Continuous Flow Synthesis of Organic Compounds

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

BY

Yachita Sharma

(Registration Number: 10CC12J26013)

Under the guidance of

Dr. Amol A. Kulkarni

Chemical Engineering and Process Development Division
CSIR-National Chemical Laboratory
Pune 411008, India

Dedicated to

My brother Ashish Sharma

सीएसआयआर–राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे – 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411008. India

Date: September 22, 2017

Dr. Amol A. Kulkarni
Scientist
Chem. Eng. & Proc. Dev. Div.
aa.kulkarni@ncl.res.in
Phone: +91 20 2590 2153

Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Continuous Flow Synthesis of Organic Compounds"** submitted by **Ms. Yachita Sharma** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Yachita Sharma
(Research Student)

Dr. Amol A. Kulkarni
(Research Supervisor)

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Continuous Flow Synthesis of Organic Compounds''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Amol A. Kulkarni**, Scientist, Chemical Engineering and Process Development Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

Yachita Sharma

August 2017 **(Research Student)**

CSIR-National Chemical Laboratory

Pune 411 008

Content

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…Yachita Sharma

PFR	Plug flow reactor
CSTR	Continuous stir tank reactor
RT	Residence time (minute or second)
FR	Flow rate (mL/min)
RV	Reactor volume
SS	Stainless steel
PTFE	Polytetrafluoroethylene
BPR	Back pressure regulator
MFC	Mass flow controller
NMR	Nuclear magnetic resonance spectroscopy
IR	Infrared spectroscopy
GC	Gas chromatography
GC-MS	Gas chromatography–mass spectrometry
NA	Nitric acid
FNA	Fuming nitric acid
SA	Sulfuric acid
NM	Nitrating mixture (sulfuric acid + nitric acid)
AcPh	Acetophenone
2-NacPh	2-nitroacetophenone
3-NacPh	3-nitroacetophenone
4-ClAcPh	4-chloroacetophenone
4-Cl-3-NacPh	4-chloro-3-nitroacetophenone
4-ClBA	4-chlorobenzoic acid
3-ClAcPh	3-chloroacetophenone
5-Cl-2-NAcPh	5-chloro-2-nitroacetophenone
OX	o-xylene
3-NOX	3-nitro-o-xylene
4-NOX	4-nitro-o-xylene
DNOX	di-nitro-o-xylene
FB	Fluorobenzene
4-NFB	4-nitrofluorobenzene
2-NFB	2-nitrofluorobenzene
ClB	Chlorobenzene
4-NClB	4-nitrochlorobenzene
2-NClB	2-nitrochlorobenzene
BrB	Bromobenzene
4-NBrB	4-nitrobromobenzene
2-NBrB	2-nitrobromobenzene
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Hypo	Sodiumhypochlorite
2-IPP	2-isopropylphenol
4-IPP	4-isopropylphenol
o/m	Ortho/ meta ratio
o/p	Ortho/pera ratio

1. Analytical grade Solvents was used.

2. Organic layers after every extraction were dried over anhydrous sodium sulfate.

4. Column Chromatography was performed over silica gel (60-120 & 230-400 mesh) and neutral alumina.

5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.

6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.

7. ^{1}H spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard.

8. GC and GCMS data were recorded on a Ultra Trace GC.

9. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

11. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

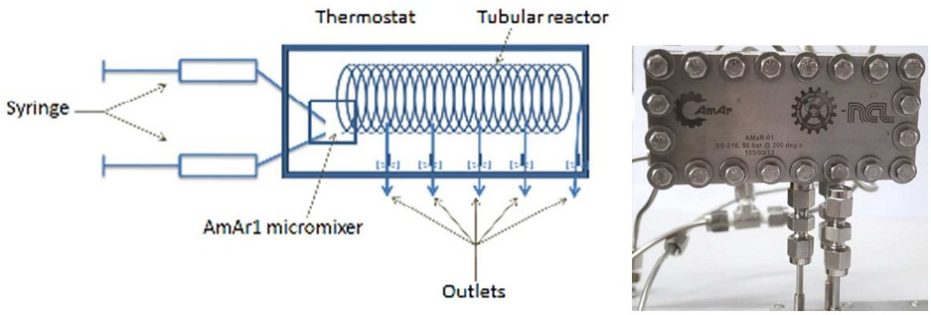
Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Yachita Sharma
Degree Enrolment No. & Date	Ph. D. in Chemical Sciences (10CC12J26013); January 2012
Title of the Thesis	Continuous Flow Synthesis of Organic Compounds
Research Supervisor	Dr. Amol A. Kulkarni (AcSIR, CSIR-NCL, Pune)

Introduction; Continuous flow synthesis using micro-reactors is now a well known reaction engineering tool that facilitates rapid mixing due to small dimensions, large heat transfer area and narrow residence time distribution. An accurate control on the residence time of the reactants and the possibility of addition of one of the substrate along the length of the reactor help to minimize sequential reactions. Several reactions have been reported in literature with better yield and selectivity when carried out in micro-reactor as compared to the conventional batch mode operations.[1] [2] The reactions that are selectivity sensitive (including polymerization reactions), radical reactions, reactions involving unstable intermediates, reactions involving toxic reagents, exothermic reactions etc. are among the most suitable reactions that can be conducted in microreactors or flow reactors.

1. Continuous Flow Nitration of *o*-Xylene

Continuous flow nitration of *o*-xylene is studied for different nitrating agents over a wide range of conditions for different parameters such as temperature, residence time and concentrations. Nitrating mixture comprising of sulfuric acid and fuming nitric acid was seen to yield higher selectivity for isomer 2,3-dimethyl-3-nitrobenzene than 2,3-dimethyl-4-nitrobenzene and also non-negligible quantity of di-nitro derivatives of *o*-xylene. With only fuming nitric acid as nitrating agent selectivity for 2,3-dimethyl-4-nitrobenzene was higher than 2,3-dimethyl-3- nitrobenzene. Impurities mainly come from nitration of mono-nitro derivatives and that too more from nitration of 3-nitro isomer due to its higher reactivity with nitric acid. The optimal condition to achieve maximum yield of 4-nitro-*o*-xylene with minimum dinitro derivatives of *o*-xylene for nitration using only FNA was found to be at 20 ºC and a residence time of 33 s, which gives 99% conversion with 0.91 m/p ratio.[4]

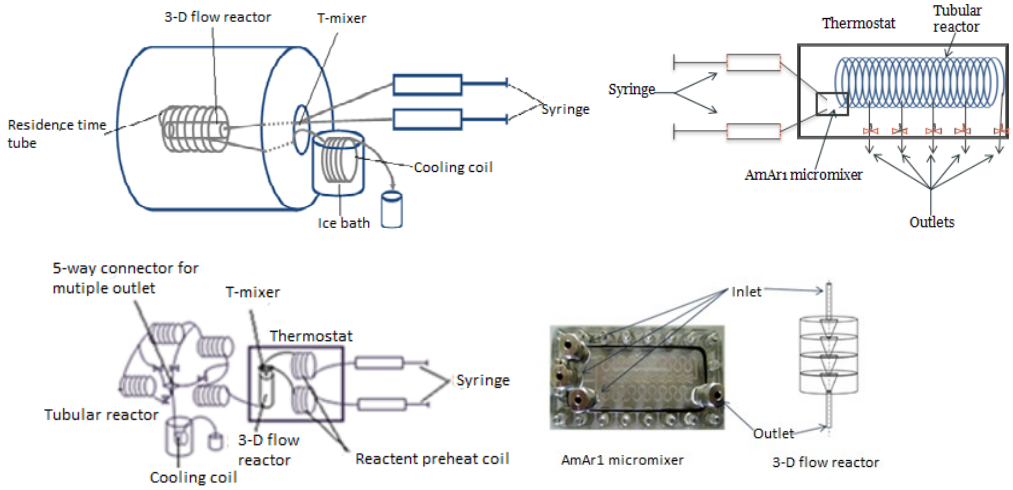


Schematic 2: Continuous flow nitration of *o*-xylene

2. Continuous Flow Nitration of Benzene and it's Halo-derivatives

Nitrobenene is used for the synthesis of paracetamol (drug), urethanes , pesticides, dyes, explosive, agriculture and horticultural flowering from centuries. Pharmaceutical industries have also large interest in nitro-halobenzenes as these are intermidiates for many drugs and exhibits Mutagenic activity. Similarly, nitrofluorobenzene is used as antiarrythmic, antihypertensive and antiischemic drug agent, also it is in demand as an intermediate for antioxidant for rubber and anti-leprosy drug – Dapsone. Nitrobromobenzene is in demand for drug manufacturing for hypnotic, sedative and antiemetic feature.

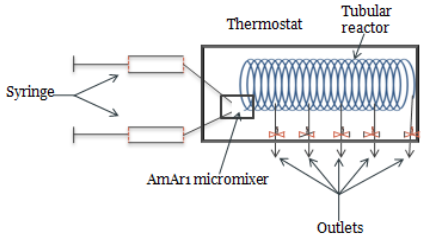
Continuous flow nitration was studied using fuming nitric acid as a nitrating agent and with a catalytic amount of sulphuric acid. Benzene nitration was performed with complete consumption of used fuming nitric acid where 2w% of sulphuric was used. Over 99% conversion was achieved for fluorobenze, chlorobenzene and bromobenzene in 2.34, 3.63 and 4.89 min resulting in 87%, 69% and 92% *p*-isomer selectivity respectively.



Schematic 3: Reaction setup a) Furnace b) Isothermal setup c) Adiabatic setup with reactant preheating, and AmAr1 and 3-D flow reactor

3. Continuous Flow Nitraton of Acetophenone and Chloro Substituted Acetophenones

The continuous flow nitration of acetophenone & substituted acetophenone was carried out in a safe manner in a shorter reaction time than the conventional approach. The choice of micromixer was seen to affect the performance of the nitration reaction. The effect of different parameters on the yield of the desired product was studied.[3] In this case 94 to 99% conversion achieved with higher selectivity, using solvent free conditions. Results are summerized in Table.



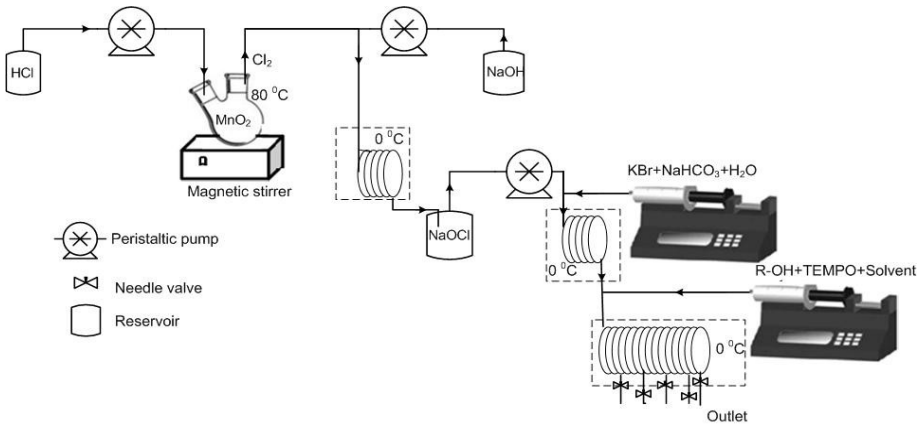
Schematic 1: Continuous flow nitration setup of acetophenone and substited acetophenones

Table1: parameters studied and results

Substrate	N. A. Moles (FNA)	Residance time (min.)	Temperature (^oC)	Optimal condition	Result
AcPh	1.8 & 8 (H_2SO_4 in some cases)	3 - 10	-10 - 20	Temp.: 10 ºC R.T. : 10 min	Conv.-: >99% o/m: 2.2
3-Cl-AcPh	3 – 7	2 - 10	10 - 70	Temp .: 50 ºC R.T. : 5.8 min	Conv. : 94% 5-Cl-2-NAcPh Yield : 56.4
4-ClAcPh	2 –10	2.63 – 20.00	-10 - 70	Temp .: 0 ºC R.T. : 10 min	Conv. : 96% 4-Cl-3-NAcPh Yield : 40%

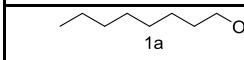
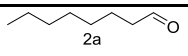
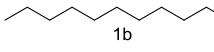
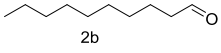
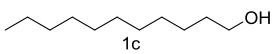
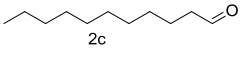
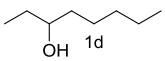
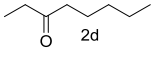
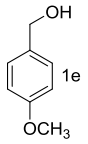
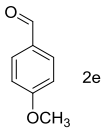
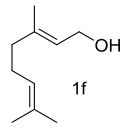
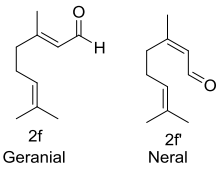
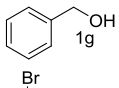
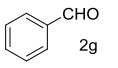
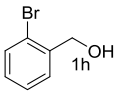
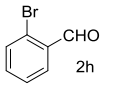
4. Continuous Flow Telescopic Oxidation of Alcohols via Generation of Chlorine and Hypochlorite

A three-step continuous flow oxidation of alcohol is demonstrated with continuous chlorine generation as the first step followed by its use for the flow synthesis of high strength sodium hypochlorite. The solution is subsequently used for oxidation of alcohols in presence of catalytic amount of nitroxyl radical "TEMPO", which inhibits oxidation at the aldehyde stage- Selective
oxidations of eight different alcohols.[5] For achieving identical yields the aromatic alcohols containing electron withdrawing groups needed longer residence time than aliphatic alcohols.



Schematic 4: Three-step continuous flow alcohol oxidation (1.5 equivalent of hypochlorite, pH = 9.5, adjusted by addition of saturated NaHCO3, 5 mole% KBr, 3 mole% TEMPO)

Table 2: 3 mole% of TEMPO, 1.5 equivalent of hypochlorite (PH= 9.5, adjusted by addition of saturated $NaHCO_3$), 5 mole% KBr . [For 1g and 1h, TEMPO is 5 mol% and 7 mol%, respectively] [For entries 1e and 1h, yield is based on GC area%]

Reactants	product	% Conversion of alcohol	Impurity (area %)	% yield of Aldehyde	Residence time (min)
 1a	 2a	99.35	5.0	95	8.67
 1b	 2b	94.14	2.5	90	6.57
 1c	 2c	100	-	95.3	5.56
 1d	 2d	99.18	-	99	4.88
 1e	 2e	96.3	-	89	5.05
 1f	 2f Geranial 2f' Neral	100	20	80 (Gerenial/Neral 0.29)	6.67
 1g	 2g	100	-	99.82	4.05
 1h	 2h	99	8	90.1	15

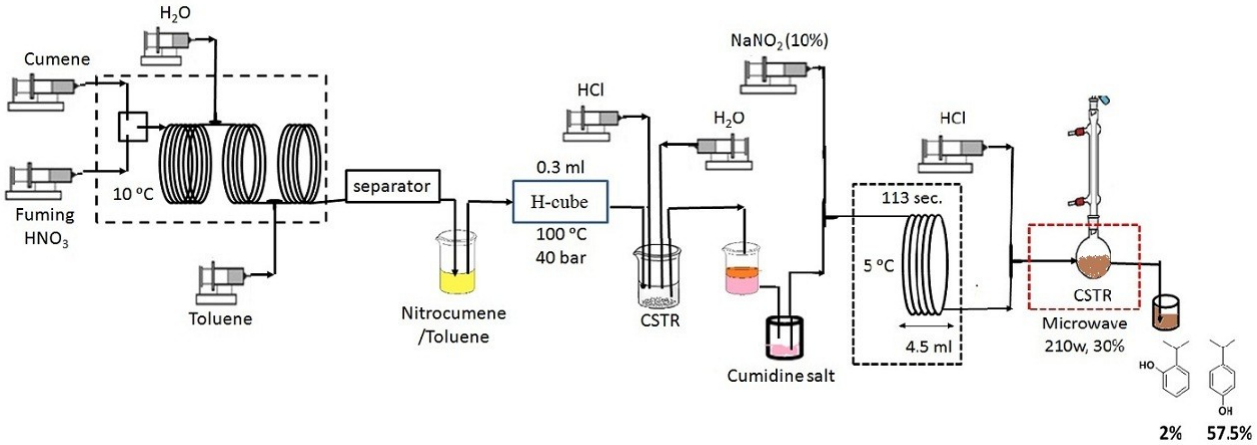
5. Multi-step flow synthesis of isopropyl phenol

Isopropyl phenol is an intermediate for the manufacture of agrochemicals, UV stabilizers, polymerization inhibitors and anti-oxidants etc. It may also be use for the production of phosphorus containing plasticizers instead of cresol, as diphenylisopropylphenyl phosphate is less toxic then tricresylphosphate. Generally isopropyl-phenols are synthesized by either rearrangement of saturated alkylphenylethers or by the selective oxidation of di-isopropylbenzene.

Here a **c**ontinuous multi-step flow synthesis of isopropyl phenol is demonstrated via nitration of cumene followed by reduction, diazotization and hydrolysys.[6] The first step nitration of cumene with fuming nitric acid gives 2 and 4-nitrocumene, which upon continuous separation of organic layer followed by reduction using H-cube with Pd/Ni gives cumidine. Followed by diazotization in acidic environment and hydrolysis at higher temperature it gives 2-isopropyl phenol and 4-isopropyl phenol. All steps give good yield of desired product.

Table 3: Results of nitration, reduction, diazotization and hydrolysis steps

Reaction	**Reaction condition**	**Conversion %**	**2-isomer yield %**	**4-isomer yield%**
Nitration	10 ºC temp., 10 min	99.9	18	60
Reduction	100 ºC temp, 40 bar, 1.5 min	100	85.28	74.67
Diazotization	0 ºC temp, 1.9 min	100	100	100
Hydrolysis	Microwave 240 w, 35%,6.7 min		13.3	96.7
	PFR, 16 equi. H_2SO_4, 80 ºC, 10 min.		33.76	6.05



Schematic 5: Integrated multi step flow synthesis setup of iso-propylphenole

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A Process for the Preperation of Isopropylphenol from Nitrocumene. Indian Patent, 2014.

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Chapter 1

Introduction to Continuous Flow Synthesis

1.1 Introduction

Chemistry plays an extremely important role in our day to day life. Our day starts with chemicals like calcium carbonate and sodium fluoride present in toothpaste, after that soap which is made up of esters. Mouthwash, detergent, cleaner, medicines, food, our surrounding like plastic containers, chairs, clothes, paint, door, fragrances, fan, drinks, TV, laptop, etc. are some very important things without which we can't imagine our life. These all essential things are made up of some organic or/and inorganic chemicals, so chemistry is an essential part of our day to day life. Table 1 shows a brief list of some essential chemicals of our day to day life

Table 1. 1: Chemicals present in day to day life things[$]

	Everyday life material	Chemicals in
1	Mouthwash	hydrogen peroxide and fluoride
2	Toothpaste	calcium carbonate and sodium fluoride
3	Deodorant stone	potassium aluminium sulfate
4	Soap	sodium stearate
5	Salt	sodium chloride
6	Aspirin	salicylic acid
7	Vinegar	Acetic acid
8	Antifreeze	Ethylene glycol
9	Batteries (car, bike)	Sulphuric acid
10	Furniture polish	Ammonia, naphtha, nitrobenzene, petroleum distillates, and phenol
11	Drain cleaners	Lye and sulphuric acid
12	Dishwashing detergents	Anionic,cationic, or non- ionic solutions plus phosphates
13	Whole grains	antioxidants, B vitamins, phytochemicals, carbohydrates, protein, healthy fats and minerals like iron, copper, zinc, magnesium
14	Vegetables/fruits	Sodium, potassium, iron, magnesium, carbohydrate, vitamins,
15	Sugar	glucose and fructose
16	Bbaby's toys, shower curtains cosmetics and most of the plastic products	Phthalates and PVC (Polyvinyl Chloride)
17	Badminton strings	Vectran an aromatic polyester of 4-

		hydroxybenzoic acid and 6-hydroxynaphthalene-2-carboxylic acid
18	Golf balls	Surlyn copolymer a high-performance ethylene copolymers containing acid groups partially neutralized using metal salts such as zinc, sodium and others.
19	Cricket helmet	Titanium, Polycarbonate, ABS plastic, Polyester
20	Bleach	Sodium hypochlorite solution
21	Mothballs	Naphthalene, P-Dichlorobenzene
22	Candle	paraffin
23	Engine antifreezes	Ethylene glycol
24	Drug to reduce the risk of heart disease and stroke	Fenofibrate, Clopidogrel
25	Anticonvulsant drug used in the treatment of epilepsy bipolar disorder, and clinical depression	Lamotrigine
26	Medication for the treatment of type 2 diabetes	Metformin
27	Nonsteroidal anti-inflammatory drug (NSAID)	Ibuprofen

[$]Compiled from various sources

Almost each and everything in our surrounding is the result of some organic and inorganic reactions, for which typical batch processes has been in tradition from centuries, which are very crucial in term of time and labor consumption.

1.2 Methods in organic synthesis

i. Batch Reactions
ii. Semi-batch
iii. Continuous flow synthesis

i. Batch reactions: Typically batch reactor has larger volumes, where mixing is achieved by vigorous stirring. Materials are charged in one go in a batch reactor, and the reaction proceeds with time, it does not attain a steady state, and control of temperature, pressure and volume is necessary. In a batch reactor mixing generates

inhomogenety of energy distribution in reactor which causes hot spot and by product. A 250 mL round bottom flask has surface to volume ratio is around 80 m^2m^{-3} which is very less for proper heat dissipation.[1] Reaction time can be explained as the time spent under specific reaction conditions. A Huge quantity of solvents used in reactions to control fast reaction, or generate homogeneity in the reaction mixture.

By-product formation, industrial waste adds extra steps of separation and purification which adds on the unnecessary economical burden to the process in terms of energy consumption, labor cost and time. Lose of tons of material if something goes wrong in one batch, which hikes the production cost and market prices.

ii. **Semi batch reactor:** Semi batch reactor can be explained as a combination of batch and flow reactor. The reaction takes place in a single stirred tank reactor which modified to allow reactant addition and/or product removal in time. It has several advantages over the batch reactor. Exothermic reactions can be easily taken care in semi batch reactor as it allows the continuous slow addition of one of the reactor which controls reaction rate and heat removal. It controls the selectivity of product in parallel reaction by slow addition of reactant, or series reaction by continuous removal of the product.

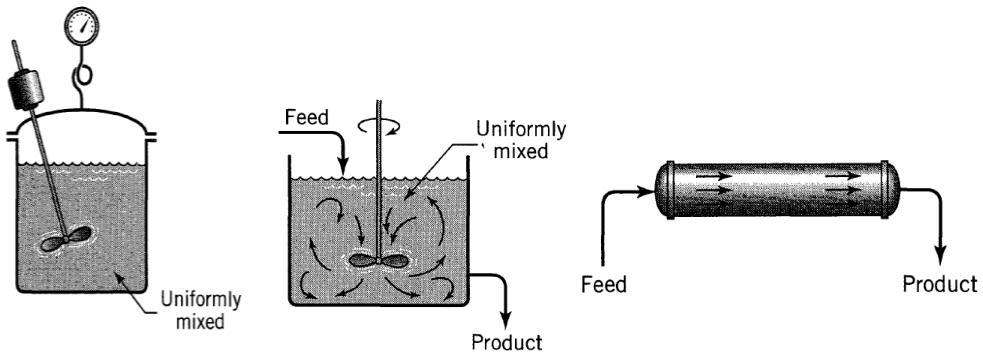

Figure 1. 1: a) Batch reactor, b) Semi-batch reactor, and c) Continuous flow reactor[2]

iii. **Continuous flow reactor:** In a continuous flow reactor, all reactants flow together throughout the inlet to the outlet of the reactor and their volumes are very less. They run at steady state and reaction mixture composition doesn't change with time. Residence time can be defined as time interval in-between inlet and outlet of the reactor.

1.3 Continuous Flow / Microreactor:

Continuous flow reactors can be of various dimensions viz. miniaturized channels with diameters in the range of 10 – 500 micron or tubular reactors in various forms (viz. straight tubes, coils, spirals etc.) of 1 mm to 100 mm tube diameter, etc. They are typically made up of non-reactive material like glass, acryl, silicon, stainless steel, quartz or polymers. In flow, reaction proceeds as the substances/reactants travels through the reactor and the composition of the reaction mass continues to vary along the reactor length. In the absence of any radial in-homogeneity the concentration remains uniform over the tube cross-section at any location along the reactor length. The residence time of a reaction in flow is associated with the total time spent in the reactor and is estimated as the ratio of reactor volume and the total flow rate. Residence time can be controlled by changing reactor volume or by changing the total flow rate. Here in flow set up residence time and the time needed to process certain volume are not same as in the case of most of the batch reactions. Flow rates of individual substances are calculated by their volumetric ratios, which basically come from molar ratios.

$$\text{residence time (min)} = \frac{\text{volume (ml)}}{\text{flow rate (ml/min)}}$$

1.3.1 Advantage of flow reactors:

Microreactor technology provides rapid process development with higher purity, conversion and yield. This technique is reproducible because of automated parameter control over the reaction. Excellent mixing and heat transfer can be achieved with its unique characteristic of small channel dimensions.

i. **Control over fast reactions:** For proper conversion and selectivity, control over mass and heat transfer is the necessity of a chemical reaction. In batch mode fast reaction can be controlled by either decrease in reaction temperature or by the dilution method which decreases the frequency of effective collisions, leads slower reaction rate. In both cases reaction becomes mixing dependent. In continuous flow, the reaction can be controlled by decreasing residence time without any change in reaction rate or concentration. Due to small diffusion path it provides excellent mixing, and heat transfer which is unattainable in big reaction vessels.

ii. **Improved mixing:** Mixing takes place with the diffusion of molecules in the reaction vessel. Mixing time is proportional to the square of the length of diffusion path and

hence smaller diffusion paths in microreactors help to achieve very small mixing times. In batch reactors mixing is achieved by stirring which creates non-homogeneous energy distribution in reaction vessel with turbulence and chaotic mixing. Microchannel with shorter diffusion path and small volume provides excellent mixing with laminar flow. In case of homogeneous reactions where reactants, products, catalyst all are in the same phase, mass transfer effect can be avoided.[3] However, in case of heterogeneous reaction where reactant species are immiscible (viz. gas-liquid, liquid-liquid, gas-liquid-solid, etc.) the reaction rate relies on mass transfer between the two phases. In order to understand conversion, product formation and reaction rate, mixing plays an important role.

iii. **Precise temperature control:** Heat transfer in between interior of the reactor and surrounding takes place via reactor surface. Higher the value of surface area to volume ratio, more efficient will be the heat transfer. Standard microreactors come with channel diameter of 1 mm which have higher surface to volume ratio that helps rapid heat dissipation. This helps for carrying out highly exothermic reactions *viz.* Ozonolysis reaction to be performed even close to 0 ºC and even higher temperature in shorter reaction time instead of -78 ºC over several hours.[4] A temperature profile of can also be applied with excellent control for the continuous-flow process for the Synthesis of 2-ethylphenylhydrazine hydrochloride.[5] Heat transfer depends on the heat transfer per unit time (Q/t), the conductivity of the material (k), surface (S), distance between two ends, (d) higher temperature end (T_1), and lower temperature end (T_2). Reaction kinetics (rate, conversion, selectivity) can be calculated depending upon heat transfer calculations.

$$\frac{Q}{t} = -kS\frac{T1 - T2}{d}$$

iv. **Selectivity:** Reactions which give more than one product are usually temperature sensitive. The activation energy for each reaction is different and so is also the heat of reaction. While a typical batch reaction usually gives a broader temperature distribution profile and hence inefficient heat transfer, a microreactor offers very narrow temperature distribution with its unique characteristics of rapid heat dissipation and restricts the formation of undesired products.[6]

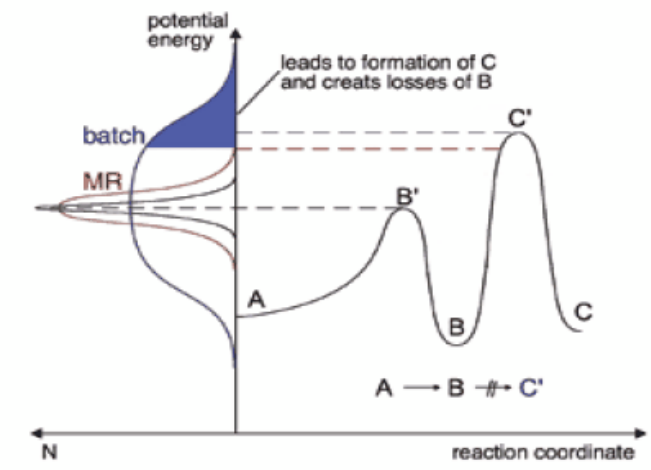

Figure 1. 2: Temperature distribution profile and selectivity in batch and flow

v. **Shorter reaction time:** There is an approximate correlation between the reaction time and size of the reaction environment i.e. reactor volume. In continuous flow reactors with smaller diffusion lengths, it provides excellent mixing and rapid heat dissipation with the help of higher surface to volume ratio and hence can be operated at a very different condition than a typical batch reactors.[7] For example, highly exothermic Grignard reactions require reaction temperature -20 ºC in batch with the reaction time of 55 min, same reaction was successfully performed in a flow reactor at room temperature in a residence of 33 min, with 1.2 equivalence of Grignard reagent in the place of 2 equivalents.[4] Similarly bi-phasic bromination reaction using hypobromite as brominating reagent requires 22 hrs in batch at 38 ºC, while it gets completed just in a residence time of 3 minutes using a continuous flow reactor at 85 ºC and excellent mixing provided by glass static mixture.[3a]

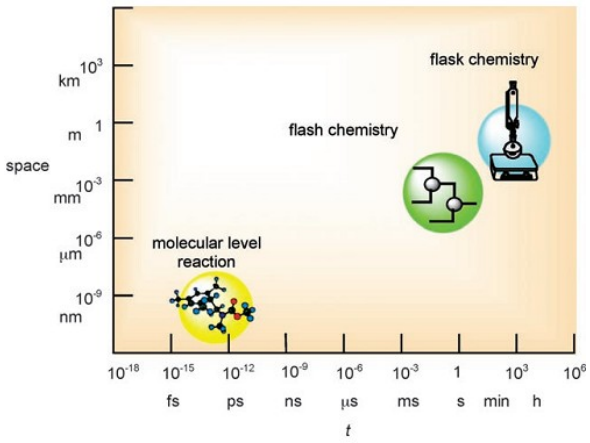

Figure 1. 3: Time/space relationship of chemical reactions[1]

vi. **Reproducibility:** Continuous flow processes are usually reproducible because in addition to the controllable parameters like initial/inlet reactant concentration, temperature and flow rate etc., the residence time, flow pattern result in giving consistent results. Further to this, automation also helps to improve the reproducibility. Flow rate is controlled by pumps, reaction temperature controls by reactor type and heating cooling bath, MFC controls inlet gas flow rate while back pressure regulators take care of pressure inside the reactor, mixing and heat transfer controls by a microreactor, so all parameters remain consistence and there is no chance of manual error due to operator independent control. As much time it will be operated, it will give the reproducible result.

vii. **Safety:** Proper heat dissipation is the necessity of exothermic reactions to avoid thermal run away, which is taken care by higher surface to volume ratio of microreactores. In general, the level of safety precautions increases with increasing process volumes. Continuous flow synthesis avoids the need of large inventories of reactants. Any times these include toxic chemicals, reactive gases, air or moist sensitive and unstable reagents, and shock sensitive intermediates and those can be handled with better precautions in flow[8]. Even the short reaction times and very different operating conditions reduce the reactor volumes significantly and it provides a much safer platform for hazardous reaction at lab scale as well as at industrial stage.

viii. **Scale up:** Heat transfer, mass transfer, thermodynamics and overall reaction rates strongly influence the performance of a flow reactor. Systematic numbering-up approach can be used for quick translation of a laboratory scale process to an industrially feasible process.[8c, 9]

1.3.2 Limitations of flow reactors:

Continuous flow synthesis also has a few specific limitations that can be overcome through systematic engineering analysis of the problem. Some of the limitations are discussed below.

i. **Solid handling and clogging:** Introduction of solid compound in flow reactor is very challenging. In batch reactions, solids can be directly added to the reaction mass

without adding additional solvent. For the reaction of the same solid compound in continuous flow manner, it has to be dissolved in some solvent, which makes it more diluted and decreases the rate of reaction. Some organic compounds are partially soluble in solvents and remain as slurry like naphthalene which has MP of 80.26 ºC is partially soluble in 1,2-dichlorobenzene and 1,2-dichloroethane, on other hand some reaction like bromobenzene nitration forms solid product p-nitrobenzene of MP 124 ºC, performing this kind of reactions in flow manner may clog the reactor depending upon solubility.

ii. **Material compatibility:** all chemicals are not compatible with all material of construction, so during reactor designing, construction material should be chosen very carefully keeping reaction chemistry in mind. For example, sulphuric acid (98%) and hydrochloric acid (37%) are not SS-316 compatible, while Fluoroelastomer (FKM), PTFE and PVDF are some construction material which shows excellent compatibility towards these chemicals. Similarly, PVDF shows excellent compatibility for nitric acid (69%) but non-compatible with fuming nitric acid (98%)

1.4 Type of flow reactor:

I. **Continuous Stir Tank Reactor (CSTR):** Continuous Stir Tank Reactor, also known as a backmixed reactor, is a cylindrical vessel of constant reactant volume. It runs with a continuous flow of the fluid that enters and exits. For the agitation of the fluid, it is equipped with an impeller blade or magnetic stirrer. It is assumed to be an isothermal and steady state, with consistent composition throughout the reactor same as the outlet of the reactor. The reaction can be controlled by changing in and out flow rates, which will basically change residence time. It is basically used for the reaction involves slurry, solid or precipitation, which cannot be handled in microchannels, where mixing achieved by stirring.

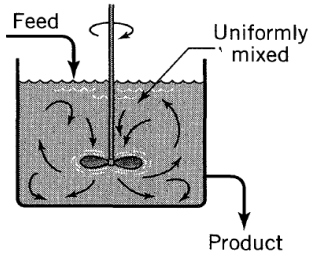

Figure 1. 4: Continuous flow stir tank reactor

II. **Plug flow reactor (PFR):** Plug flow reactor is also known as a continuous tubular reactor. The reaction proceeds as reactants travel through the reactor. At the inlet of PFR reaction rate is very high which decreases throughout the reactor as reactant concentration decreases. Reaction mixture composition varies with the length of reactor and it gives constant composition at same length even after several hours of reaction time

In reality, not every flow reactor is a PFR and it is usually a combination of PFR and CSTR based on the extent of backmixing in the reactor. The backmixing has severe consequences on fast reactions and hence the analysis of extent of backmixing for bench scale (50 mL < volume < 200 mL), pilot scale (200 mL < volume < 500 mL) and commercial scale reactors (volume > 500 mL) is essential. However all the reactions reported in this thesis are based on lab scale synthesis and hence no quantitative analysis of extent of backmixing was performed.

1.5 Reactor equipment:

To make a perfectly working continuous flow setup residence time tube, union, expender, reducer, sampling valve, non-return valve, micromixer, gas filter, tools for connection, temperature and pressure sensor, back pressure regulator, pump, constant temperature bath etc. are some of the necessary things.

Figure 1. 5: Equipment of continuous flow reactor

i. **Fittings and tubing:** To perform flow chemistry in the lab, firstly separate parts of the reactor have to be assembled to make a working flow set up. It requires tubes and different fittings which come in stainless steel and polymer materials, should be chosen considering chemistry. For lab scale commonly used tubes and fittings are of 1/16", 1/8" and 1/4" outer diameter.

ii. **Pump:** Pump is a device that facilitates physical or mechanical action of moving fluids (liquid or slurries) by consumption of energy, commonly rated by flow rate, pressure, and horsepower. On the basis of their diasplacement, they can be classified into positive displacement, dynamic, velocity, valveless, steam, impulsive and gravity pumps. Out of these centrifugal and positive displacements are two basic pumps.

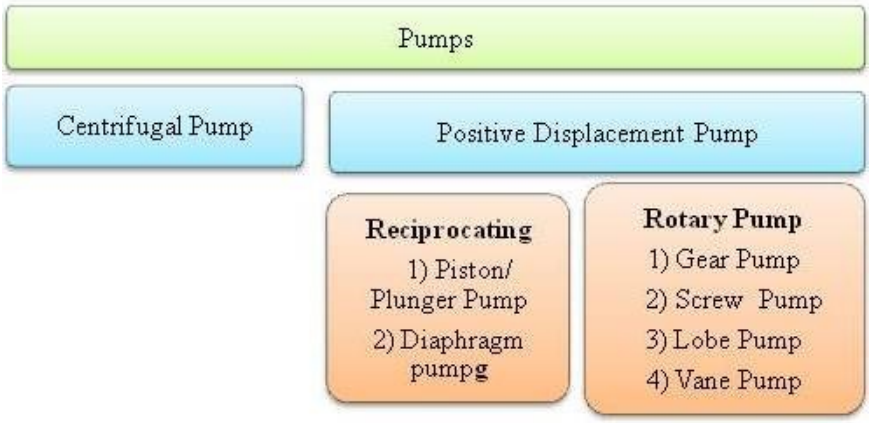

Figure 1. 6: Classification of pump

a. **Centrifugal pump:** Centrifugal pumps are valveless pumps with torque characteristics, available in various materials like cast iron, steel and stainless steel alloy, ceramic and plastic. They provide high flow rates at low pressure, commonly use for sewage, water, petroleum and petrochemical pumping. Cavitation, corrosion due to fluid property, impeller failure, spills, leakage along rotating the shaft and overheating due to low flow are some limitations of centrifugal pumps.

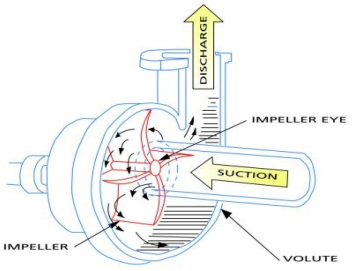

Figure 1. 7: Centrifugal pump[10]

b. **Positive displacement pump:** In positive displacement pump, fluid flows with the action of expanding cavity and decreasing cavity at suction zone and discharge zone respectively. It gives approximately constant flow despite the pressure. Positive displacement pump are of two types 1) rotator pump and 2) reciprocating pump depending on the flow of the fluid from the discharge side. Reciprocating pump has a pulsating manner while the rotary pumps results in a smooth flow. At lab scale syringe pump, piston pump and peristaltic pumps are of more interest.

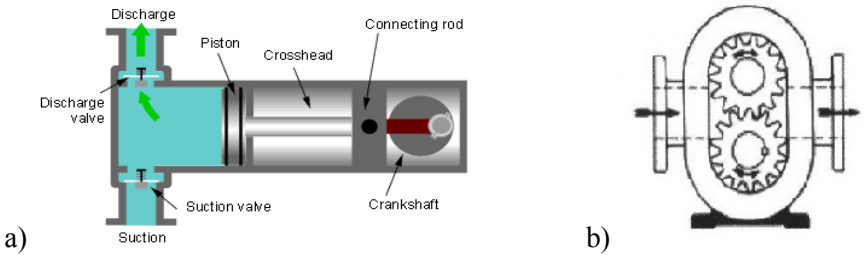

Figure 1. 8: a) Reciprocal pump, b) Rotatory pump

Table 1. 2: Selection criteria of pumps on the basis of required flow rate and pressure

Pump	Flow rate	Pressure	General criteria
Syringe Pump	pl/min to few mL/min	up to 15 bar	When very accurate and pulseless flow is required
Peristaltic Pump	few mL/min to few L / min	up to 16 bar	contamination-free pumping suitable for use in high purity applications
Diaphragm Pump	few L/min	up to 10 bars	Handling Aggressive media including gasses and gas/liquid mixtures.
Piston & Plunger Pumps	few mL/min to few L/min	wide range	High Head requirements. Select a plunger pump for high-pressure applications
Gear Pump	few mL/min to L/min	wide range	Internal Gear: Moderately viscous fluids External Gear: Highly viscous

iii. **Constant temperature bath:** Organic reactions are highly temperature sensitive, should be carried out at a constant temperature. A slight change in temperature can be change into a ratio of products and by-products. Constant temperature bath is a fluid circulating device with heating and chilling units, which maintains a constant temperature by heat transfer. Flow set up can be placed inside this bath or fluid may be circulating to the jackets of CSTR. Some assembled reactors like vapor tech come with its own heating and cooling assemblies within the system.

iv. **Back pressure regulator (BPR):** Some chemical reactions where gas generates as one of the products or side product,or solvents heated higher than their boiling point generates some pressure inside the system. Back pressure regulator sense pressure inside the reactor and keeps it constant by an opening one way valve to remove excess pressure generated in the system and provides constant outlet flow rate. Zhang et. al. used acetonitrile (BP 82 ºC) as solvent at 150 ºC reaction temperature for ullmann coupling,[11] with BPR of 250 psi. Selection of back pressure regulator depends on the reaction temperature, pressure, flow rate, type of gaseous stream and pump.

v. **Mass flow controller (MFC**): Mass flow controller control and measure the flow of gas. It's based on the principal of thermal sensor. It gives constant flow without being affected by surrounding conditions as gas pressure, temperature etc.[9, 11] It is generally made up of SS316 with viton as sealing material.

vi. **Temperature sensor:** Temperature sensor moniters the in and out temperature of the reaction mixture and the coolent fluid which helps in reaction monitoring and energy balance calculations. Constant temperature indicates the steady state in the system.

1.6. Choice of parameters:

Chemical reaction can be explained by the braking old bond and new bond formation which leads to the generation of new chemical formula. This bond breaking and bond generation affects by many parameters, like reaction temperature, as an increase in temperature provides more energy for bond breaking, solvent, reaction pressure, residence time etc.

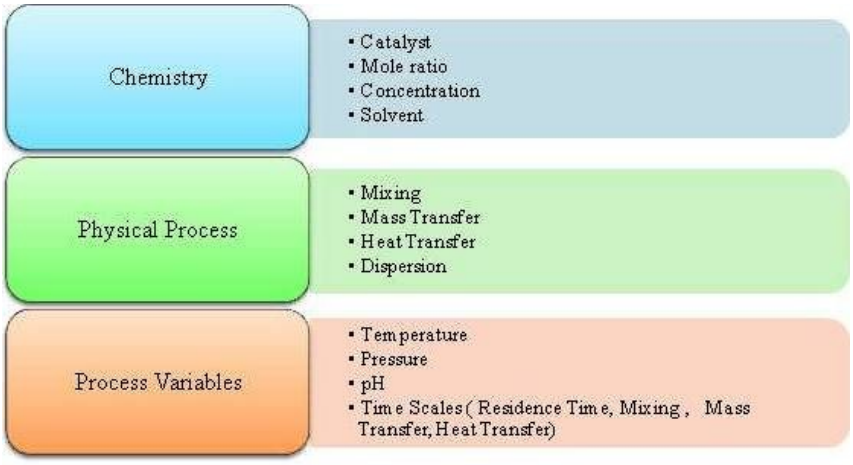

Figure 1. 9: Parameters affects the reaction rate

I. **Catalyst:** Catalysts accelerate reaction rate by providing an alternative pathway of lower activation energy without undergo any change itself. Enzymes are the most common and efficient catalysts occur in all living body for proper functioning. As well in chemistry, catalyst plays an important role in the bulk production of chemicals, specialty chemicals, pharmaceuticals etc. They may be heterogeneous or homogeneous depending on chemistry, out of which heterogeneous preferred in industries due to easy of separation. Choice of catalyst and its quantity depends on reaction chemistry and compound to be treating. For example for the reduction of ethyl nicotinate Pd/C is used, it gives partially and fully reduced products. On using 5mol% catalyst 90.7% of partially reduced and 8.3% fully reduced products were achieved, while on using 10mol% catalyst, fully reduced product increased to 14.7% with 84.2% partially reduced product.[9]

II. **Mole ratio:** Stichiometry of reactants plays an important role for reaction to proceed. The reaction rate can be accelerate or reduce by changing catalyst moles. A Higher ratio may lead by-product formation while lower can limit the reaction. More reagent quantity requires in batch as compare to flow because of poor mixing.[4]

III. **Solvent:** Solvents can affect solubility, stability and reaction rates and can control thermodynamics and kinetics of the reaction.[6a, 8b] For example rate of exchange reaction of sodium acetate with methyl iodide to give methyl acetate and sodium iodide is 10 million times faster in DMF as compared to methanol. It's because of the tendency of hydrogen bond formation of methanol with acetate ion, which reduces the rate of reaction by decreasing reactivity of oxygen of acetate ion. In case of hydrogenation of ethyl nicotinate, 49.5 and 90.7% complete hydrogenated product was achieved with ethanol and ethyl acetate solvent respectively.[9] Viscosity of solvent also affect reaction rate by controlling its colloidal frequency.

IV. **Temperature**: According to Arrhenius equation, the rate of reaction is severely influenced by the reaction temperature. In continuous flow synthesis much higher temperature can be controlled as compare to batch due to its unique capability of rapid heat dissipation.

V. **Pressure:** In the gaseous reactions, increase in pressure increases the rate of reaction as pressure indicates the concentration of gaseous substances according to ideal gas law. And it affects the reaction rate according to Le Chatelier's Principle.

$$P = \frac{n}{V} * RT$$

P- Pressure

n- Number of moles

V- Volume

RT - Constant at constant temperature

VI. **Residence time:** In a batch reactor, the reaction time is the total time spent by reactants under defined condition, while in a flow reactor, the residence time can be explained as the time spent in reactor zone which basically determined by the ratio of reactor volume (mL) and bulk flow rate (mL/min). When two reactants come in contact they react and form product and by-product, a specific time is required for completion of the reaction, if reaction time is lesser than the residence time then the conversion will remain incomplete. On providing higher residence time more by-products can also get formed for network of reactions kind of a system (viz. halogenations, nitration, oxidation, etc.).

1.7 Selection criteria for the reaction:

An exothermic reaction, multiphase reaction, reactions involve unstable or sensitive intermediates, reactions where mixing or heat transfer comes in the picture, reactions deals with selectivity issue, reactions involving safety concern, all these types of reactions can be easily transferred from batch to flow.

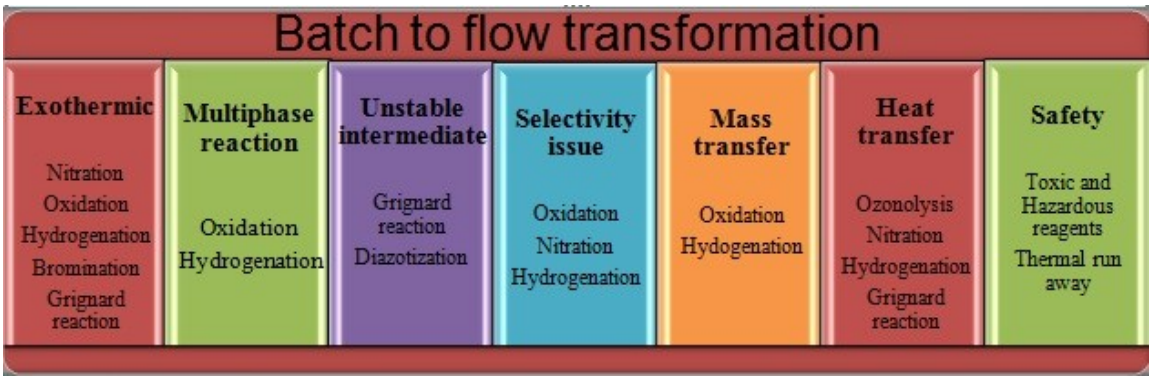

Figure 1. 10: Selection criteria for choosing reaction from batch to continuous flow

1.8 Case study:

According to kinetics a chemical reaction can be classified into three categories. The first category is a very fast reaction which requires milliseconds to few seconds for completion, rate/mixing dependent reactions. The second class of reaction also comes in the category of fast reactions which completes in several seconds to minutes, and these are mainly rate limiting, can be affected by temperature, concentration, pressure and solvent. And the third type of reaction is slow reactions which require several minutes to hours for completion, associated with autocatalysis and thermal accumulation.

On the basis of reacting phase these can be further classified into two categories, homogeneous reaction and heterogeneous reaction.

I. Homogeneous reaction:

When all reactants, catalyst lies in the same physical state either aqueous, organic or gaseous, known as a homogeneous reaction. These reactions are mostly mass transfer independent and kinetically controlled.

a. Synthesis and purification of Ibuprofen

A multi step three minute continuous flow synthesis of Ibuprofen drug was established with through put of 8.09 g/h,[7a] which is an essential medicine in the list of World Health Organization (WHO). It's continuous synthesis includes five steps including three chemical transformation (Friedel-Crafts acylation, oxidative 1,2-aryl migration, simultaneous quench of excess oxidant and saponification of ester) , one work-up and one in-line liquid-liquid separation. $AlCl_3$, acid chloride and arene in dichloromethane are typical reagent of Friedel-Crafts reaction, very explosive on using neat and generates heterogeneity in the mixture, can clog the flow reactor. In order to remove the solvent, Jamison et al. have used 1:1 ratio of propionyl chloride and $AlCl_3$ with a slight excess of $AlCl_3$, where propionyl chloride itself act as a solvent to deliver $AlCl_3$. Aluminum is not compatible with oxidative 1,2-aryl migration and it is soluble in aqueous phase below pH 4.5 so reaction was quenched in-line using HCl which generates 2 immiscible liquids, , separated by an in-line liquid-liquid separator. A PFA reactor of 600 µl was used for this first step at 250 psi pressure. ICl, the polymorphic solid was used for the second step which is soluble in a little amount of solvent. It generates I_2 which may clog reactor so DMF was added to TMOF feed to dissolve it. This step was carried out in 120 µl PFA reactor. Excess ICl may harm back

pressure regulator, so it was quenched using 2-mercaptoethanol, it doesn't dissolve sodium halide salts and create clogging but it is essential as phase transfer reagent of the substrate to transfer in the aqueous phase, so 1:3 mixture of methanol and water was used in the reaction. This mixture provides a suitable condition for hydrolysis. A PFA reactor of 200 µl was used at 250 psi pressure for this final step. This synthesis demonstrates the ability of continuous flow mode to handle extreme reaction conditions in the production of pharmaceutical compounds at lab scale as well as at large scale.

b. Reaction using Grignard reagents

Grignard reactions are an important tool for C-C bond formation. These reactions are highly exothermic and sensitive towards air and moist, apart from this, Grignard reagent shows exceptional reactivity towards a wild range of electrophilles. This excellent reactivity and exotherm can be easily control by encrypting flow method, which provides homogeneous mixing and narrow temperature distribution profile for restricting to the target product. Riva et al.[4] used a commercially available vapourtec flow unit to explore reactions involving Grignard reagent. 4-isopropylbenzaldehyde was chosen as an initial compound for the screening of reaction. 4-isopropylbendaldehyde and (2-methylallyl)magnesium chloride in THF was stored under N_2 atmosphere and directly pumped to the reactor. A short column of polymer-supported benzeldehyde was assembled at the outlet of the main reactor for scavenging of the excess Grignard reagent. Multiple parameter combinations of reaction temperature, residence time, Grignard equivalent were applied to the optimized reaction. 98% conversion was achieved on using 1.2 equivalent of Grignard reagent in residence time of 33 min at room temperature, while in batch just 29% conversion was achieved by applying the same condition in much longer reaction time of 120 minutes. For 95% conversion, batch requires 2 equivalents of Grignard reagent and 50 minutes at -20 ºC. In conclusion a library of secondary and tertiary alcohols was established in safer and controlled manner using continuous flow method.

II. Heterogeneous reaction:

Heterogeneous reaction (multiphase reaction) can be defined as gas-liquid, liquid-liquid, liquid-solid, gas-liquid-solid and gas-liquid-liquid, playas an important role in chemical and pharmaceutical industries. These reactions known to be mass transfer

dependent, in batch mixing is achieved by vigorous stirring, while in flow diffusion in small channels provides excellent mixing.

i. **Biphasic (liquid-liquid, gas-liquid, solid-liquid, solid-gas) reaction:** Heterogeneous catalytic reaction where the reaction takes place at the surface of the catalyst, gas-liquid reaction, reactions of two immiscible liquids all comes under the category of biphasic reactions. Here we will discuss some examples of these reaction basically which performed in the flow.

A. **Heterogeneous catalytic reaction:** Reactions in which solid catalyst is used with liquid or gaseous main stream comes under this category. Leaching, quenching and separation are crucial steps in such type of reaction which can be overcome by using catalyst column.

a.Coupling and decarboxylation reactions promoted by copper tubing

Presence of copper catalyst is essential for some chemical transformations. For the transformation of such kind of reaction into the flow, Zhang[11] used commercially available Vaopotec flow reactor in which they used copper tube reactor. This copper tube can be heated upto 250 ºC. Firstly they tried Ullmann coupling which required higher catalyst loading, higher reaction temperature and longer reaction time. They used tertra-n-butylammoniumacetate (TBAA) as base aand acetonitrile as a solvent for reaction no additional catalyst was used. Reaction heated to 150 ºC temperature, acetonitrile has a boiling point 82 ºC, so back pressure regulator was used at the end of the reactor. 100% conversion was achieved in 120 minutes. To verify the role of copper tube, some experiments were repeated in PFA tube with the same condition, no reaction was observed. After this Sonogasira coupling was performed in this reactor where no Pd catalyst was used, here DMF was used as solvent with TBAA base.

B. Gas-liquid reaction: Rate of gas-liquid reaction depends on the dispersion of gaseous phase into liquid phase where mixing plays an important role. In batch reactors mixing is achieve by stirring which takes longer time for completion of the reaction.

a. Ozonolysis using a semi-permeable Teflon AF-2400 membrane

Gaseous reaction are mass transfer depended and requires vigorous mixing, flow reactor provides excellent mass transfer but it requires proper control over gas flow rates and back pressure, tube reactor of semi-permeable membranes are the new invention in this series, which allows gases to pass through it. Steven et al.[8b] used Teflon AF-2400 semi-permeable membrane which is an amorphous copolymer of perfluorodimethyldioxolane and tetrafluoroethylene, allows gases to pass through it, used for gas- liquid reactions involving ozonolysis of alkenes. Explosive and shock sensitive ozonides and peroxy intermediates form during ozonolysis have been safely handled in this membrane flow reactor. As a preliminary experiment, tube reactor of Teflon AF-2400 was filled with sudan-red 7B dye which has tendency to be bleached while contacting ozone. This filled tube was placed in a glass bottle filled with ozone gas, the dye becomes color less in few minutes. Various solvents have been screened and methanol found to be most suitable with bleaching time of 1.15 minute. Ozonolysis of 11 alkenes has been performed using same Teflon AF-2400 tube reactor using methanol solvent, resulted good to excellent yields of desired product.

b. Ketones synthesis from carbon dioxide and organolithium/Grignard reagents

In the synthesis of agrochemicals, natural products, pharmaceuticals and functional materials, ketones are the fundamental structural moiety. Ketones are generally synthesized by the Friedel-Crafts acylation, oxidataion of the secondary alcohols or reaction of carboxylic acid derivatives with anhydrides, nitriles and acid chlorides in the presence of a metallic reagent. One-pot batch synthesis of ketone from direct carboxylic acid associated with some issues of symmetric ketone, and alcohol by-product formation which significantly decreases the yield of desired product, removal of excess CO_2, and longer reaction time. All these limitations of batch reactor overcome by Jamison[6a] using three step continuous flow reactor. PFA tube reactor with PEEK Y-mixer was used for as a flow setup for this reaction. In first step organolithium compound was carboxylated by treating it with the stichiometric quantity of CO_2, and its second step, it reacted with a second organolithium compound to generate asymmetric ketone. THF was used as a solvent for the first organolithium to avoid symmetric ketones and diethyl ether solvent was used for the second organolithium compound to enhance the reaction rate. In some cases where excess CO_2 was used, degasser was used to remove it and the final product was quenched by drop

by addition in HCl. In parallel they also performed some high exothermic lithium-halogen exchange, lithiation and magnesium-halogen exchange reaction which was further integrated with ketone synthesis.

C. Liquid-liquid reaction:

a. Preparation of aromatic fluorides

Aromatic fluorides are in high demand in medicinal industries.[12] These Fluorinated aromatic compounds generally synthesized by Balz-Schieman reaction which is a 2 step reaction, diazotization of aromatic compounds followed by fluorodediazoniation. In aqueous phase, diazotization carried out at low temperature, while on using ArN_2BF_4 or in the presence of some ionic complex it can be performed at a higher temperature, but due to poor mixing and poor thermal control it gives undesired coupling products. While on other side, fluorodediazonitation is performed by direct heating of solid powder of ArN_2BF_4, due to improper temperature management and presence of some water it also gives several by-products. So basically batch procedure has some limitations of high energy consumption, unstable yields and regiospecific fluorination. Several modifications like the use of a nonreactive solvent for heating ArN_2BF_4, thermal, photochemical[13], ultrasound[14] or microwave irradiated decomposition of aryldiazonium fluorides were tried to overcome these issues but they came with new limitations of solvent recycling, added separation steps, yield dependency on aryl substrate, and scale-up limitations.

Yu et al.[8a] transformed this batch procedure to continuous flow mode which provides higher mass transfer and excellent thermal control over the period of completion. Both steps optimize separately and then integrated. For diazotization a tube reactor of 1 mm id was used. Solution A (2M amine was dissolved in 1.8 equivalent hydrochloric acid and 1.2 equivalent fluoroboric acid) and solution B (2.1M sodium nitrite) reacts and generates diazonium salt in residence time 15 seconds at 25 ºC, which further converted into more stable solid diazonium tetrafluoroborate, which was obtained by cooling, filtering and drying. It makes slurry after dissolving in co-solvent ,a tube reactor of 1.5 mm id was used for continuous fluorodediazoniation step, gives higher yield at 125 ºC temperature in residence time of 1 min.

b. Continuous flow bromination and synthesis of hypobromide

Halomethylsulfonyl group is significantly important in several industries in the form of antifouling paints for fishing nets and ships, fungal infection of the skin, herbicide to agricultural products, controlling microbial degradation in adhesives, textiles, paper coatings and plastics. Continuous flow bromination in industrial relevance, Stevens[3a] and his coworkers used hypobromide for bromination of methansulfonates and methylsulfones. It is a water-toluene biphasic system where tetrabutylammoniumbromide was used as phase transfer catalyst. Initially one experiment was performed in batch, complete conversion was achieved in 22 h. During the transformation of flow of this reaction, initially potassium hypobromide was synthesized in batch by addition of Br_2 in KOH. This hypobromide was subsequently used for bromination. Initially self assembled PFA reactor was used where various parameter combinations of reaction temperature, residence time, hypobromide equivalence were tried but failed to achieved complete conversion. Then PFA reactor was switched to glass static mixture, which improves mixing by forming an emulsion and excellent heat and mass transfer in the biphasic mixture. 100% Tribromo product was obtained using 4 equivalent hypobromide in residence time of 3 minutes at 85 ºC. At the longer time (low flow rates) there is no sufficient mixing and shorter time doesn't provide sufficient time to reaction takes place. In next step they continuously synthesized hypobromide using CSTR and this freshly prepared hypobromide subsequently used for bromination. This integrated setup was tested for 5.5h, with through put of 53g/day. Different halogenated methylsulfones and methanesulfonates were synthesized in excellent isolated yields using this safe and efficient method.

ii. **Gas-liquid-solid reaction:** These reactions are mainly mass transfer dependent, where the reaction takes place at the surface of the solid catalyst.

a. Hydrogenation of ethyl nicotinate

Scale up involving gaseous reactants deals with some issues like safety, mixing and gas solubility. Hydrogenation is one of the important reaction which needs scale up for which many reactors are available in market like H-cube, but it has limitation of 10 g/day, H-cube Midi with limit of 500 g/day, so in order to safe and easy scale up from gm scale to kg scale, Steven[9] used a commercially available trickle bed reactor

HEL FlowCAT for hydrogenation of ethyl nicotinate. Capacity of tickle bed is 3 mL where 2.6 gm Pd/C can be charged. This system provides a wide range of parameters such as temperature, pressure, and gas and liquid feed. The initial experiment was performed in a batch where 85% conversion with partially and completely reduced product in ratio 7:1 was obtained in 38 h at room temperature. In flow, catalyst particle size should be in the range of 0.1 mm to 0.8 mm because too small particles lead blockage and too longer particles affect mixing. They tried different parameter combinations of temperature, pressure, H_2 flow rate, reactant morality and solvent. A throughput of 1219g/day of partially reduced products and 1524g/day for completely reduced products was optimized using 5% and 10% Pd/Al_2O_3 catalyst respectively.

b. Hydrogenation in micro-channels

In another case of hydrogenation, Kobayashi[3b] used catalyst immobilized glass micro-channel reactor of channel size 200um x 100um with 45 cm length. First amine group introduce onto the surface of glass channels to encapsulate Pd catalyst, then microencapsulated Pd in colloidal solution was pass through the channel and it was kept at 150 ºC for 5 h. Due to heating, polymer cross linkage takes place which immobilized Pd onto the surface of glass micro reactor. Substrate dissolved in THF and H_2 gas passed to this Pd-immobilized reactor using talon tube and the sample was collected at the outlet of the micro channel. Reactions performed at much crucial condition then batch, 140 ºC temperature with reducing reaction time from 10 h to 90 s. The annular gas flow was preferred here and no leaching of catalyst was reported. A library of products in pure form was obtained with high reactivity and efficiency. On the basis of the reaction channel volume and the amount of the catalyst, the space-time yield was 140,000 times higher than those produced by ordinary laboratory flasks.

Table 1. 3: Comparison of batch and flow reaction

Action/ Reactors	Batch Reactors	Continuous Reactors
Operation	Changes occur in the concentrations of reaction mixture over time (unsteady)	At all locations throughout the reactor length, conditions are different but constant over time (steady)

Reaction time	Time spent under defined conditions	Time spent in reactor, determine by the ratio of reactor volume and total flow rate
Types of materials	Can be used with all types of materials (slurries, it is easier to use the batch process).	Easier for use with flowing materials
Type of reaction	Represents an effective and economic solution for slow reactions	Due to small volume fast reactions can be handled very effectively
Mixing	Due to larger volume mixing throughout the vessel is poor	Due to smaller volume higher mixing rates are possible
Control of the set of actions in the system	Complex control. Control of reactor conditions is more difficult.	Easier to control reaction conditions (pH, pressure, temperature)
Product(s)	Extractions of materials only after all the actions are finished with the conclusion of the reaction.	Continuous extraction of products at all times during the reaction.
Product development stage	Preferable when the process is relatively new and still unfamiliar. In this case the initial investment is in a smaller batch reactor, and thus the economic risk is smaller.	Preferable after the conclusion of all the stages of grossing-up and economic feasibility tests.

1.9 Work Outline

After proper understanding of continuous flow synthesis we actually wanted to apply it practically in our lab. So we started with single step, exothermic nitration for proper understanding of continuous flow synthesis, and make a chemistry flow. *o*-xylene was chosen a as model reaction as reduced form of its nitro-derivative is useful intermediate in APIs. Continuous flow nitration of *o*-xylene is studied for different nitrating agents over a wide range of conditions for different parameters such as temperature, residence time and concentrations. An economic analysis of the

continuous flow reactor for production of 100 kg/hr and 500 kg/hr of 2,3-dimethyl-4 nitrobenzene in a jacketed tubular reactor showed that numbering-up is a more economical approach for higher production capacity.

Continuous flow nitration of benzene and its halo derivatives was revisited using fuming nitric acid (FNA) as a nitrating agent and with a catalytic amount of sulphuric acid. Where as in literature higher amount of sulphuric acid requires for the higher yield and completion of reaction, which also generates spent acid that creates disposal and recycling problems. In similar way, in terms of atom economic, use of only fuming nitric acid is ~1.7 times higher for benzene nitration and ~ 1.5 times higher for nitration of halobenzenes.

After enough understanding we moved towards two step integrated reaction, the continuous flow nitration of Acetophenone followed by reduction of the meta isomer using simple tubular reactors. Because of ease of separation of the desired isomer from the first step, both steps are made continuous, but separately. The choice of micromixer was seen to affect the performance of the nitration reaction. The effect of different parameters on the yield of the desired product was studied. Both steps were demonstrated for several hours, yielding a sufficiently large quantity (~100 g) of m-aminoacetophenone at lab scale in a single day using simple tubular reactors.

In order to understand selectivity issues and mass transfer limitations and to overcome it we chosen a 3-step continuous flow oxidation of alcohol with continuous chlorine generation as the first step followed by its use for the flow synthesis of high strength sodium hypochlorite. The solution is subsequently used for oxidation of alcohols in presence of catalytic amount of nitroxyl radical “TEMPO”, which inhibits oxidation at the aldehyde stage.

As the last project, a multi-step integrated **c**ontinuous flow synthesis of isopropyl phenol is demonstrated by continous sequential exothermic, endothermic, and temperature sensitive reactions like nitration, reduction, diazotization and hydrolysis. As a model system cumene was selected as the initial substrate. Cumene upon nitration gives 2 and 4-nitrocumene which gives respective cumidines by the reduction. Upon diazotization of cumidines in acidic environment followed by high temperature hydrolysis it gives 2-isopropyl phenol and 4-isopropyl phenol with complete elimination of in between separation, isolation and purification steps.

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Chapter 2

Continuous Flow Nitration of *o*-Xylene: Effect of Nitrating Agent

2.1 Introduction

Continuous flow synthesis using micro-reactors is now a well known reaction engineering tool that facilitates rapid mixing due to small dimensions, large heat transfer area and narrow residence time distribution. Having narrow RTD and an accurate control on the residence time of the reactants on reaction can help to avoid sequential reactions in such systems. Several reactions have been reported in literature with better yield and selectivity when they carried out in micro-reactor as compare to conventional batch mode operations. A comprehensive account of several such single step and multistep reactions including nitration can be found in the literature[1 2 3 4 5]. The reactions that are selectivity sensitive (including polymerization reactions), radical reactions, reactions involving unstable intermediates, reactions involving toxic reagents, exothermic reactions etc. are among the most suitable reactions that can be conducted in microreactors or flow reactors. Among many exothermic and selectivity sensitive reactions that are demonstrated in microreactors, aromatic nitrations forms an important class of reactions. In general, the aromatic nitration reactions are highly exothermic and the heat of reaction per electrophilic substitution by a nitronium ion is typically ~ -100 kJ/mol. The nature of exotherm depends upon the functional groups on the aromatic ring and the rate of heat generation depends up on the rate of reaction and hence on the rate of mixing. Being selectivity sensitive the secondary and tertiary nitrations cannot be avoided if the reaction is not controlled properly. There is also a large number of patented literature describing industrial applications of flow nitration.

Nitro derivatives of *o*-xylene find use in dyes, pharmaceutical intermediates, agricultural intermediates, explosive chemical and in fragrances. This nitration yields mono-nitro derivatives viz. 3-nitro-*o*-xylene (2) and 4-nitro-*o*-xylene (3). Reduction of 4-nitro-*o*-xylene yields, which is 4-amino-*o*-xylene (xylidine) is used as a starting material for the synthesis of riboflavin (vitamin B_{12}).[6] Import market of riboflavin alone is ~18,862,005$, china is largest supplier of it. It is also used as a precursor for high performance polyurethane resin, 6-Dimethylaminonaphthalimide (6-DMN)[7] and an intermediate for pre mergence herbicides (germination of seeds by inhibition of a key enzyme).[8] Another product isomer 3-nitro-*o*-xylene is used for the formation of mefenemic acid, the synthesis of herbicide topramezone (4,5-dihydro-3-isoxazolyl--2methyl--4methylsulfonylphenyl-5-hydroxy-1--methyl-1-H-oxazol-4-ylmethanone)[9], and for 1,4-dihydrobenzo[d][1,2]dithiin-5-ylamin (an electron-conductive polymer with a high disulfide density)[10].

In the present work, we demonstrate the relative performance of *o*-xylene nitration using different nitrating agents in continuous mode using simple tubular reactors. We have studied the synthesis of mono-nitro as well as dinitro derivatives and have brought out the impact of observations on the different tubular reactor configurations.

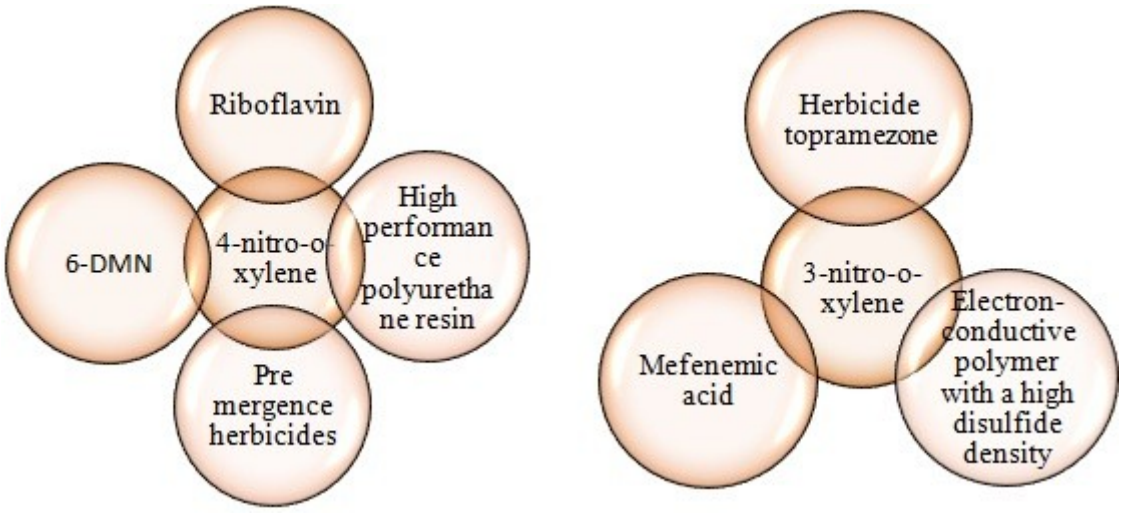


Figure 2. 1: 4-nitro-*o*-xylene and 3-nitro-*o*-xylene as intermidiate for some important synthesis

2.2 Reaction mechanism

A nitration reaction follows electrophillic substitution mechanism, in which nitronium ion is the reactive species. The kinetics as well as the mechanism of nitration of organic substrates is a well studied subject. As can be seen in the below Schemes related to the generation of nitronium ions, and subsequent electrophilic substitution, it involves many different steps. Once the nitronium ion is generated, it attacks at sterically preferred double bond and yields the isomers. The analysis of literature shows that with nitrating mixture as the nitrating agent, the number of nitronium ions generated is significantly more than the case of fuming nitric acid alone.[11] Thus, the values of the relative rates of following individual steps play an important role in governing the selectivity of the product: (i) Generation of nitronium ions by self-dehydration of nitric acid if only fuming nitric acid is used, (ii) Generation of nitronium ions by dehydration of nitric acid by sulfuric acid if mixed acids are used, (iii) Hydration of nitronium ions and (iv) Attack of nitronium ion on the aromatic ring for its electrophilic substitution. While some of these steps are reversible, each has its own rate constant and activation energy. Thus a combination of these parameters governs the overall conversion as well as the selectivity.

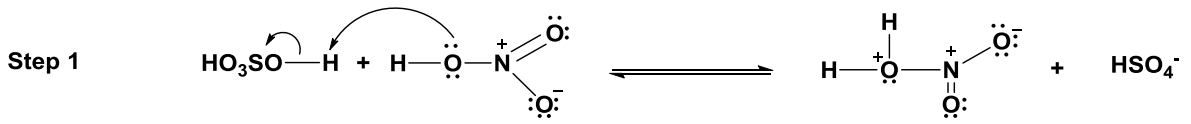


Figure 2. 2: Nitronium ion generation in presence of sulphuric acid:

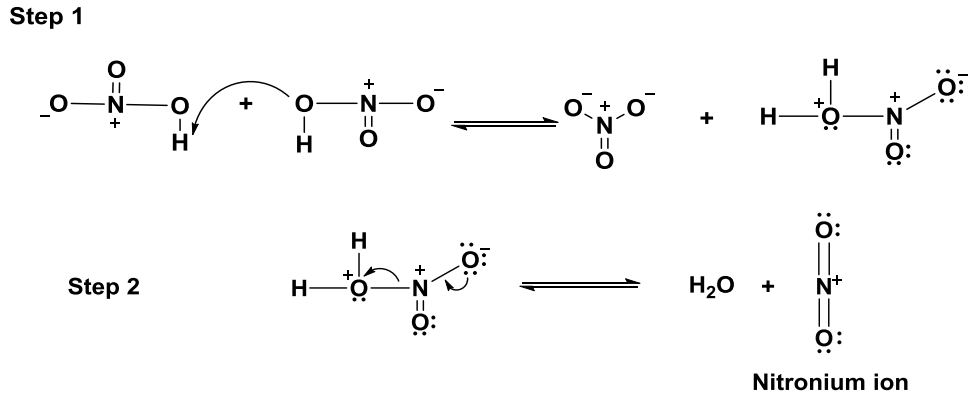


Figure 2. 3: Nitronium ion generation from nitric acid alone:

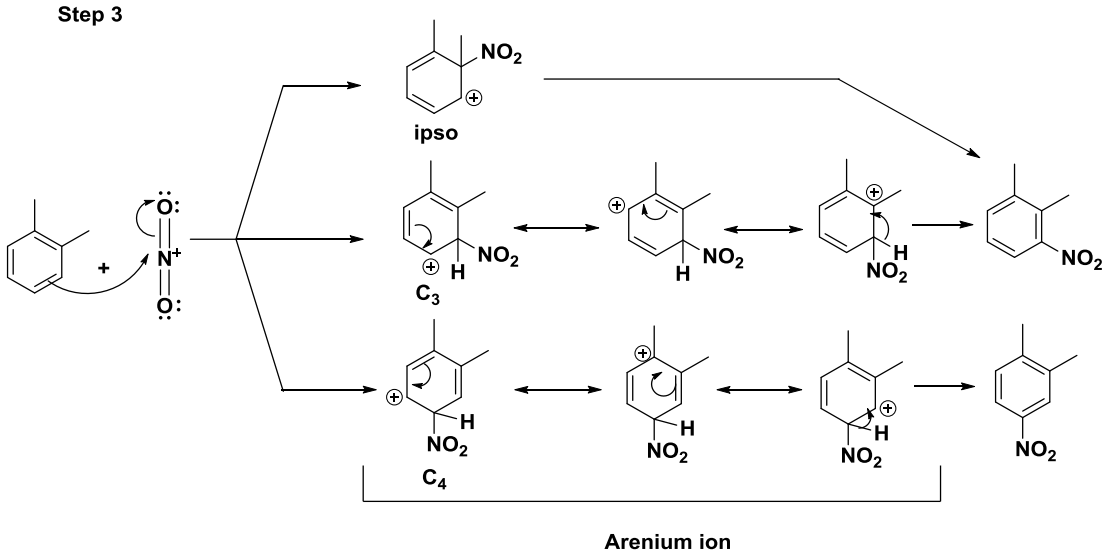


Figure 2. 4 : Nitration of *o*-xylene

Nitration of *o*-xylene (1) yields mono nitro derivatives as well as dinitro derivatives (Figure 2.5). In general unlike the mono nitration of *o*-xylene, which needs low reaction temperatures to control the reaction, the nitration of mono-nitro derivatives has higher activation energy and needs higher temperatures to initialize the reaction.

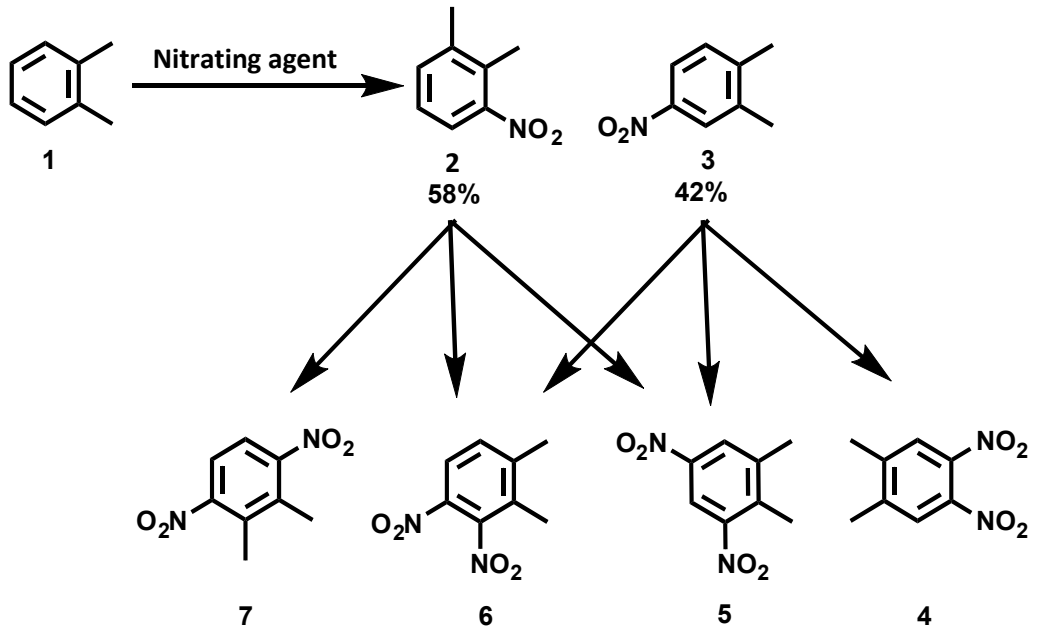


Figure 2. 5: Nitration of *o*-xylene (1), giving 1,2-dimethyl-3-nitrobenzene (2), 1,2-dimethyl-4-nitrobenzene (3), 1,2-dimethyl-4,5-dinitrobenzene (4), 1,2-dimethyl-3,5-dinitrobenzene (5), 1,2-dimethyl-3,4-dinitrobenzene (6), and 1,2-dimethyl-3,6-dinitrobenzene (7)

2.3 Literature analysis

In general the mole ratio of isomers 2:3 varies in between 1.22 to 2.22 depending upon the experimental conditions. Among these two isomers, 3 is the most desired isomer due to large number of intermediates it is needed, however conventional process approach yields poor selectivity for 3. The import market of 3-nitor-*o*-xylene (2) and 4-nitro-*o*-xylene (3) in India is around 11,399,897 $, out of which 11,390,940 $ market is covered only by 4-nitro-*o*-xylene. China is the largest supplier for 4-nitro-*o*-xylene which supplies >99% of it. So it is necessary to re-examine the nitration of *o*-xylene and find an approach that with the advantage of a flow reactor can make it economically as well as environmentally friendly.

In conventional batch mode of *o*-xylene nitration mixed acids are frequently used as the nitrating agent. The presence of sulphuric acid helps to generate the nitronium ions (NO_2^+) which is the reactive species that does the electrophilic substitution of the substrate. The literature shows the possibility of getting 80% yield of 3-nitro-*o*-xylene of a nitrating mixture[12] and only 4-nitro-*o*-xylene if fuming nitric acid is used in 10 equivalents of the *o*-xylene.[13] Table 2.1 shows the analysis of yields of the isomers for different nitrating agents under different conditions.

Table 2. 1: Analysis of literature on o-xylene nitration (the last three entries are heterogeneous catalytic reactions)

author	T (ºC)	H_2SO_4:1 (w/w)	nitrating agent	yield (%)	isomer ratio	
					2	3
Nolting and Forel[12]	0	1.96	HNO_3	80	a	--
Crossley[14]	0	1.94	HNO_3	61.8	88	11
Emerson and Smith[15]	-10 to 0	1.94	HNO_3	85.6	a	--
Farmer and Sutton[16]	-10 to 0	1.94	HNO_3	41.4	a	--
Batchelder et al.[17]	43.3	2.17	HNO_3	87.9	--	--
Griesheim plant[18]	0 to 15	1.19	HNO_3	72.3[b] 62.3[c]	55	45
Kobe and Pritchett[19]	25	2.15	HNO_3	90	58	42
Lavy and Rauch et al.[20]	60	0.5	0.5 mol HNO_3		55	45
	25 – 80[e]	-	N_2O_4+ O_2 / gas	75	18 - 27	82-73
Olah et al.[21]	25	-	FNA[d]+ CH_3NO_2		47	53
Liu et al.[22]	35[f]	-	Liq. NO_2	81	11	89
Sengupta et al.[23]	50[g]	-	FNA	85	-	71

[a]Only this isomer was reported. [b]Crude. [c]Purified. [d]FNA = fuming nitric acid. [e]Catalyst mercuric acetate in glacial acid. [f]H-β zeolite catalyst with Si/Al_2 and molecular oxygen. The percent yield is for both isomers, and the percent selectivity is the fractio on GC. [g]H-Y zeolite catalyst, 115% H_3PO_4, FNA.

Use of spent sulphuric acid in the nitrating mixture creates major issues on scale up. It is highly miscible with water, very corrosive and also acts as a strong dehydrating agent, which upon dilution also dissolves many metals. After the reaction is over the acid mixture containing sulfuric acid cannot be discharged as it is and needs to be neutralized, which generates salts.

In an attempted to avoid spent sulfuric acid, Sengupta et al[23] reported nitration of *o*-xylene using FNA with 115% polyphosphoric acid, nitrobenzene, and H-Y zeolite catalyst, which yields 85% conversion and 71% selectivity for 4-nitro-*o*-xylene. However, the use of polyphosphoric acid makes this approach uneconomical. Recently Liu et al[22] reported 89% of 4-nitro-*o*-xylene using liquid nitrogen at 35^0 C, in the presence of molecular oxygen & zeolite H-β with Si/Al 500. These reactions over zeolite, although green, are time consuming (12 to 24 hr) and are not economically viable. In view of these issues it is necessary to develop an alternate approach for the nitration of *o*-xylene.

2.4 Batch experiments

2.4.1 *o*-xylene nitration with nitrating mixture: 34 gm *o*-xylene was taken in 250 mL round bottom flask and mixed with 17.8 gm of concentrate sulfuric acid and 3.6 gm water followed by the slow addition of nitrating mixture (11.7 gm HNO_3 and 11.8 gm H_2SO_4) in 6 min at 20 ºC temperature. It's a two phase reaction, samples taken out from this reaction mixture at 0, 15, 30, 50 and 70 min and analyzed by GC, maximum 58.6% conversion was achieved in 70 min with major 3-nitro derivative. Results are summarized in Table 2.2.

Table 2. 2: Reaction proceeding with time on using nitrating mixture at 20 ºC

	GC area %			
Time (min)	OX	3-NO_2	4-NO_2	impurity
0	42.375	27.103	21.631	7.645
15	49.542	23.588	19.003	6.428
30	44.278	27.567	21.148	6.031
50	44.283	27.901	21.231	4.829
70	41.418	28.815	22.421	5.357

2.4.2 *o*-xylene nitration with fuming nitric acid: 20 mL *o*-xylene was taken in 50 mL round bottom flask, 7.27 gm fuming nitric acid added in 15 min at 0 ºC reaction temperature followed by stirring of 3.25 hr. samples taken out in between and analyzed by GC, maximum 29.51% conversion achieved with major 4-nitro derivative. Results are summarized in table 2.3.

Table 2. 3: Reaction proceeding with time on using fuming nitric acid at 0 ºC

	GC area %			
Time (min)	OX	3-NO_2	4-NO_2	Impurity
15	90.03	3.99	5.98	0.00
30	77.44	5.09	8.09	1.17
75	85.72	4.95	7.50	1.83
90	85.30	5.52	8.35	0.82
120	78.92	6.11	9.48	5.48
150	84.40	5.73	8.69	9.38
175	75.84	6.11	9.71	8.33
195	70.49	7.09	11.46	10.97

2.5 SOP for preparing continuous flow setup and experiments

For making a continuous flow set up, first and most important step is to choose a chemistry (reactant, reagent, product, intermediate, solvents etc.) compatible material. During assembling a setup, teflon tape should be warped around the threads of female fitting and all fittings should be tighten enough to prevent leakage, over tightening may harm thread and cause leakage. Leakage check is necessity before performing any experiment to prevent any misshaping, it can be done by passing water at high flow rate, or for gaseous phase reaction, set-up can be placed in water and can be done by passing air.

For making multiple outlet set-up volume of each section should be known and calculation of flow rates and residence time will be based on cumulative volume of reactor. Residence time of each section will be calculated on the basis of volume of the section and cumulative flow rate. Sample collection should be done after reaching steady state, which nearly takes twice of residence time, and it should be quenched immediately. Volume of

collected sample (reactant) should be constant while collection time may vary with changing flow rates or residence time.

2.6 Flow setup and experimental procedure

Fuming nitric acid, nitrating mixture, *o*-xylene, and mono nitro derivatives of 1,2-dimethylbenzene are compatible with SS316, so we used 1/8" SS316 tubing, fitting and syringes. Although 4-nitro-*o*-xylene lies in solid phase but it was completely soluble in nitrating agent and 3-nitro-*o*-xylene. There was no solid formation and clogging issue through the reaction, it was directly transformed from batch reaction to continuous flow. After setup assembling, leak test was done with the solvent and once all the pumps are ON and solution comes at the outlet, flow rate measure to check if the pumps are giving the required flow rate.

For the continuous flow experiments, the experimental setup (Figure 2.6) consisted of two syringe pumps (Holmarc Optomechtronics, India), loaded with stainless steel syringe (SS316 syringe, 29 mm i.d., 50 mL volume), one containing nitric acid, and another containing *o*-xylene, connected to SS316 tubes (1/8 in. o.d.). The outlet of pumps was connected to AmAR1 micromixer (1 ml) (Figure 2.6) followed by a residence time tube (3.12 mm outer diameter and 2.1 mm inner diameter, 5.5 ml volume). The entire assembly had five outlets (one immediately after the micromixer and remaining along the length at equal distance.) with needle valves for sampling. The entire assembly was immersed in a heating/chilling thermostat (Julabo, ME12) to maintain the system under isothermal condition.

The flow rates of both reactants *o*-xylene (1) and nitrating agent were varied to achieve the desired mole ratio and residence time. Samples were collected at the different outlets (corresponding to different residence times), in a fixed quantity of ice-cold-water. Known quantity of toluene (Merck) was used to extract the organic phase from samples. It was washed twice with water and then with brine to remove residual nitric acid. Trace quantity of water was removed by passing organic phase through a bed of anhydrous sodium sulfate

A separate set of experiments, the nitration of mono-nitro derivatives of *o*-xylene (3-nitro-*o*-xylene and 4-nitro-*o*-xylene) was also studied. The setup consisted of three syringe pumps, loaded with stainless steel syringe containing nitric acid, and o-xylene, and a PTFE syringe containing water. Rest of the set-up was kept same as discussed previously. Samples were collected from various ports in a finite quantity of ice-cold-water and later extracted in toluene with same workup process.

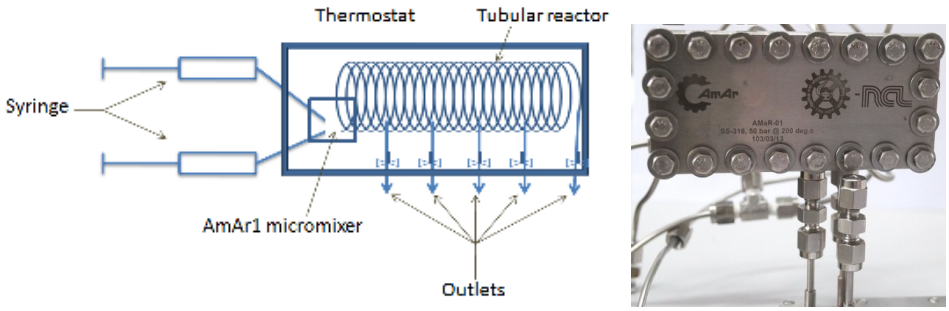


Figure 2. 6: Schematic reaction setup

2.7 Parameters to be studied

The rate of reaction increases with an increase in reaction temperature. Longer reaction time provides more contact to react and formation of products and by-products. More amount of nitrating reagent will provide more nitronium ions to reacts. So reaction temperature, residence time, nitrating agent and nitric acid equivalents all can make different parameter combinations that may influence the conversion and yield of 4-nitro-*o*-xylene in their own way. Different combinations studied for *o*-xylene nitration are listed in table 2.4. It needs to be noted that the reaction of *o*-xylene is a two phase reaction and hence mass transfer limitation needs to be overcome.

Table 2. 4: Different parameter combinations studied for optimization of 4-nitro-o-xylene

Sr No	Nitrating agent	Molar ratio (Nitrating agent : OX)	Temperature (ºC)	Residence time (min)
1	Nitrating mixture (1:1 moles)	1	0 to 70	20
			20	0.61 to 2.00
		2	40 & 50	4.60 to 29.00
			60	20.00
		3	40 , 50	20.00
2	Nitrating mixture (40, 60 v/v)	2	40	4.60 to 20.00
		3		
		4		
		1	40	1.47 to 5.18
		0.66		1.47 to 20.72
		0.5		1.47 to 5.18
3	Fuming nitric acid	1	40	4.60 to 29.00

			30	2.50 to 34.00
		2	30	2.30 to 10.00
			40	2.30 to 20.00
			50 60	3.90 to 10.00
		3	40	2.30 to 10.00
			30	2.50 to 10.00
		4	0 , 10 , 20	0.33 to 2.00
		1	40	1.47 to 5.18
		1.5		
		2		
		0.5		
		0.66		1.47 to 20.72

In a separate set of experiments, the nitration of mono-nitro derivatives of *o*-xylene (2 and 3) was studied at concentrations that mimic the conditions at the outlet of various experiments performed in the nitration of *o*-xylene.

2.8 Analysis

The samples were analyzed using gas chromatography with an HP5 capillary column and an FID detector. Nitrobenzene was used as internal slandered for GC analysis. Di-nitro impurities were identified using GCMS. And products confirmed via NMR. For the conformation of product formation, NMR of column purified 3-nitro-*o*-xylene and 4-nitro-*o*-xylene was done with Bruker AV 200 instrument in solvent $CDCl_3$. For confirmation of di-nitro-*o*-xylene impurities, NMR of nitration reaction mixture of 3-nitro-*o*-xylene and 4-nitro-*o*-xylene was done separately.

2.9 Result and discussion

2.9.1 Mono nitration of o-xylene

Initially number of experiments were carried out using the nitrating mixture NM (HNO_3:H_2SO_4 ~ 40/60 v/v), at 40 ºC. Results are summarised in Table 2.5. Sulphuric acid acts as a catalyst and being a weak base it protonates nitric acid and generates nitronium ion while also acting as a dehydrating agent.[24] On using excess nitric acid sequential nitration of mono-nitro derivatives can be expected which reduces the selectivity of the desired products and

needs more separation stages. On using 4 molar equivalents of NM, only di-nitro derivatives of *o*-xylene were observed.

Further, experiments were carried out by decreasing the quantity of sulfuric acid. Nitrating mixture comprising of FNA and H_2SO_4 (1:1 moles) was used. Flow rates of *o*-xylene and nitrating mixture were maintained to achieve identical molar flow rates of *o*-xylene and FNA. Experiments carried out with a residence time of 20 minutes over a temperature range of 0 ºC to 70 ºC. It was observed that although it is expected that the reaction will get completed early with increase in the temperature, no complete conversion was achieved due to the lack of sufficient nitronium ion concentration. Moreover the impurities formed were significant (Figure 2.7). This implied that equimolar concentration of nitric acid needs significantly higher amounts of sulfuric acid to continuously generate nitronium ions and also absorb water.

Table 2. 5: Nitration of *o*-xylene using nitrating mixture (40/60, v/v concentrated HNO_3 and concentrated H_2SO_4) at 40 ºC with different amount of nitrating agent; impurities include the di-nitro derivatives.

mole ratio (1: NA)	residence time (min)	Impurity (%)	Conversion (%)
2:1	1.5 – 5.28	3 – 7	56- 57
1.5:1		5 – 7	66– 70
1:1		7 – 12	76 – 90
1:2	4.6 – 20	18 - 27	96 - 100
1:3		18 - 61	98 - 100
1:4		39 - 97	96 - 100

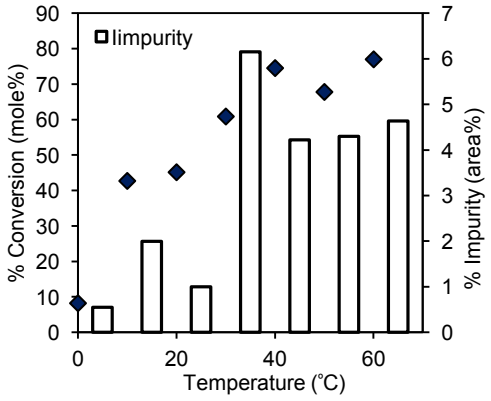


Figure 2. 7: Effect of temperature on conversion and impurity formation in nitration of *o*-xylene with 1:1:1 molar ratio of o-xylene:HNO_3:H_2SO_4 in a residence time of 20 minutes.

In the subsequent experiments 2 and 3 mole equivalents of nitrating agent (FNA + H_2SO_4) were used. Experiments were carried out at higher temperature (40 ºC, 50 ºC and 60 ºC for 2 mole equivalents of FNA and 40, 50 ºC for 3 mole equivalents of FNA respectively) with a residence time of 20 minutes at the final outlet. Over 91% conversion was achieved (Figure 2.8). The above observations indicated that having equimolar or excess sulfuric acid is not suitable for achieving complete conversion and acceptable (less than 5%) impurities, all further experiments were carried out using only fuming nitric acid as the nitrating agent.

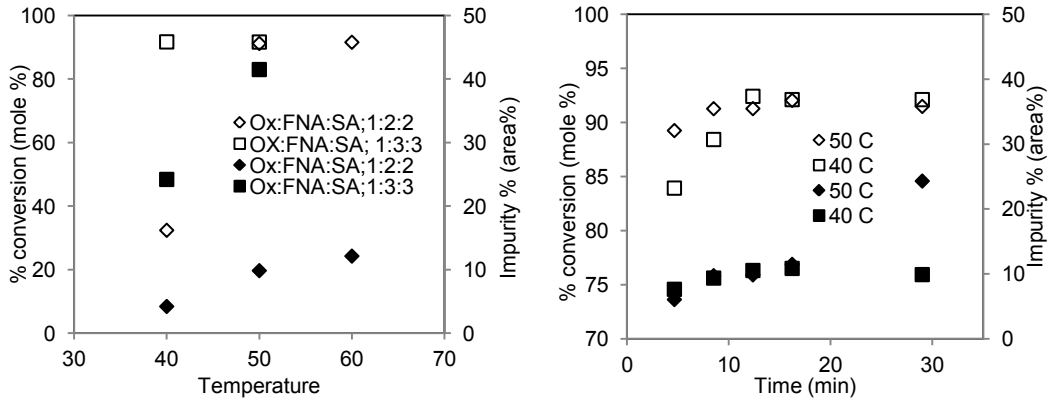


Figure 2. 8: (A) Residence time = 20 min, (B) OX:FNA:SA; 1:2:2. Open symbols - % Conversion, closed symbols - % Impurities.

Initial experiments with complete elimination of sulphuric acid performed at 40 ºC using 1 mole of FNA resulted in only 38 % conversion of *o*-xylene in 4.46 minutes, which increased to 90% with 3 mole equivalent of FNA. Increasing concentration of fuming However the yield of dinitro derivatives also increased. The observations are shown in Figure 2.9A-B). Thus, while higher quantities of FNA will help achieve complete conversion of *o*-xylene, it will severely affect the selectivity of mono-nitro derivatives.

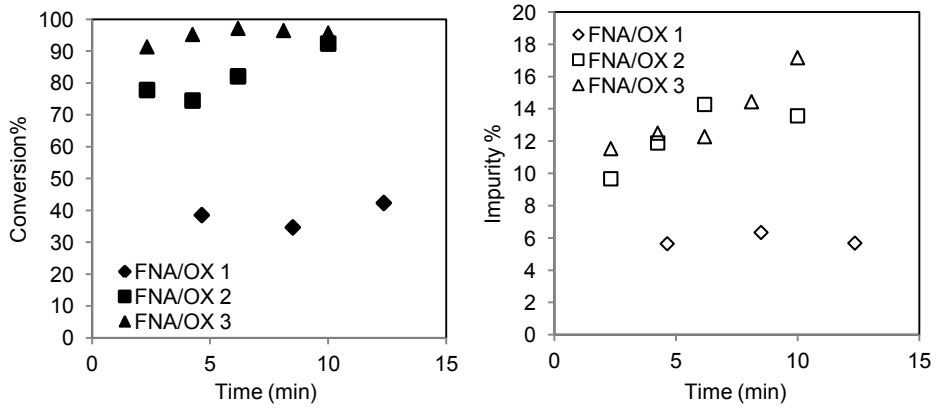


Figure 2. 9: Effect of FNA concentration and residence time on the conversion and impurity formation (mainly di-nitro derivatives) at 40 °C

In order to get the maximum conversion and minimum dinitro derivatives of *o*-xylene and other impurities, further experiments were carried out to screen a wide range of conditions at a fixed mole ratio of *o*-xylene to FNA (1:4). The residence time was varied between 20 s to 600 s, and the temperature was varied from 0 ºC to 30 ºC. It was observed that at 20 ºC, 99% conversion and only 7.2 % di-nitro impurities were observed in less than 40 s. While using only FNA as the nitrating agent selectivity for 4-nitro-*o*-xylene was found to be higher than that for 3-nitro-*o*-xylene. The observations on the effect of nitrating agent on the conversion and yield of the undesired products are shown in Figure 2.10. With constant moles of nitric acid in both the nitrating agents, nitrating mixture leads to higher conversion as well as higher quantities of the impurities. The nitronium ion concentration predicted for FNA only and for the nitrating mixture (69% HNO_3, 40/60 v/v) are 4.7 and 20 mole % respectively, which support these observations.[11]

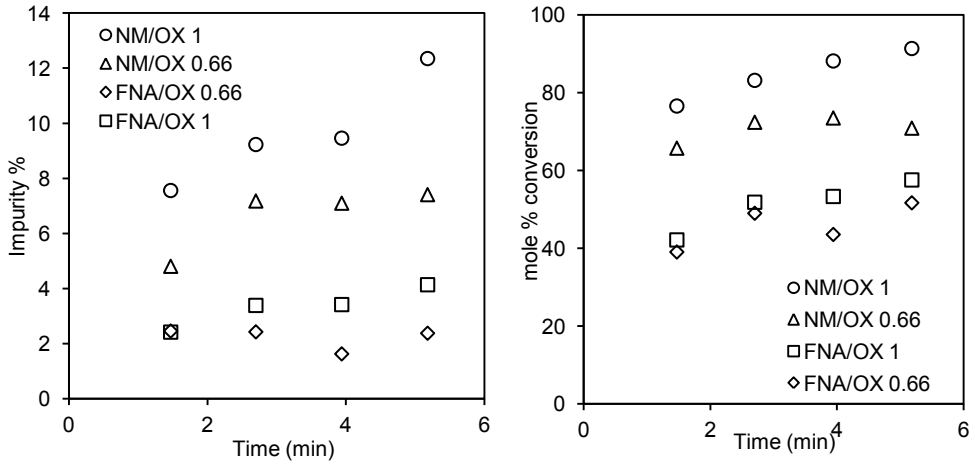


Figure 2. 10: Effect of presence of sulfuric acid on conversion of *o*-xylene and di-nitro formation, using 1:1 (mol/mol) nitrating mixture at 40 ºC. Legends show the mole ratio of nitric acid in the NM or fuming nitric acid (FNA) to *o*-xylene (OX).

In all the experiments it was observed that with FNA as nitrating agent, the selectivity of 4-nitro-*o*-xylene was higher than that of 3-nitro-*o*-xylene, which was a complete contradiction to the observations based on experiments that use sulphuric acid. In some cases the selectivity of 4-nitro-*o*-xylene is higher even with nitrating mixture, but it is mainly because of rapid sequential reactions of 3-nitro-*o*-xylene, which reduced its selectivity. Increasing acidity substantially increases the proportion of reaction at C_4, and to a smaller degree that at C_3, both at the expense of ipso-nitration. The estimated possible percentage of initial attack at C_{ipso}, C_3 and C_4 are 64, 11and 25 with 50%; 55, 15 and 30 with 60% and 45, 18

and 37% with 70% H_2SO_4. Barnett et al[25] observe that above the acidity of 72% H_2SO_4 at which wheland intermediate rearranges rapidly it favours the formation of 3-nitro-*o*-xylene. Hence the ratio of 3-nitro-*o*-xylene to 4-nitro-*o*-xylene can change depending upon the acidity at that instant, which can be seen from the observations from Figure 2.11.

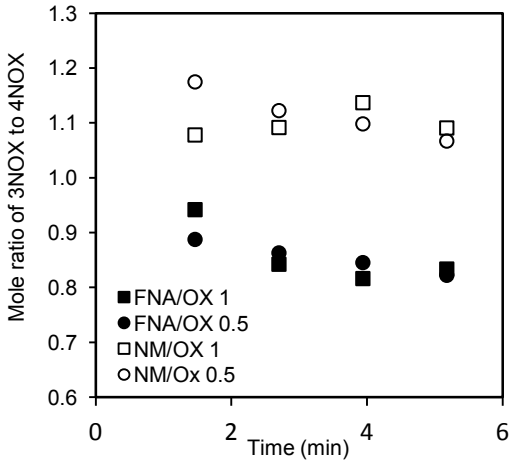


Figure 2. 11: Effect of sulphuric acid on the selectivity at 40 ºC

The selectivity of the mono-nitro derivatives and the impurities vs. the conversion of *o*-xylene for different experiments is shown in Figure 2.12. These observations can be used to outline general observations for comparing the effect of nitrating mixture and fuming nitric acid. It is quite clear that the selectivity of 4-nitro-*o*-xylene is higher with fuming nitric acid than the nitrating mixture. Also the % impurities were less with fuming nitric acid than with nitrating mixture. While in-general the % impurities increased with increasing temperature, the higher values of impurities observed with nitrating mixture were mainly because 3-nitro-*o*-xylene underwent further rapid reactions in the presence of excess nitrating agent. This implies that the relative rates of generation of nitronium ions make a difference in the selectivity of nitronium attack on the aromatic ring. Also, since the electron density is higher for the 4 position of *o*-xylene it is a more obvious product when using only fuming nitric acid. However the rate of protonation of the substrate and attack of nitronium ion in the presence of sulfuric acid would yield different isomer composition.

Upon looking at the data and ignoring the experiments where 3-nitro-*o*-xylene got further nitrated, which restricts the impurities below 20% of the overall nitrated substrate. It was observed that % impurities increased linearly at lower conversions and then increased exponentially with higher conversion. This implies that even in isothermal conditions and with

possibly no mass transfer limitations, the sequential nitration or decarboxylation reactions of specific products are more pronounced even at relatively lower temperatures and in the presence of excess nitrating agent. Thus while the further nitration of all the mono-nitro derivatives may not be possible and even the desired isomer may not undergo further rapid reactions (and its yield may remain unaffected), conditions that encourage the undesired isomers to undergo further reactions will have serious implications on the process.

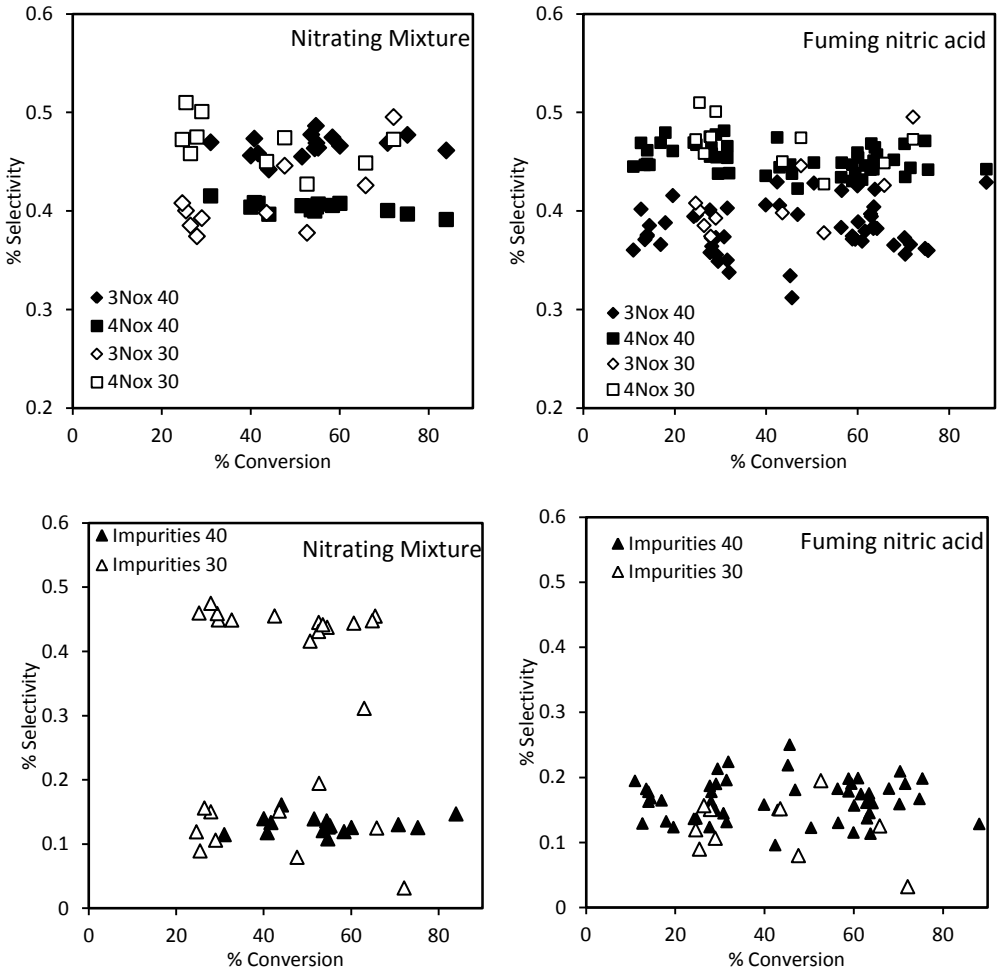


Figure 2. 12: Variation in the % selectivity of the products and impurities at 30 and 40 ºC as function of conversion of *o*-xylene . Only the points up to 90% conversion are included.

2.9.2 Nitration of mononitro *o*-xylene

The impurities observed in the mono-nitration of *o*-xylene were the dinitro derivatives (mainly coming from the sequential nitration of 3-nitro-*o*-xylene and 4-nitro-*o*-xylene) and trace quantities of phenolic impurities. It was observed that at specific reaction conditions the

concentration of impurities was high and hence it was necessary to understand the conditions that lead to the formation of dinitro derivatives from mono-nitro *o*-xylenes.

In the experimental observations discussed earlier, *o*-xylene nitration was carried out using 4 moles of fuming nitric acid, where in the mono-nitration step 1 mole of nitric acid gets consumed and one mole of water gets generated . This basically leads to a relatively diluted nitric acid when 3-nitro-*o*-xylene and 4-nitro-*o*-xylene undergo further nitration. In view of this, in order to maintain consistency in the approach, the synthesis of dinitro derivatives using 3-nitro-*o*-xylene and 4-nitro-o-xylene was carried out using 3 moles of FNA and one mole of water as nitrating agent. For the nitration of 3-nitro-*o*-xylene, temperature was varied in the range of 10 ºC to 60 ºC, while for the nitration of 4-nitro-*o*-xylene experiments were done over 30 ºC to 50 ºC. In both the cases the residence time was changed from 16 to 300 s. Increase in temperature as well as residence time resulted in higher conversion of 2. However the selectivity of dinitro derivatives was lesser than the extent of conversion of mono-nitro derivatives. In the presence of fuming nitric acid, the mono-nitro o-xylenes can undergo partial oxidation leading to phenols, and nitrophthalic acid. In general, the solubility of nitrophthalic acid in water is very high. In order to confirm the formation of nitrophthalic acid in aqueous layer, it was extracted separately using ethyl acetate. The solid product was found to char immediately upon concentration, which confirms with the observations given in the literature.

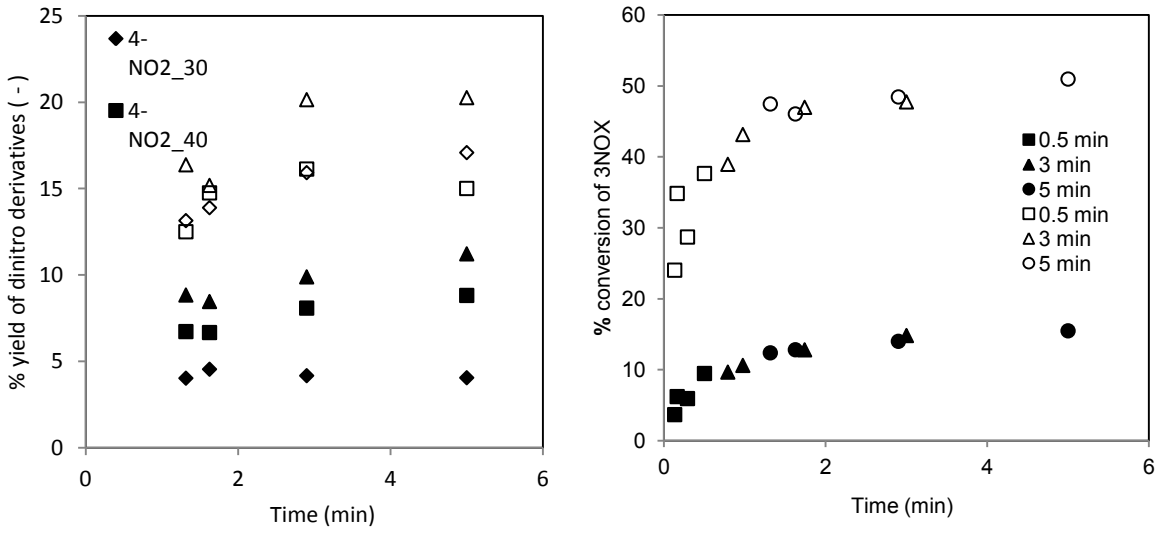


Figure 2. 13: (A) comparison of overall yield of the dinitro derivatives of *o*-xylene from the nitration of 3-nitro-*o*-xylene and 4-nitro-*o*-xylene, (B) Effect of residence time on conversion of 3-nitro-*o*-xylene using 3 moles of FNA & one mole of water. Open symbols correspond to conversion while closed symbols indicate impurities.

The analysis of the product at different temperatures as well as residence times showed that the yields of dinitro derivatives resulting from nitration of 3-nitro-*o*-xylen were always higher than that of 4-nitro-*o*-xylene (Figure 2.13). The analysis of the product composition showed that that reactivity of 3-nitro-*o*-xylen to undergo nitration is relatively higher than 4-nitro-*o*-xylene. Further 4-nitro-*o*-xylene was found to have higher tendency to yield an oxidative products, however the rates of these oxidation reactions were relatively lower than the nitration. With 3-nitro-*o*-xylene as substrate undergoing nitration to yield dinitro derivatives, the prominent impurities formed include formic acid, 3-methyl-2-nitrophenyl-methyl ester, while with 4-nitro-*o*-xylene as substrate the prominent impurities were Pyridine-3-carbamidoxime (MW = 123.23 gm/mol). In order to see the effect of dispersion and nature of flow (with 3 moles of FNA, 1 mole of water and 1 mole of 3-nitro-*o*-xylene, it becomes a two phase flow) experiments the extent of mixing was varied by changing the flow rates. It was observed that the extent of conversion was independent of the nature of mixing and at identical residence time, even achieved at different lengths inside the reactor the conversion was almost the same. This also implied that the micromixer followed by a tubular reactor offered a system without any mass transfer limitations, which makes it suitable for studying the reaction kinetics.

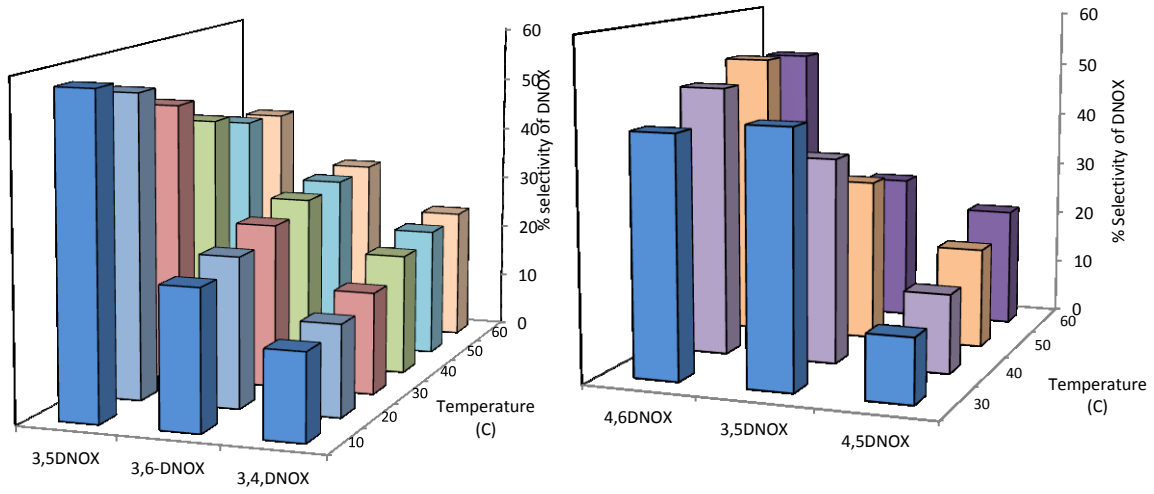


Figure 2. 14: Variation in the % selectivity of different di-nitro derivatives obtained after nitration of 3-nitro-*o*-xylene and 4-nitro-*o*-xylene at different temperatures.

Upon analysis of the data obtained at different temperatures in continuous mode at different residence time it was observed that the % selectivity of different dinitro derivatives

from both 3-nitro-*o*-xylene and 4-nitro-*o*-xylene shows different kinetics. When 3-nitro-*o*-xylene undergoes nitration the % selectivity of 5 decreased while the selectivity of 7 and 6 increased with increasing temperature. This implies that while the pre-exponential factors for the reactions giving 5 is higher than the other two isomers, the activation energy for the later two is lower, while allows its selectivity to increase with increasing temperature. For the case of nitration of 4-nitro-*o*-xylene, 5 gets formed more than other isomers and it continuously increases with increase in the temperature, however the yield of 5 continues to decrease. These observations are important if one wants to exclusively synthesize any of these dinitro derivatives of *o*-xylene. On the other hand it also indicates that at a given reaction temperature for the mono-nitration of *o*-xylene, the residence time should be restricted to ensure that a complex mixture of dinitro derivatives is not formed. The literature shows that the melting points of these dinitro derivatives. For example, the melting points of 7 (89 ºC), 6 (82 ºC), 5 (75 ºC) and 4 (115 ºC) vary closely and also over a wide range. This will need specific and controlled crystallization protocols to recover the pure mono nitro derivatives.

Table 2. 6: Number of experiments performed

	Batch experiments *o*-xylene	*o*-xylene nitration	3-nitro-*o*-xylene nitration	4-nitro-*o*-xylene nitration
Number of experiments	7	180	36	12

2.10 Economics of a continuous flow reactor for nitration of *o*-xylene

Considering that the continuous flow nitration of *o*-xylene is to be carried out for production of 100 kg/hr of 3, i.e. about 72 TPM, here we present a simple analysis of economic feasibility of this nitration reaction in a jacketed tubular reactor. The conditions (residence time, temperature) that yield maximum selectivity for 3 was considered as the design basis. As a simple system, it was considered that the reactor is to be fabricated using a combination of different sections made from SS316 tubes of 2.5 mm inner diameter (i.e. 3.175 mm or 1/8” outer diameter) and 4 mm inner diameter (i.e. 6.3 mm or 1/4” outer diameter). While the smaller diameter tube (3.175 mm) is cheaper than 6.3 mm diameter tube, it would offer higher pressure drop at identical flow rates to produce a fixed quantity of 3. Also, in order to produce a fixed quantity of 3 in a given time, with the knowledge of specific residence time the total reactor volume gets fixed. This implies that one would need

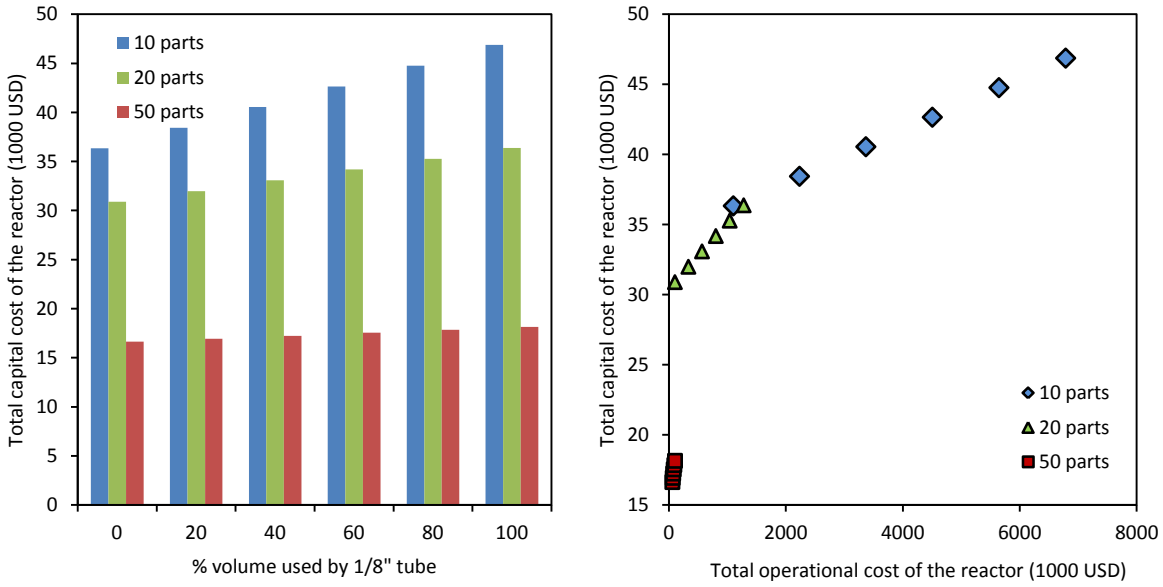
significantly longer length of the small diameter tube than the larger tube size. Smaller tube size will also yield higher heat transfer area and also relatively higher mass transfer rates. Thus depending up on the heat generation rate in a specific region along the length of the reactor it is necessary to ensure that adequate heat transfer coefficient is ensured by providing the necessary heat transfer area as well as the Nusselt number on tube as well as shell side. Thus it is always possible to design a flow reactor that can take care of location specific heat duties as the reaction proceeds. In the present exercise, it was assumed that for a fixed capacity and for a given condition the % selectivity is independent of the reactor design and hence the downstream processing costs will remain the same. Similarly, for a given throughput the pumps will also have a possible narrow variation in the pressure drop and hence the cost of the pumps of specific material of construction will not vary significantly.

Considering the above criteria, here we give a quick approach that allows one to evaluate the possible design of a flow reactor. On the basis of the volume fraction of reactor that yields a specific heat duty (or heat generation rate), its length can be estimated depending upon its diameter, which eventually yields the cost of the specific section of the reactor. Thus, depending upon the fraction of the reactor used for different heat loads, the total capital cost of a reactor (including the cost of jacket depending upon the geometrical configuration of reactor, viz. coil, double coil, triple coil, etc.) can be obtained. The cost of the connectors can be added to the capital cost (tubular reactor + jacket) and then one can move to estimate the operating costs. The operating costs are primarily the cost of pumping due to pressure drop at a given flow rate in different sections of the reactor and the cost of utility and its pumping through the jacket. Usually, the single long tubular reactors are uneconomical, and hence are run by numbering up, which reduces the flow rate through each reactor and hence also the resulting pressure drop. Thus, while the capital cost of the reactor can be retained more of less same, the operating costs can be reduced. Also, the capital costs and peripherals including the control system are one time investment it usually depreciates and also needs maintenance, which adds to the recurring costs of a plant.

Here we have followed the above approach discussed in detail in Joshi and Doraiswamy[26] for the design of a flow reactor for production of 100 kg/hr of 3. Back of the envelop calculations showed that a tubular reactor is split in *N* parallel reactors (i.e. numbering-up) would yield much lower pressure drop due to lower velocities in individual tubes. In Figure 2.15, we have shown the observations for tubular reactor having 10, 20 and 50 units running in parallel to achieve the desired production rate at varying volume fractions of 3.175 mm diameter tube

(rest being the 6.3 mm diameter tube). It can be seen that the capital cost of reactor having less number of parallel units continued to increase significantly as the volume fraction of reaction mixture through the smaller diameter tube increased. With 50 parallel reactors, this increase was not significant. Upon plotting the total capital cost of the reactor (including reactor cost, peripherals, control system, etc.) vs. the total operating cost, it showed a positive correlation with the steepness in the increasing with number of parallel units used for fabricating the reactor. Also, the steepness in the trend decreases at higher CAPEX and OPEX, which implies that the OPEX plays a significant part in the overall costing right from the in the first year of reactor operation. It further implies that having more continuous reactor units running in parallel is always economical as it decreases the OPEX by a few orders of magnitude rather than having a single flow reactor. Typical such assemblies from tubular reactors can be seen in the literature.[27] In the present case, the typical costing was done based on the present cost of the reactants, products and material of reactor from various resources.

The estimated net profit for a period of 5 years only from the reactor is shown in Figure 2.15C-D. The standard depreciation rates, escalation in prices of raw materials and products, maintenance and repair costs and the down-time costs of the reactor (for 300 days of operation in a year) were taken into account. It can be seen that if the reactor is made only of 6.3 mm diameter tubes, the net profit will continue to increase with time. However if the reactor is made only of 3.175 mm diameter tubes, the overall net profit will always be lesser, which will lead to very long payback period. On the other hand, if the reactor is made of 6.3 mm diameter reactor, the net profits are positive right from the first year of its operation.



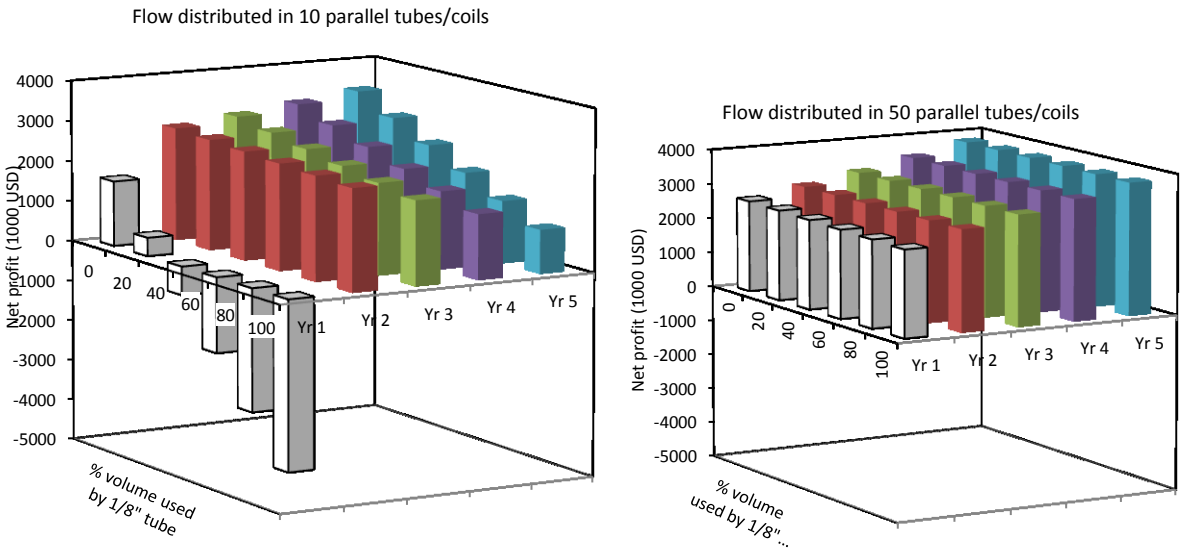


Figure 2. 15: Economic analysis of the continuous flow nitration of *o*-xylene using SS316 tubular reactors. (A) Variation in the CAPEX with the volume fraction of 1/8" o.d. tube used for constructing a flow reactor (remaining volume is occupied by ¼" tube). (B) Effcet of numberin-up on the variation of CAPEX vs. OPEX, (C – D) Net profit from the flow reactor under the assumption of complete recovery of products and complete conversion of *o*-xylene for numbering-up with 10 and 50 parallel units.

Also, numbering-up can be seen to increase the profit and hence reduce the payback period significantly. However these possibilities exist only if the flow is distributed uniformly in the reactor, without which it will be difficult to attain identical residence time in all the parallel units.

2.11 Conclusions

Continuous flow nitration of *o*-xylene (1) is studied for different nitrating agents over a wide range of conditions for different parameters such as temperature, residence time and concentrations. The effect on the conversion and yield of 3 has been investigated in detail.

On using 4 molar equivalents of NM (HNO_3:H_2SO_4 ~ 40/60 v/v) at 40 ºC only di-nitro derivatives of o-xylene were observed within 10 minutes of reaction time. At a residence time of 20 minutes with an equimolar nitrating mixture (1:FNA:H_2SO_4 = 1:1:1) no complete conversion was achieved even at higher temperatures (50 - 70 ºC) due to the lack of sufficient nitronium ion concentration.

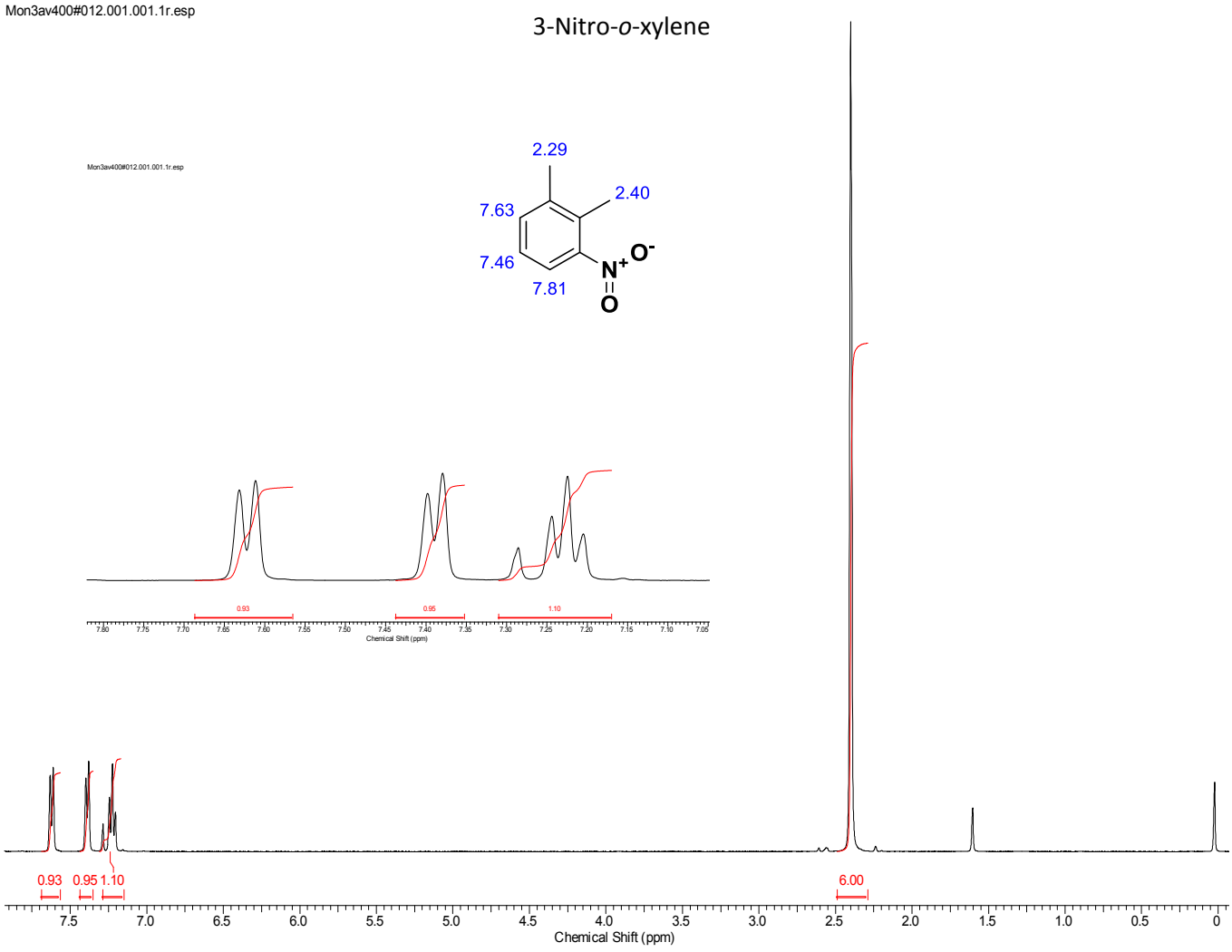
With only fuming nitric acid in excess as nitrating agent at 20 ºC, 99% conversion and only 7.2 % di-nitro impurities were observed in less than 40 s. This also resulted in higher

selectivity for 3 when compared to 2, which is a complete contradiction to the observations based on experiments that use sulphuric acid. In the presence of fuming nitric acid, the mono-nitro *o*-xylenes can undergo further nitration to yield different dinitro derivatives of *o*-xylene (viz. 5, 7, 6 and 4) and it also undergoes partial oxidation leading to phenols, and nitrophthalic acid.

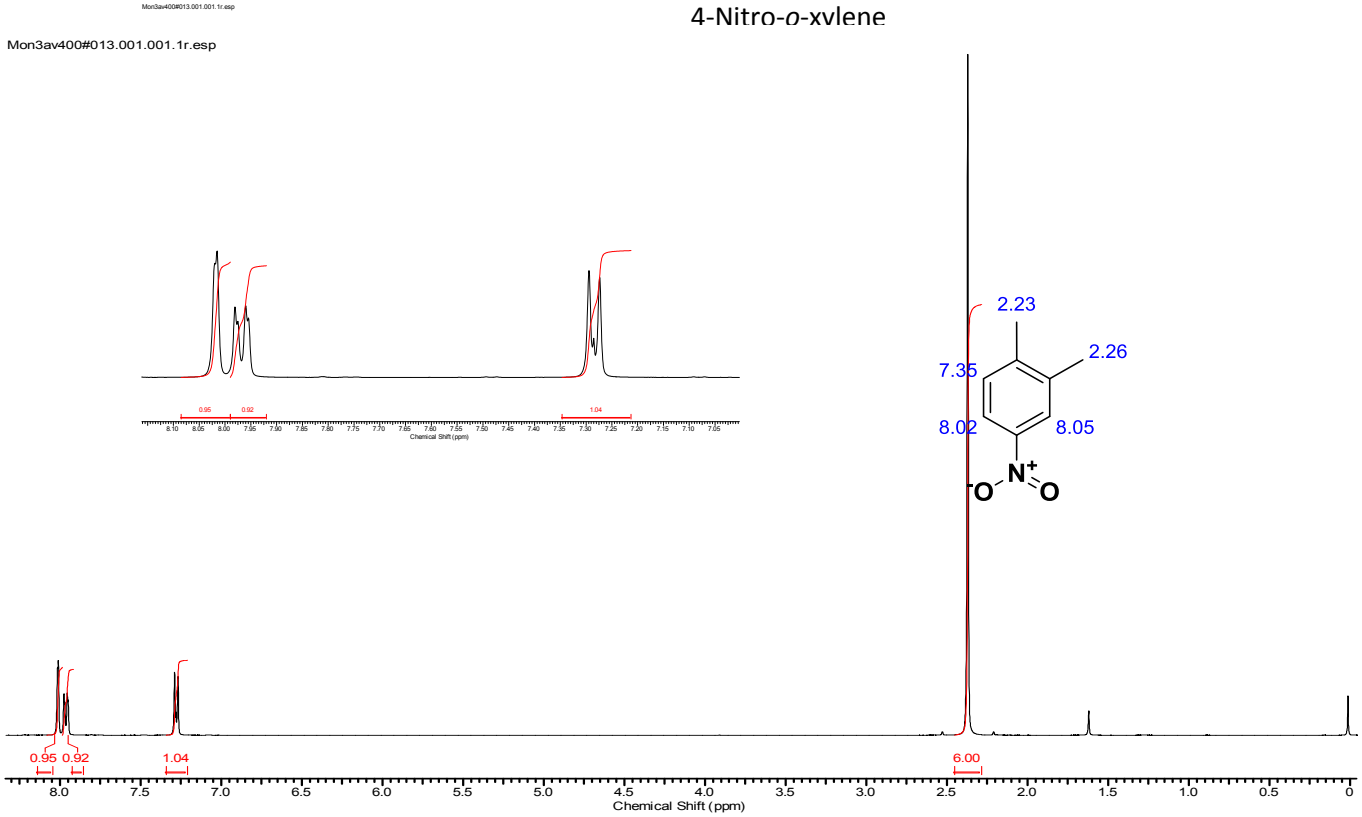
An economic analysis of the continuous flow reactor is also presented for continuous production of 100 kg/hr of 3, i.e. about 72 TPM in a jacketed tubular reactor. The analysis showed that having more continuous reactor units running in parallel is always economical as it decreases the OPEX by a few orders of magnitude rather than having a single flow reactor. If the reactor is made only of 3.175 mm diameter tubes, the overall net profit is found to be always lesser than the reactors is made out of 6.3 mm diameter tubes. The choice of suitable tube size needs to be made based on the overall heat transfer coefficient (usually limited by tube size heat transfer coefficient) and the ability to remove the heat efficiently throughout the reactor. Importantly what comes out from the analysis is to have a combination of small size and large size tubes for constructing such a flow reactor, which will be better in terms of safe operation and cost effective than using only small size tubes throughout the reactor. The analysis also showed that numbering-up helps to increase the profit and hence reduces the payback period significantly.

Analytical Data

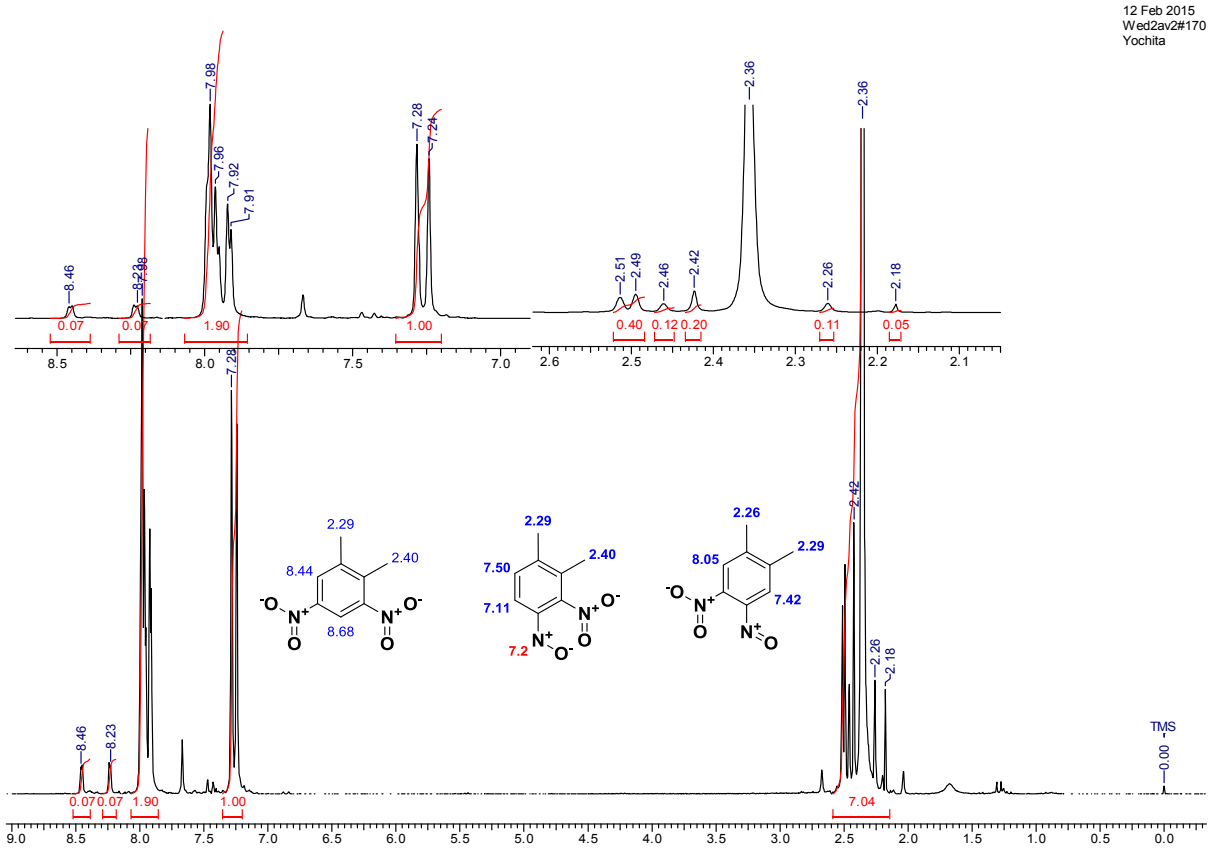
i. NMR data



4-Nitro-*o*-xylene



Mixture of 4-Nitro-*o*-xylene nitration



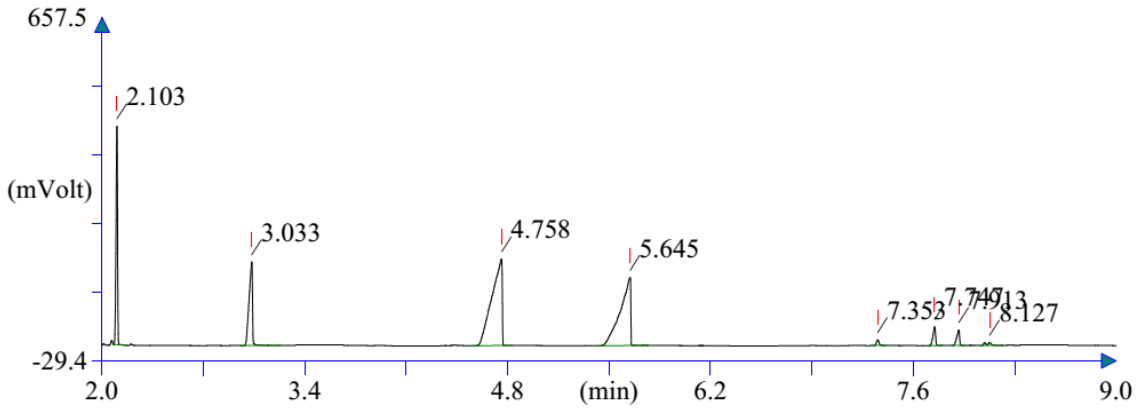
ii. GC and GCMS of nitration reaction mixture

GC method: HP5 column with FID detector as used for the analysis of all experiments. Nitrobenzene was used as internal standard. Initial oven temperature kept 70 ºC and temperature rise with the ramp 30 ºC/min up to 140 ºC temperature with hold time of 0.20 min, second ramp with 2 ºC/min up to temperature 146 ºC, peaks of o-xylene, 3-nitro-*o*-xylene, 4-nitro-*o*-xylene and nitrobenzene comes in this range. Finally temperature rose to 250 ºC and hold for 3 min, with ramp 40 ºC/min.

Table 5: GC and GCMS retention time of substrates

Substrate	GC Retention time	GCMS retention time
o-xylene	2.12	
Nitrobenzene (I S)	3.02	
3-nitro-*o*-xylene	4.64	6.74
4-nitro-*o*-xylene	5.48	7.96
di-nitro-*o*-xylene	7.30	11.16
di-nitro-*o*-xylene	7.74	11.48
di-nitro-*o*-xylene	7.91	12.02
di-nitro-*o*-xylene	8.12	12.42

I. GC report of *o*-xylene nitration reaction mixture



II. GC report of mono-nitro-*o*-xylene nitration reaction mixture

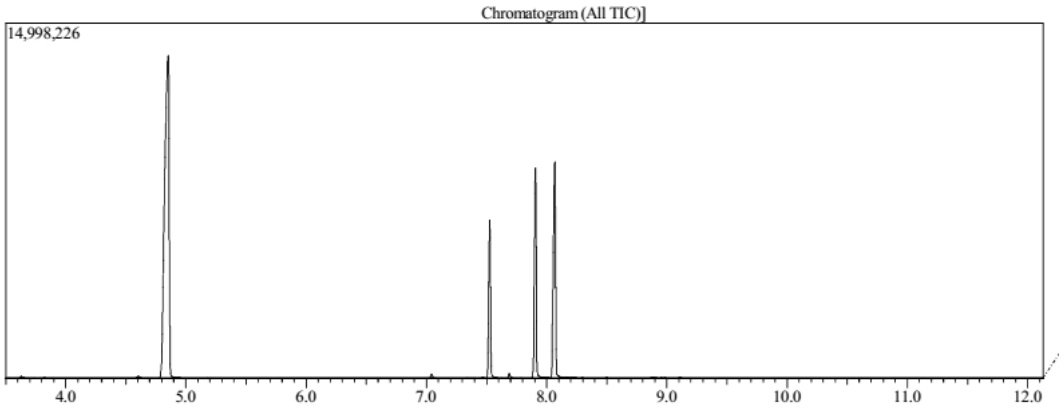


Figure: GC of 3-nitro-*o*-xylene nitration reaction mixture (it forms three di-nitro-*o*-xylene)

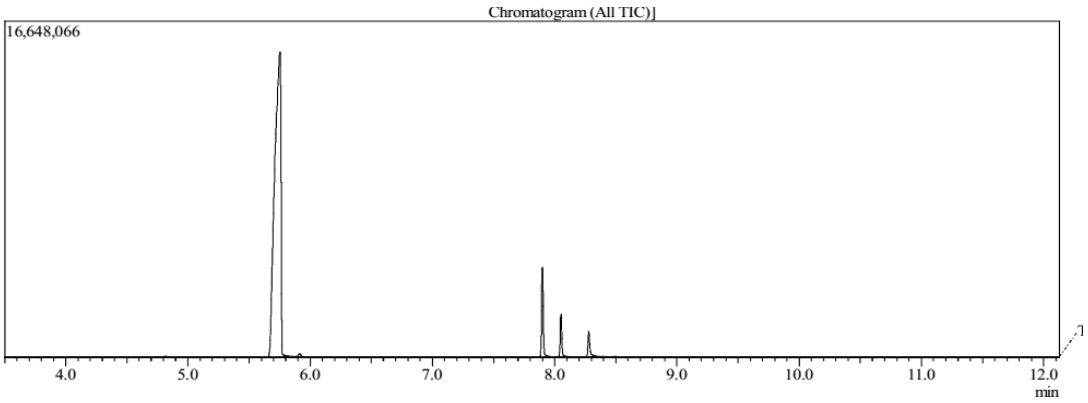
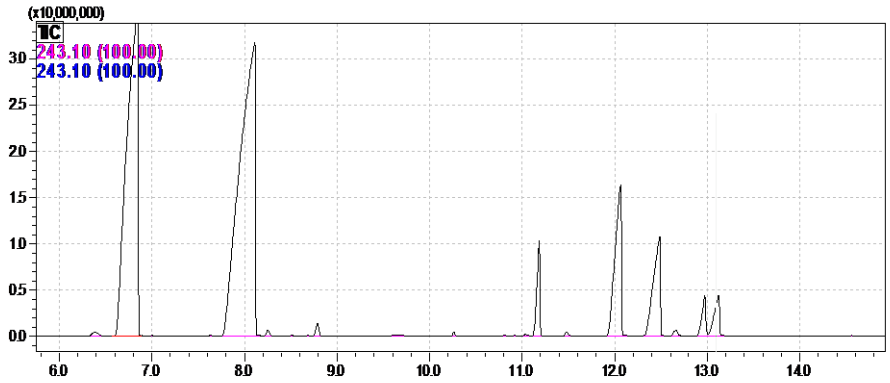


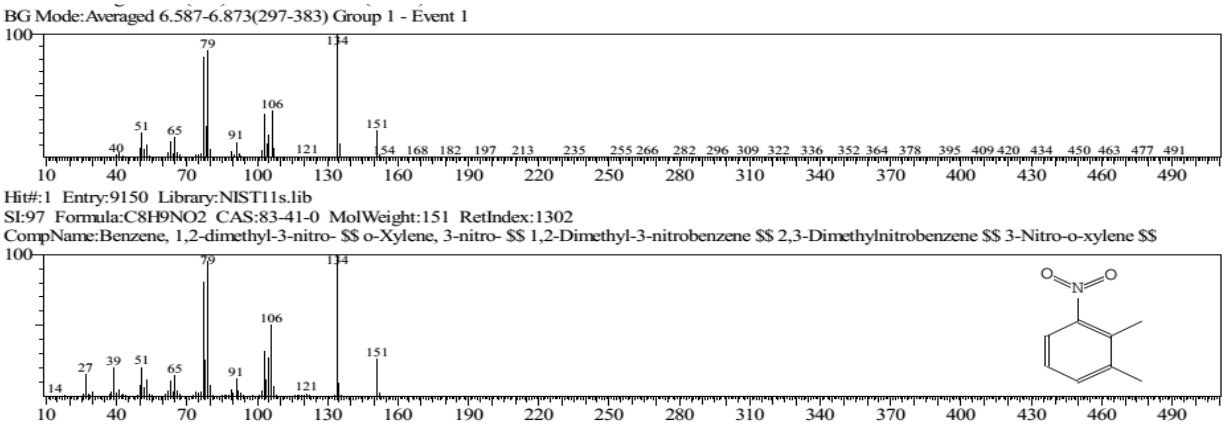
Figure: GC of 4-nitro-*o*-xylene nitration reaction mixture (it forms three di-nitro-*o*-xylene)

GCMS data:

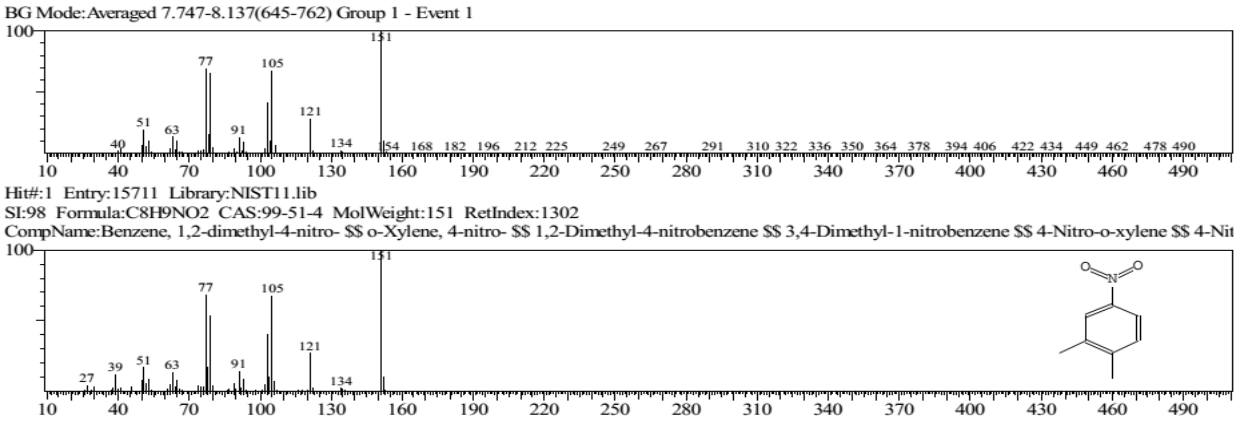


i. 2 mono-nito signal:

1) Single at R.T. 6.743 min
   Base Peak: 134.15
   3-nitro-*o*-xylene



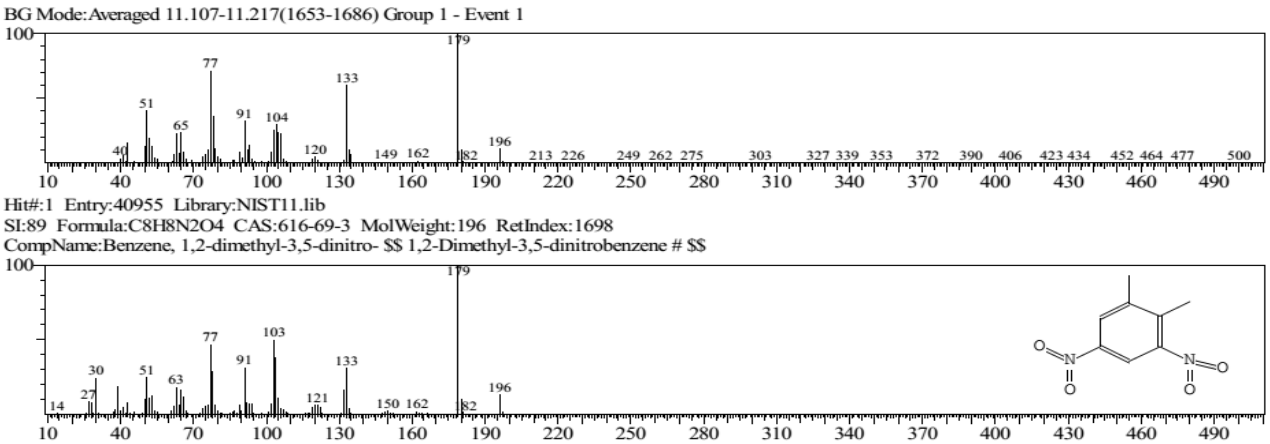
2) Single at R.T. 7.967 min
Base Peak: 151.20
4-nitro-*o*-xylene



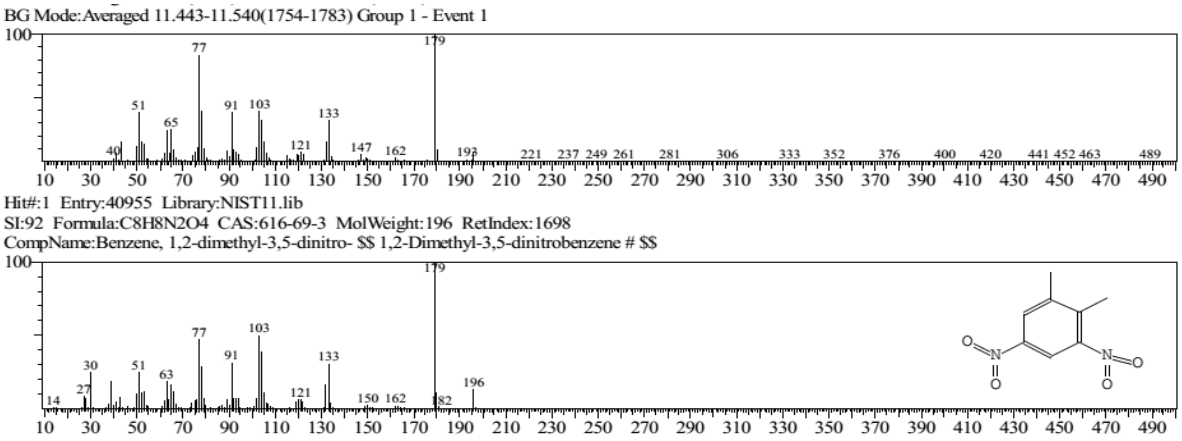
ii. 4-di-nitro signal:

(There is just one di-nitro-o-xylene derivative present in GCMS library, for all four dinitro compounds it shows same structure isomer)

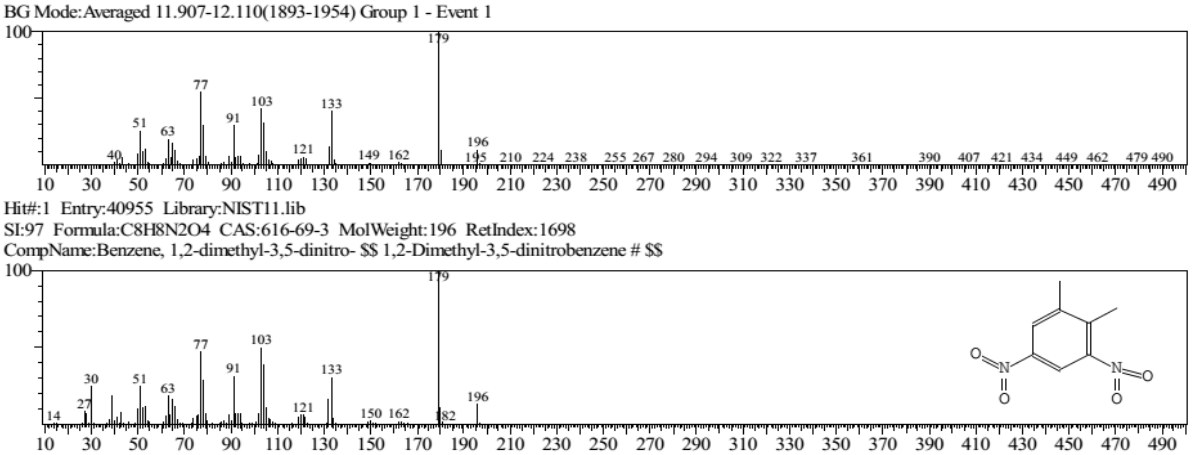
1) Single at R.T. 11.160 min
Base Peak: 179.10)
di-nitro-*o*-xylene



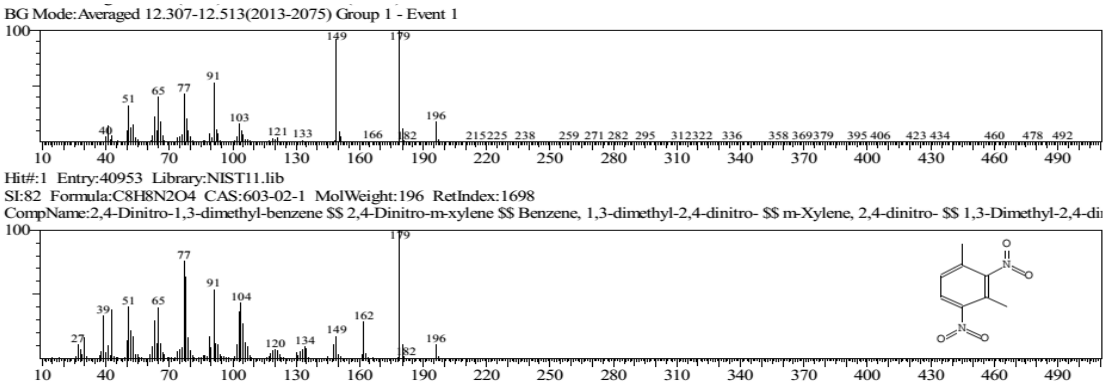
2) Single at R.T. 11.483 min
Base Peak: 179.10
di-nitro-*o*-xylene



3) Single at R.T. 12.020 min
Base Peak: 179.10
di-nitro-*o*-xylene



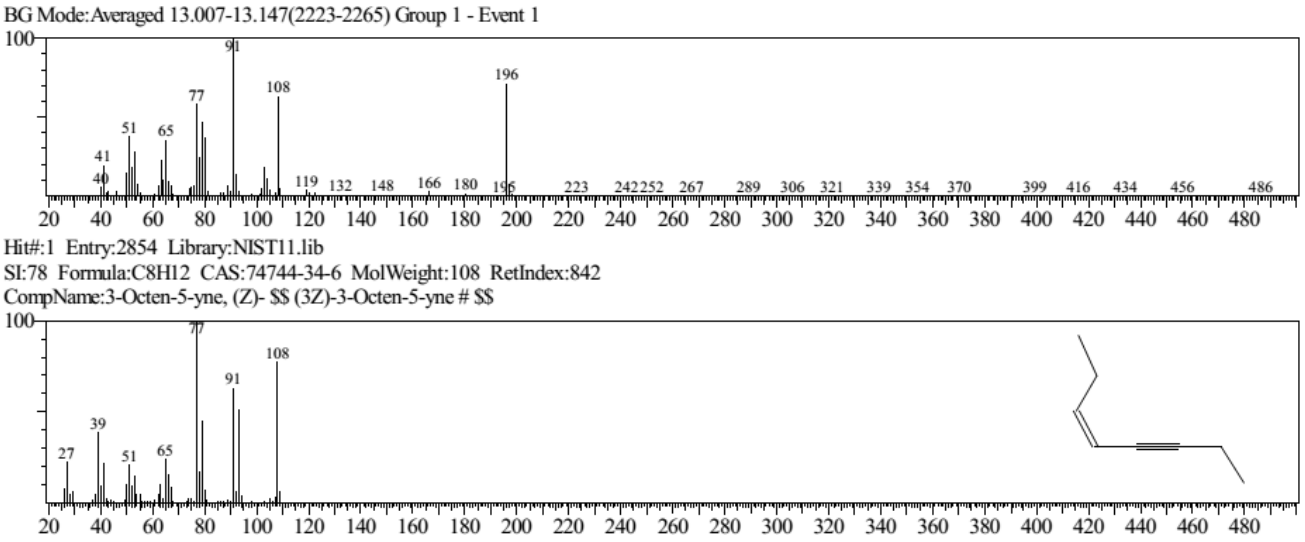
4) Single at R.T. 12.420 min
Base Peak: 179.10
di-nitro-*o*-xylene



iii. Some impurity:

Single at R.T. 13.093 min

Base Peak: 91.10



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Chapter 3

Revisiting Continuous Flow Nitration of Benzene and Its Halo-derivatives

3.1 Introduction

Nitration is an important class of organic reactions which introduce nitro (NO_2) group into any organic compounds. It is also one of the most basic reactions used for functionalizing the aromatic substrates. The first nitration was done in 1834 by *Mitscherlich*[1] where he synthesized nitrobenzene using fuming nitric acid. The first patent on benzene nitration using nitrating mixture was filed by Mansfield[2]. A large numbers of organic compounds are nitrated using different nitrating agents and solvents. Literature shows that the nitrating mixture (HNO_3 + H_2SO_4) is the reagent of choice as more than 30% nitrations are performed using nitrating mixture.[3] Nitro derivatives are useful intermediates in pharmaceutical, agriculture, dye, explosive, perfumery, rubber industries. Industries usually carry out nitration reactions in semi-batch mode. Usually the semi-batch mode is adapted because of better control on heat management through very slow addition of one of the reactants. Reaction being very fast and exothermic, addition rate helps to control the heat generation rate that should correspond to the heat removal rate from the reactor. The former depends upon the reaction rate and heat of reaction while the later one depends on the heat transfer coefficient of the reactor, heat transfer area and the cooling fluid (flow rate and temperature). Although the semi-batch mode helps to control the temperature inside the reactor, prolonged contact time between the organic substrate and the products (usually isomers) with the nitrating agent leads to formation of dinitro and trinitro derivatives. Depending upon the stability of these byproducts and their reactivity with nitric acid, the chances of thermal run away are also high.[4] In addition to these issues related to the intrinsic kinetics of the reaction, being immiscible (organic substrate and aqueous nitrating agent phases) need very high mass transfer coefficient or need exceedingly large volumes of fuming nitric acid to achieve a highly reactive homogeneous mass. In several cases even large volumes of solvents are used to avoid rapid reactions with neat substrates, which make the reaction rates further get affected by dilution. Most of these issues that do not allow a nitration reaction to be carried out at its intrinsic kinetics can be overcome by using a continuous flow synthesis approach using flow reactors having at least an order of magnitude higher heat transfer area and mass transfer coefficients. Smaller dimensions give shorter diffusion path and higher surface to volume ratio, which enhance mixing and gives better heat transfer to restrict the formation of desired products by making it a close to isothermal operation.[5]

One of the most basic nitrations is the nitration of benzene and halobenzens. Nitrobenene is used for the synthesis of paracetamol, urethanes , pesticides, dyes, explosive, agriculture and horticultural flowering from centuries.[6] Pharmaceutical industries also have large interest in nitro-halobenzenes as these are intermediates for many drugs and exhibits Mutagenic activity.[7] Similarly, nitrofluorobenzene is used as antiarrythmic, antihypertensive and antiischemic drug agent, also it is in demand as an intermediate for antioxidant for rubber and anti-leprosy drug – Dapsone. Nitrobromobenzene is in demand for drug manufacturing for hypnotic, sedative and antiemetic feature. However, benzene, halobenzene and their nitro derivatives are not environmental friendly. This work presents the nitration of benzene and halobenzene in safer, eco and environmental friendly way with complete elimination of solvents.

3.2 Literature analysis

For the synthesis of nitrobenzene, Vaughan et al.[8] used Perfluorosulfonic acid polymer membrane, under 82.34 kPa N_2 pressure. This polymeric membrane preferably comprising sulfonic acid groups, pendant to the polymeric backbone which catalyzed reaction. Membrane helped to control diffusion and hence the overall reaction rates. Alexanders et al.[9](1978) used nitrating mixture for adiabatic benzene nitration. Used nitric acid was completely consumed and spent acid was recycled to 68% concentration under vacuum, at 90 °C temperature and 60 mm pressure. Umbarkar et al.[10] have reported the use of silica supported MoO_3 catalyst to facilitate nitration with dilute nitric acid. Dilute nitric acid over 20% MoO_3/SiO_2 is reported to show more than 90% benzene conversion with 99.9% selectivity for nitrobenzene. The catalyst showed stability for more than 1000 h on-stream.

Apart from these batch literature, a vast body of literature is reported on benzene nitration using different microreactors to overcome a few issues viz. mixing, heat transfer, formation of byproducts viz. dinitrophenol and dinitrobenzene etc. In 1942 Othmer[11] and his co-workers reported continuous process for benzene nitration using only nitric acid (61%) and suggested a plant of capacity 5 ton/day on the basis of these optimizations. Vapour phase nitric acid was assumed stronger then liquid phase because it uniformly distributes in reaction mixture and gives almost twice the yield when compared to liquid phase nitration. Burns and Ramshaw[12] achieved 94% nitrobenzene yield in residence time of 24.4 s by using a capillary reactor of 178 μm at 90 ºC temperature, higher amount of sulphuric acid (77.7%) was used to enhance rate of reaction in this case. Quadros et. al.[13] have studied an adiabatic continues pilot

plant for the production of nitrobenzene using higher sulphuric acid quantity. They studied effect of different parameters including stirring speed, flow rates, temperature of feed stream, reaction temperature and reactant ratio and found strong dependency on these. A detailed analysis based on reaction engineering models is presented to explain their observations. In the case of nitration of halobenzens, o/p ratio varies with change in solvent and nitrating agent, as shown in Table 3.1, which is always <1 (o/p <1). Reactivity order of these halobenzens shows a "U" profile (F, I> Br, Cl). Iodine is more reactive then bromine and chlorine because of its low electronetivity. There is poor lone pair overlap in bromine and chlorine which is good in fluorine so fluorine is more reactive then bromine and chlorine.[14]

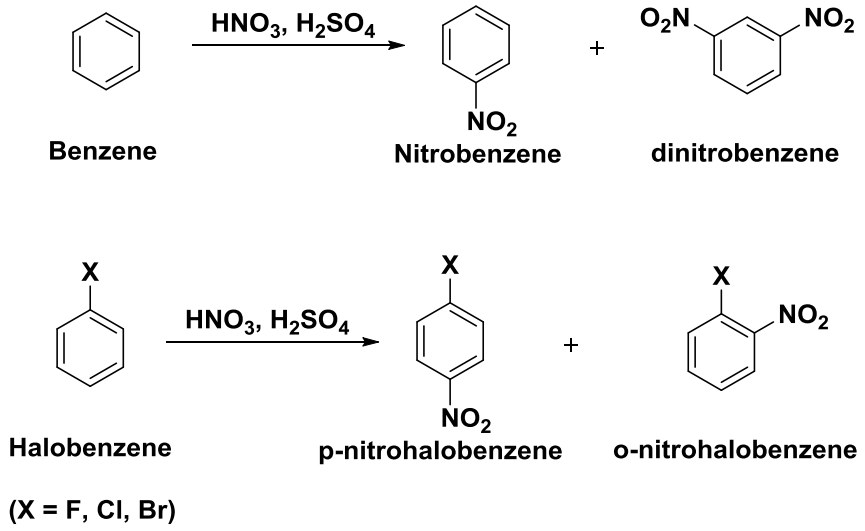


Figure 3. 1: Nitration of benzene,Chlorobenzene, fluorobenzene and bromobenzene

Table 3. 1: Literature analysis of benzene and halobenzens nitration

Substrate	Author and year	System	Nitrating agent	Temp (°C)	Reaction Time	% Conv.	o/p selectivity
Benzene	Vaughan (US Patent3,976,704) 1976[8]	Perfluorosulfonic acid polymer membrane (12 psi N_2 pressure)	90% HNO_3 (NA/B 1.15) 70 % HNO_3 (NA/B 0.73)	85 85	--	82 18	--
	Umbarkar et al. 2006[10]	MoO_3/SiO_2 catalysts	70% HNO_3 NA/B 0.90	140	--	90	--
	Quadros et al. 2004.[13]	67%H_2SO_4+23 %H_2O+	70%HNO_3 NB/B 0.86	117 (adiab	2 min	86	--

		10%HNO_3		atic)			
	Smith et al. 2002[15]	zeolite Hß in 1,2-Dichloroethane	N_2O_4 and O_2	0	43hr	55	--
		zeolite Hß 200 psi air pressure (solvent free)	N_2O_4	25	22 hr	100	--
	Alexanders et al. 1978[9]	58-66%H_2SO_4+28-37%H_2O+ 3-7%HNO_3	HNO_3	136 (adiabatic)	11.2 min	99.5	--
Chlorobenzene	Olah et al., 1961[16]	Sulfuric acid	Nitric acid	25	--	--	0.43
		Nitromethane	Acetyl nitrate	25	--	--	0.42
		TMS	NO_2BF_4	25	--	--	0.30
	Sparks et al.,1964	Sulfuric acid	Acetyl nitrile	25	3 hr	67	0.24
	Sebastian, et al. ,1976	Sulfuric acid + phosphoric acid (0.01:0.99)	Nitric acid	80	3 hr	--	0.76
	Olah et al., 1981[17]	BF_3 catalyst	Silver nitrate with acetonitrile	25	10 hr	--	0.80
	Smith et al., 1998[18]	B-zeoite catalyst, Acetic anhydride	90% HNO_3	--	30 min	--	0.07
	Smith et al. 2002[15]	zeolite Hß in 1,2-dichloroethane	N_2O_4 and O_2	0	48 hr	98	0.16
		zeolite Hß 200 psi air pressure (solvent free)	N_2O_4	25	14 hr	100	0.18
Fluorobenzene	Olah et al., 1961[17]	BF_3 catalyst	Silver nitrate with acetonitrile	25	10 hr	--	0.37
	Olah et al., 1961[16]	H_2SO_4	HNO_3	18	--	--	0.14
		Acetic anhydride	HNO_3	25	--	--	0.09
		TMS	NO_2BF_4	25	--	--	0.09
	Smith et al., 1998[18]	B-zeoite catalyst, Acetic	90% HNO_3	-	30 min	99	0.06

		anhydride					
	Smith et al. 2002[15]	zeolite Hß in 1,2-dichloroethane	N_2O_4 and O_2	0	48	100	0.08
		zeolite Hß 200 psi air pressure (solvent free)	N_2O_4	25	16 hr	100	0.10
Bromobenzene	Olah et al., 1981[17]	BF_3 catalyst	Silver nitrate with acetonitrile	25	10 hr	--	0.34
	Olah et al., 1961[16]	H_2SO_4	HNO_3	18	--	--	0.60
		Nitromethane	Acetyl nitrate	25	--	--	0.58
		TMS	NO_2BF_4	25	--	--	0.35
	Smith et al., 1998[18]	B-zeoite catalyst, Acetic anhydride	90% HNO_3	--	5 min	99	0.14
	Smith et al. 2002[15]	zeolite Hß in 1,2-dichloroethane	N_2O_4 and O_2	0	48 hr	99	0.28
		zeolite Hß P = 200 psi (solvent free)	N_2O_4	25	14 hr	97	0.24
Iodobenzene	Olah et al., 1981[17]	BF_3 catalyst	Silver nitrate with acetonitrile	25	10 hr	-	0.21
	Smith et al. 2002[15]	zeolite Hß in 1,2-dichloroethane	N_2O_4 and O_2	0	48 hr	99	0.60

Analysis of literature data shows that generally nitrating mixture is the most common choice for the nitration reaction. Here sulphuric acid also act as a dehydrating agent, solvent and catalyst which is used in high amount and it subsequently generates large volume of spent acid. It may cause plant corrosion, it is highly reactive, dissolves most of metals, highly miscible in water, highly corrosive and also an oxidizer. Discharge of this spent acid is not an acceptable solution and neutralization generates large volumes of solids (salts). Reusing spent acid is rarely possible due to organic contaminates and presence of residual nitrous/nitric species. Considering above disadvantage it is advaisable to avoid use of sulphuric acid and other solvents. A few solid catalyst based nitration reactions have been reported in the literature but they require typically much longer reaction time around 10 - 48 hr and catalyst

stability is an issue. In view of this, here we revisit nitration of benzene and halobenzene to find the possibilities of avoiding or minimizing the use of spent acid and longer reaction time. Objective was to achieve the nitro-derivatives in a residence time of few a seconds to few minutes with complete elimination of sulfuric acid and other solvents except in case of benzene nitration where 2 wt% sulfuric acid was found necessary.

3.3 SOP for preparing continuous flow setup and experiments

From batch to flow transformation of any reaction first perform one batch experiment to check if there is any solid formation, if yes then use quantitative amount of solvent to dissolve that, observe temperature raise and phase change in reaction mixture throughout the reaction. All these plays important role during process transformation.

For making a continuous flow set up, first and most important step is to choose a chemistry (reactant, reagent, product, intermediate, solvents etc.) compatible material. During assembling a setup, teflon tape should be warped around the threads of female fitting and all fittings should be tighten enough to prevent leakage, over tightening may harm thread and cause leakage. Leakage check is necessity before performing any experiment to prevent any misshaping, it can be done by passing water at high flow rate, or for gaseous phase reaction, setup can be placed in water and can be done by passing air.

For making multiple outlet setup, volume of each section should be known and calculation of flow rates and residence time will be based on cumulative volume of reactor. Residence time of each section will be calculated on the basis of volume of the section and cumulative flow rate. Once all the pumps are ON and solution comes at the outlet measure the flow rate initially, to check if the pumps are giving the required flow rate Sample collection should be done after reaching steady state, which nearly takes twice of residence time, and it should be quenched immediately. Volume of collected sample (reactant) should be constant while collection time may vary with changing flow rates or residence time.

3.4 Continuous flow synthesis set-up and experiment

For the continuous flow experiments, the experimental setup (Figure 3.2) consisted of two syringe pumps (Holmarc Optomechatronics, India), loaded with two stainless steel syringes (SS316 syringe of 50 ml volume from Amar Equipment Pvt. Ltd., India), one

containing nitric acid, and another containing substrate, connected to a SS316 tubes (1/8" o.d.). The outlet of pumps were connected to Amar3 SS316 3D flow reactor cum micromixer (0.3 ml volume) followed by a residence time tube (3.12 mm outer diameter and 2.1 mm inner diameter). The entire assembly (Figure 3.2) had five outlets (one immediately after the micromixer and remaining along the length at equal distance) with needle valves for sampling. The entire assembly of tubular reactors was immersed in a heating-chilling thermostat (Julabo, ME12) to maintain the system at isothermal condition. A high temperature furnace was used for higher temperature nitrations (T > 110 ºC), with a single outlet. Benzene has boiling point of 80 °C, and reactions were carried out at much higher temperature, To avoid pulsating effects due to boiling a cooling coil (coil in ice bath) was used immediately after the furnace, which helped to prevent mass loss in the vapor phase. Some experiments were carried out at adiabatic conditions with reactant preheating in a tubular reactor made of Teflon tube.

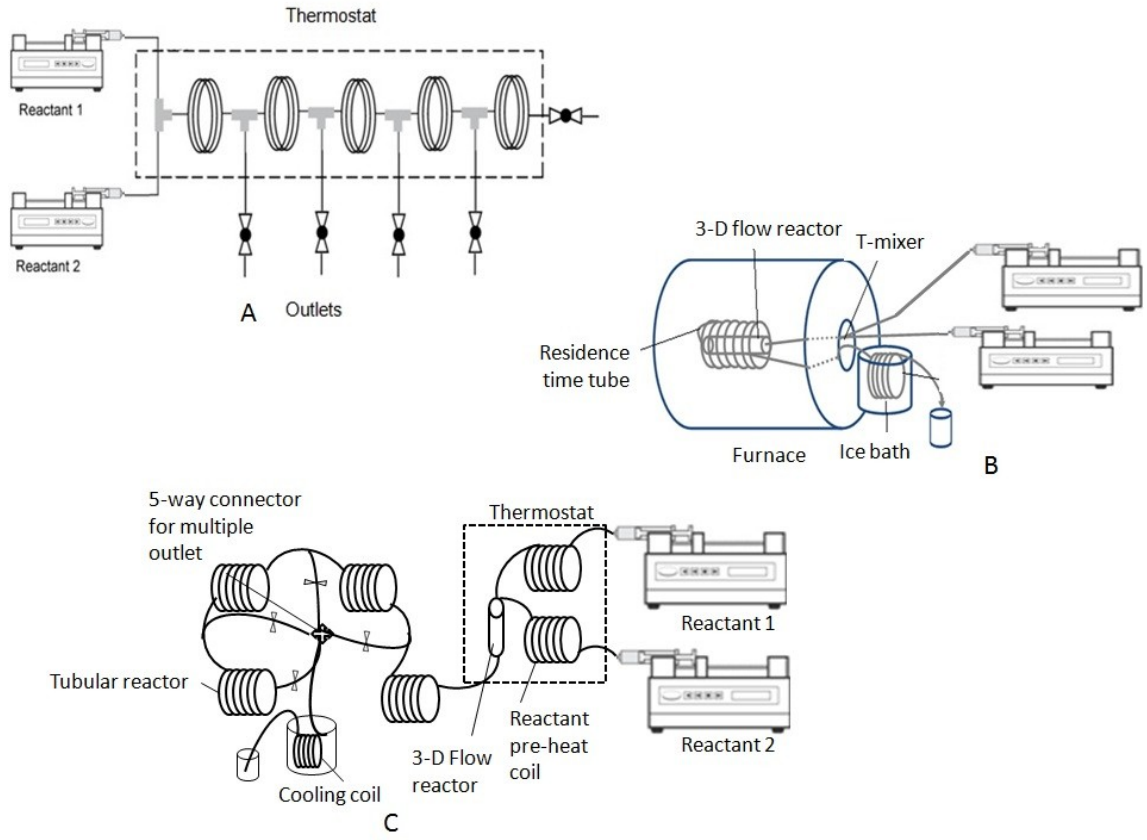


Figure 3. 2: Schematic reaction setup of benzene and halobenzene nitrations a) Isothermal setup b) Setup using furnace for higher temperature c) Adiabatic setup with reactant preheating

The flow rates of reactants and nitrating agent were varied to achieve different residence time as well as a range of mole ratios of the reactants. Samples were collected at

different outlets (corresponding to different residence times), in a fixed quantity of ice-cold-water. A known quantity of toluene (Merck) was used to extract the organic phase from these samples. The extracted organic phase was washed two times with water and separated by gravity. It was further washed with brine to make them free of residual water. Trace quantity of water was removed by passing the organic phase through a bed of anhydrous sodium sulphate. The samples were analyzed using gas chromatography with an HP5 capillary column and an FID detector. Di-nitro impurities were identified using GCMS. The influence of different parameters (viz. temperature, residence time, nitrating agent [H_2SO_4, 0 - 100 wt% of fuming nitric acid]) on the conversion and selectivity of isomers was studied.

3.5 Analysis

Analysis of nitration reactions of benzene and halobenzene was done using GC with HP-5 capillary column and FID detector. Initially all products and reactants calibrated on GC and then conversion and yields were calculated on molar basis using calibration curve. *o*-xylene was used as internal standerd. GC data has been added at the end of chapter.

3.6 Result and discussion

3.6.1 Benzene nitration

Typical nitrating agent used for benzene nitration is the mixed acid having composition of 58.5-66.5% sulfuric acid, 28–37% water and 3–7.5% nitric acid (69% concentration)[19]. The nitronium ion concentration estimated for only FNA is 4.7 mole%. While for nitrating mixture (69% HNO_3 : concentrated H_2SO_4 ~ 40/60 v/v) the nitronium ion concentration is 20 mole %, which increases with an increase in quantity of sulfuric acid[20]. The present work aim at significantly reducing the sulfuric acid quantity or possibly eliminate it. In view of this, initial experiments of benzene nitration were performed using only fuming nitric acid as a nitrating reagent. A maximum of 49% yield of **2** was achieved in 8 s residence time on using 0.95 moles of NA at 90 ºC. Since sulfuric acid act as a catalyst and dehydrating agent in this nitration reaction, catalytic amount (2 wt% with respect to FNA) of sulfuric acid was used in next experiment where only 50% yield was achieved instead of 49%. These results conclude that nitric acid is a limiting reagent here, further experiments were carried out using higher moles of FNA upto 2 mol with 2 wt% of sulfuric acid and maximum 93% yield was achieved with 94.5% conversion in residence time of 26.4 s on using 2 moles of fuming nitric acid. The results are summarized in Figure 3.3.

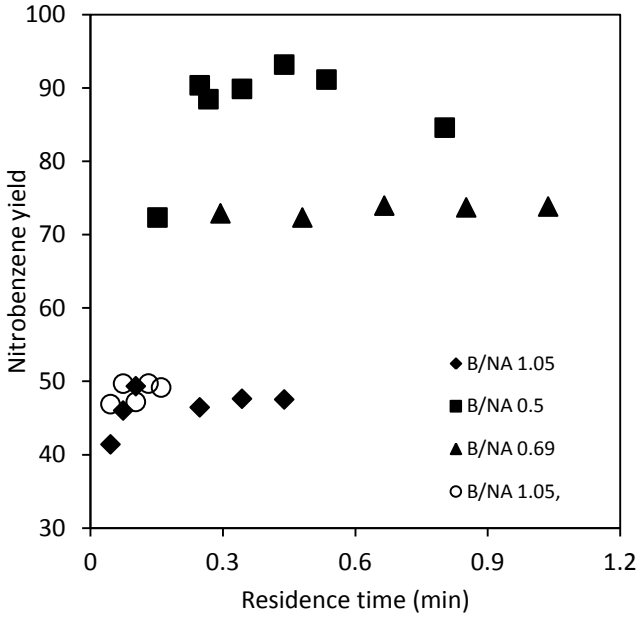


Figure 3. 3: Effect of nitric acid quantity and presence of sulfuric acid on benzene nitration at 90 ºC, solid legend corresponds to use of 2w% sulfuric acid, and empty legend corresponds to absence of SA

The quantity of sulfuric acid was further optimized to regulate the generation of nitronium ions and their consumption to achieve the stoichiometric conversion of benzene. Experiments were carried out using 3 different molar ratios 0.5, 1 and 2 of nitric acid with different sulfuric acid wt% in the range of 0 – 100 wt%. The results are summarized in Figure 3.4. Using 0.5 moles and 1 mole of the fuming nitric acid with 25 wt% SA, % yield of nitrobenzene **2** increased from 35% to 66%. At identical mass ratio of sulfuric acid and fuming nitric acid (w/w) the yield of **2** was 92% in 15.6 s residence time. Further enhancement in the quantity of sulfuric acid resulted in formation of di-nitro derivatives. Use of higher quantities of sulfuric acid also generates spent acid that creates disposal and recycling problems. In the absence of higher amounts of sulfuric acid, presence of active nitronium ion limits the reaction. For complete conversion of benzene, 2 mole of fuming nitric were used with 2 wt% and 50 wt% of sulfuric acid which resulted in >95% yield in both cases in residence time of 33.9 and 9.6 sec respectively at reaction temperature of 110 ℃. Reaction condition of benzene with 2 moles of fuming nitric acid and 2 wt% sulfuric acid at 110 ºC reaction temperature gave 96% 2 yield in 33 s.

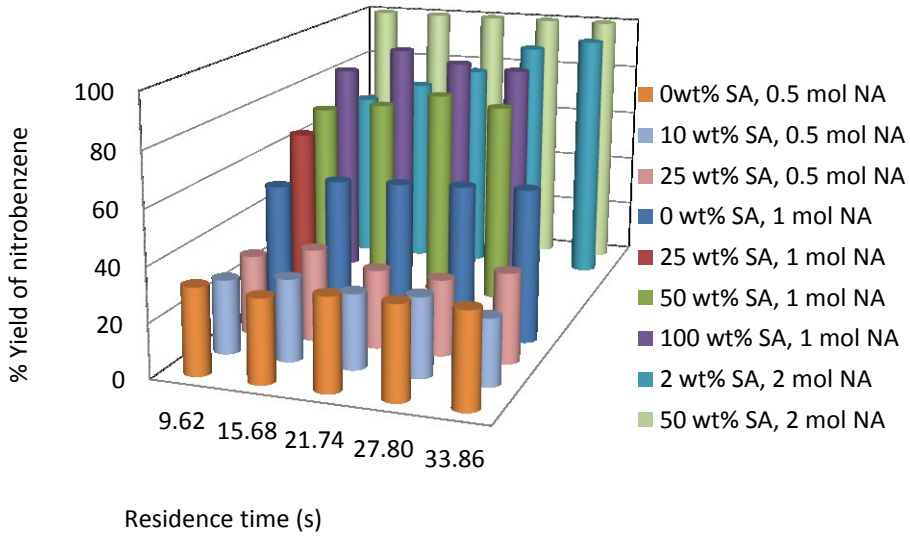


Figure 3. 4: Effect of nitric acid and sulfuric acid quantity on benzene nitration at 110 ºC temperature.

From these sets of experiments, the sulfuric acid quantity was optimized to 2 wt% of fuming nitric acid, but it requires 2 moles of fuming nitric acid for complete conversion. In order to reduce the quantity of fuming nitric acid while achieving maximum conversion, the sulfuric acid quantity was further varied in range of 2 -10 wt% while nitric acid moles were retained at 0.5 where complete consumption of used fuming nitric acid was expected. On the basis of previously done experiments, 25 wt% SA and 0.5 mol NA at a reaction temperature of 110 ºC, resulted in only 34% yield of nitro benzene and hence higher temperature was necessary. Experiments were carried out in temperature range of 120 ºC to 221 ºC for a fixed residence time of 30 s. The observations indicated an increase in the yield with increasing reaction temperature (Figure 3.5).

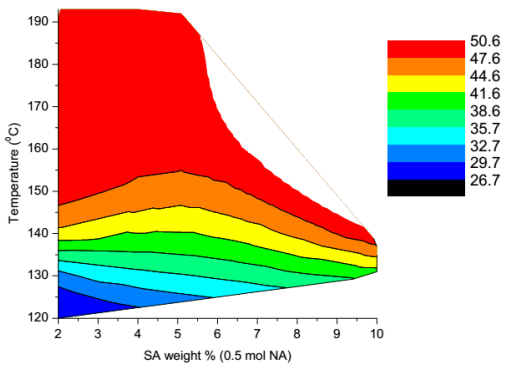


Figure 3. 5: Effect of reaction temperature and SA quantity on benzene nitration with 0.5 mole of nitric acid and residence time of 0.30 minute. (No experiment has been performed for longer residence time at temperature below 130 and above 145 ºC

Complete consumption of nitric acid can be achieved at a reaction temperature above 145 ºC with 2 wt% of sulfuric acid, which also resulted in 50% conversion of benzene to nitrobenzene with no dinitro derivatives.

Nitration reactions are generally carried out at 60 to 70 ºC and being exothermic, cooling is a necessity to control temperature. In order to avoid cooling, adiabatic nitration is an optimal way to carry out benzene nitration. Highly exothermic nature of the reaction releases large amount of heat, which if not removed actually helps to enhance the reaction rate despite decreasing concentration of the limiting reactant. In literature adiabatic benzene nitration is generally carried out using nitrating mixture (3 -7.5% nitric acid, 58.5 – 66.5% sulfuric acid and 28 – 37% water), with 10% excess of benzene, in temperature range of 80 – 120 ºC under such condition reaction temperature does not exceed 145 ºC. On using 3% nitric acid, which is lower limit in literature for adiabatic condition, higher sulfuric acid is required, which generates spent acid in large amount and makes it uneconomical as well as environmentally unsustainable. On the other hand using 7% nitric acid generates excessive heat which results in temperature raise above 145 ºC, which tend to give dinitro derivatives. Similarly in the presence of less than 28% water in nitrating mixture, more dinitro forms and above 38% the reaction rate decreases[19].

In order to check feasibility of fuming nitric acid in adiabatic mode, experiments were planned with 2 wt% of sulfuric acid and no water. In this series initial experiments were carried out at a relatively low temperature in the range of 30 – 80 ºC using 0.5 mol of nitric acid. Residence time for such experiments was varied from a few seconds to a maximum of 14 minutes. Over this

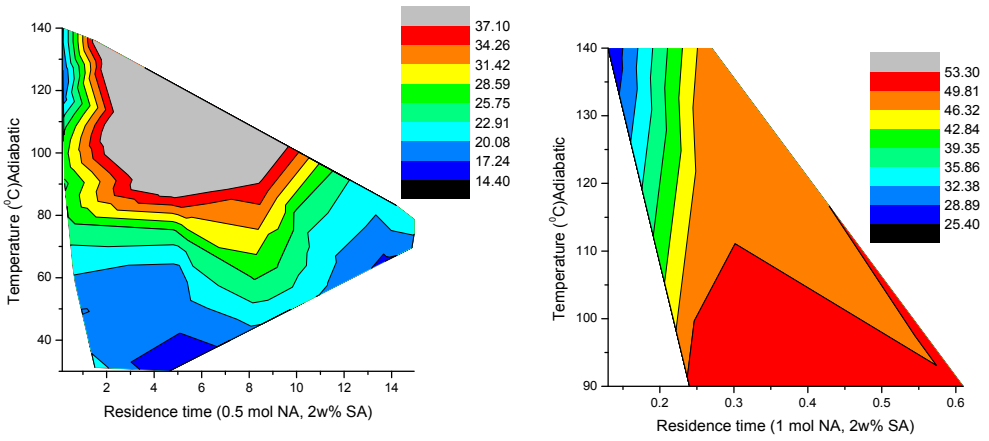


Figure 3. 6: Effect of residence time and temperature on adiabatic nitration of benzene

Temperature range reaction showed two-phase flow as boiling point of nitric acid and benzene both are below 90 ^{0}C and remain immiscible. At 80 ^{0}C, the yield of **2** was 36.7% in 30 s. At higher temperatures in range of 90 – 140 ºC, the reaction was seen to show very rapid fluid movement resulting from almost an instantaneous phase change with no improvement in yield and conversion. This was primarily because of significant reduction in the residence time at higher temperatures due to phase change. On using 1 mole of fuming nitric acid and 2 wt% sulfuric acid in temperature range of 90 – 140 ºC and in residence time range of 7.8 – 36 s, maximum 53% yield of **2** was achieved at 90 ºC in residence time of 24 s. Thus, in addition to mode of reaction and the composition of nitrating agent, the relative rates of heat transfer, phase change, reaction and flow rate (i.e. residence time) govern the conversion of benzene and the yield of mono-nitrobenzene.

For an isolate yield of mononitrobenzene, experiment carried out using 0.5 mole of fuming nitric acid with 2w% SA at 90 ºC and 57.8 gm of sample was collected. Organic and aqueous layers were separated by simple liquid-liquid extraction. Organic layer was given water wash followed by drying over sodium sulphate. 42% of mononitrobenzene and remaining benzene was isolated after evaporation on a rotavap (Heidolph GmbH.). Complete consumption of FNA was confirmed by titration with sodium hydroxide.

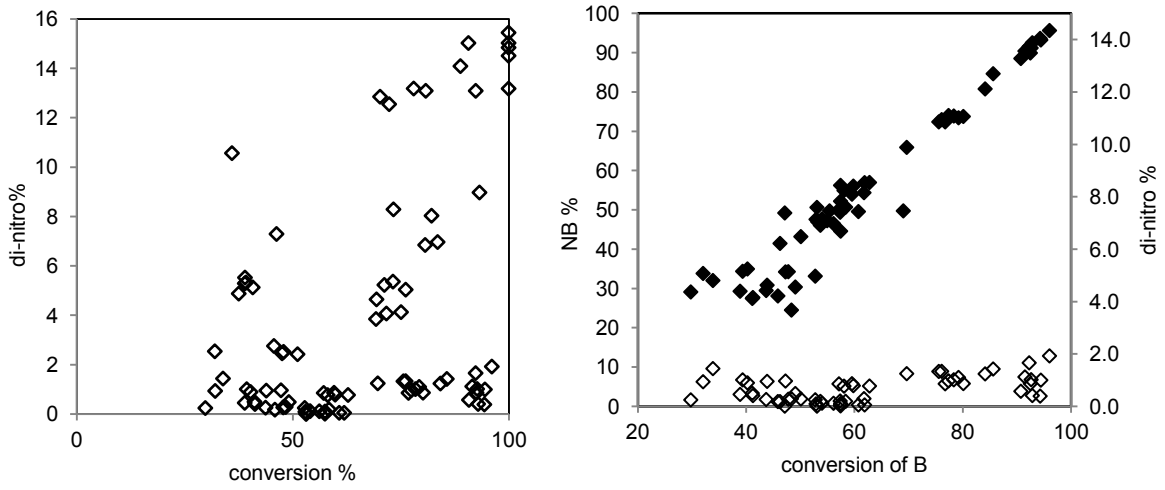


Figure 3. 7: a) Mole% dinitro impurities with conversion, SA used in range of 0-200w%, b) Nitrobenzene yield with increasing conversion & >2% impurities, 0-25w% SA used

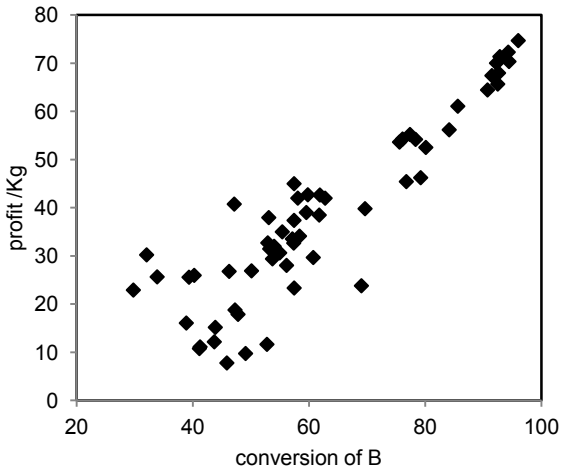


Figure 3. 8: Conversion- profit profile with >2% di-nitro impurities

On using more than 2w% of sulfuric acid (SA), >2 % di-nitro-benzene formed. 95.6% yield of nitrobenzene with 1.92% di-nitro impurities achieved on using 2 moles of fuming nitric acid (FNA) with 2w% SA. Reaction carried out at 110 ºC with residence time of 10 minutes, with the maximum profit of 74.69 Rs/kg.

3.6.2 Halobenzene nitration

Halobenzenes show a "U" profile in terms of reactivity in nitration reaction. On nitration it gives 2 main nitro derivatives, o-nitro and p-nitro with traces of m-nitro derivative., it is The deactivating and ortho, para directing nature of halogens towards nucleophilic substitution reaction lead to the value of ratio of o/p always below 1. This isomer ratio (o/p) depends on the nitrating reagent and solvent used. Among the available halobenzenes, only nitration of fluoro, chloro and bromobenzene was carried out. Since iodobenzene is highly hazardous (mainly for skin and eye contact), and highly combustible, storage and its frequent use in lab is not a safe practice, we have not carried out the nitration of iodobenzene.

The isothermal experimental setup with 3D Flow microreactor[21] shown in Figure 3.2 was used for nitration of halobenzenes. SS syringe (i.d. 29 mm, vol. 50 ml) for nitric acid and PTFE syringe (i.d. 30 mm, vol. 60 ml) for halobenzene was used. This reactor has 4 outlets at definite length. Samples were collected at different outlets, in a fixed quantity of ice-cold-water. A known quantity of toluene (Merck) was used to extract the organic phase from these samples. The extracted organic phase was washed two times with water and separated by

gravity. It was further washed with brine to make them free of residual water. Trace quantity of water was removed by passing the organic phase through a bed of anhydrous sodium sulphate.

Table 3. 2: Experimental conditions for halobenzene nitration

	Mole ratio (FNA/ Substrate)	Temperature (°C)	Residence time (min.)	Conversion (%)	Para Selectivity (%)
Fluorobenzene	1.5	30 - 50	0.71 - 10.00	73.9 - 96.8	87
	2.0			95.1 - 97.9	
	3.0			98.7 - 99.87	
Chlorobenzene	2.0	65 - 75	0.16 – 15.00	60.67 – 74.2	69
	3.0			48.5 – 99.9	
Bromobenzene	5.0	70	4.89	100	92

The samples were analyzed using gas chromatography with an HP5 capillary column and an FID detector. Experiments were carried out over a wide range of combinations of temperature, residence time and molar ratio as shown in Table 3.2.

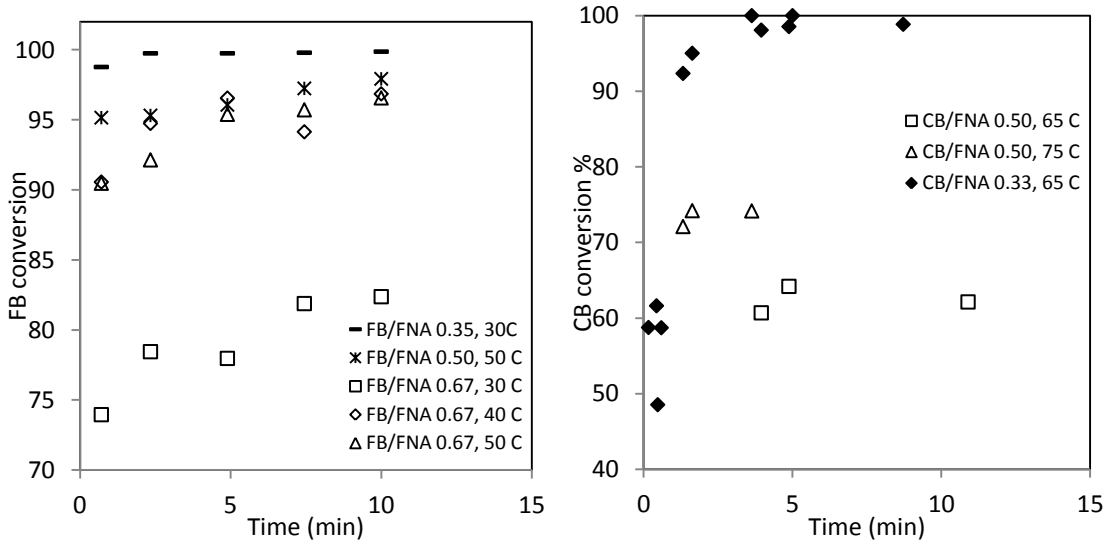


Figure 3. 9: Effect of residance time and temperature on nitration of a) fluorobenzene b) chlorobenzene

First experiment of chlorobenzene nitration was performed with 2 mole of fuming nitric acid at 65 ºC in residence time range of 3.95 to 10.9 minutes. maximum conversion of 64% was achieved in 4.88 minute. Longer residence time did not show any further increase in conversion. In order to enhance rate of reaction same experiment carried out at higher temperature 75 ºC where maximum conversion increased to75.2% in 1.63 minute. Fuming nitric acid has boiling point of 83 ºC hence further temperature rise was not advisable and we increased fuming nitric acid moles. Complete conversion with 69% *p*-nitrochlorobenzene selectivity was obtained on using 3 moles of fuming nitric acid at 65 ºC in residence time of 3.63 minutes.

In an effort to study the feasibility of Continuous flow nitration of bromobenzene, experiments were done using 5 moles of fuming nitric acid at reaction temperature of 70 °C. Complete conversion of bromobenzene with 92% selectivity of *p*-nitrobromobenzene was obtained in a residence time of 4.89 min. para-nitrobromobenzene has boiling point 252 ºC, and it remains in solution form in excess nitric acid. Reactor clogging was observed upon carrying out the reaction with less than 5 moles of nitric acid, which helps to keep *p*-nitrobromobenzene in solution. The key observations are summarized in Table 3.2.

These observations indicate that although nitration of benzene and halobenzene is a well established process and commercially implemented for large scale manufacturing, it is necessary to revisit such basic reactions to find new operating windows to transform them in sustainable processes. More work on development of detailed reaction engineering models for these reactions is in progress and will be reported separately.

Table 3. 3: Number of experiments performed

Reactions	Batch experiments	Flow experiments
Benzene nitration	8	192
Bromobenzene nitration	4	3
Chlorobenzene nitration	4	24
Fluorobenzene nitration	4	25

3.7 Conclusion

In general, nitric acid is a limiting reagent for benzene nitration. Higher moles of nitric acid or large volume of sulfuric acid are required for achieving complete conversion and high

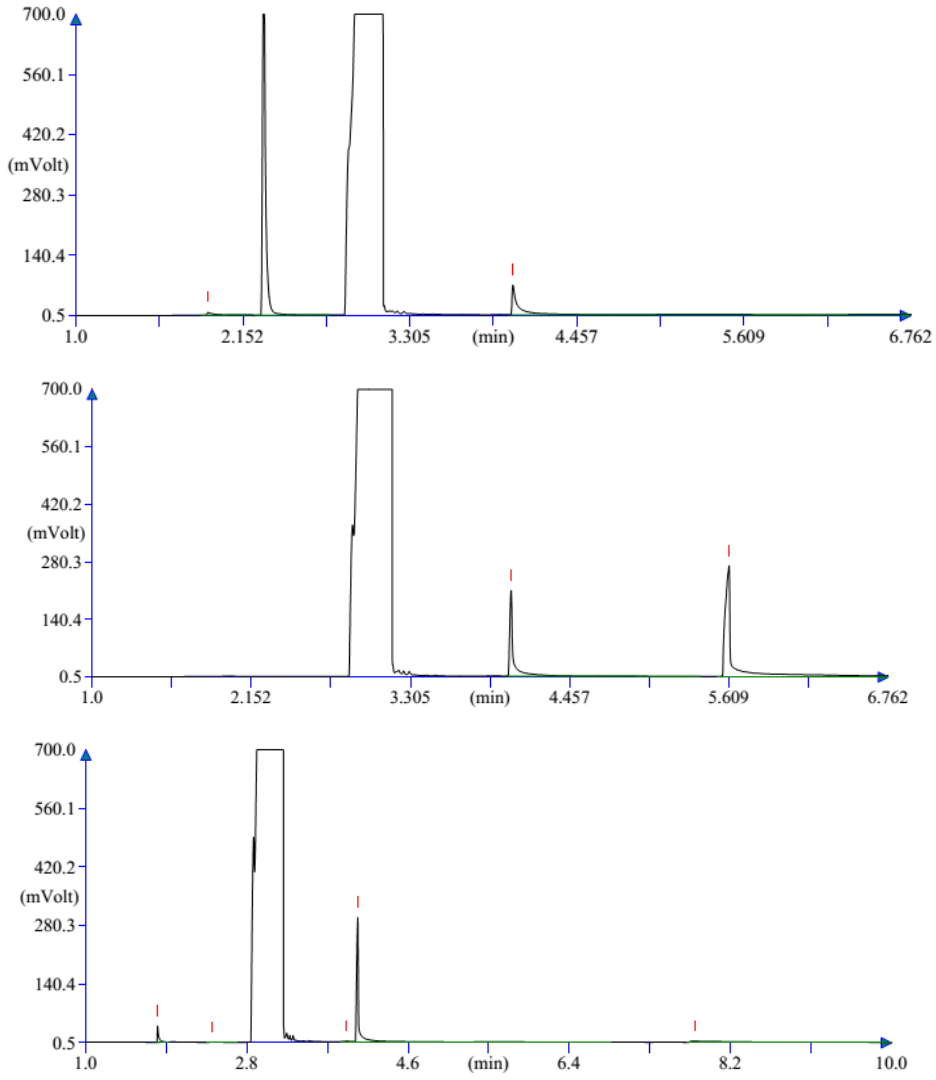
yield. Using fuming nitric acid alone makes this process rapid as well as sustainable. Only for benzene nitration 96% yield of nitrobenzene was achived on using 2 moles of fuming nitric acid with only 2 wt% sulfuric acid at 110 ^{0}C reaction temperature in reaction time of 33 s. On the other hand at 145 ^{0}C with 0.5 mole of fuming nitric acid and 2 wt% sulfuric acid also resulted in complete consumption of nitric acid along with 50% conversion of benzene and 50% yield of nitrobenzene. 87%, 69% and 92% *p*-selectivity with >99% conversion was achieved for the nitration of fluorobenze, chlorobenzene and bromobenzene using only fuming nitric acid in residence time of 2.34, 3.63 and 4.89 minute respectively, with complete elimination of solvent and catalyst.

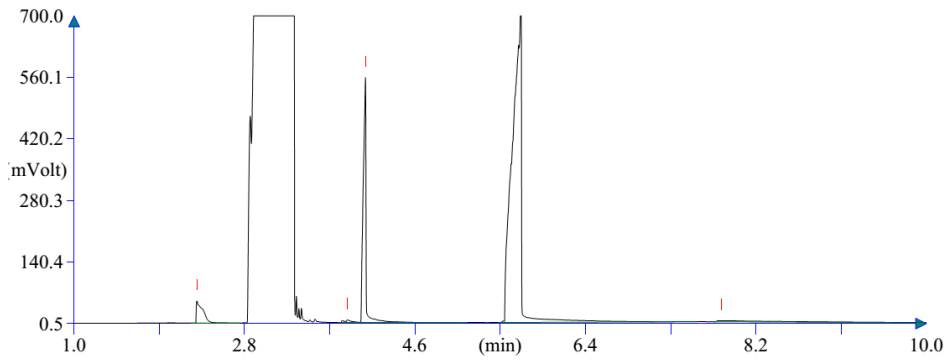
Analytical Data

1) GC and GCMS spectra

1. **Benzene:** GC method: Initial oven temperature kept 65 ºC and temperature rise with the ramp 5 ºC/min up to 80 ºC temperature, second ramp with 35 ºC/min up to temperature 280 ºC and hold for 2 min.

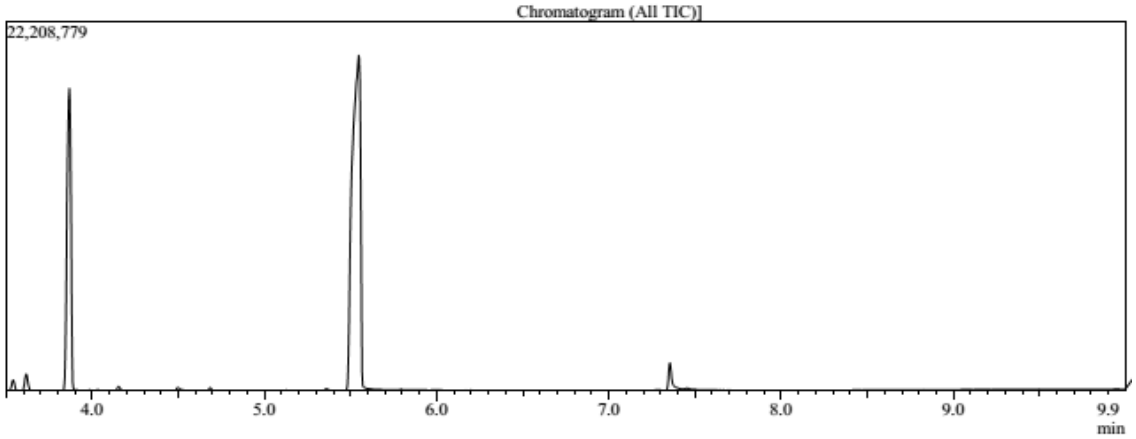
	GC retention time
Internal standard	4.0
Benzene	2.3
nitrobenzene	5.6
Metadinitro benzene	7.8





GC spectra of a) Benzene, b) Nitrobenzene, c) Di-nitrobenzene and d) Reaction mixture

GCMS of Benzene nitration reaction mixture



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RawMode:Single 5.540(613) BasePeak:77.05(10000)
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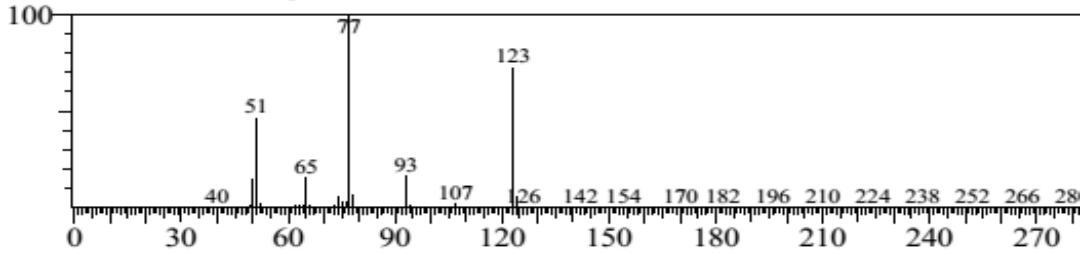

Line#:1 R.Time:7.353(Scan#:1157) MassPeaks:461
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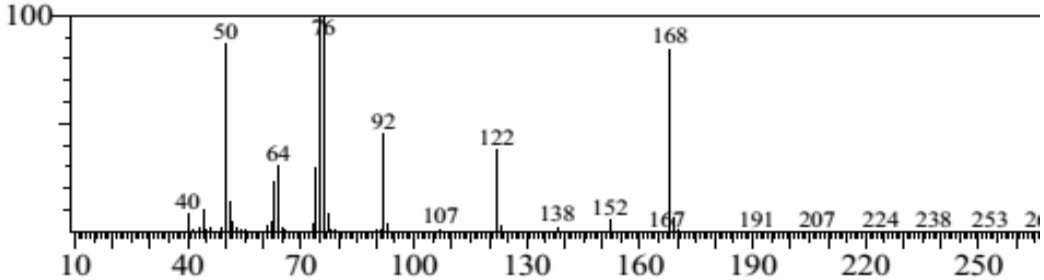
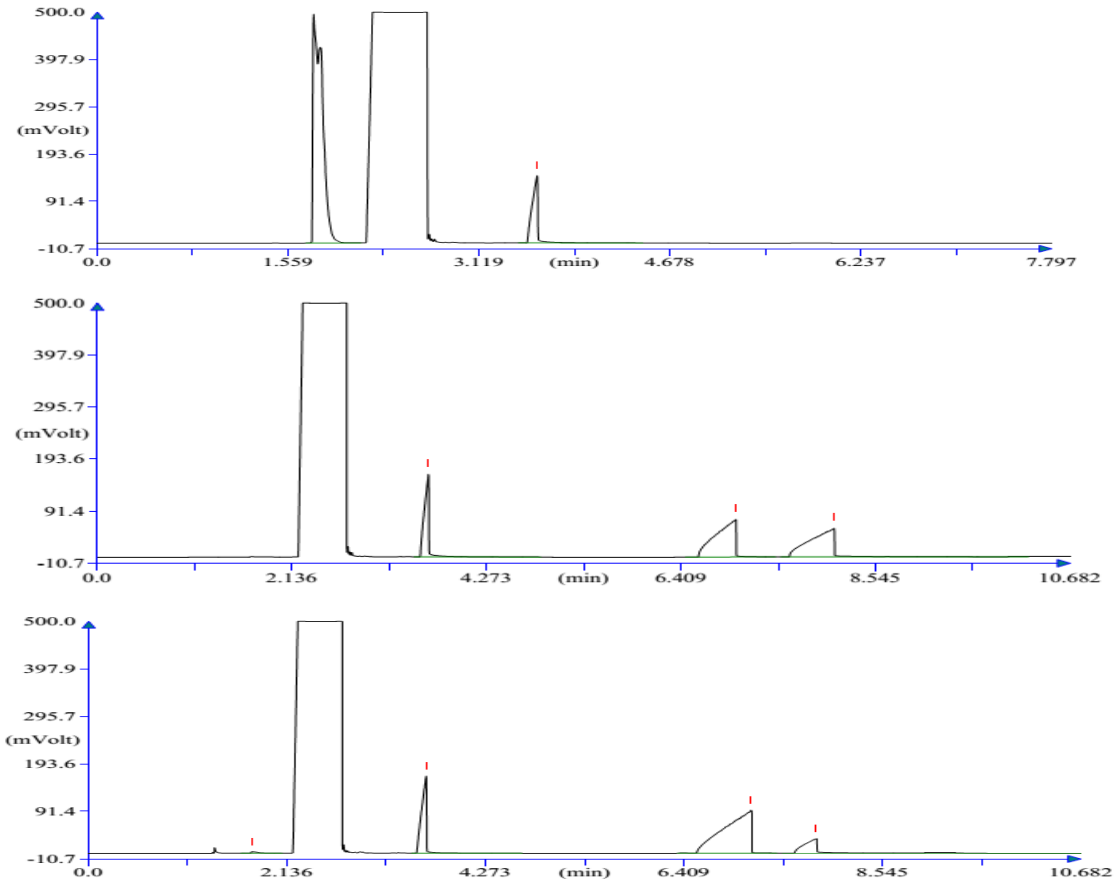
BG Mode:None Group 1 - Event 1



2. **Fluorobenzene:** GC method: Initial oven temperature kept 65 ºC and temperature rise with the ramp 5 ºC/min up to 108 ºC temperature, second ramp with 30ºC/min up to temperature 280 ºC and hold for 1 min.

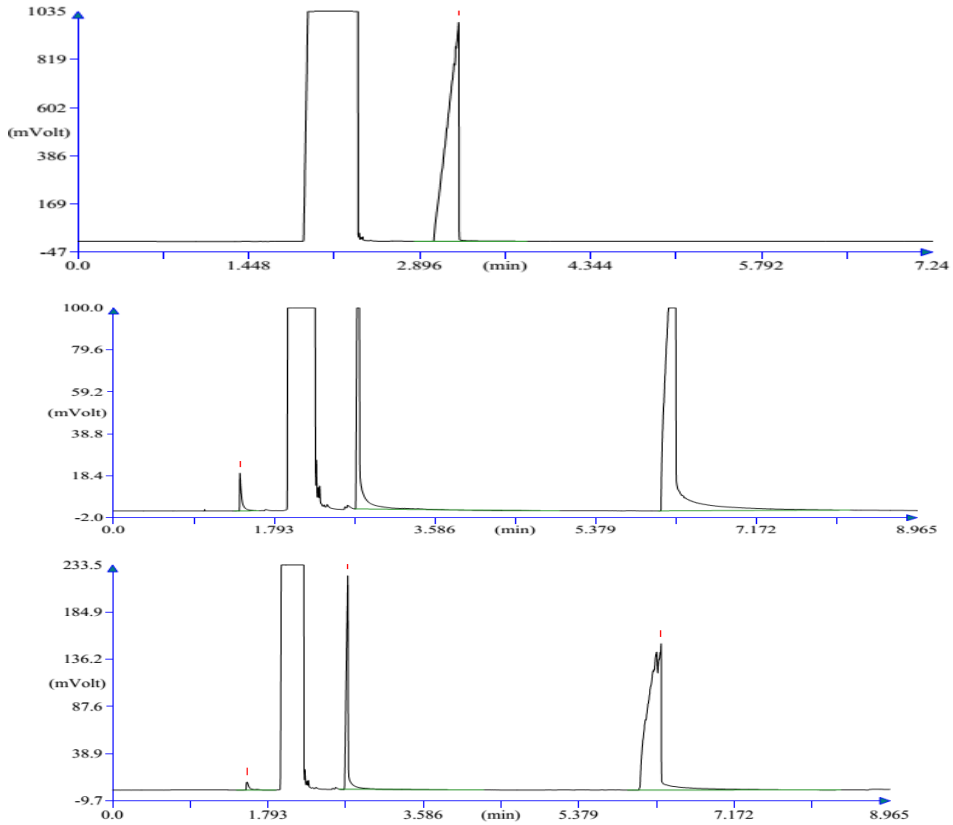
	GC retention time
Internal standard	3.5
Fluorobenzene	1.7
2-nitrofluorobenzene	7.8
4-nitrofluorobenzene	7.1



GC spectra of a) Fluorobenzene, b) Nitrofluorobenzene, c) Reaction mixture

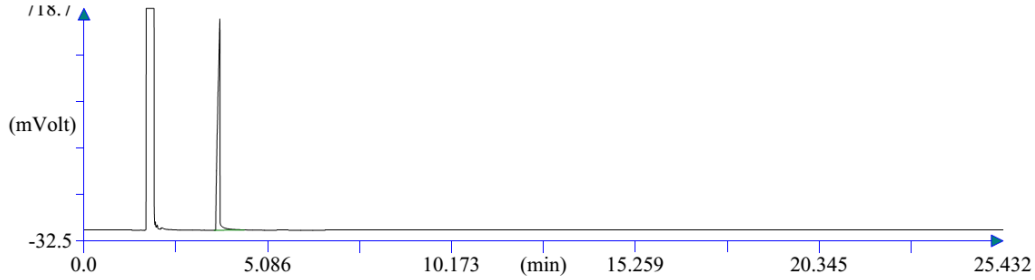
3. **Bromobenzene:** GC method: Initial oven temperature kept 65 ºC and temperature rise with the ramp 2 ºC/min up to 180 ºC temperature, second ramp with 10 ºC/min up to temperature 250 ºC and hold for 5 min.

	GC retention time
Internal standard	2.7
Bromobenzene	3.2
4-nitrobromobenzene	6.2



spectra of a) Bromobenzene, b) 4-nitrobromobenzene, c) Reaction mixture

4. **Chlorobenzene:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 0.5 ºC/min up to 65 ºC temperature, second ramp with 30 ºC/min up to temperature 132 ºC with hold time of 1 min, third remp with the of 0.1 ºC/min upto 133 ºC with hold time of 1 min and final temperature remp with 45 ºC upto 250 ºC with hold time of 2 min.



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Chapter 4

Discontinuous two-step Flow Synthesis of *m*-Amino Acetophenone

4.1 Introduction

The nitro derivatives of aromatic compounds find applications in the manufacture of dyes, API's, pesticides and fine chemicals. One of the most common ways for inserting a nitro group in the organic structure is by nitration using different nitrating agents, the nitrating mixture (HNO_3 + H_2SO_4) being the most practiced. The synthesis of nitro aromatic compounds is usually associated with relatively high heat of reaction (usually of the order of -100 kJ/kmol per nitro group[1]). Also, since the presence of sulfuric acid largely drives the reaction by generating the nitronium ions, the concentration of sulfuric acid in the nitrating mixture also helps decide the isomer ratio. However since the sulfuric acid usually does not participate in the reaction, it is not included in the reaction kinetics. Usually, the nitro aromatics are further reduced to obtain the respective amines which are relatively stable. Since the nitration using nitrating agents is usually non-specific in terms of isomers, the mononitro derivatives primarily includes a mixture of different isomers. Since the amines from individual isomers have different applications and are difficult to separate, the nitro derivatives are isolated and then reduced using variety of reducing agents.

Continuous flow aromatic nitration using microreactors[2-6] is now a well established fact and a comprehensive Review on the topic can be found in Kulkarni[7]. The advantages of miniaturized process devices or microreactors such as high heat transfer area, efficient mixing, better mass transfer rates and precise control on the residence time etc. help achieve better conversion and much higher selectivity of the mononitro products. Several such examples from the literature on homogeneous and two phase nitration reactions in continuous flow miniaturized devices mainly aim at reducing the byproduct formation and enhancing the product yield [3-5, 8-15]. While the use of microfabricated devices is encouraged for laboratory scale syntheses, simpler approaches such as using simple tubular reactors [3-5, 8] which also offer the required heat transfer area per unit volume of the reacting mass also help to carry out exothermic reactions having and issues of selectivity. In continuation with our efforts to study the nitration of reactive aromatic substrates[3, 4], the nitration of acetophenone (**1)** was taken up in the microreactor system.

4.2 Literature analysis

The major product from mononitration is meta-nitroacetophenone which is an important raw material for the commercial production of fine chemicals and active pharmaceutical ingredients. The reduction of meta-nitroacetophenone to meta-

aminoacetophenone, followed by diazotization and thermal decomposition of diazonium salt gives meta-hydroxyacetophenone. The meta-hydroxyacetophenone is the staring material in the production of important drugs like Rivastigmine which is used for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease[16 17] and fenoprofen drug used for symptomatic relief for rheumatoid arthritis, osteoarthritis, and mild to moderate pain.[18] Here in present work we bring out the lab scale approach that can be scaled up to a few kilograms from a single tubular reactor for the synthesis of **3**. The system can be easily scale-up to achieve higher capacity. The entire process involves nitration followed by reduction, both the steps can be made continuous but separately. The paper also brings out the reasons that do not support a continuous process that comprises both the steps in a continuous manner.

The conventional route for the manufacture of **2** is through the nitration of **1** using nitrating mixture.[19] The reaction is extremely exothermic and needs to be carried out at 5 ºC with controlled addition of acetophenone over several hours. Typical production scales in the industry for the *m*-nitro-acetophenone in India are of the order of few tens of tons per month (typically if to be converted in continuous mode it comes to be anywhere from 5 to 25 gm/min depending upon the requirement of individual industries). Being a highly exothermic reaction, conventionally, addition of nitrating agent in semi-batch manner is preferred. The addition time period is crucial because the additions over longer time lead to the decomposition of raw material giving a poor yield. Also, very efficient stirring is required to achieve good mixing that helps achieve reasonable yields of the desired product. These constraints make the nitration of acetophenone difficult to scale up while retaining the stoichiometric selectivity. In this paper, we focus on the nitration and reduction steps (Figure 4.1). In the first step of nitration, the literature reports indicate that a second order kinetics apply for this reaction[20] and the rate constant decreases with increase in the concentration of nitric acid, thus needing an optimal concentration of nitric acid that would help achieve maximum reaction rate. The presence of sulfuric acid is necessary even to activate the organic substrate for nitration reaction thereby helping to accelerate the reaction and hence sulfuric acid is used in much excess.

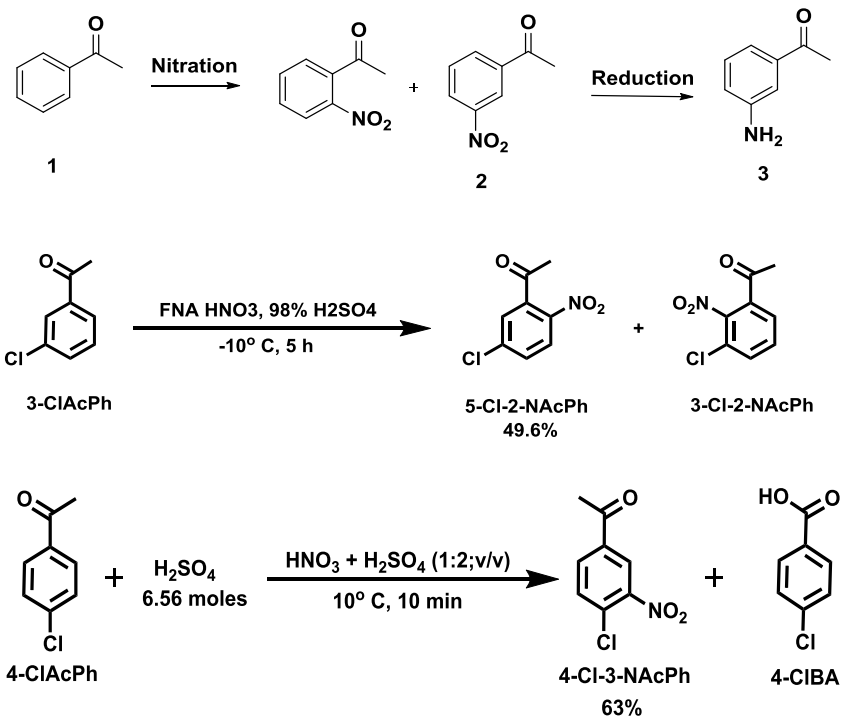


Figure 4. 1: Nitration of acetophenone, *m*-chloroacetophenone and *p*-chloroacetophenone

4.3 SOP for preparing continuous flow setup and experiments

For making a continuous flow set up, first and most important step is to choose a chemistry (reactant, reagent, product, intermediate, solvents etc.) compatible material. During assembling a setup, teflon tape should be warped around the threads of female fitting and all fittings should be tighten enough to prevent leakage, over tightening may harm thread and cause leakage. Leakage check is necessity before performing any experiment to prevent any misshaping, it can be done by passing water at high flow rate, or for gaseous phase reaction, setup can be placed in water and can be done by passing air.

For making multiple outlet setup, volume of each section should be known and calculation of flow rates and residence time will be based on cumulative volume of reactor. Residence time of each section will be calculated on the basis of volume of the section and cumulative flow rate. Sample collection should be done after reaching steady state, which nearly takes twice of residence time, and it should be quenched immediately. Volume of collected sample (reactant) should be constant while collection time may vary with changing flow rates or residence time.

4.4 Experimental

The experiments were performed in two steps, as shown in the Figure 4.1. Individual steps were studied separately. Batch as well as continuous flow experiments were performed to synthesize **3** and were later optimized for the highest quantitative yield at lab scale. The details of the experimental procedure are given as follows.

4.4.1 Nitration of acetophenone: Experimental set-up and experimental procedure

1. **Preparation of solutions:** A solution of acetophenone (Loba Chemie) in concentrated sulfuric acid (Thomas Baker) was prepared in a beaker in ice-salt bath at a temperature between -5 to 0 ºC. The addition of acetophenone to sulfuric acid was done drop wise such that the mixture temperature does not rise above 2 ºC. Because of the low melting point of acetophenone (19 ºC), during the addition it was kept at room temperature to retain it in liquid state. Addition of acetophenone at lower temperature to sulfuric acid is not advisable as the heat of dissolution creates hotspots and even the solid powder gets accumulated on the stirrer thereby causing significant variability in the dissolution time. At low temperature the dissolution becomes liquid-solid mass transfer controlled. With higher mixture volumes lumping of solids was seen to yield larger flocks, which take very long to dissolve/react. Hence mixing of acetophenone at room temperature (> 25 ºC) in cold sulfuric acid was preferred and was found to be very exothermic. The heat generation rate was in the range of 3.9 to 4.2 ºC/ml, which limits the mixing volumes and also indicates the need for having either longer mixing time to avoid rapid heat generation or rapid heat removal from the system. Nitrating mixture was prepared by mixing concentrated nitric acid with concentrated sulfuric acid and was maintained at 0 ºC in a v/v ~ 40/60 proportion. The mixture compositions were varied depending upon the need for experiments.

2. **Batch experiments:** In a typical batch experiment, the nitrating mixture was added drop wise to the mixture of acetophenone in sulfuric acid over 30 - 45 min and care was taken to maintain the temperature at 0 ºC. This was done in a jacketed stirred glass reactor. After complete addition the solution was stirred for 15 min and then it was dumped into a 500 mL beaker containing 150 gm of crushed ice. This resulted in quenching of the reaction and a yellow solid product was seen to get precipitated. The product was filtered (which contains almost > 90% meta isomer and rest of ortho isomer) and dried and later recrystallized in ethanol to get pure meta isomer. Only at

higher temperatures, phenolic byproducts as well as the byproducts due to cleavage of the ketone group were observed. Melting point of the dried product was checked for several batches and was ~ 76 - 77 ºC and was confirmed by NMR as **2** (the value from the literature is 77.8 ºC). The above procedure for isolation was also followed for the continuous flow experiments.

3. **Continuous flow experiments:** The typical experimental setup consisted of two syringe pumps (Longer – LSP02-1B), a constant temperature bath (Julabo GmbH), a micromixer and a tubular reactor. The residence time was controlled by choosing the flow rates and the reactor tube outside the constant temperature bath (the outlet portion about 60 mm) was maintained at constant temperature by insulating it using glass-wool. Typical experimental set-ups are shown in Figure 4.2.

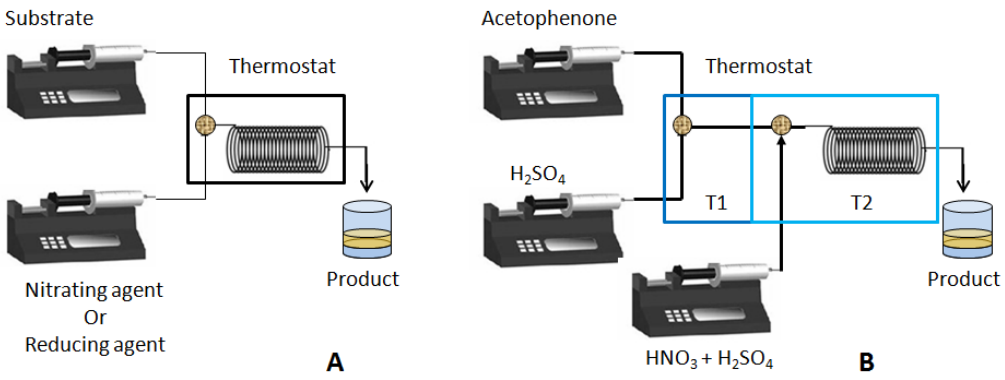


Figure 4. 2: Schematic of the experimental set-up. (A) Nitration of organic substrate 1 with nitrating agent or reduction of the nitroaromatic 2 with the reducing agent. (B) Mixing of 1 with sulfuric acid followed by nitration with nitrating agent.

After preparation of solutions, both the solutions were taken in glass syringes. For the continuous flow experiments, tubular reactors of three different sizes (1/16” mm. o.d. hastelloy tube, 1/8” and 1/4” SS316 tubes) were used. While the first one resulted in a clogged reactor due to precipitation of the product/ polynitrated byproduct due to very large surface available for precipitation per unit reactor volume, the latter two tubes did not clog. In all the cases, flow rates were adjusted to achieve the desired residence time. For the selection of suitable micromixer for this reaction, a simple T-mixer, a split and recombine type planar micromixer and a caterpillar IMM micromixer were used. Unless explicitly stated, most of the experiments were carried out at 5 ºC. The samples were collected on crushed ice and the

product was filtered and washed with two times 20 mL of ice cold water. Then residue was dried for an hour and the filtrate was extracted by using diethyl ether. From that extracted layer 1mL was taken in a sample vial and analysis was done on GC (Thermo Trace Ultra GC) with a HP5 column (30 m x 0.25 mm ID, 0.2 μm film). Experiments were also carried out without filtration and all the product was extracted using diethyl ether. After extraction with ether, mixture was concentrated on Rotavapor (Buchi) and the product weight was monitored until it reached a constant value. Experiments were also carried out by mixing **1** and sulfuric acid continuously at 0 ºC and then further mixing it with the nitrating mixture using another micromixer immersed in the constant temperature bath just before it reaches the tubular reactor. A few experiments were also carried out using only fuming nitric acid for the nitration of Acetophenone, *p*-chloroacetophenone and *m*-chloroacetophenone.

4.4.2 Reduction of *m*-nitroacetophenone

1. **Batch Experiment:** Reaction of *m*-nitroacetophenone (2 gm) with granulated tin (Thomas Baker) (4 gm) dissolved in 40 mL of 10% HCl (Thomas Baker) in a batch reactor at 95 ºC for 2 hours was monitored. The reaction mixture was brought to room temperature and was filtered to remove any undissolved tin. A 40% NaOH (SD Fine Chemicals) solution (24 mL) was added to the filtrate with stirring and cooling. The resultant yellow precipitate was filtered and washed with water (20 mL). After drying on suction pump for 2 hours, it was recrystallized from water. The melting point of the product was 96-97 ºC which matches with the melting point from literature and was confirmed by NMR as **3**.

2. **Continuous flow reduction:** The reaction was carried out in a silicone tube (1/8" OD) having 8.5 mL volume. For 1 gm acetophenone in 20 ml methanol and 5 gm $SnCl_2.2H_2O$ in 20 ml 10% HCl pumped using syringe pumps with a residence time of 22 min at 100 ^oC. However since the Tin chloride system is not a green approach, all further experiments were carried out using Sodium sulfide (Na_2S) as a reducing agent. Details are given in the next Section.

4.5 Analysis

Final products of nitration of nitration of acetophenone, chloro-substituted acetophenones and reduction of nitroacetophenone were analyzed using GC, GCMS and

NMR. NMR was done using Bruker AV200 MHz and AV400 MHz, NMR spectrometer in $CDCl_3$ solvent, and GC analysis was done with HP-5 capillary column with FID detector.

a) 3-Nitroacetophenone
b) 3-Aminoacetophenone
c) 5-Chloro-3-nitroacetophenone
d) 4-Chloro-3-nitroacetophenone

Analytical data has been shown at the end of this chapter, before references.

4.6 Results and Discussions

4.6.1 Nitration of acetophenone

As mentioned previously, for the continuous flow experiments tubular reactors of three different sizes were used. While the smallest tube diameter (1.38 mm i.d.) got clogged due to precipitation of the product, the latter two tubes did not clog for a range of residence times studied in these experiments. Hence further experiments were carried out using a 1/8" tube. For the selection of the right micromixer, experiments were carried out at 50 ºC and residence time of 10 min with 2 m long, 1/8" o.d. tubular reactor (i.d. = 2.7 mm). The micromixer and the reactor were immersed in a constant temperature bath. The observations on the yield of the meta and ortho isomers are shown in Figure 4.3. The reaction needed excellent mixing between the two reactants and the conversion was 78%, 86% and 100% respectively with T-mixer (0.8 mm bore size), planar split and recombine type of mixer (0.5 mm characteristic channel dimension) and the IMM's Caterpillar micromixer (R600). The planar split and recombine mixer was an in-house design with obstacles in the flow path that would just split and recombine the fluid streams in the same plane. The mixture of acetophenone in sulfuric acid and the nitrating agent have different density and viscosity values and that makes this reactive mixing challenging. At flow rates that need about 10 min residence time in the tubular reactor, mixing of these two streams was seen to be the limiting factor. Better mixing will always help in completion of the reaction. In all the subsequent experiments, IMM's Caterpillar micromixer (R600) was used before the tubular reactor.

The effect of residence time was studied at a reaction temperature of 5 ºC. The higher yield of the desired meta isomer was obtained at a residence time of 5 min. Longer residence time yielded impurities, which resulted in reduction in the yield of the desired meta product. The effect of volume of nitrating mixture (at identical composition) was studied at 10 ºC and

10 min residence time. The product yield increased with the increasing volume of nitrating mixture. However the maximum yield was still lower than that of the previous experiment at 5 ºC with 5 min residence time, indicating the formation of impurities (mainly deacetylation followed by di-nitro benzene derivative and was confirmed by GCMS) at higher temperature. The effect of reaction temperature was studied by carrying out the reaction at 0 ºC to 25 ºC. The observations are given in Table 4.1. Lower temperatures were seen to reduce the yield in a given reaction time, while the higher temperature yielded more impurities.

Based on these observations, the optimized conditions for the reaction were 10 ºC, 10 minutes residence time, w/v ratio of **1** to sulfuric acid of 1:2.5, v/v ratio of substrate mixture to nitrating mixture of 1:1.66 (with standard nitrating mixture), that yields 98.55% of the expected yield of mono-nitro derivative and complete conversion of acetophenone.

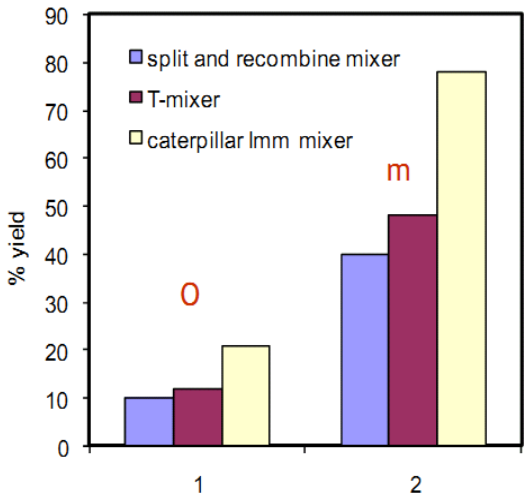


Figure 4. 3: Effect of micromixer on the product yield.

A few experiments were also carried out for nitrating acetophenone with fuming nitric acid. It was observed that 1.8 mole equivalents of fuming nitric acid gave around 80% conversion in 20 minute residence time at 20 ºC. However the selectivity of m-isomer decreased with increasing temperature as well as increasing reaction time (Figure 4.4). To optimize complete conversion longer residence time and higher temperature does not work so we increase nitric acid moles and achieved >99 % conversion at 10 ºC in 10 min residence time with m/o ratio of 2.20. Selectivity of m-isomer increases with increasing sulfuric acid equivalents in nitrating mixture, which is 2.52 with 3.2 equivalent sulfuric acid (Figure 4.4).

Table 4. 1: Screening experiments for the nitration of acetophenone (Q_1 = AcPh + H_2SO_4 ~ 1:2.58 v/v at 25 ^{0}C, Q_2 = HNO_3:H_2SO_4 ~ 1:1.5 v/v, Tube size: Expt. No. 1 -13: $^1/_8$" o.d., 2.7 mm i.d., 14-16: ¼" tube, 5.3 mm i.d.)

Expt. No.	Q_1:Q_2 (v/v)	τ (min)	T (ºC)	Conversion (%)[a]	*o* (%[b])	*m* (%[b])	Impurity (%[b])
1	0.8	10	0	75.8	12.8	62.8	0.0
2	0.8	10	5	98.7	17.1	81.3	0.3
3	0.8	10	10	100	18.9	75.8	5.3
4	0.8	10	15	100	17.5	70.2	12.3
5	0.8	10	20	100	15.5	62.5	22.1
6[c]	0.8	10	25	-	-	-	-
7	0.8	5	5	93	21	78	0.0
8	0.8	8	5	97	19	73	5.0
9	1	10	0	68	11.8	44.1	0.28
10	1	10	5	73	16.4	56.2	0.34
11	1	10	10	100	21.0	77.0	1.96
12	1.34	10	10	97.1	28.2	68.8	0
13	2	10	10	71.7	15.6	56.2	0
14	0.8	3	5	98.1	22.1	75.7	0.3
15	0.8	5	5	99.0	17.2	81.0	0.8
16	0.8	10	5	99.7	18.8	77.8	1.1

[a]Conversion is estimated based on the unreacted amount of acetophenone obtained from the GC analysis. [b]Area percentage determined from GC, [c]at room temperature, the reactor got clogged without yielding any product at the outlet. The reactor could not be cleaned even after keeping it for several hours in acetone and also by sonicating it in an ultrasound bath.

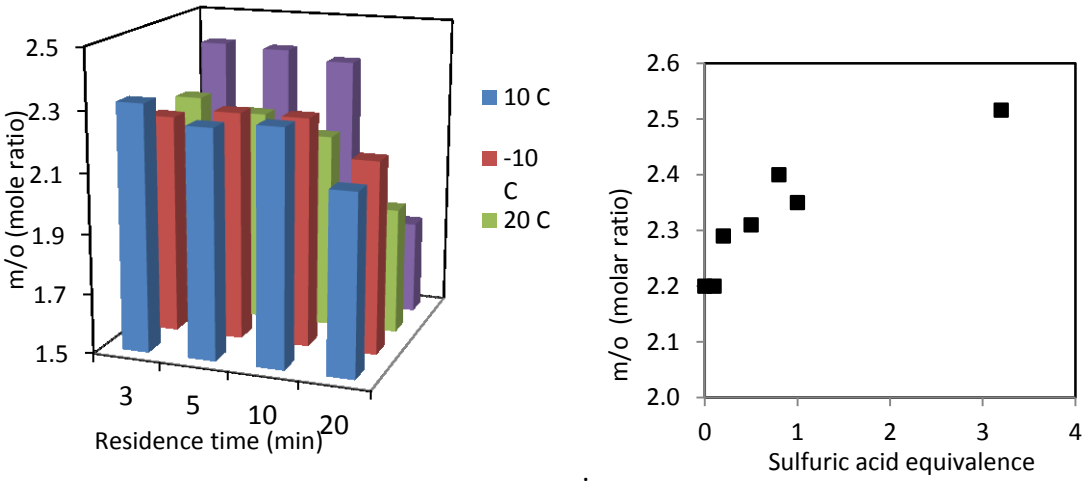


Figure 4. 4: 1) Effect of residence time and temperature on yield of 3-nitroacetophenone (1.8 mole fuming nitric acid), 2) effect of sulfuric acid equivalent on selectivity of 3-nitroacetophenone (8 mole fuming nitric acid)

4.6.2 Reduction of *m*-nitro acetophenone

The reduction in batch mode used *m*-nitroacetophenone **2** (2 gm), 4 gm granulated tin metal, 40 mL 10% HCl, 24 mL of 40% NaOH (used for work-up). At 85 to 95 ºC, the reduction over 2 hrs yielded 74% of **3** (M.P. ~ 96-97 ºC). The product was confirmed by NMR. In the presence of substrate, tin was soluble in 10% HCl at 85 ºC and the reaction mixture became homogeneous within 45 minutes. The reaction was conducted by following the above dissolution procedure and sample was taken after 24 hours. Eventually, the solution was in slurry form with some amount of undissolved tin. The experiment was repeated and six samples were taken with 15 minutes interval after the solution became homogeneous. The samples were quenched with 40% NaOH and then extracted by ether and the analysis showed that all the samples contained only the product. Additional experiments were carried out using 1.9 gm of the catalyst $SnCl_2.2H_2O$ (S D Fine Chemicals), methanol (Thomas Baker) and 10% HCl. The reaction was kept for reflux at 78 ^oC for 4 hrs and the reaction was still incomplete. Higher catalyst quantity (3.87 gm) and reflux at 110 ^oC yielded 95% conversion of **2** in 30 min.

Typical experimental set-up for continuous flow reduction consisted of two syringe or peristaltic pumps and a thermostat (Julabo). Experiments were carried out at 100 ºC in a 1/16" o.d. tube (1.38 mm i.d.) having 8.5 mL volume. Experiments yielded 100% reduction for a residence time of 22 min. Since the use of SS316 tubular reactor may give a colored product

all the experiments were carried out in a silicone tube. The experiments in a silicone tube (4.4 ml volume, 1.5 mm i.d.) at 100 ºC yielded 70% yield of the product. The reaction was further optimized to yield 100% yield in 5 minutes using higher catalyst quantity. Since the process of reduction using tin chloride is not economical and also environmentally challenging at large scale due to sludge formation, all further experiments were carried out using sodium sulfide as reducing agent.

The reduction reaction was carried out in a SS316 of 1/8" o.d. tube (2.8mm i.d., 8.5 mL volume) with **2** (2 gm) in ethanol (37 mL) and Na_2S (2.5 gm in 8 mL water) at 70 ^oC. Residence time was maintained at 20 min. The reaction achieved complete conversion of **2** yielding only a single product at the outlet. Yield of the **3** in crystalline form from the first stage of crystallization was 89%. Remaining was obtained as the second crop. In another set of experiments, both the precursors (**2** and Na_2S) were mixed in aqueous solution of ethanol and pumped using a single peristaltic pump either using a silicone tube or a SS316 tube immersed in a constant temperature bath at 70 ºC. Ethanol-water mixture was recycled and reused. This gives a perfect reduction reaction where only selective reduction of nitro group takes place giving an E-factor of 0 as the salt formed in the reaction can be used for many applications.

These studies indicate that, while nitration of an aromatic substrate can be done efficiently in continuous mode, reduction in the continuous mode is feasible only when the mono-nitro derivatives are used in isolated/separated form. While this reduction may not be greener than the catalytic hydrogenation, using simple reducing agents viz. Na_2S with a completely recyclable solvent make it an economically viable option. The product from this reduction is also sodium sulphate, which is used in large quantities for the manufacture of detergents, in the Kraft process of paper pulping, drying and storage of moisture sensitive items and in the manufacture of glass. Being a non-corrosive salt it is used in large quantities in textiles. Thus, although use of Na_2S may not be as greener an approach than the hydrogenations, use of recyclable solvent, consumption of generated salt, makes it a far greener and economical approach.

The recent trends of development of integrated processes[21, 22] are definitely a forward going approach. After every reaction, separation of isomers is critical and should be done at the stages where the separation is possible without much hassle (viz. different melting points, very different boiling points, very selective solubility in solvents, etc.). Incidentally, the products from all reactions do not show such features and the integration of reaction and

separation remains limited. In such cases, while individual steps in the syntheses do show merits of going continuous, the feasibility of separation and the economics will drive such recommendation.

4.6.3 3-Chloroacetophenone nitration

3 moles of fuming nitric acid was used in initial set of experiment, residence time was maintained in between 2.63 to 10 minutes and temperature raise in range of 10 ºC to 30 ºC, which gave maximum 40% conversion with 7.44% yield of 5-chloro3-nitroacetophenone. Nitric acid moles increased to 7 moles in order to get complete conversion and good yield. It resulted 97% conversion at temperatures as high as 70 ºC. Conversion increases with increasing reaction temperature and residence time, while 5-chloro3-nitroacetophenone starts decomposing at temperature above 50 ºC and at longer residence time. 56.39% yield of 5-chloro-2-nitroacetophenone, with 94%conversion was achieved at 50 ºC, in residence time of 5.8 min.

Table 4. 2: Reaction proceeding with different residence time, temperature and moles of fuming nitric acid

3-ClAcPh: FNA	Temp. (ºC)	Time (min)	Conversion %	% Yield of 5-Cl-2-NAcPh
0.33	10 - 30	2.63 - 10	23 - 40	4.14 - 7.44
0.20	50 - 70	2.63 - 10	69 - 96	15.35 - 23.05
0.14	50 - 70	2.63 -10	89 - 97	36.50 - 56.39

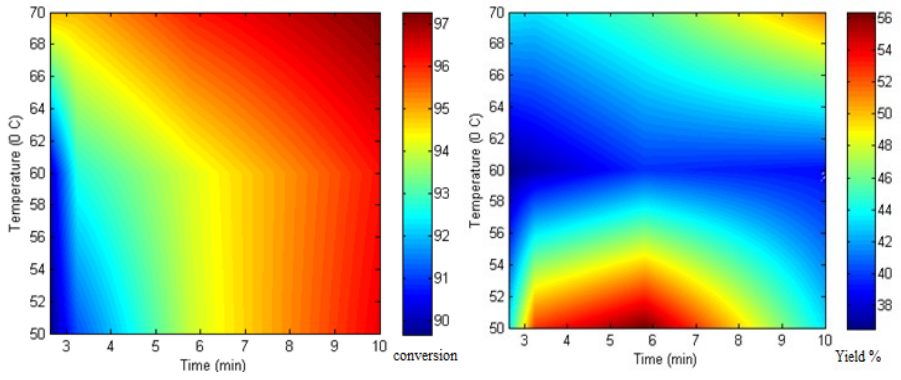


Figure 4. 5: 3-Chloroacetophenone nitration with 7 moles of FNA

4.6.4 4-Chloroacetophenone nitration

100 gm of 4-chloro-3-nitroacetophenone costs around 1800 rs. In batch it gives 63% yield of 4-chloro-3-nitroacetophenone in just 10 minutes on using higher amount of sulfuric acid which involves separation steps. Here we aimed towards complete elimination of solvents. 2 moles of fuming nitric acid was used for initial screening, only 3% yield was achieved. Fuming nitric acid favors oxidation over nitration at higher temperature and longer residence time and Cl-benzoic acid forms as side product. To increase yield, further nitric acid concentration was increased up to 10 moles at lower reaction temperature. Maximum 40.30% yield of 4-chloro-3-nitroacetophenone obtained in 10 minutes residence time at 0^0 C, using 10 moles of FNA.

Table 4. 3: Reaction proceeding with different residence time, temperature and moles of fuming nitric acid

4-ClAcPh: FNA	Temp(ºC)	Time (min)	Conversion (%)	Yield (%)	Remarks
0.50	10 - 60	2.63 - 10	31 - 77	1.60 - 3.16	oxidation is favored over nitration
0.33	60 - 70	2.63 - 10	61 - 84	8.47 - 3.11	
0.20	-10	2.63 - 10	59 - 86	2.89 - 15.53	
0.10	-10 - 10	2.63 - 20	63 - 98	8.96 - 40.30	

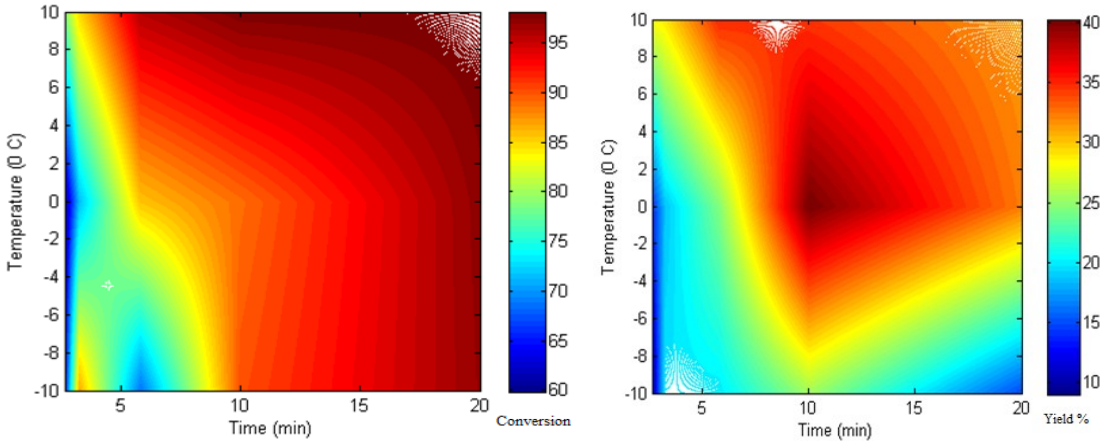


Figure 4. 6: 4-chloroacetophenone nitration with 10 moles of FNA

Table 4. 4: Number of experiments performed

	Batch experiments	Continuous flow experiments
Acetophenone nitration	25	126
m-Aminoacetophenone reduction	5	54
3-Chloroacetophenone nitration	2	30
4-Chloroacetophenone nitration	3	40

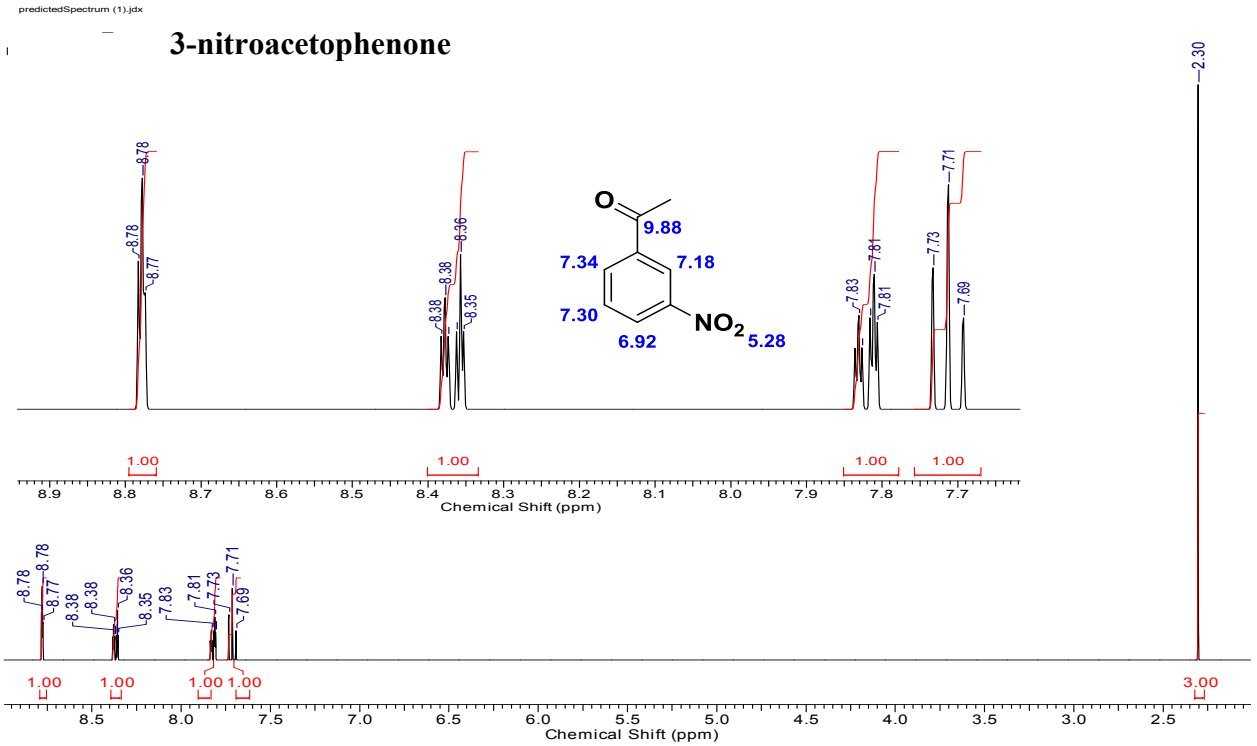
4.7 Conclusions

Two-step, discontinuous, flow synthesis of *m*-aminoacetophenone is demonstrated using simple tubular reactors (SS316 and silicon tube). The yields from continuous flow reactions were comparable with the batch reactions. The flow synthesis approach for nitration step yields a safer process even at enhanced temperatures with shorter reaction time to achieve consistent performance. Both the steps involved homogeneous solutions (in contrast to typical two phase aromatic nitration). Using a good micromixer is essential to achieve the activated aromatic substrate with the nitrating agent while for the reduction a simple T micromixer was sufficient to achieve the desired mixing. The formation of di-nitro derivative as an impurity was seen to have a strong dependence on temperature, residence time and the internal composition of nitrating mixture. The reduction with sodium sulfide is recommended due to lower costs which makes the process economical. From the simple set-up as described here, both the steps can be scaled to make a few 100 gm quantity of **3** at lab scale in a single day. Since the solutions are homogeneous, scaling up of this process will be relatively easy so far the necessary heat transfer area is made available to control the reaction. Continuous flow nitration of other aromatic ketones using variety of nitrating agents including fuming nitric acid is also reported.

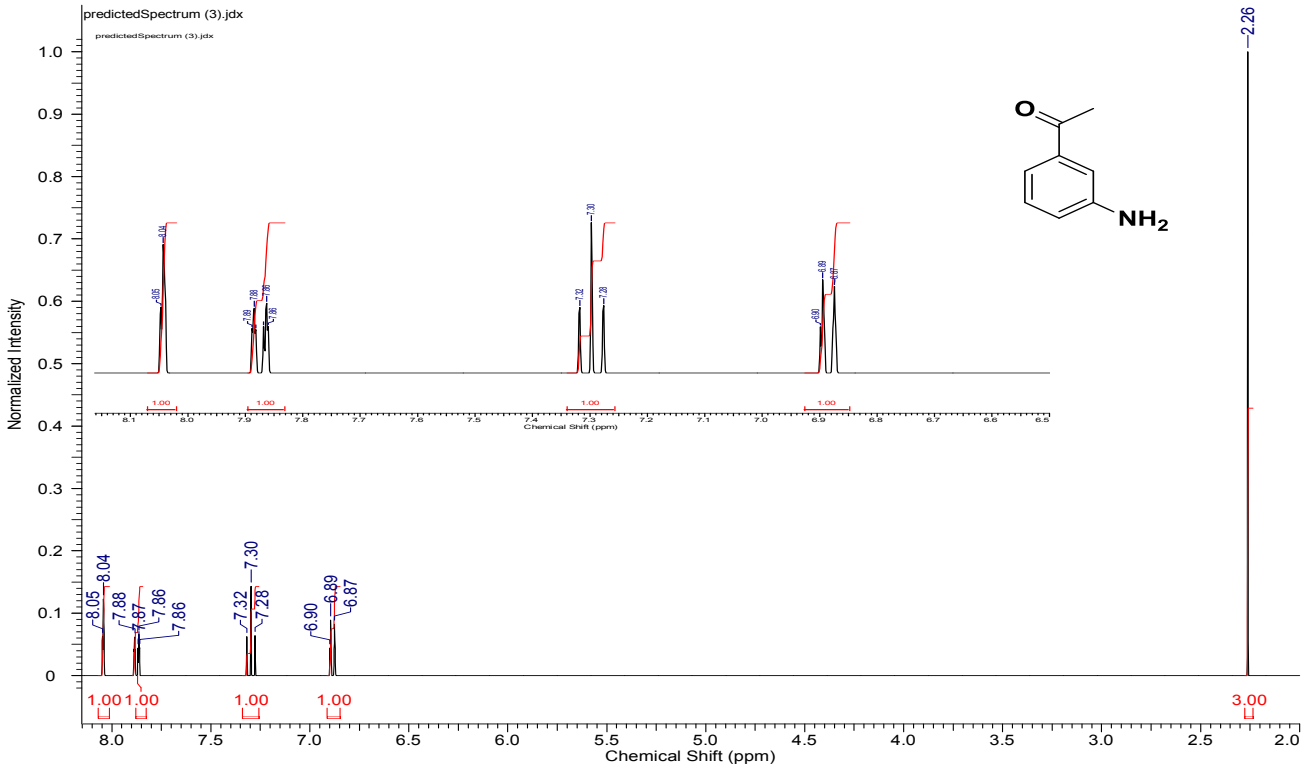
Analytical Data

NMR

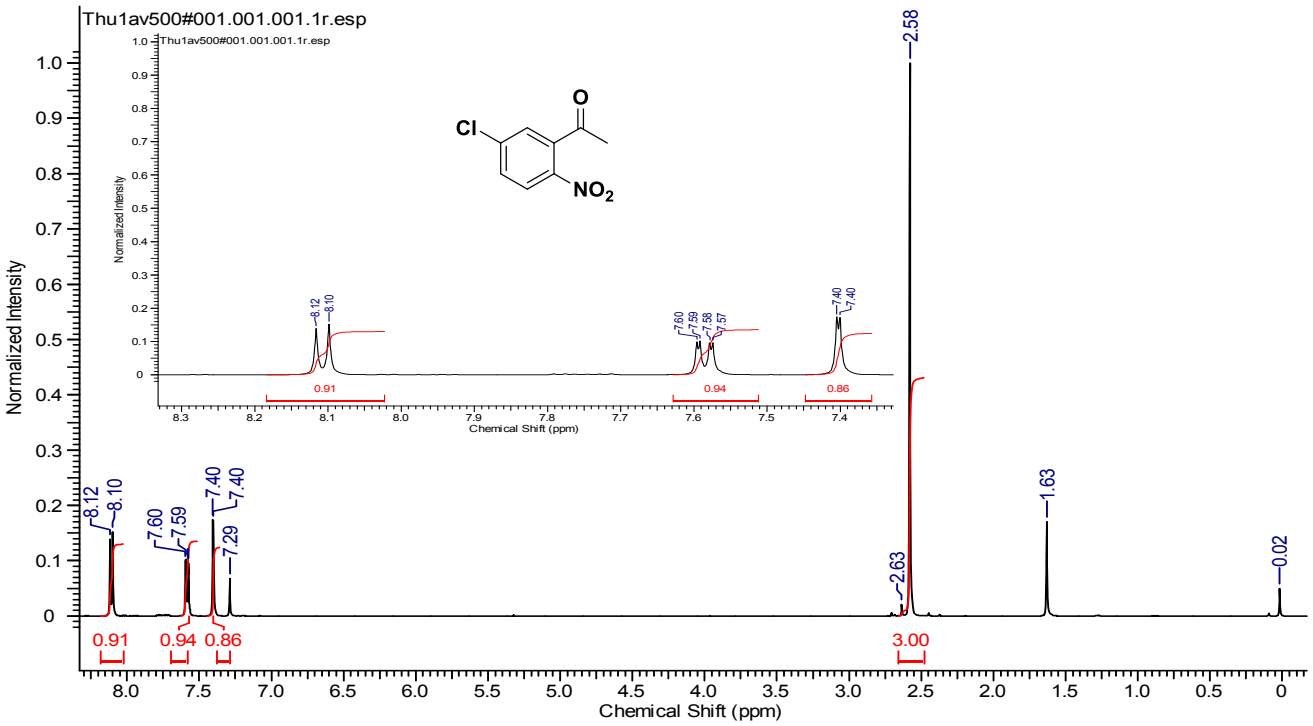
3-nitroacetophenone



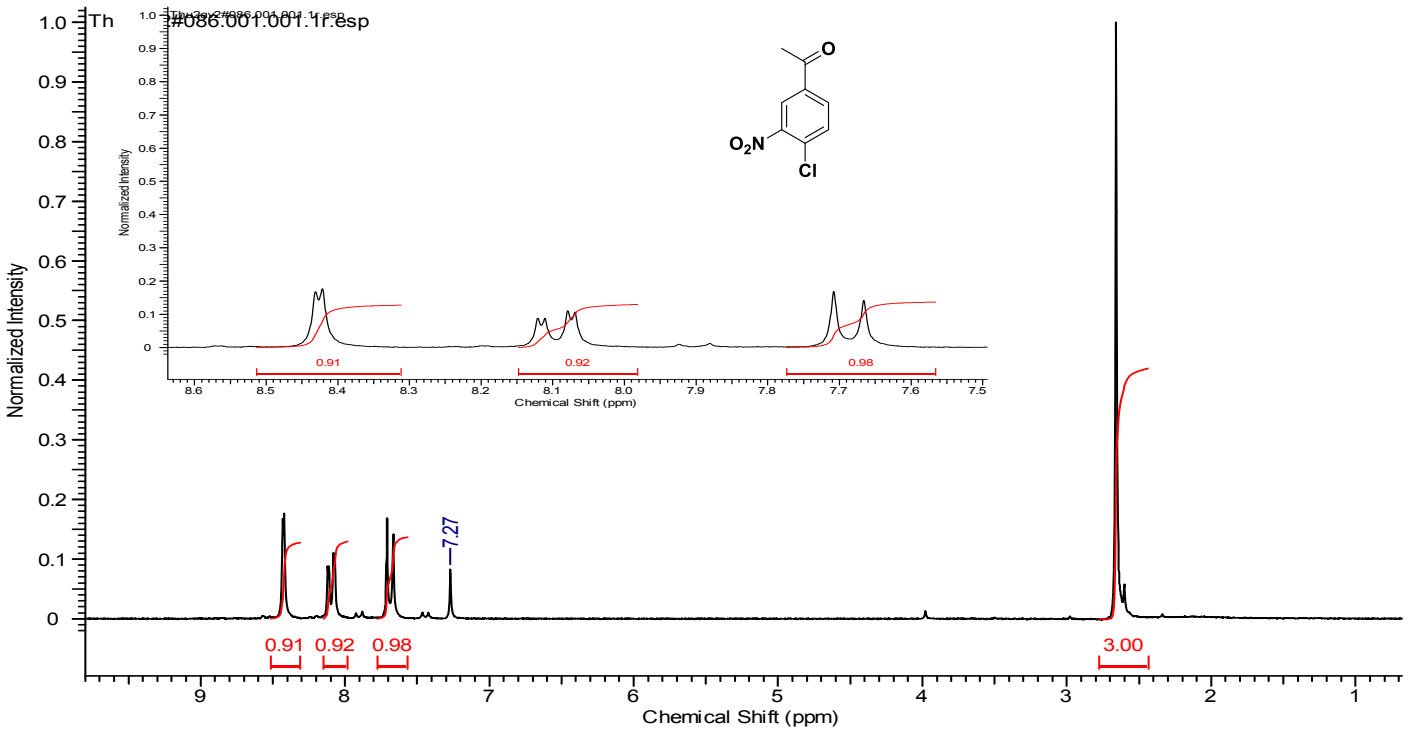
II. 3-Aminoacetophenone



III. 5-Chloro-2-nitroacetophenone



IV. 4-Chloro-3-nitroacetophenone



GC and GCMS

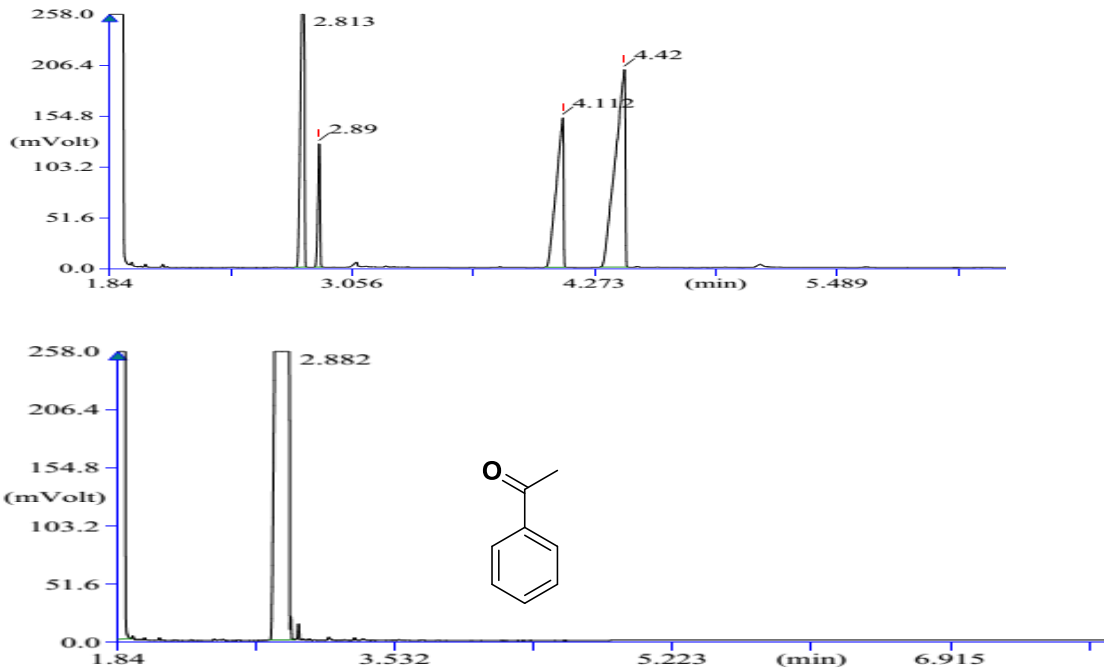
I. Acetopenone nitration

GC method: HP5 column with FID detector as used for the analysis of all experiments. Nitrobenzene was used as internal standard. Initial oven temperature kept 70 ºC and temperature rise with the ramp 35 ºC/min up to 199 ºC temperature with hold time of 0.00 min, second ramp with 1 ^{0}C/min up to temperature 200 ºC, all peaks of comes in this range. Finally temperature rose to 250 ºC and hold for 0.5 min, with ramp 40 ºC/min.

Table 5: GC retention time of substrates

Substrate	GC Retention time
Nitrobenzene	2.81
Acetophenone	2.89
2-Nitroacetophenone	4.12
3-Nitroacetophenone	4.42

GC chromatogram:



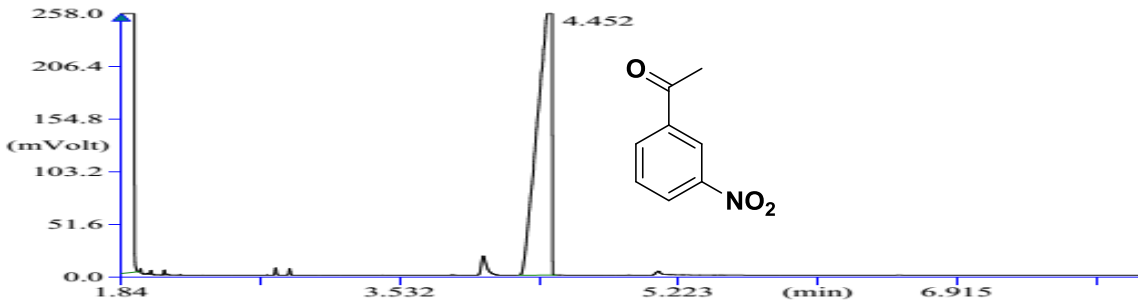


Figure: GC spectra of a) acetophenone nitration reaction mixture, b) Acetophenone and c) *m*-nitroacetophenone

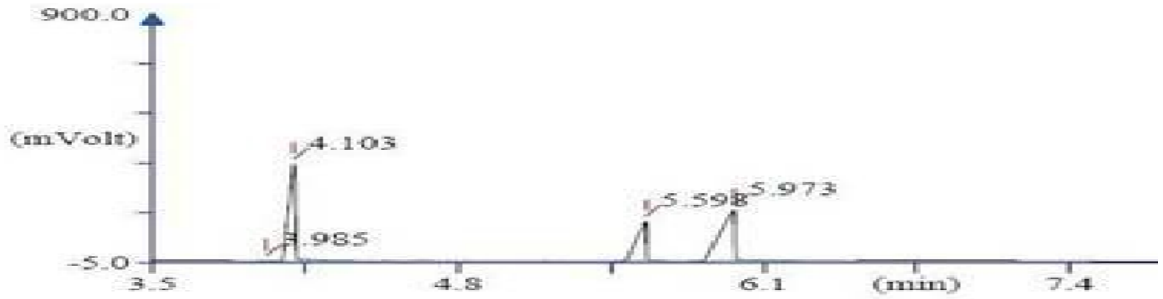
II. Nitroacetophenone reduction

GC method: HP5 column with FID detector as used for the analysis of all experiments. Nitrobenzene was used as internal standard. Initial oven temperature kept 60 ºC and temperature rise with the ramp 35 ºC/min up to 199 ºC temperature with hold time of 0.00 min, second ramp with 1 ºC/min up to temperature 210 ºC, all peaks of comes in this range. Finally temperature rose to 250 ºC and hold for 0.5 min, with ramp 40 ºC/min.

Table 5: GC retention time of substrates

Substrate	GC Retention time
2-Nitroacetophenone	3.98
3-Nitroacetophenone	4.10
2-Aminoacetophenone	5.59
3-Aminoacetophenone	5.98

GC chromatogram:



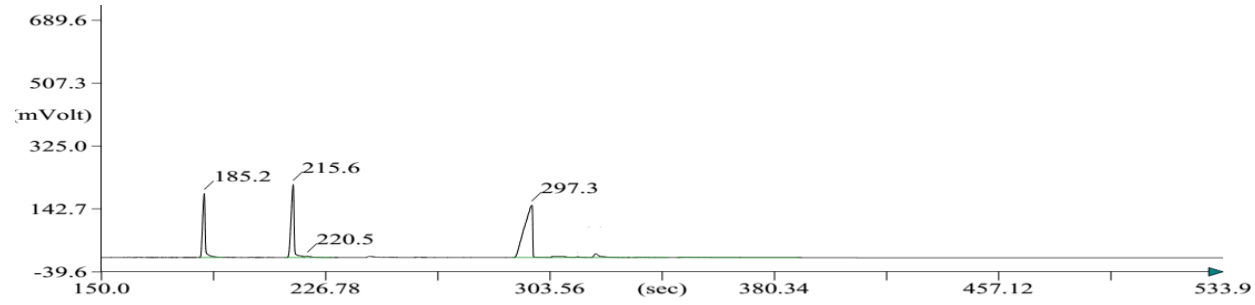
III. Nitration 3-chloroacetophenone

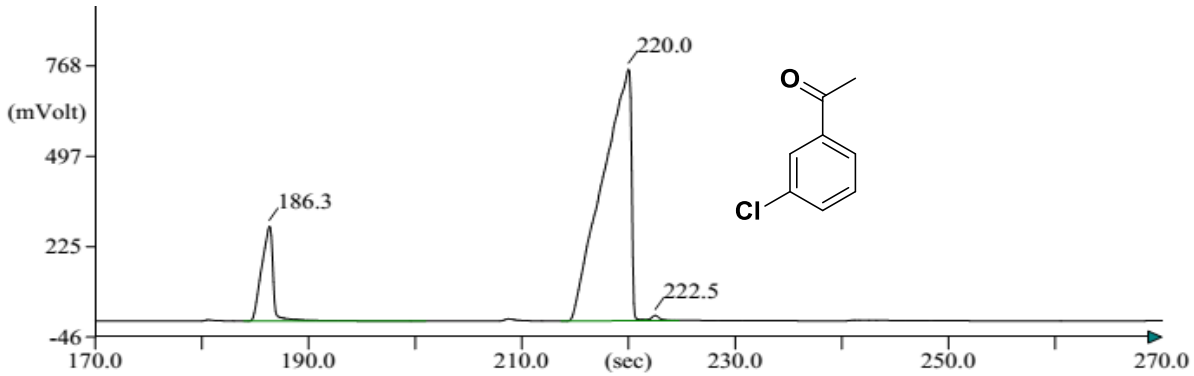
GC method: HP5 column with FID detector as used for the analysis of all experiments. Nitrobenzene was used as internal standard. Initial oven temperature kept 70 ºC and temperature rise with the ramp 40 ºC/min up to 199 ºC temperature with hold time of 0.00 min, second ramp with 1 ºC/min up to temperature 203 ºC, all peaks of comes in this range. Finally temperature rose to 250 ºC and hold for 0.5 min, with ramp 40 ºC/min.

Table 5: GC retention time of substrates

Substrate	GC Retention time
Nitrobenzene	3.10
3-Chloroacetophenone	3.66
5-Chloro-3-nitroacetophenone	4.92

GC chromatogram:





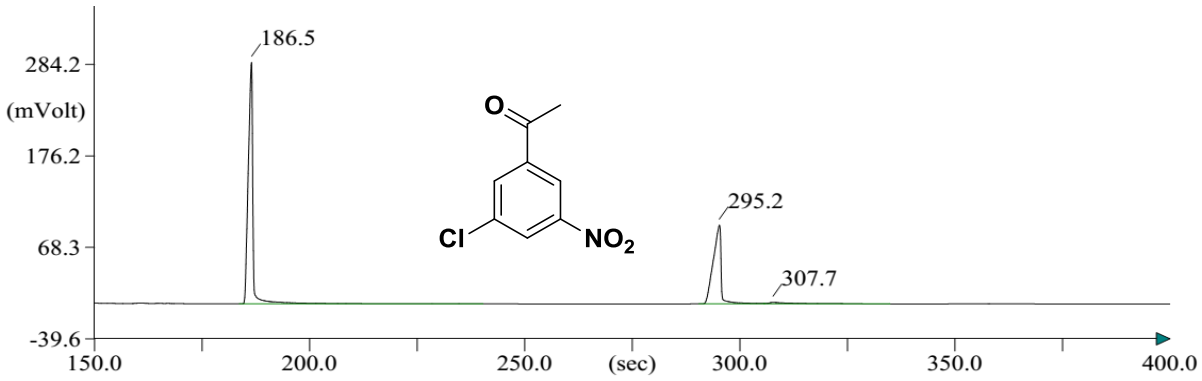


Figure: GC of 3-chloroacetophenone nitration reaction mixture,b) 3-chloroacetophenone and c)5-chloro-3-nitroacetophenone

IV. Nitration 4-chloroacetophenone

GC method: HP5 column with FID detector as used for the analysis of all experiments. Nitrobenzene was used as internal standard. Initial oven temperature kept 60 ºC and temperature rise with the ramp 50 ºC/min up to 182 ºC temperature with hold time of 0.30 min, second ramp with 0.4 ºC/min up to temperature 185 ºC with hold of 0.50 min, all peaks of comes in this range. Finally temperature rose to 250 ºC and hold for 0.50 min, with ramp 50 ºC/min.

Table 5: GC and GCMS retention time of substrates

Substrate	GC Retention time	GCMS retention time
Nitrobenzene	3.10	
4-Chloroacetophenone	3.54	3.49
4-Chlorobenzoic acid		3.81
6-Chloro-3-nitroacetophenone	6.00	5.91

GC chromatogram:

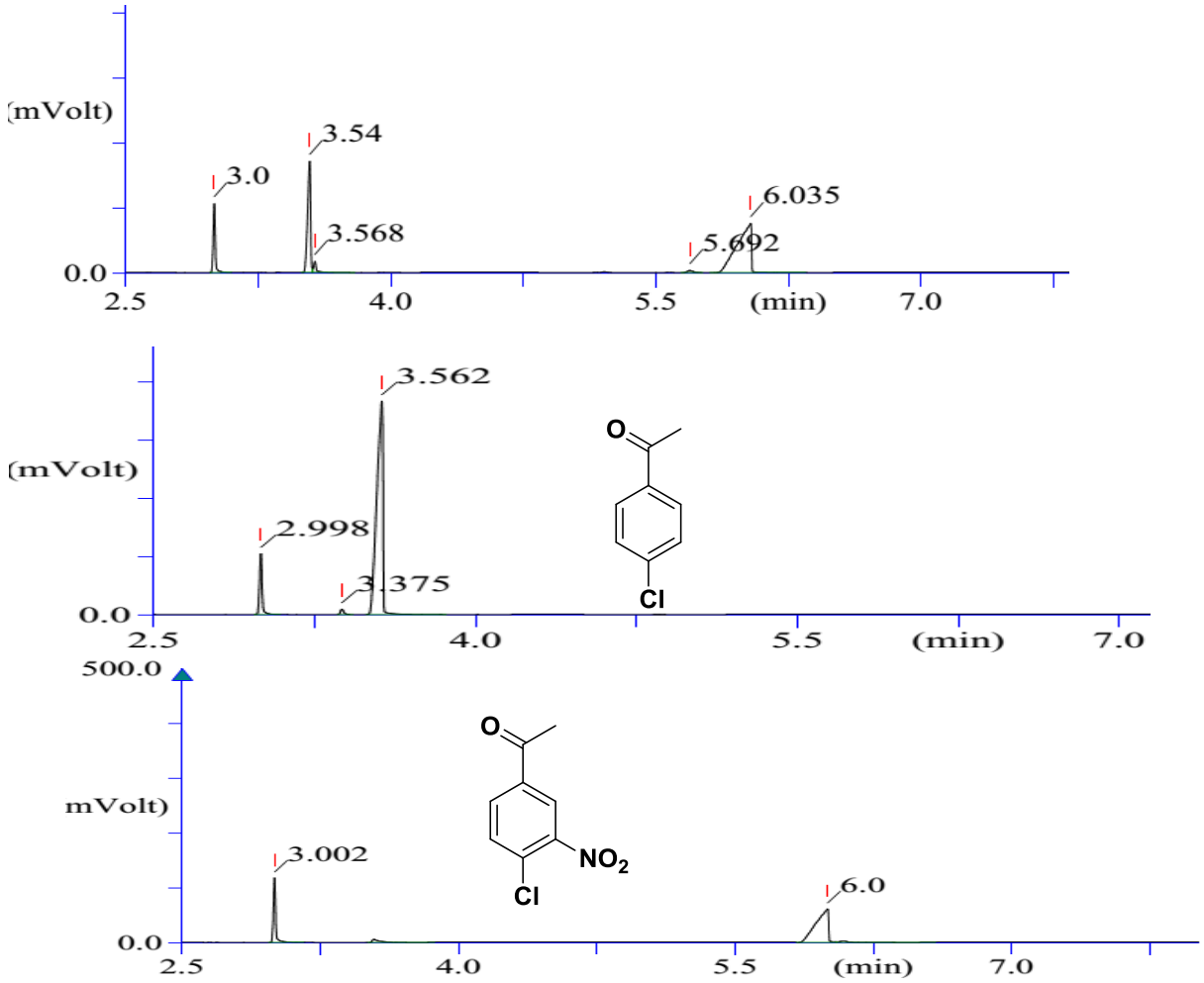
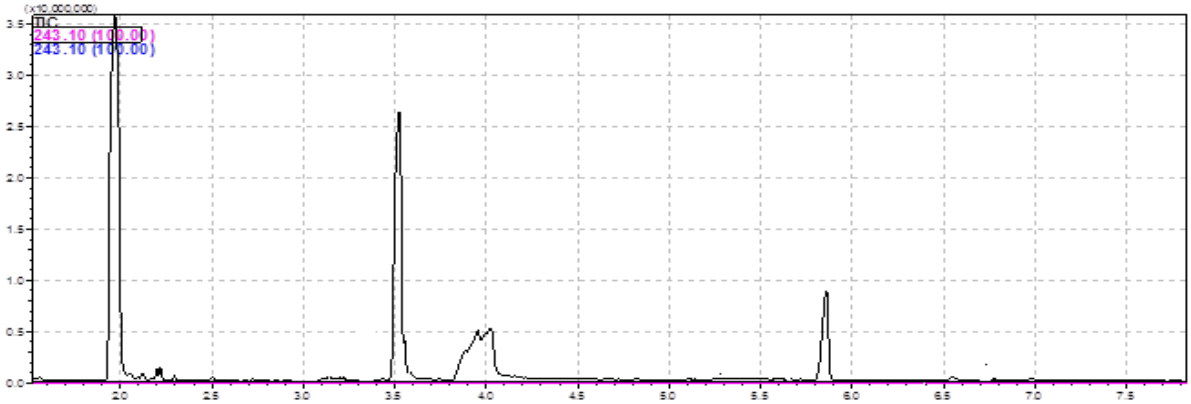


Figure: GC of a)4-chloroacetophenone nitration reaction mixture, b) 4-chloroacetophenone and c) 4-chloro-3-nitroacetophenone

GCMS

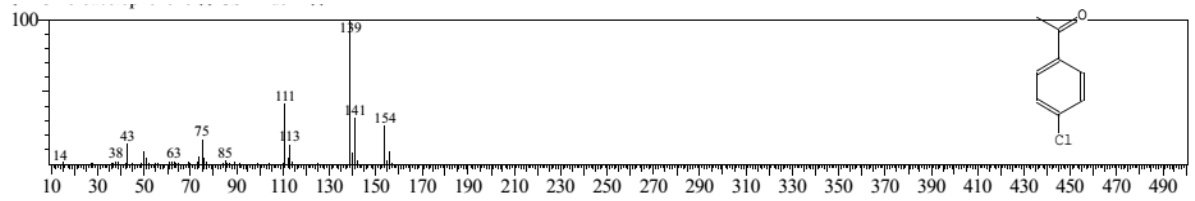
I. Reaction mixture of 4-chloroacetopnenone nitration



i. RT – 2, Toluene (solvent)

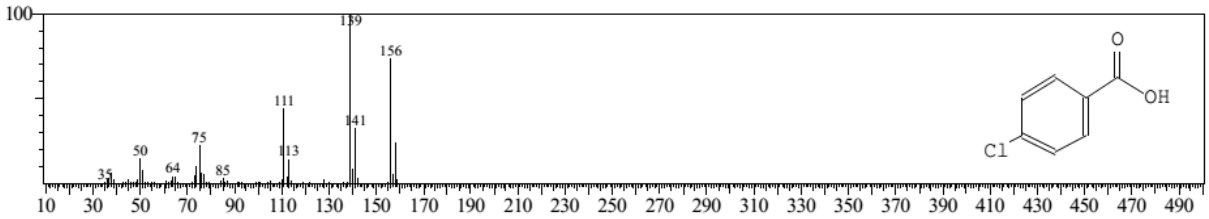
ii. RT – 3.49

Compound name – **4-chloroacetophenone**



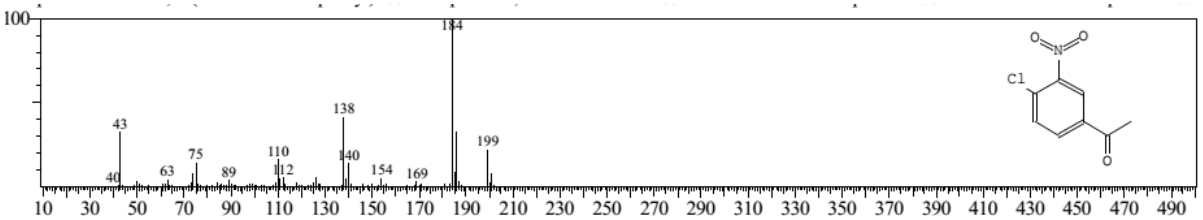
iii. RT - 3.81

Compound name – **4-chlorobenzoic acid**



iv. RT – 5.91

Compound name – **4-chloro-3-nitroacetophenone**



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Chapter 5

Continuous Flow Telescopic Oxidation of Alcohols via Generation of Chlorine and Hypochlorite

5.1 Introduction

The term oxidation may be defined as the reaction between oxygen molecules and all other different substances from metal to living tissue. With the discovery of electrons, oxidation more precisely defined as the loss of at least one electron when two or more substances react, which may or may not include oxygen. Oxidation of organic compounds may include addition of oxygen, hydrogen abstraction (removal), and/or withdrawal of electrons with or without the withdrawal of protons. Both reduction and oxidation are going side by side, this is known as redox reaction, which is basic function of life including corrosion, respiration, combustion and photosynthesis.

On oxidation, alcohols gives acids and aldehyde/ ketone out of which ketones and aldehydes are of much interest which generally identify by their sweet smell and largly used in industries like food industry, fragrance chemicals, medicines, agriculture chemicals, etc. Methyl ethyl ketone (MEK) is used in the production of plastic, varnishes, textiles, paint remover, wax, paraffin etc. For the production of nylon, cyclohexanone is essential ketone. Formaldehyde is used as germicides, fungicides as insecticides for plants, in drug testing and photography, and for the production of bakelite which is used as adhesive and coating in plastics. Benzeldehyde is used in cosmetics, dyes and perfumes, and it is also gives almond flavor to food products.

Annually aldehydes of ~19,162,084 USD is imported to India according to a survey of ZAUBA, for which China is the largest supplier followed by U.S. and Japan. For ketone this import is of ~129,459,485 USD, Taiwan is biggest supplier for it followed by Japan and South Korea.

Transformation of the highly exothermic oxidation reaction from batch process to continuous flow micro reactor technology provides a promising technique. Which decrease the equipment size, enhance heat & mass transfer, economical, and decrease production capacity ratio & energy consumption, with a dramatically decrease in reaction time Rate of gas-liquid or biphasic reactions significantly enhanced using micro reactor technology due to an improved mass transfer.

5.2 Literature analysis

Oxidation of organic substrates is typically a bi-phasic or tri-phasic reaction depending on the type of oxidizing agent, where mixing and interfacial mass transfer become a major

issue. Typically the use of stoichiometric quantities of inorganic oxidants such as $KMnO_4$, $K_2Cr_2O_7$, CrO_3 produce toxic waste.[1, 2] In greener approach is to use molecular oxygen, air, bleach or hydrogen peroxide for selective oxidation of alcohols.[3, 4] In some cases supported nanoparticales are also used with molecular oxygen or air. Shi et. al.[5] used La_2O_3-supported copper nanoparticles for transfer dehydrogenation of primary aliphatic alcohols to aldehydes with yield of 63% for oxidation of 1-octanal and 45% for the oxidation of 1-decanal under N_2 atmosphere over a reaction time of 2 hours and 10 hours, respectively. Dehydrogenation of primary and secondary alcohols to aldehydes using unsupported crystalline Re nanoparticles is also reported to give in moderate to high yield through ɣ-CH activation.[6] Dispersed platinum nanoparticles in an amphiphilic polymer is also used for aerobic flow oxidation of alcohols in water.[7] Some functional group conversions and their required oxidizing argents are summarized in Table 5.1.

Table 5.1: Oxidizing reagent & their reaction with different functional groups

Reagent	**Preferred solvent**	**Functions oxidized**
Jones reagent H_2CrO_4	Aqueous sulfuric acid and acetone	1^0-alcohol to carboxylic acid Aldehydes to carboxylic acid 2^0-alcohols to ketone Avoid amines and sulfides
Collins reagent $CrO_3 + 2C_5H_5NH$	Methylene chloride	1^0-alcohol to aldehydes 2^0-alcohols to ketone
Pyridinium chlorochromate $ClCrO_3 + C_5H_5NH$	Methylene chloride	1^0-alcohol to aldehydes 2^0-alcohols to ketone
Dimethyl sulfoxide $(CH_3)_2S{=}O$ and DCC or Ac_2O or $(CF_3CO)_2O$ or SO_3 or $(COCl)_2$		1^0-alcohol to aldehydes 2^0-alcohols to ketone
Potassium permanganate $KMnO_4$	Water or aqueous mixtures	Aldehyde to carboxylic acid 20-alcohol to ketone Alkenes to vicinal-diols Alkynes to carboxylic acid Avoid amines and sulfides
Osmium tetraoxide OsO_4	Pyridine, often used catalytically	Alkenes to vicinal-diols
Periodic acid HIO_4	Water or aqueous mixtures	Vic-glycols to carbonyl compounds
Lead tetraacetate $Pb(OCOCH_3)_4$	Benzene or acetic acid	Vic-glycols to carbonyl compounds
Peracids CH_3CO_3H, $C_6H_5CO_3H$	CH_2Cl_2 or ethers	Alkenes to epoxides Ketones to esters Avoid amines and sulfides

Ozone (O_3)	CH_2Cl_2 or $CHCl_3$	Cleaves alkenes and alkynes Avoid benzene derivatives amines and sulfides

Over last two decades the use of 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) based selective oxidation has attracted a great attention. It is a heterocyclic stable radical soluble in water as well as in organic solvents and was first discovered by Lebelev & Kazarnowskii (1960). The reactive species, oxoammonium cation formed by oxidation of TEMPO in presence of either (i) a secondary oxidant such as hypochlorite at low temperatures such as 0 - 4 ºC under slightly basic conditions (Anelli-Montanari process), or (ii) O_2 along with active metal catalysts (Ru^{2+}, Mn^{2+}/Co^{2+} and Cu^{+})[8], or (iii) a mild electric potential (0.7 V versus Ag/AgCl)[9], is reported to selectively oxidize a variety of alcohols. TEMPO is expensive and is used in catalytic quantities (0.1-10 mol %). When used in relatively higher quantities it can only be recovered by costly azeotropic distillation. Alternatively, reusable polymer supported TEMPO with bleach, molecular oxygen and air is reported to be very effective for selective oxidation of alcohols to aldehyde.[4] Silica-immobilized TEMPO catalyst with catalytic amounts of HNO_3 as a NO_x source is also used as a continuous three-phase flow system with O_2.[10]

In general bleach is synthesized by reaction of chlorine gas and sodium hydroxide solution, known as Hooker process. Chlorine being highly reactive and not available on demand, safe to store in the synthesis labs, use of commercially available sodium hypochlorite solution (usually of low strength) is used for such oxidation reactions.[11, 12] The commercially available bleach requires storage temperature of 2 to 8 ºC, and its strength decrease over the time as it slowly evolves Cl_2 gas. NaOCl decomposes to NaCl and $NaClO_3$ because of its highly unstable nature. So each time before using it, one has to check the strength of this commercially available hypochlorite, which changes over the time and results will be non-reproducible. One of the ways to overcome the low strength is to prepare it freshly and consume immediately, which needs chlorine. In recent work by Strauss, et al.[13], chlorine gas continuously synthesized by reaction of HCl with NaOCl, generated chlorine was extracted by dissolving it into suitable solvent and separated by using continuous membrane separation. This high chlorine containing solvent was in situ used for chlorination and oxidation of many organic compounds. Fukuyama[14] also demonstrated same approach of continuous chlorine generation, gaseous Cl_2 was in situ used for C-H chlorination of cyclic alkenes and aromatic compounds. In an almost parallel activity, here we propose an alternate route for flow

synthesis of chlorine through the liquid-solid reaction of hydrochloric acid and manganese-di-oxide Figure 5.1. KBr is used to enhance rate of reaction as hypobromite anion is the active oxidizing agent of nitroxide.

5.3 Reaction mechanism

One mole of sodium hypochlorite is generated via the treatment of 1 mole of MnO_2 with 4 equivalence of HCl followed by the reaction of in-citu generated Cl_2 with 2 moles of NaOH. Although it's bi-phasic system, oxidation reaction takes place in organic phase. For oxidation of secondary alcohol, phase transfer catalyst is required to enhance the reaction rate.

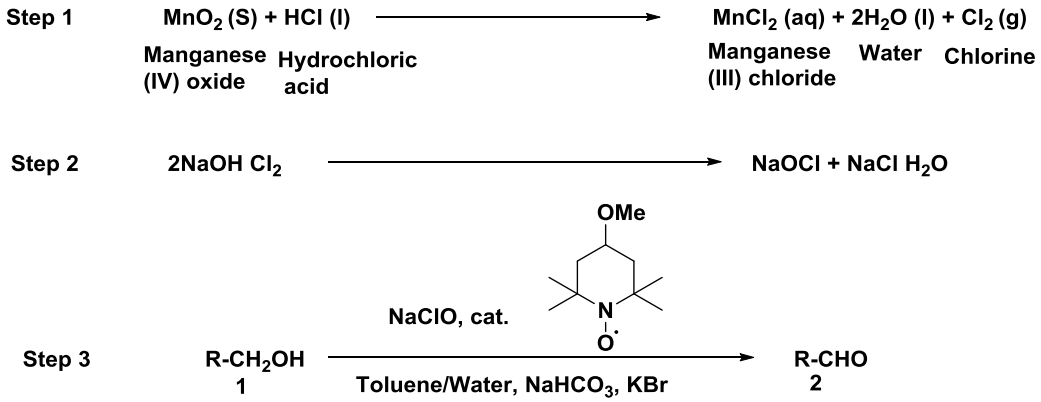


Figure 5. 1: 3-step reaction 1) chlorine generation, 2) hypochlorite synthesis, 3) alcohol oxidation using TEMPO catalyst

In TEMPO mediated oxidation, TEMPO act as a primary oxidant and stoichiometric quantity of bleach is used as secondary oxidant. Secondary oxidant transforms TEMPO into a reactive oxoammonium salt which oxidizes alcohol into aldehyde and itself converts into hydroxylamine. This hydroxyl amine transforms into TEMPO radical with secondary oxidant and completes catalytic cycle (Figure 5.2). In the presence of excess of secondary oxidant, acid forms, as secondary oxidant works as primary oxidant for further oxidation of aldehyde. In some extent, HOCl competes with oxoammonium salt and can produce chlorination in some functional groups like alkene.

Under vary basic pH the HOBr concentration decreases, which slowdowns the oxidation speed, and under very acidic condition, acid forms as a major product. So a specific pH range is necessity of TEMPO mediated oxidation.

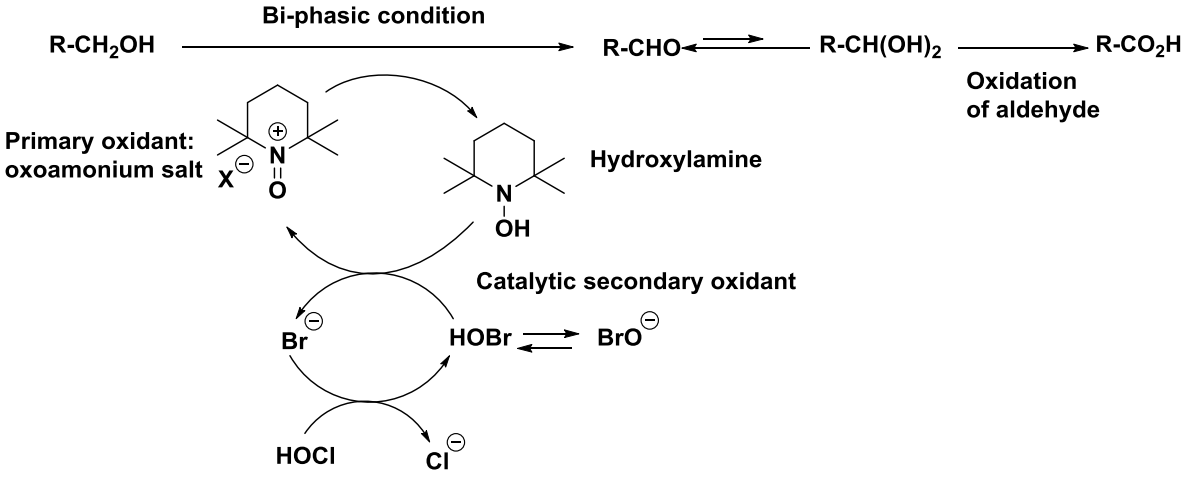


Figure 5. 2: Catalytic cycle of TEMPO mediated oxidation

5.4 Batch experiment

70 gm MnO_2 powder was taken in 250 mL RB and heated upto 80 ºC temperature followed by slow addition of HCl with continuous stirring. Generated chlorine gas was directly pass to a amberlite color bottle filled with 500 mL 10% NaOH solution for 30 minutes with continues stirring. Strength of generated hypochlorite was checked via titration with 0.1 M $Na_2S_2O_3$, using a mixture of 1.5 gm of KI, 1 mL glacial acetic acid and 1 mL of water with 1 mL NaOCl and it was found 11% with pH of 12.5. pH of this hypochlorite solution was adjusted by drop by addition of saturated $NaHCO_3$ solution.

5.4.1 Oxidation without TEMPO: 6mL of octanol and 14 mL dichloromethane solvent taken in 100 mL RB, marinated at 0 ºC temperature. 0.595 gm KBr in 14 mL water added in to this followed by slow addition of 60 mL of hypochlorite solution. Reaction quenched by addition of sodiumthio sulfate solution and it was monitored with TLC (20% ethyl acetate in pet ether) and no conversion of alcohol to aldehyde was observed even after 3 hr stirring.

5.4.2 Oxidation with TEMPO: 6mL octanol, 0.078 gm TEMPO and 14 mL dichloromethane solvent taken in 100 mL RB, marinated at 0 ºC temperature. 0.595 gm KBr in 14 mL water added into this followed by slow addition of 60 mL of hypochlorite solution. Reaction quenched by addition of sodiumthio sulfate solution and it was monitored with TLC (20% ethyl acetate in pet ether) and after 3 hr some aldehyde was observed.

5.5 SOP for preparing continuous flow setup and experiments:

For making a continuous flow set up, first and most important step is to choose a chemistry (reactant, reagent, product, intermediate, solvents etc.) compatible material. During assembling a setup, teflon tape should be warped around the threads of female fitting and all fittings should be tighten enough to prevent leakage, over tightening may harm thread and cause leakage. Leakage check is necessity before performing any experiment to prevent any misshaping, it can be done by passing water at high flow rate, or for gaseous phase reaction, setup can be placed in water and can be done by passing air.

For making multiple outlet setup, volume of each section should be known and calculation of flow rates and residence time will be based on cumulative volume of reactor. Residence time of each section will be calculated on the basis of volume of the section and cumulative flow rate. Sample collection should be done after reaching steady state, which nearly takes twice of residence time, and it should be quenched immediately. Volume of collected sample (reactant) should be constant while collection time may vary with changing flow rates or residence time.

5.6 Flow Setup and Experiment:

Silicon is not compatible with HCl so we had to use viton tube to flowing HCl, but for 10% NaOH silicon tube can be used. Bleach is SS incompatible so either glass coil or PTFE tube and joints can be used for assembling flow setup of this multistep reaction.

5.6.1 Chlorine generation: 70 gm MnO_2 powder was taken in a 250 mL round bottom flask and heated at 80 ºC. To this flask HCl was continuously added at fixed flow rate under vigorous stirring. The rate of HCl addition controlled the rate of generation of chlorine. For example, at of 2 mL/min flow rate of HCl, the reaction mixture generates Cl_2 gas at flow rate of 51 mL/min. The gas flow rate was measured using a soap film meter and was calibrated for specific inlet flow rates of HCl. The experiments were conducted for the period for which the gas generation rate was within ±1% of the desired flow rate. Every experiment lasted for maximum of 30 minutes.

5.6.2 Sodium Hypochlorite synthesis: 10% NaOH solution was used for flowing continuously for getting reacted with in-situ generated Cl_2 to yield NaOCl. For this part of experimental setup, a glass coil (1.5 mm inner diameter and total 12 mL volume) was used. Upon contacting with aqueous NaOH, yellow coloured gas was seen to get disappeared quickly due to rapid reaction. The generated NaOCl solution (of pH 13.9) was intermittently

collected in amberlite color glass bottle to measure the strength. The strength of the solution was measured through titration with 0.1 M $Na_2S_2O_3$, using a mixture of 1.5 gm of KI, 1 mL glacial acetic acid and 1 mL of water with 1 mL NaOCl. The strength of hypochlorite solution was found to vary from 7% to 13% depending upon the flow rates of the reactants and the residence time and it was further adjusted depending upon the need for selective oxidation of alcohol to aldehyde. However the stability of the solution also depends on pH.

5.6.3 Alcohol oxidation: In the third and an additional step in the flow synthesis pH adjustment was carried out to ensure that for the specific alcohol the concentration of oxidizing agent is in control. Saturated buffer solution of $NaHCO_3$ and 2 gm of KBr, dissolved in 120 mL of water was dosed using a syringe pump and mixed in-line with the NaOCl solution having pH of 13.9. The flow rate of the buffer solution was adjusted such that the pH of the outlet stream can be varied between 10 to 9.5 which was necessary to retain adequate strength of the oxidizing agent to avoid over-oxidation. Our analysis showed that hypochlorite solution of strength between 3.1 to 4.5 was sufficient to achieve controlled oxidation. The fourth and the last part of the experiment was controlled oxidation of alcohol and this section was made of PTFE tube (2 mm inner diameter and 28 mL volume). In the last step, the organic phase comprising of a solution of 3 mol% TEMPO catalyst and 3.7 mL alcohol in 30 mL solvent (toluene) was dosed using a separate syringe pump. This pH adjusted NaOCl reacted with organic solution containing alcohol. The flow rate of organic phase was decided based on concentration of alcohol and the strength of NaOCl in the second stream.

Samples were collected in a quenching solution of $Na_2S_2O_3$, which decomposed excess NaOCl. Organic phase was separated and washed with water, brine and dried over Na_2SO_4. These samples were diluted for analysis using gas chromatogram (GC). HP-5 capillary column with FID detector was used for GC analysis, and bromobenzene was used as an internal standard. Products and byproducts were confirmed with GCMS, IR and NMR.

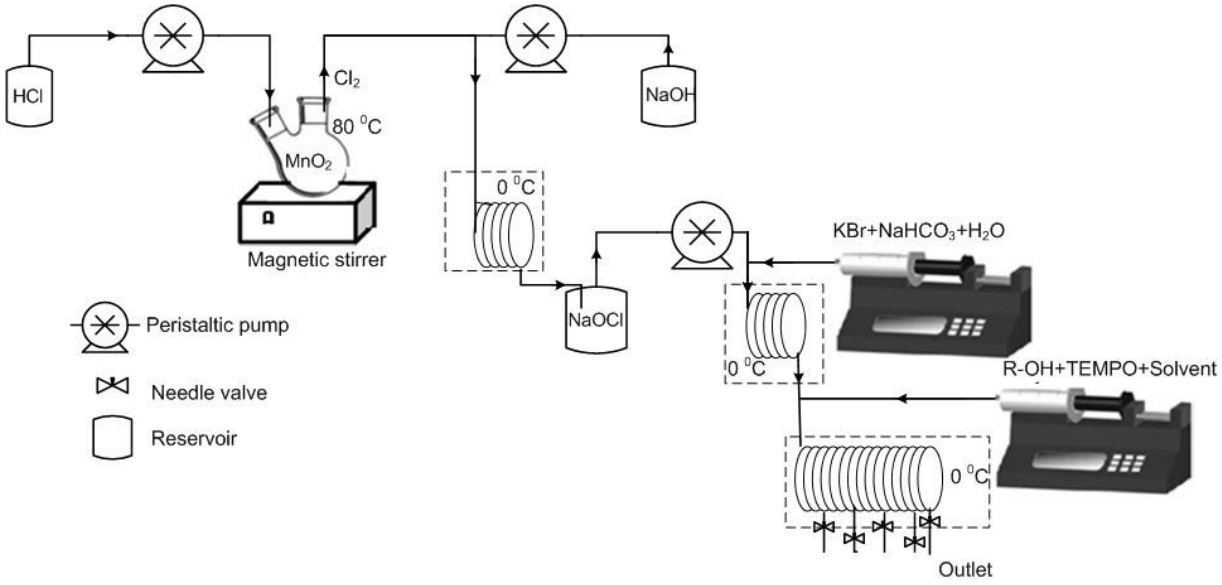


Figure 5. 3: Schematic of 3-step continuous flow alcohol oxidation (1.5 equivalent of hypochlorite, PH 9.5, adjusted by addition of saturated $NaHCO_3$, 5 mole% KBr, 3 mole% TEMPO)

5.7 Analysis

Eight different primary (**1a-c**), secondary (**1d-1f**) and aromatic (**1e, g, h**) alcohols were oxidized using this four step flow approach. Product of all these alcohol oxidation was analyzed using GC, NMR and IR. NMR was done using Bruker AV200 MHz and AV400 MHz, NMR spectrometer in $CDCl_3$ solvent, infrared spectra were recorded on a Perkin‑Elmer FT-IR spectrometer, and analysis was done using GC with HP-5 capillary column with FID detector. .Product of eight alcohols are-

1) Octanal (**2a**)
2) Decanal (**2b**)
3) Undecanal (**2c**)
4) 3-Octanone (**2d**)
5) 4-Methoxy benzeldehyde (**2e**)
6) Citral (geranial **2f** and neral **2f'**)
7) Benzeldehyde (**2g**)
8) 2-Bromobenzeldehyde (**2h**)

Analytical data has been shown at the end of this chapter, before references.

5.8 Result and discussion

5.8.1 Hypochlorite synthesis

To get rid of tedious titration of commercially available hypochlorite at each stage and for reproducibility of results, in-situ generated hypochlorite is the best alternative. It was generated with the reaction of in-situ generated chlorine gas with NaOH solution. For a fixed flow rate of chlorine, the flow rate of NaOH and its concentration in water was varied to obtain hypochlorite of various strengths. Homogeneous oxidations needed low strength hypochlorite however for bi phasic oxidation reactions solution of relatively higher strength was needed to reduce the diffusion limitations. Initially NaOH of different concentrations (5 – 20%) was used, of which 10% solution resulted in gives maximum strength of NaOCl for a fixed residence time. It required pH of 13 for the stability.

Table 5. 2: Effect of NaOH % on pH and strength of hypochlorite at 0 ºC at a fixed residence time

NaOH %	pH	strength %
5	5.11	5.83
10	13.04	7.20
15	13.05	2.06
20	13.47	0.75

In another set of experiments, in order to maintain identical flow regime during these experiments, flow rates of chlorine and NaOH solution were maintained constant while the residence time was varied by changing reactor volume. The reaction of formation of hypochlorite solution was very fast and no chlorine was seen to get escaped unreacted from the reactor. In the synthesis of sodium hypochlorite, longer residence time provides higher strength hypochlorite as more contact time helps for this exothermic reaction. A 4 mL reactor resulted in only 2% strength solution of hypochlorite in 5 s while in a 38 mL reactor that the solution strength is 11.52% with a residence time of 36 s. Thus longer residence time can help to achieve high strength hypochlorite. However the stability of the solution also depends on pH. It was observed that while one can use higher strengths of NaOH solutions for this reaction depending upon pH the strength of solution may decrease rapidly. In our experiments we had observed that for TEMPO mediated oxidation of alcohols pH of the solution should be in range of 9 to 9.8. For acidic pH, over-oxidation happens and acid forms as major product

while at higher pH no reaction takes place. For pH adjustment, saturated sodium-bicarbonate solution was used which decreases hypochlorite.

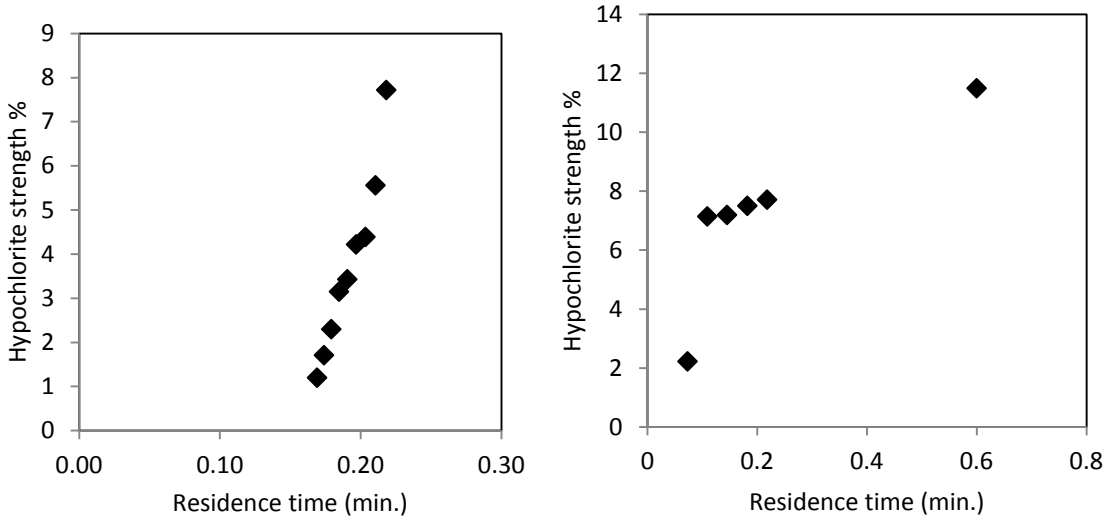


Figure 5. 4: Effect of residence time on hypochlorite strength: (A) For a fixed reactor volume (12 mL) NaOH flow rate was varied in range of 4 to 20 mL/min, (B) Reactor volume was changed from 4 mL to 38 mL at a constant flow rate of NaOH 4mL/min. (flow rate of Cl_2 was 51 mL/min, ice cold condition for both cases)

5.8.2 Oxidation of alcohols

In bleach oxidation, pH plays a major role and it is necessary to keep it in the range of 9.1 to 9.8. In highly basic conditions (pH = 13.5) no oxidation reaction takes place, while in acidic pH (< 5) acid forms as a major product. In order to understand the range of pH that is suitable for the proposed experiments, initially a few batch experiments were performed for oxidation of 1-octanol with 1.3 mole% TEMPO as primary oxidant and freshly prepared bleach as a secondary oxidant with adjusted pH of 9.5. KBr was used in reaction for enhancing the rate of reaction. Experiment carried out at 0 ºC for 3 hours resulted in 30% yield of 1-octanal. Longer reaction time resulted in significant over oxidation. Hence for all further experiments, pH was maintained at 9.5 and residence time and temperature was modified to maximize the yield of respective aldehyde.

The effect of concentration of TEMPO on the conversion and selectivity of continuous flow oxidation of 1-octanol was studied. Initially experiments were carried out without using TEMPO, which resulted in over 98% conversion with 51% impurity and 49% 1-octanol.

Experiment with 1 mole% TEMPO catalyst for identical residence time, the conversion was over 98% while the selectivity of 1-octanol was 88%.

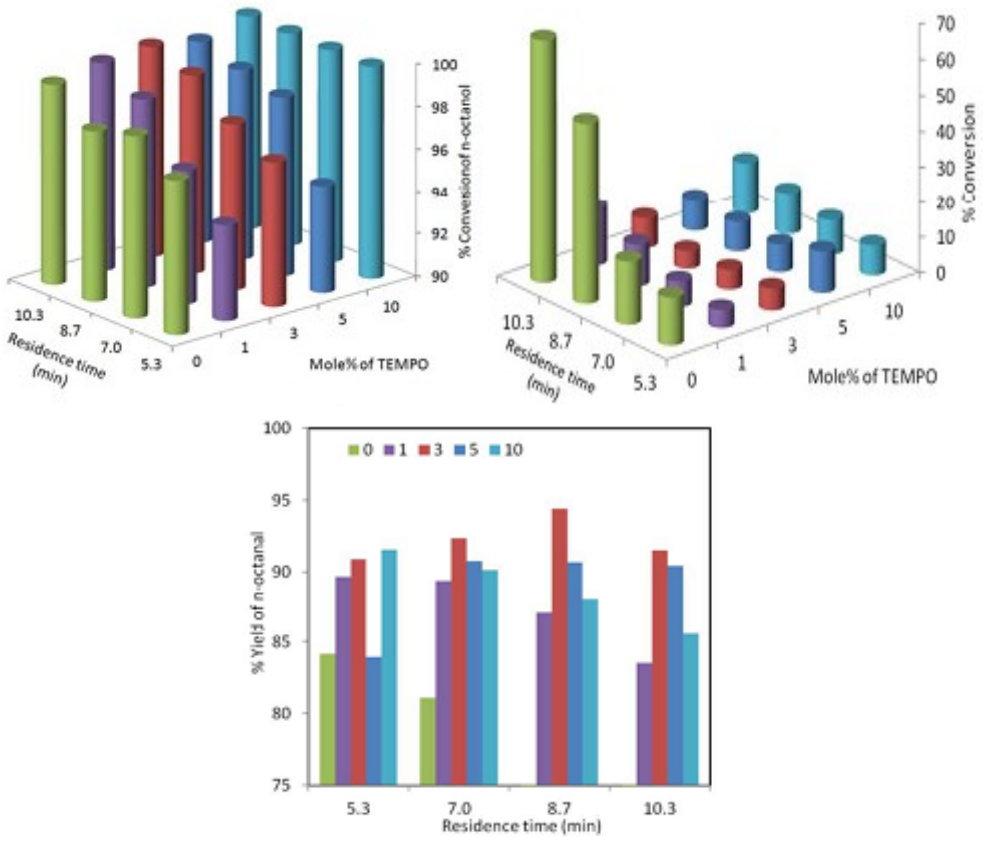


Figure 5. 5: Effect of TEMPO% and residence time on octanol oxidation (A) % Conversion of n-octanol, (B) % selectivity of impurities (mainly acid and ester) and (C) % yield of the desired aldehyde (yields lower than 75% are not shown here).

Further enhancement in the concentration of TEMPO to 3 mole% resulted in 95% yield of the desired product and over 99% conversion in a residence time of 8.6 minutes. However in the presence of excess hypochlorite, further oxidation of aldehyde is unavoidable as in this step hypochlorite acts as a primary oxidant. Octanoic acid and octyl ester are the major impurities.

In the case of oxidation of (trans)-3,7-dimethyl-2,6-octadien-1-ol (geraniol) , it gives 2 isomers, neral (**2f'**) and geranial (**2f**). Gereniol oxidation was performed with 3, 5 and 10 mol% of TEMPO which gives different isomeric ratio of neral and geranial. At a residence time of 6.75 min, with 3 mole% and 10 mole% of TEMPO, the yield of neral was 62.4% and 5.7%. However the yield of geranial did not vary much. Maximum yield of geranial was

22.3%, which was achieved at a residence time of 6.75 min with 5 mol% of TEMPO. Among the two aldehydes, neral showed more tendency to decompose with higher TEMPO%.

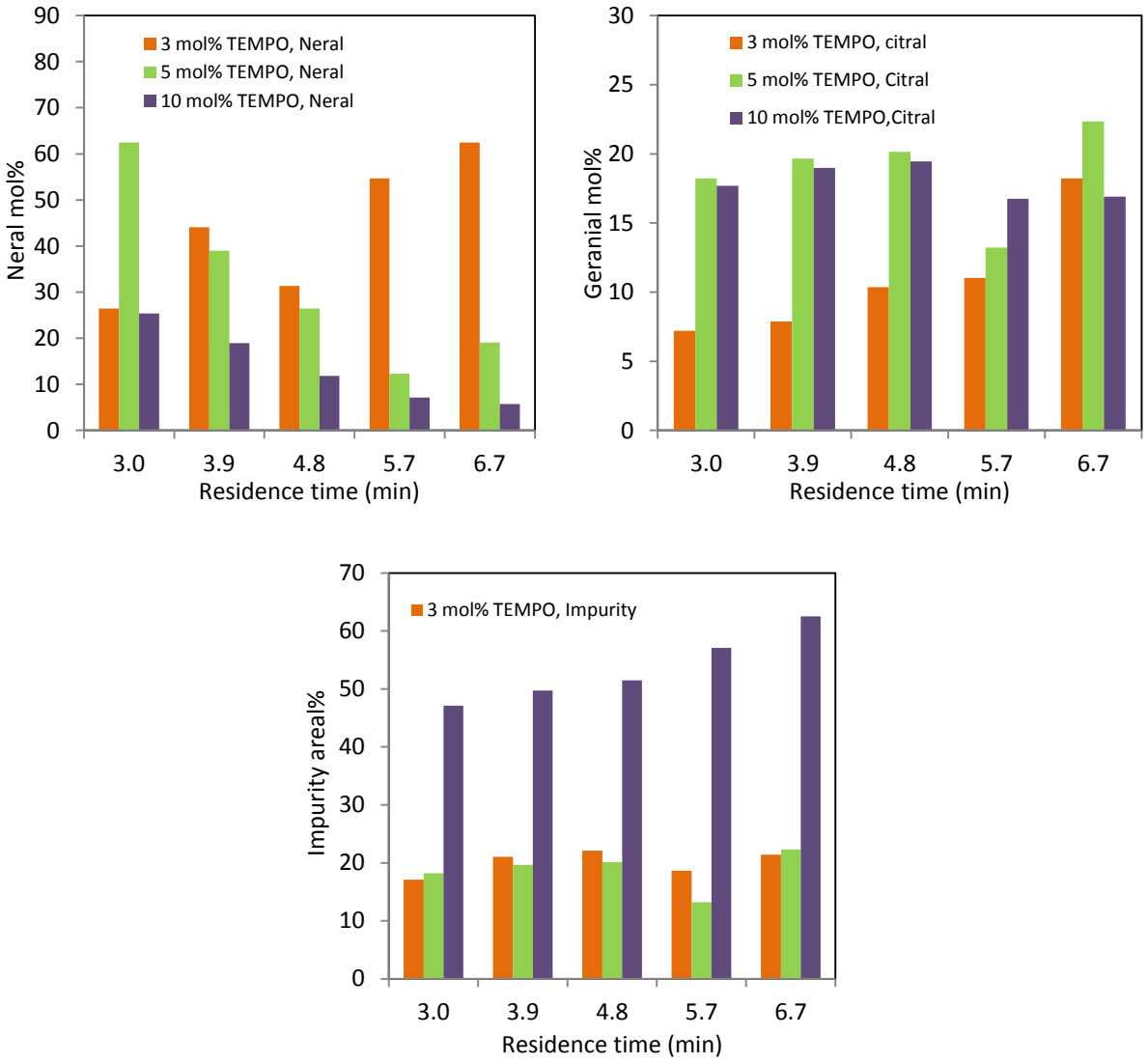


Figure 5. 6: Effect of TEMPO% and residence time on geraniol

A few more primary (**1a-c**), secondary (**1d-1f**) and aromatic (**1e, g, h**) alcohols were oxidized using this four step flow approach. The observations are given in Table 5.3. For primary and secondary alcohols this TEMPO/bleach system works efficiently giving 80- 99% yield of corresponding aldehyde and ketone. However, for aromatic alcohol, this oxidation strategy needed longer residence time and still the yield of respective aldehydes was lower than the aliphatic alcohols.

Table 5. 3: 3 mole% of TEMPO, 1.5 equivalent of hypochlorite (PH= 9.5, adjusted by addition of saturated $NaHCO_3$), 5 mole% KBr . [For 1g and 1h, TEMPO is 5 mol% and 7 mol%, respectively] [For entries 1e and 1h, yield is based on GC area%]

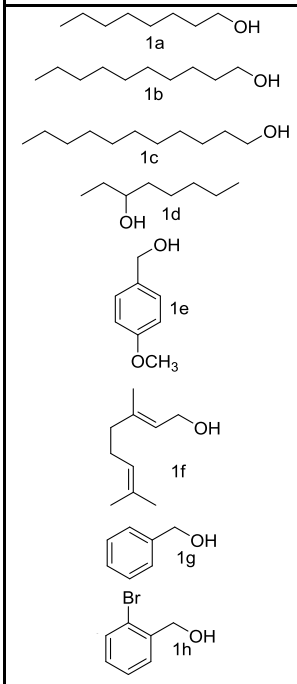
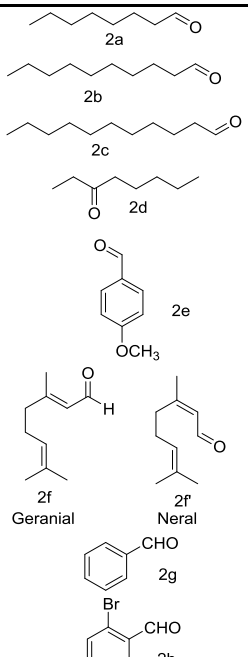
Reactants	product	% Conversion of alcohol	Impurity (area %)	% yield of Aldehyde	Residence time (min)
		99.35 94.14 100 99.18 96.3 100 100 99	5.0 2.5 - - - 20 - 6.5	95 90 95.3 99 89 80 (Gerenial/Neral 0.29) 99.82 90.1	8.67 6.57 5.56 4.88 5.05 6.67 4.05 15

Table 5. 4: Number of experiments performed

Reactions	**Batch experiments**	**Flow experiments**
Hypochlorite synthesis	10	55
Octanol Oxidation	6	31
Decanol Oxidation	4	4
Undecanol Oxidation	4	5
3-Octanol Oxidation	3	5
4-Methoxybenzyl alcohol Oxidation	4	5
Geraniol Oxidation	6	15
Benzyl alcohol Oxidation	4	5
2-Bromobenzyl alcohol Oxidation	3	5
Total experiments Oxidation	44	70

5.9 Conclusions

A four step continuous flow oxidation of alcohols is demonstrated with continuous chlorine generation as the first step through the reaction of hydrochloric acid and manganese-di-oxide followed by its use for the flow synthesis of high strength sodium hypochlorite, with continuous pH adjustment. The solution is subsequently used for oxidation of alcohols in the presence of catalytic amount of nitroxyl radical "TEMPO" which inhibits oxidation at the aldehyde stage. Selective oxidations of eight different aliphatic and aromatic alcohols have been demonstrated with high yield in range of 80 – 99% for aliphatic alcohols and relatively lower yields for aromatic alcohols containing electron withdrawing groups. The approach helps to generate high strength hypochlorite solution that can be used or variety of reactions. It is necessary to note that for specific oxidation reactions using TEMPO one would need to maintain a specific pH of the solution. This implies that just having high strength hypochlorite solution is not sufficient but pH needs to be adjusted in-line to facilitate the subsequent reaction. Since the approach generates pure chlorine in gas phase it can be used for efficient chlorination reactions in flow and relevant work will be reported separately.

Analytical data

2) NMR data

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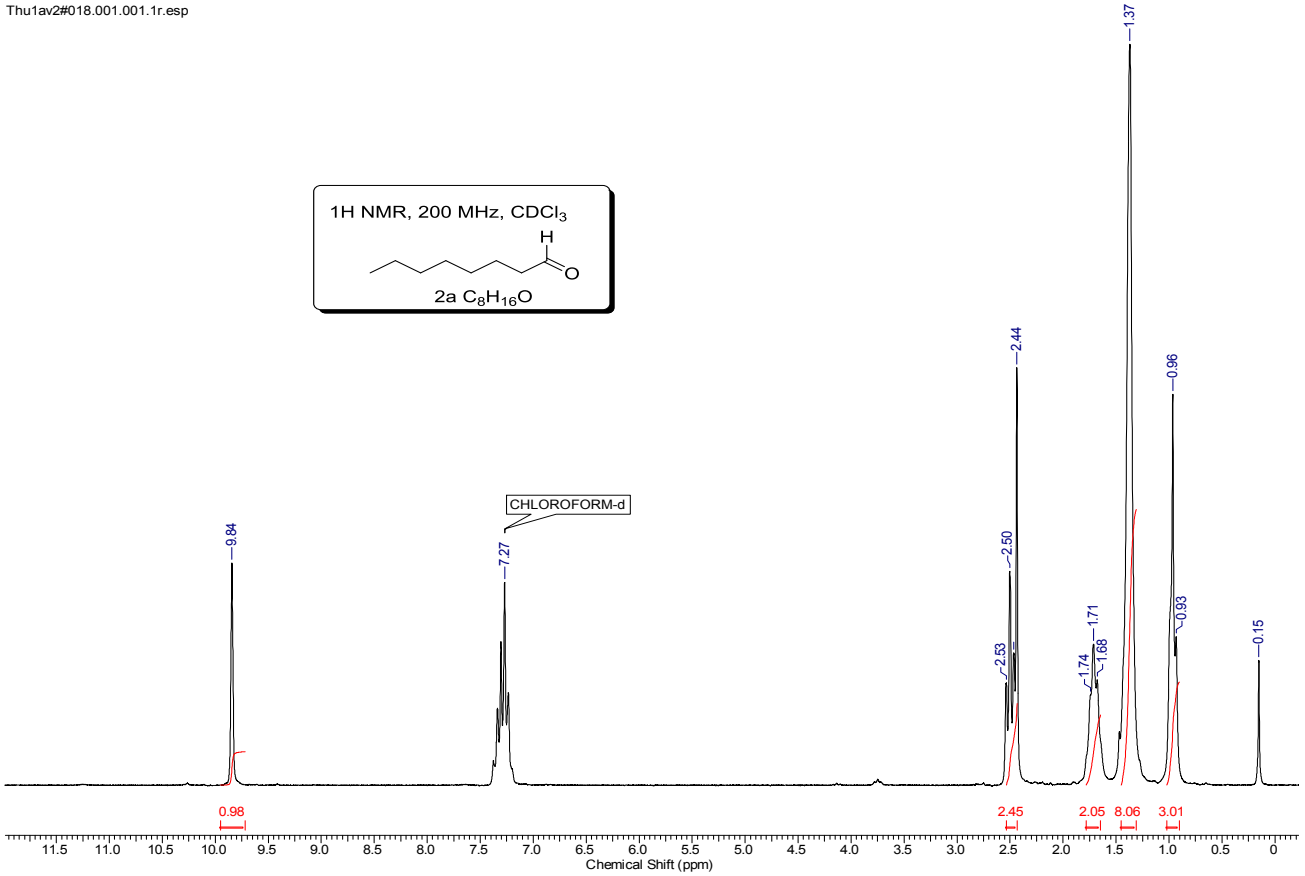

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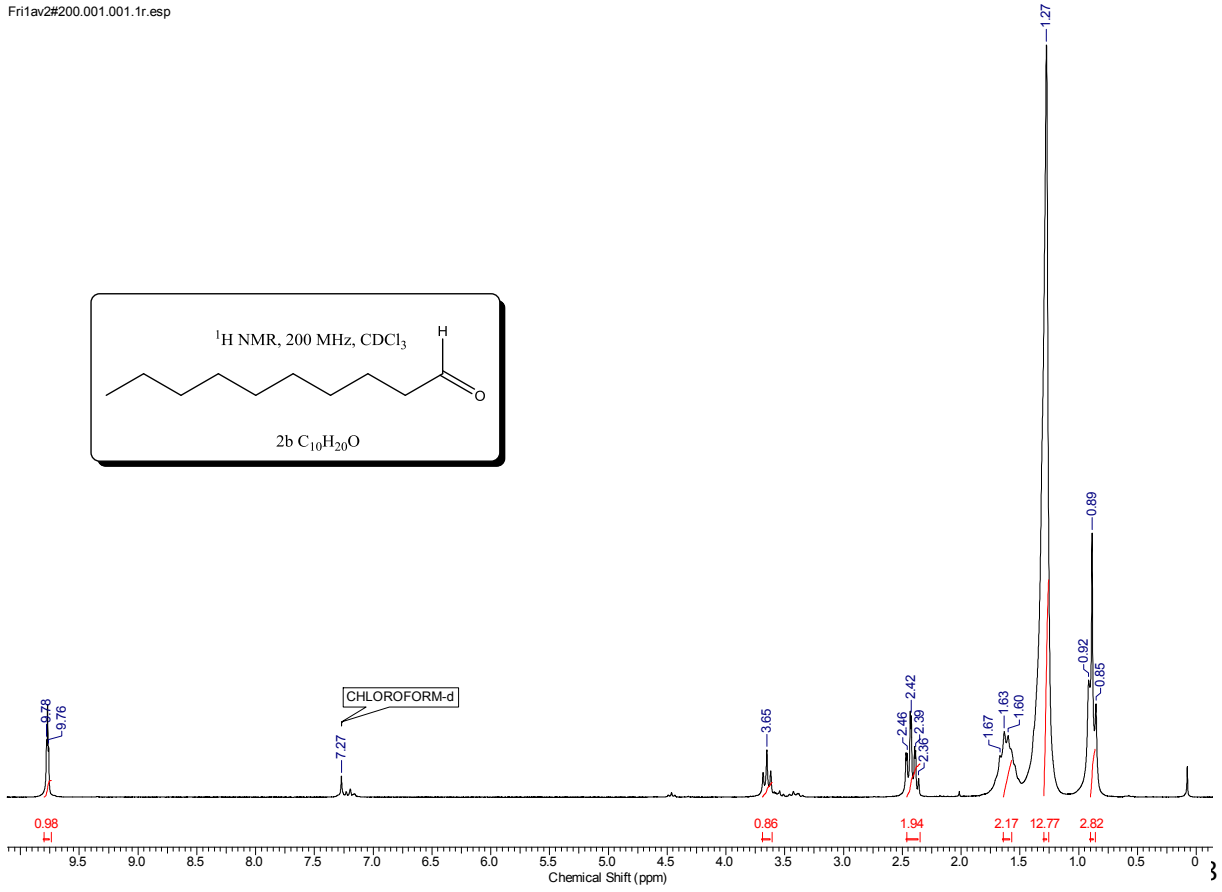

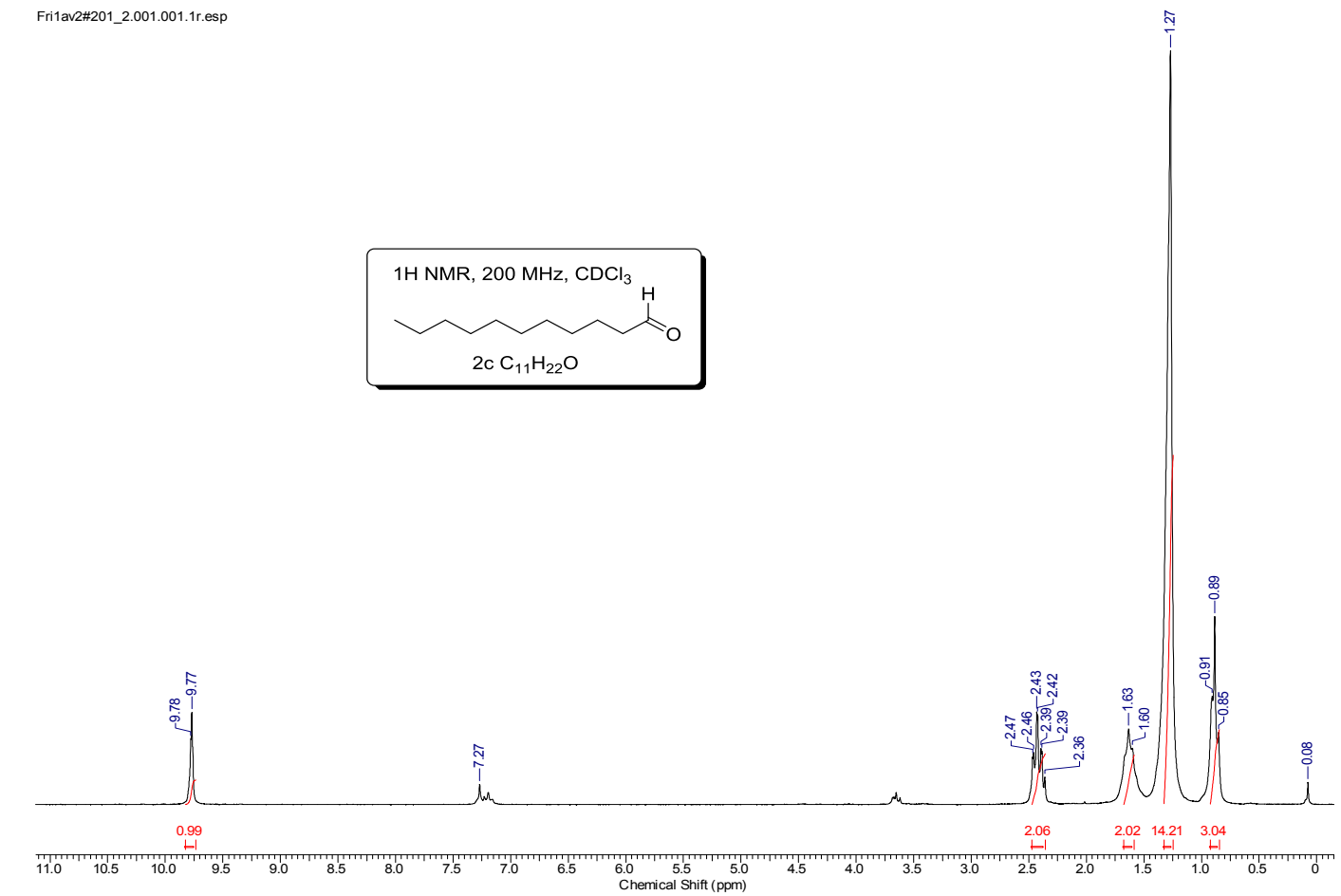
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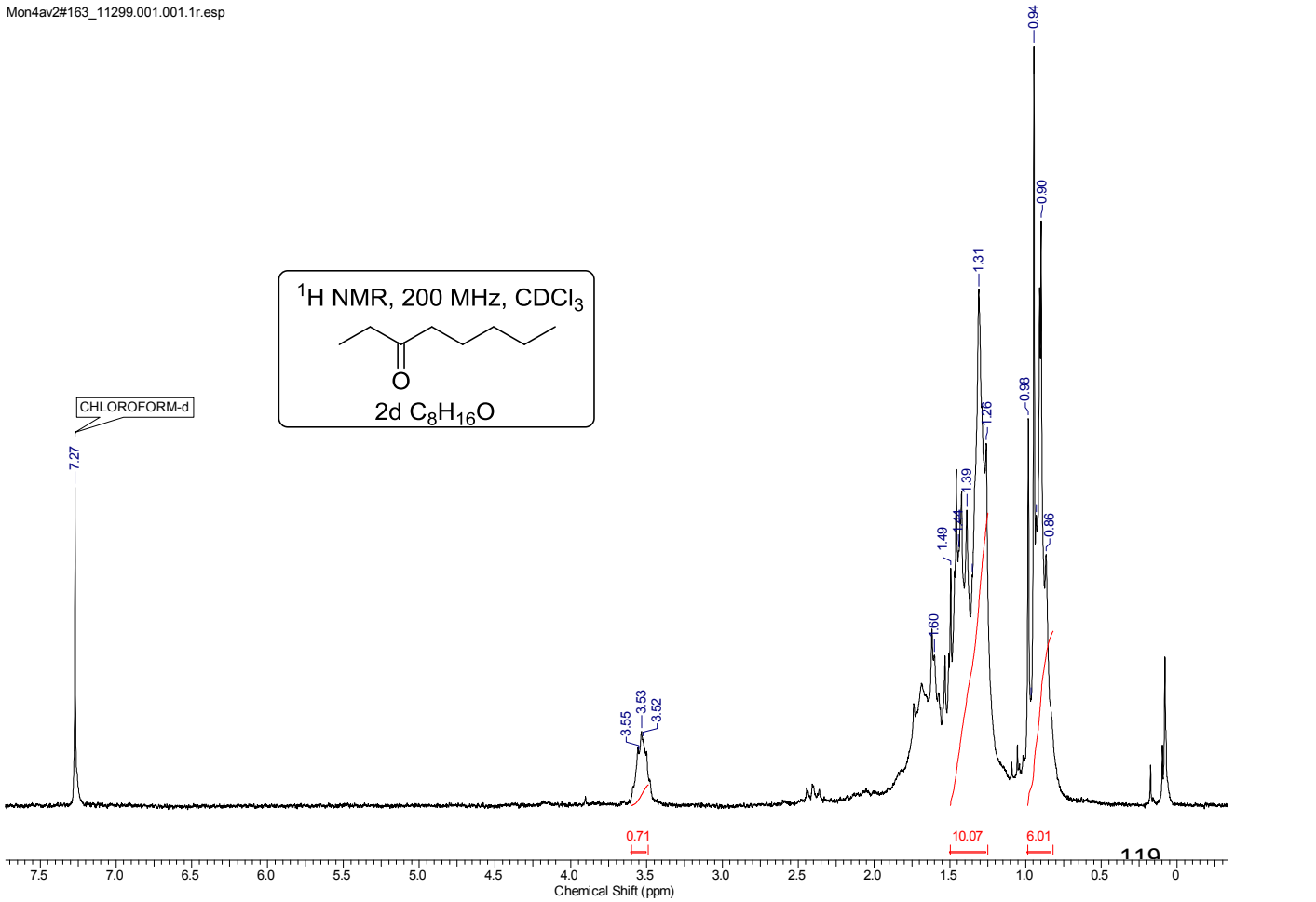
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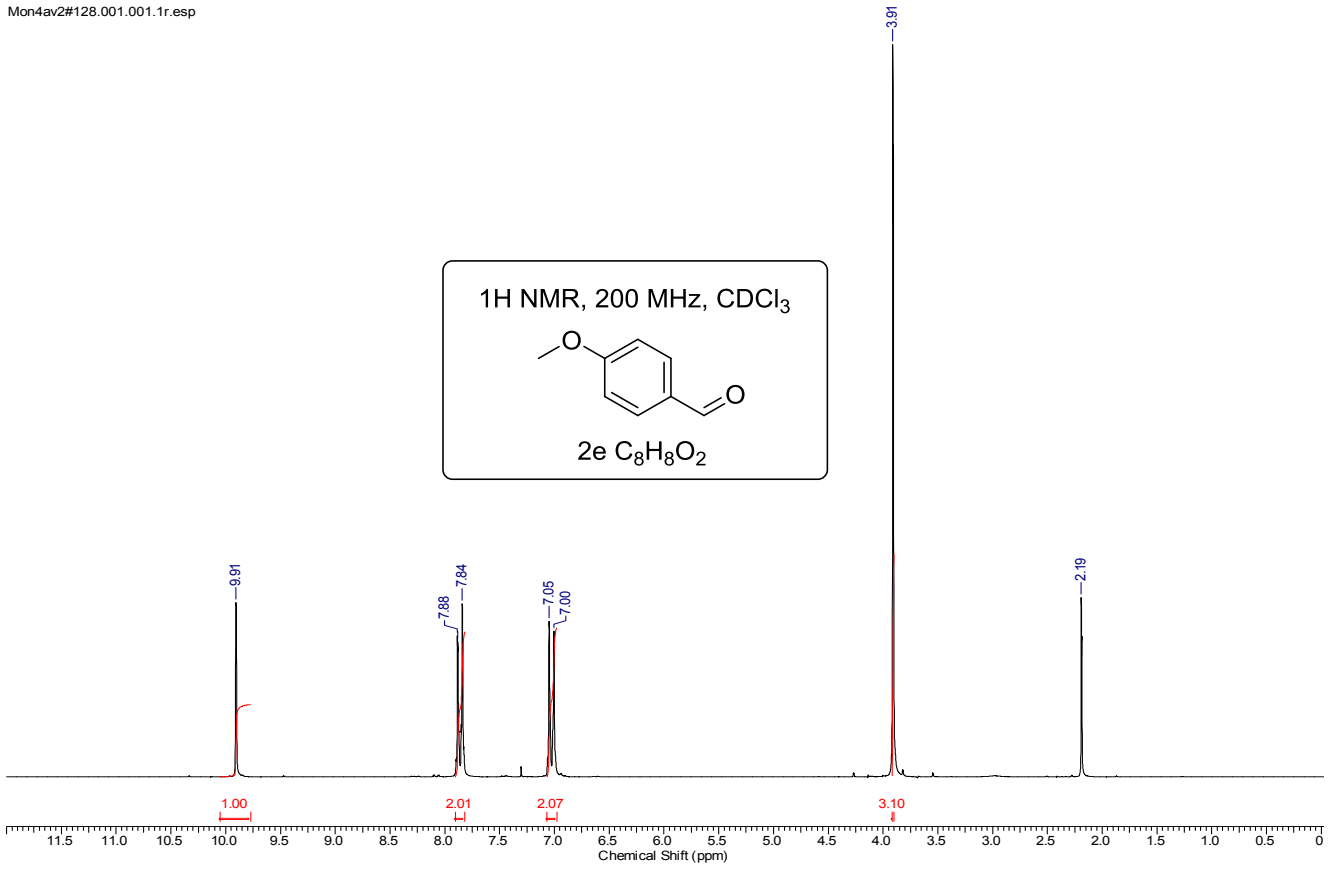
Chemical Shift (ppm)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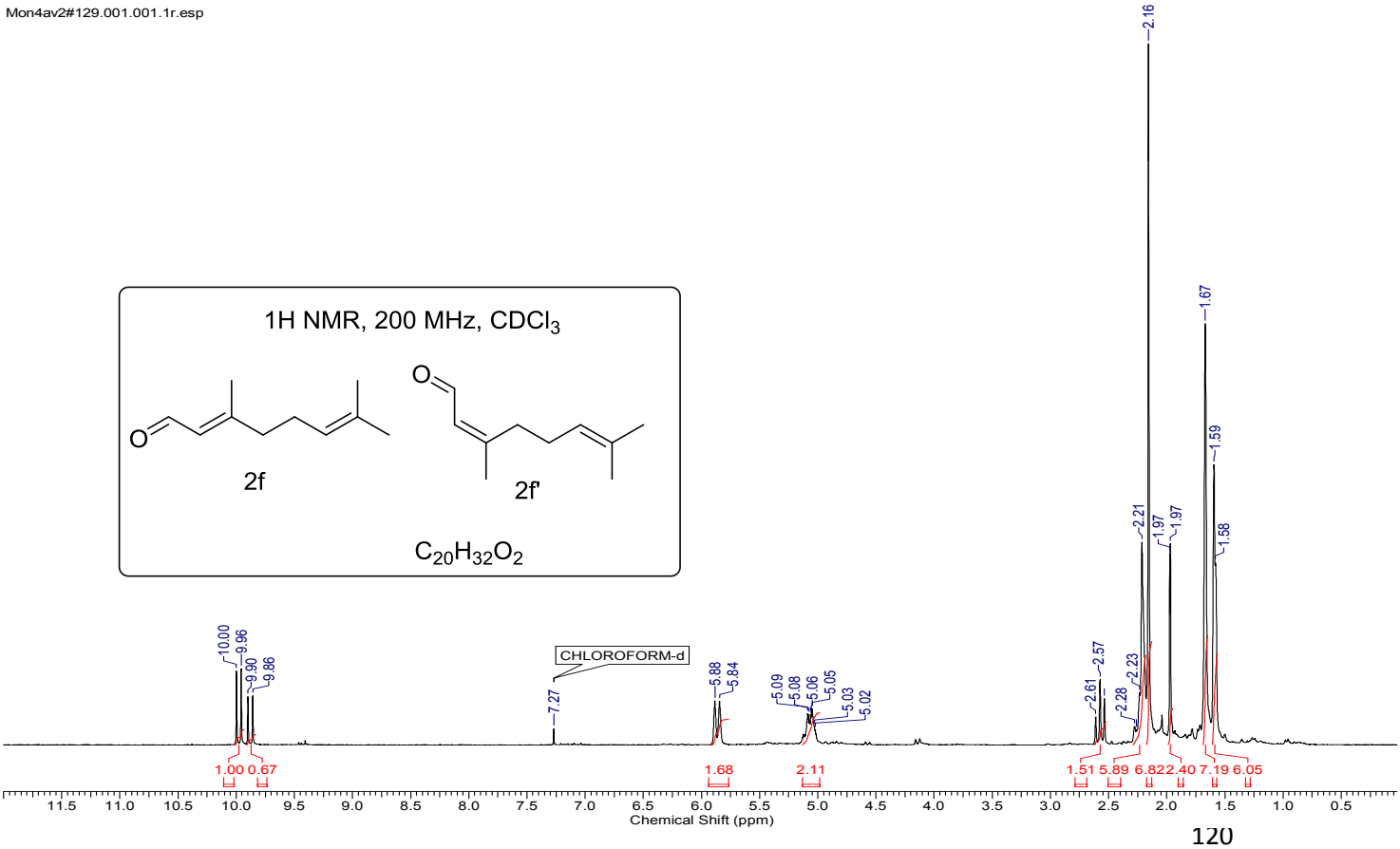
1.00
2.01
2.07
3.10
Chemical Shift (ppm)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2f'
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5.88
5.84
5.09
5.08
5.06
5.05
5.03
5.02
2.61
2.57
2.28
2.23
2.21
2.16
1.97
1.97
1.67
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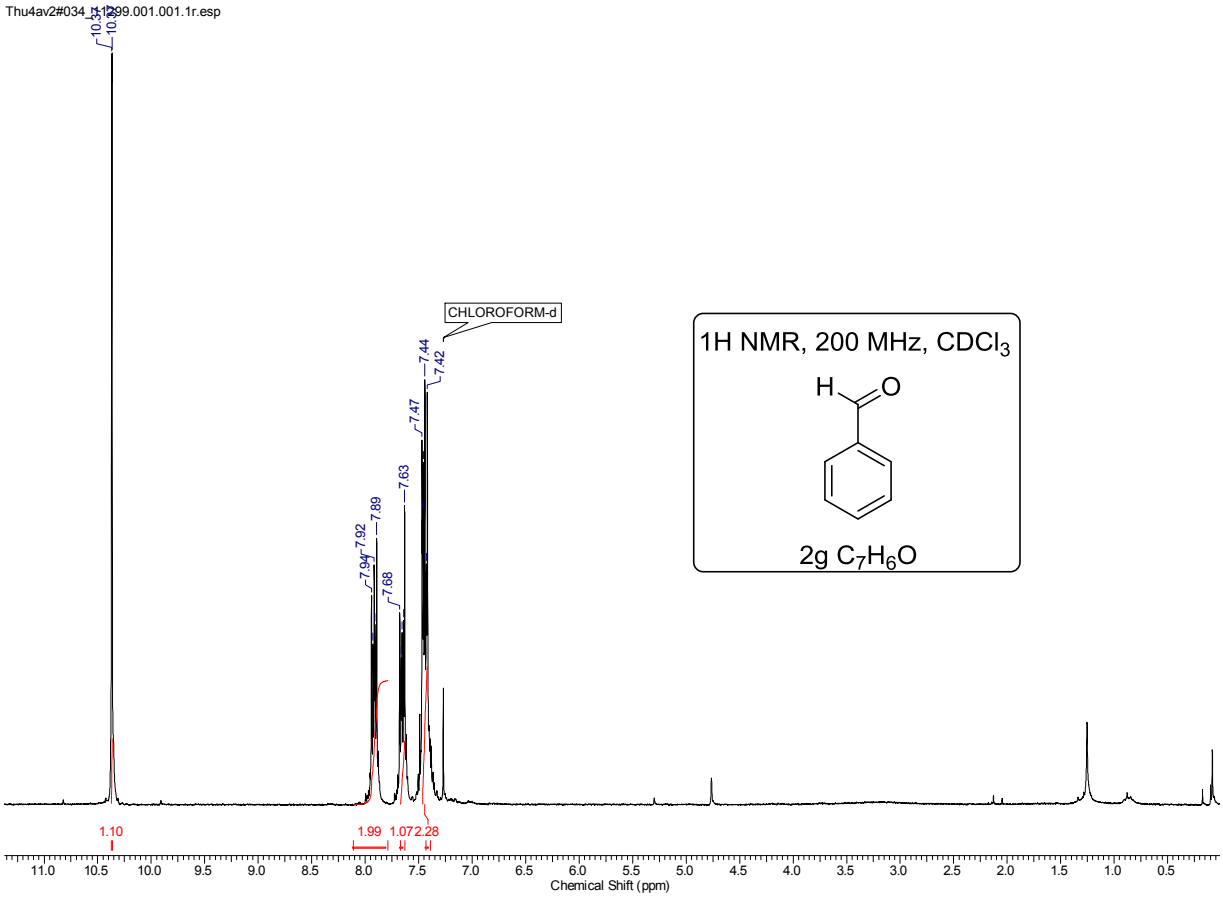
1.00 0.67
1.68
2.11
1.51 5.89 6.82 2.40 7.19 6.05
Chemical Shift (ppm)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O
2g C7H6O
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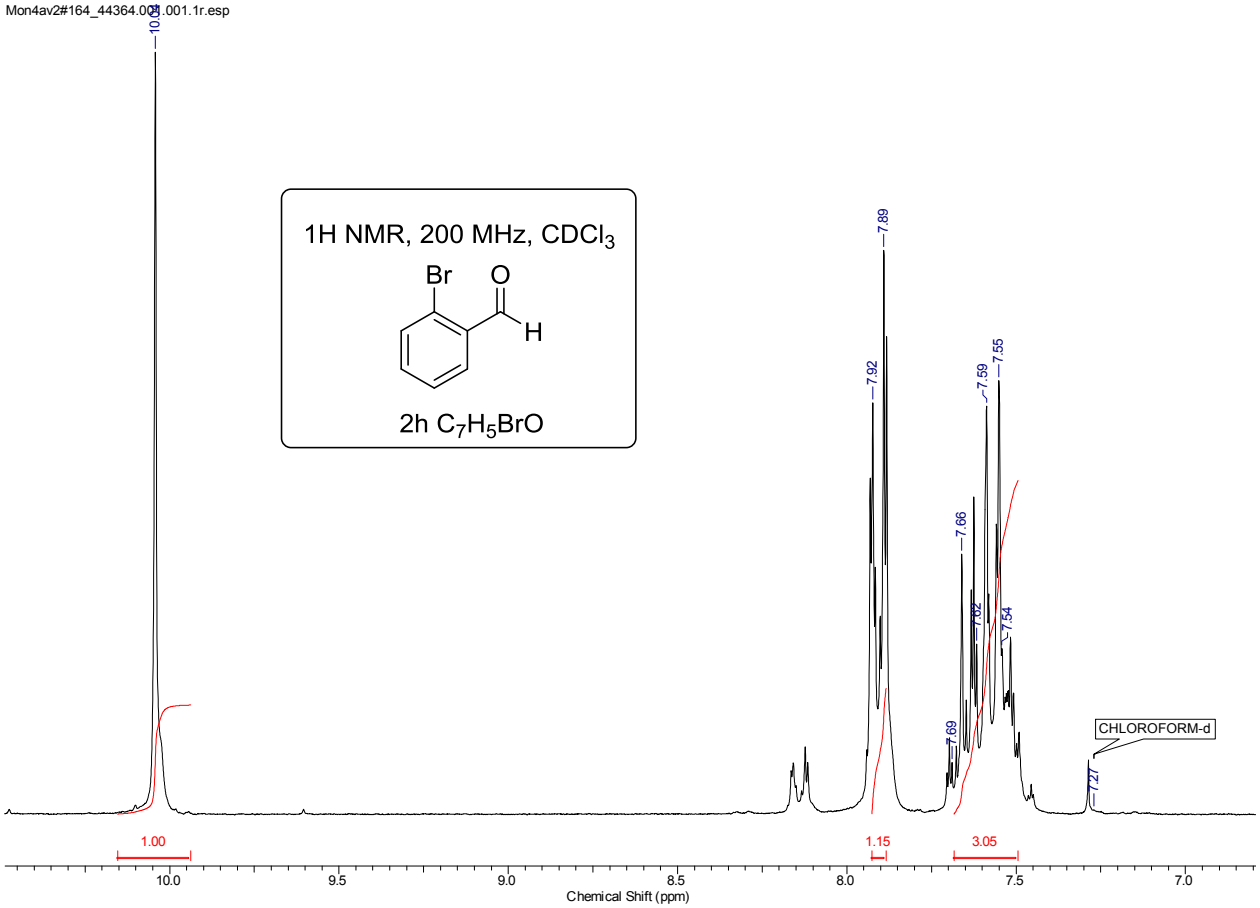
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O
H
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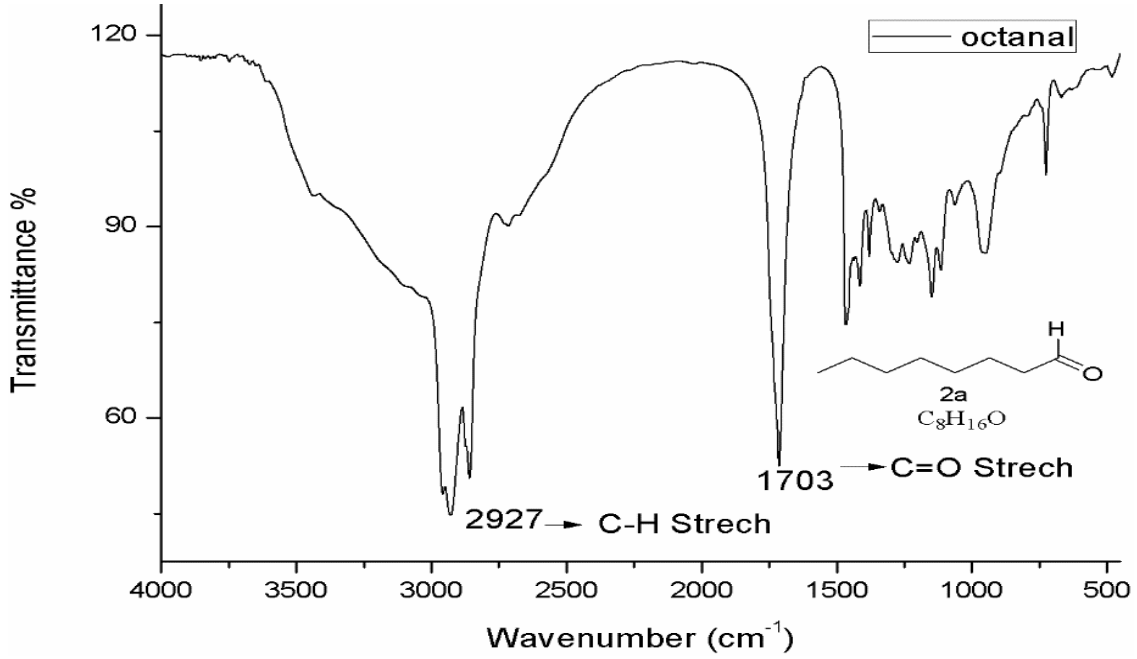
Chemical Shift (ppm)

3) IR data


octanal
Transmittance %
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90
60
1703
C=O Strech
2927
C-H Strech
4000
3500
3000
2500
2000
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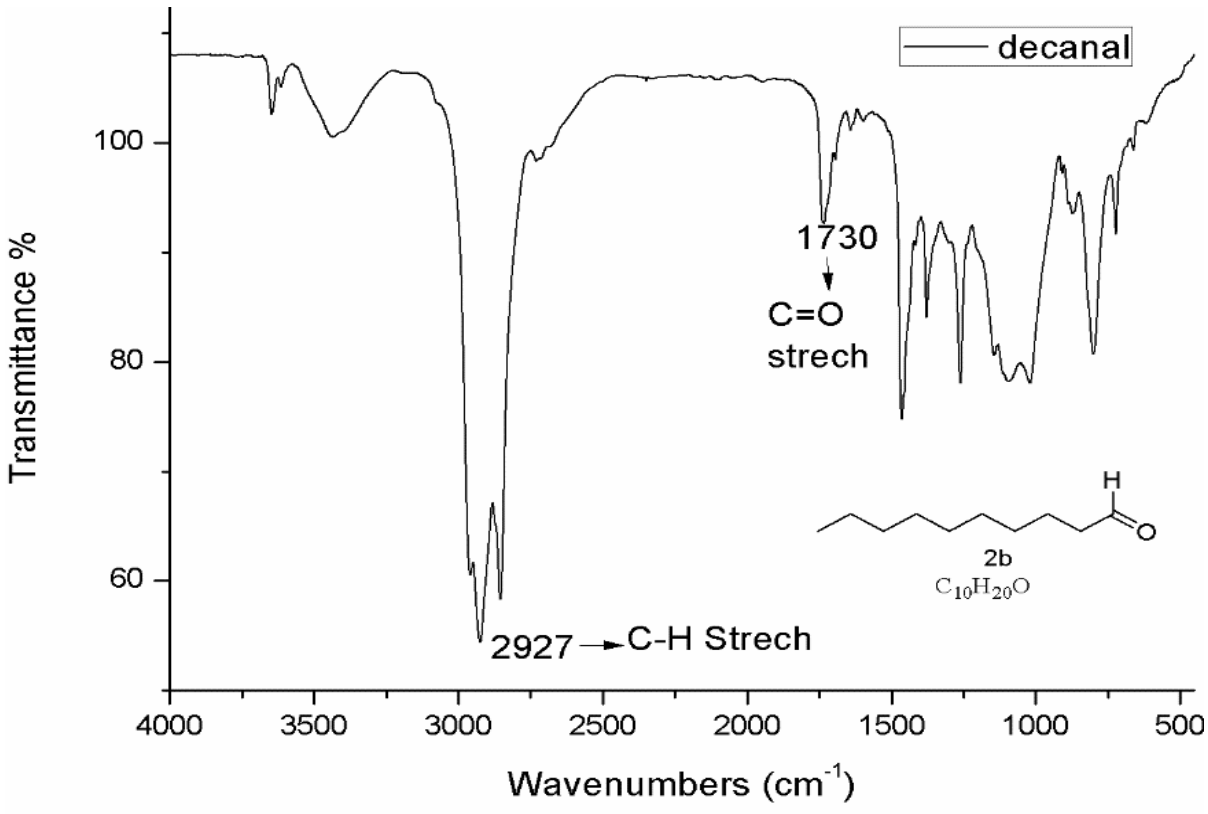
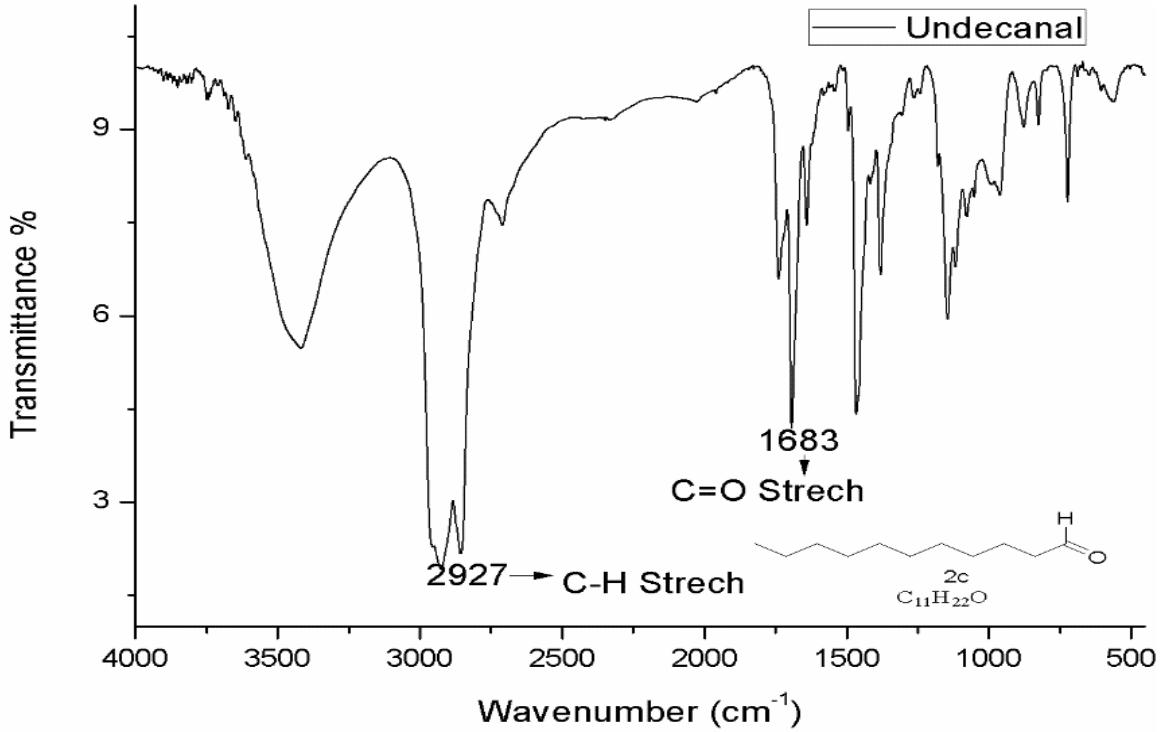
500
Wavenumber (cm-1)
H
O
2a
C8H16O


decanal
Transmittance %
100
80
60
1730
C=O
strech
2927
C-H Strech
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
H
O
2b
C10H20O


Undecanal
Transmittance %
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6
3
1683
C=O Strech
2927
C-H Strech
H
O
2c
$C_{11}H_{22}O$
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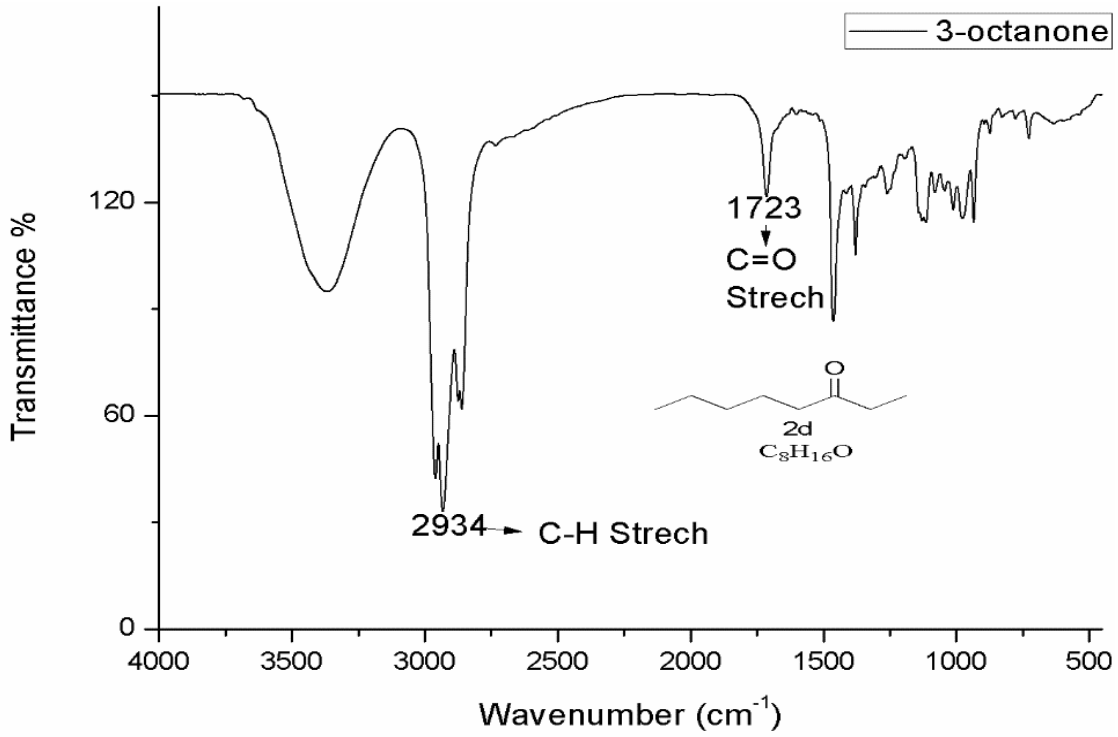
3000
2500
2000
1500
1000
500
Wavenumber (cm^{-1})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Strech
O
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C-H Strech
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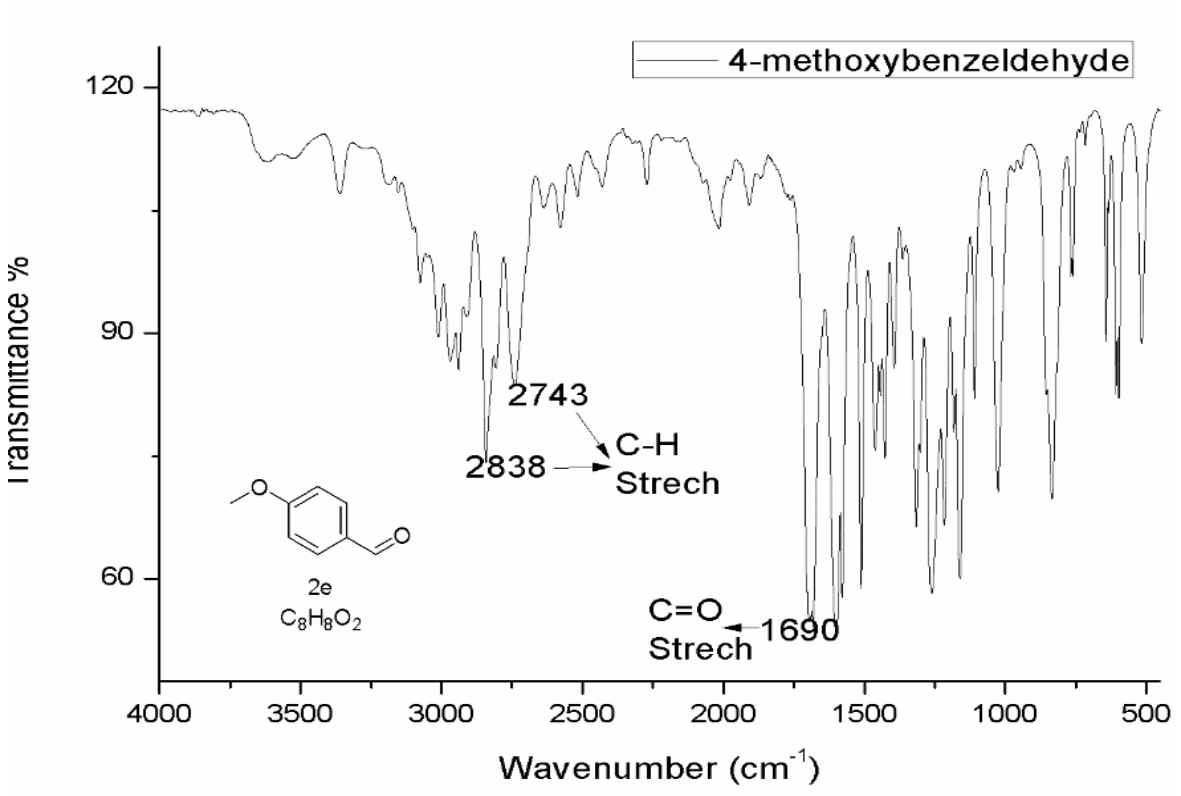
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm^{-1})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Transmittance %
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2838
C-H
Strech
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C8H8O2
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3500
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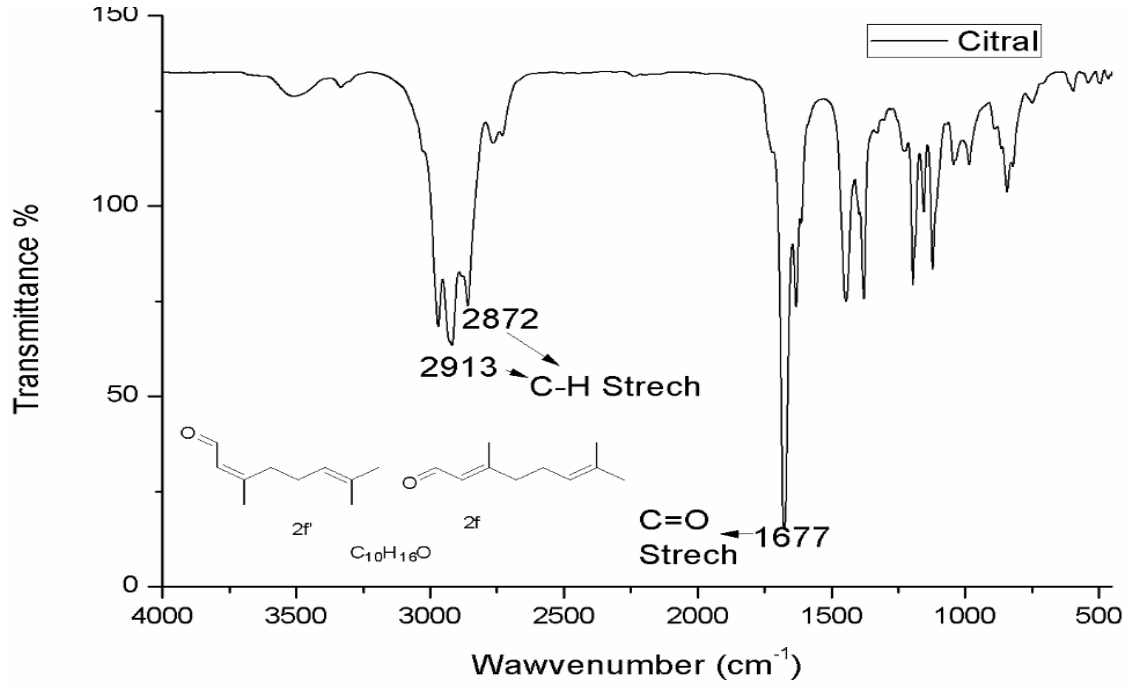
1000
500
Wavenumber (cm-1)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Transmittance %
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0
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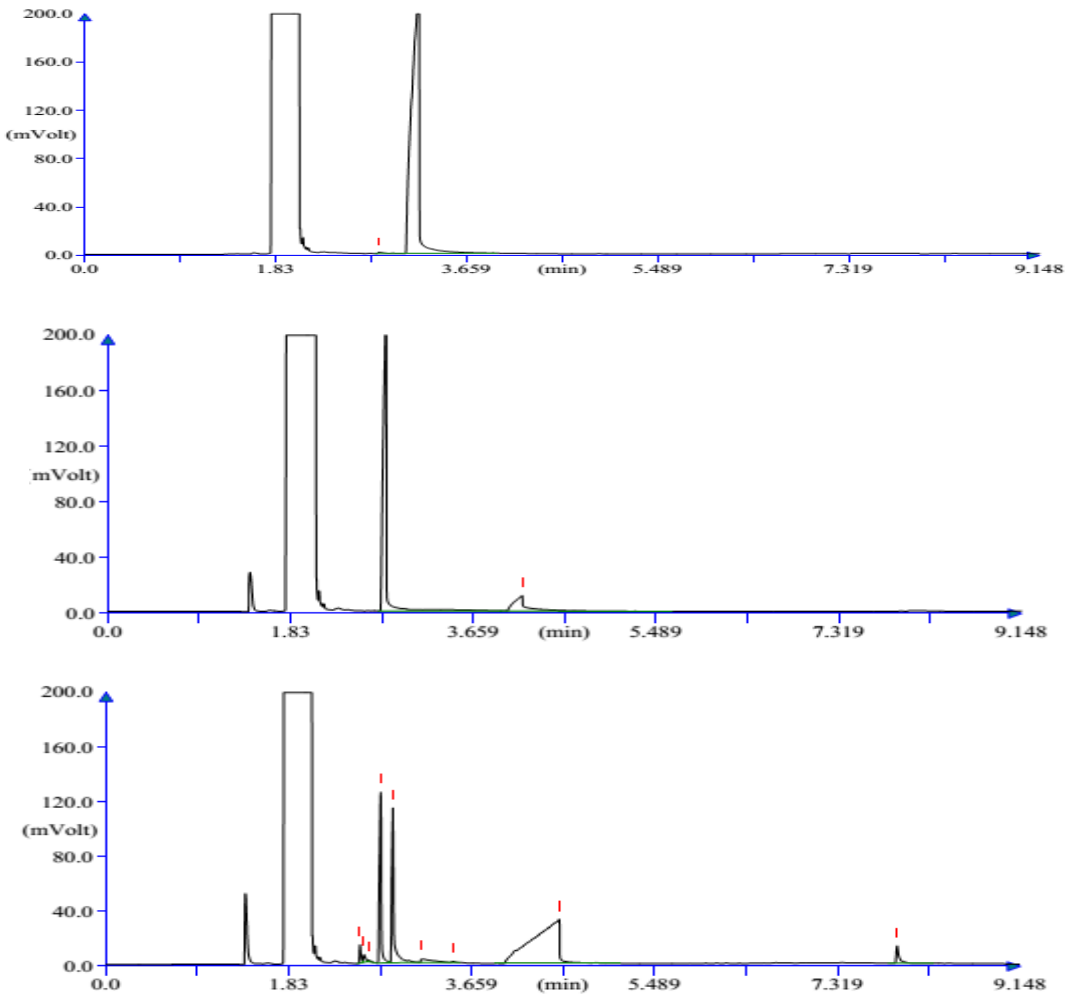
2913
C-H Strech
2f'
2f
C10H16O
C=O
Strech
1677
4000
3500
3000
2500
2000
1500
1000
500
Wawvenumber (cm-1)

4) GC and GCMS spectra

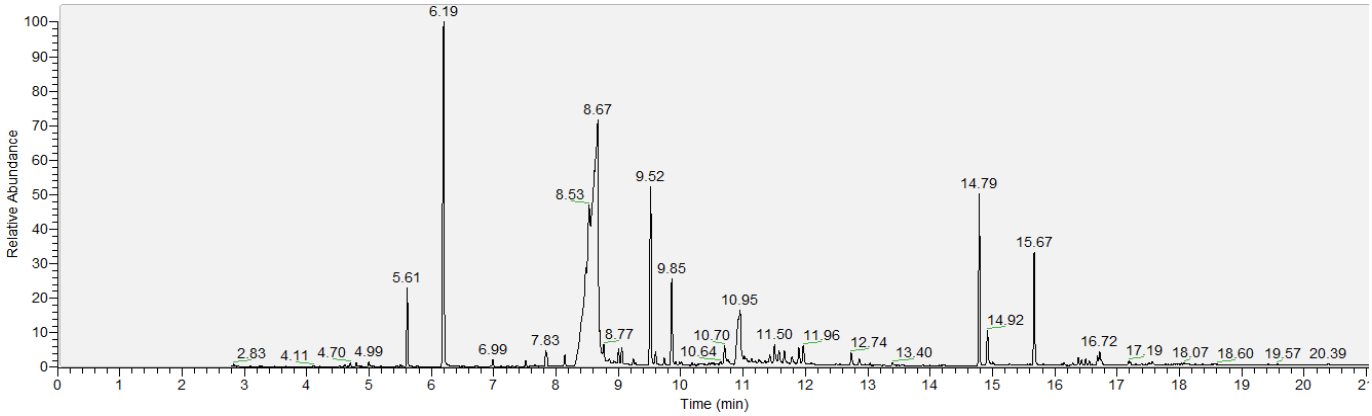
5. **Octanol:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ^{0}C and hold for 1 min, with ramp 35 ºC/min.

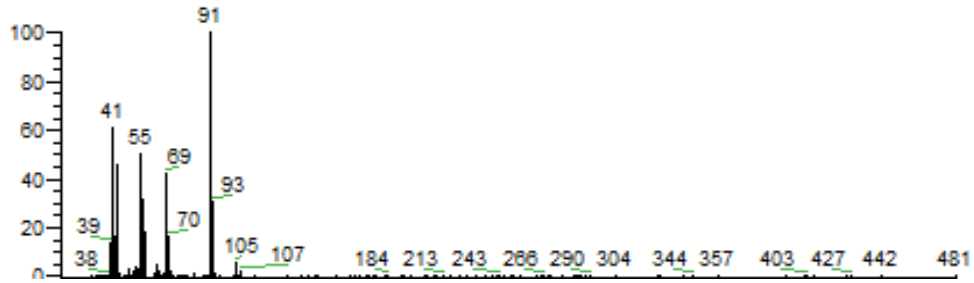
	GC retention time	GCMS retention time
Internal standard	2.7	
Octanol	3.1	
Octanal	4.1	6.1
Impurity (acidic impurity)	7.9	8.6
(Furanone impurity)		9.5
Ester impurity		14.7
Impurity (from solvent)		5.6



GC spectra of a) Octanol, b) Octanal, and c) Octanol oxidation reaction mixture

GCMS of octanol oxidation reaction mixture





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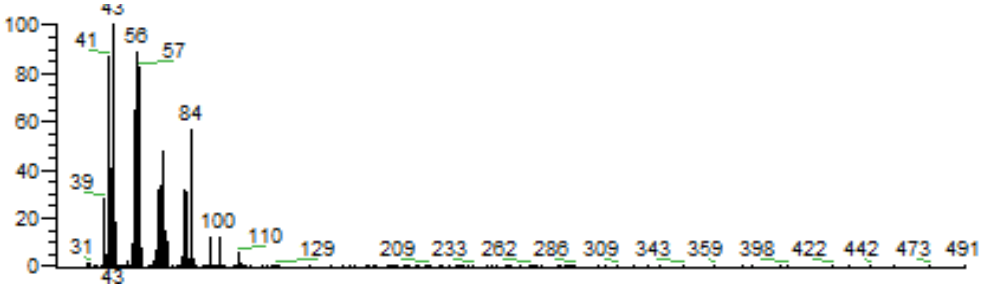

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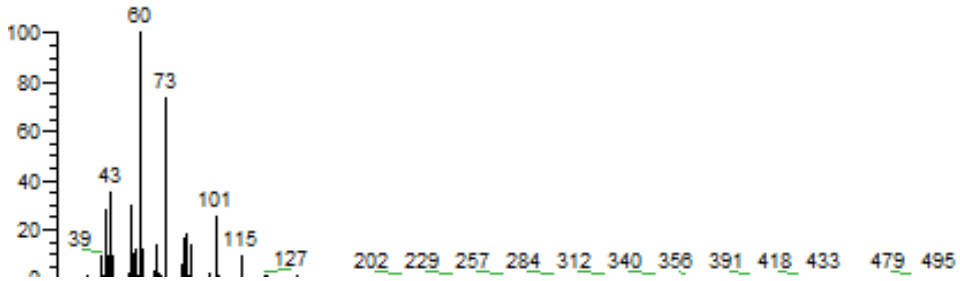
NL: 9.99E2



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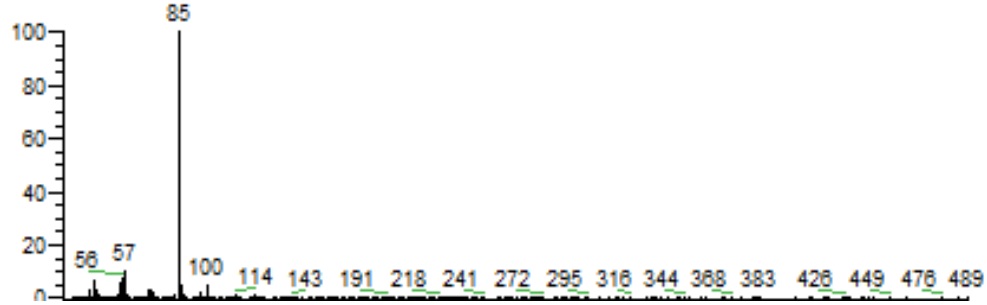

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+ c EI Full ms
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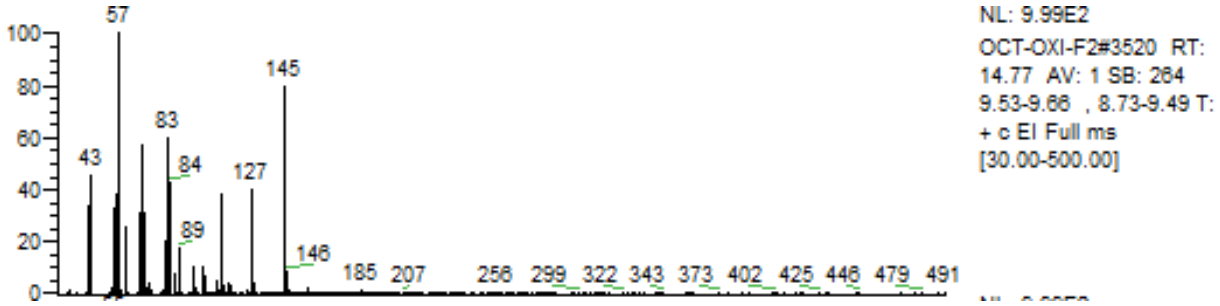
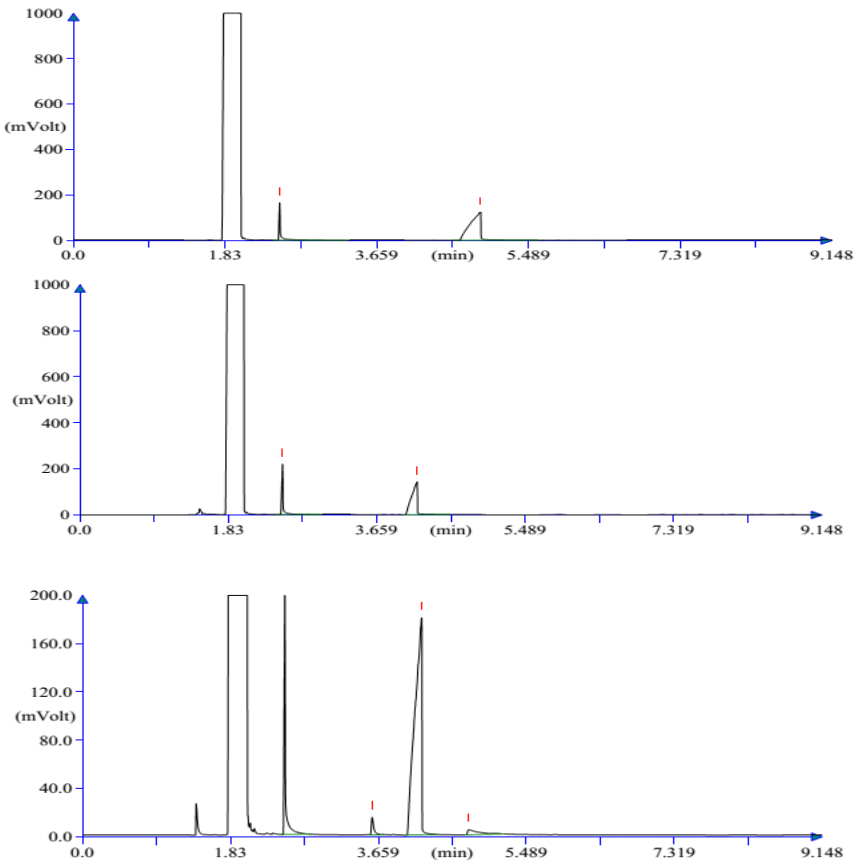


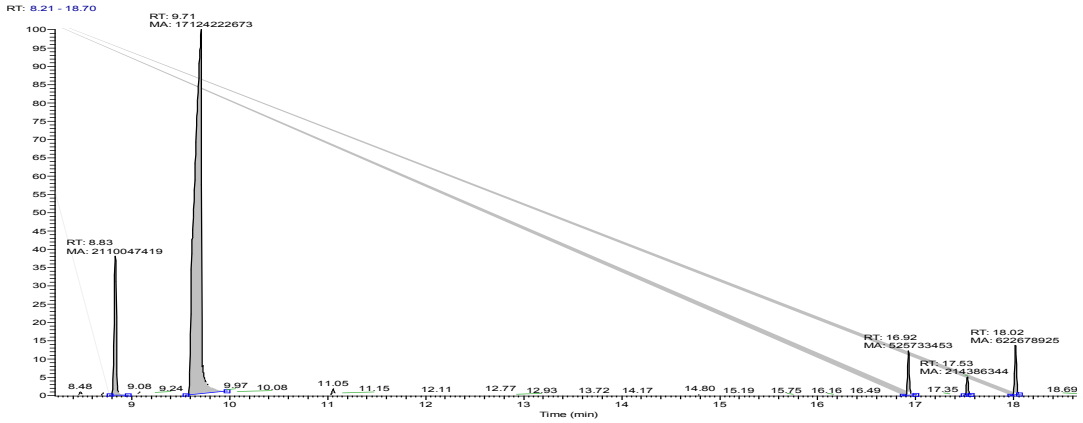
6. **Decanol:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ºC and hold for 1 min, with ramp 35 ºC/min.

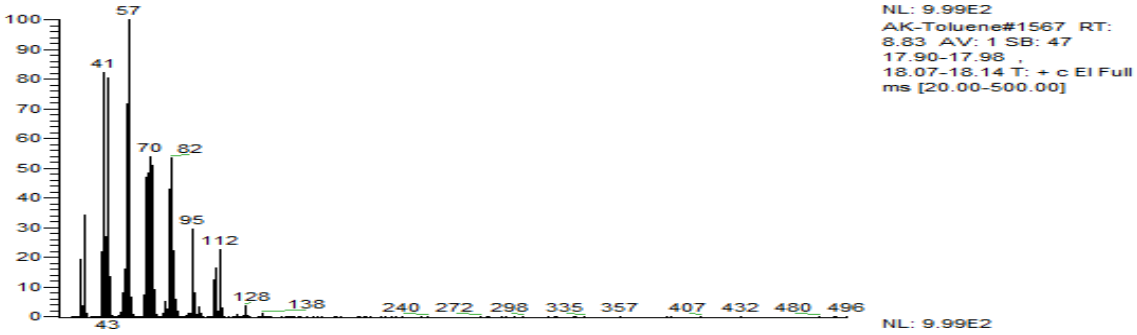
	GC retention time	GCMS retention time
Decanol	4.9	9.7
Decanal	4.1	8.8
Internal slandered	2.4	
Impurity (trans-2-dodecen-1-ol)		16.9
Impurity (trans-2-dodecen-1-ol)		17.5
Impurity (decanoic acid decyl ester)		18.2

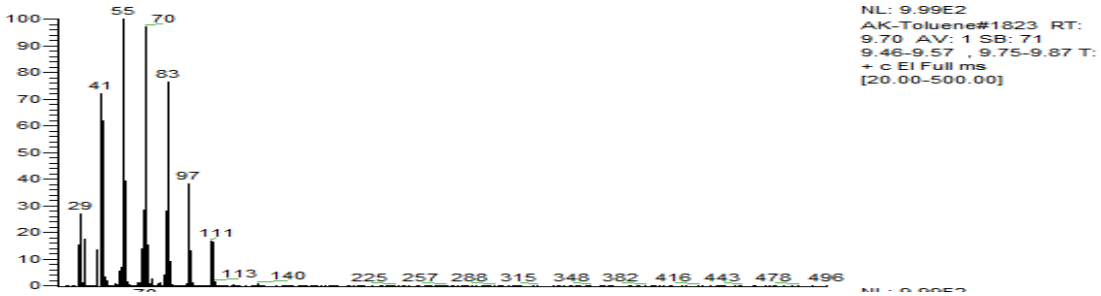


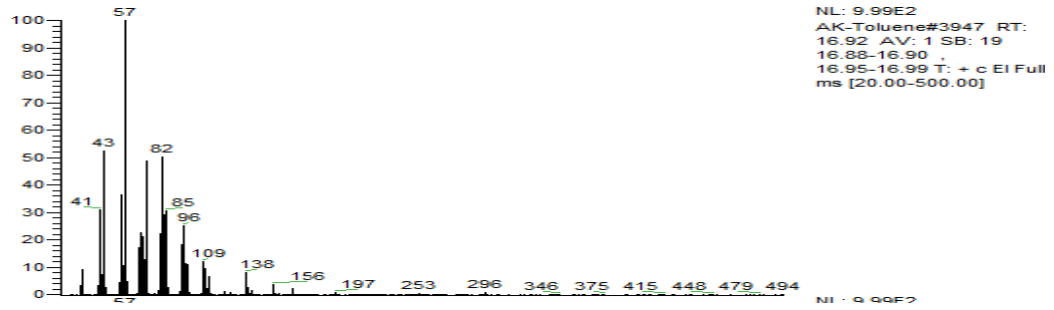
GC spectra of a) Decanol, b) Decanal, and c) Decanol oxidation reaction mixture

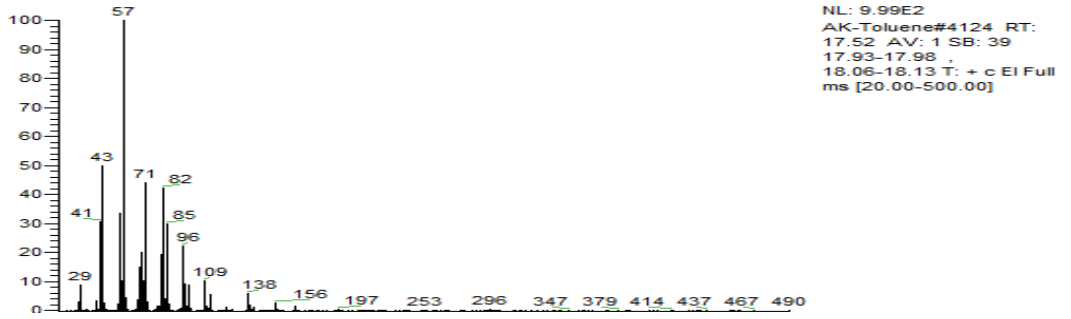
I. GCMS spectra of decanol oxidation reaction mixture

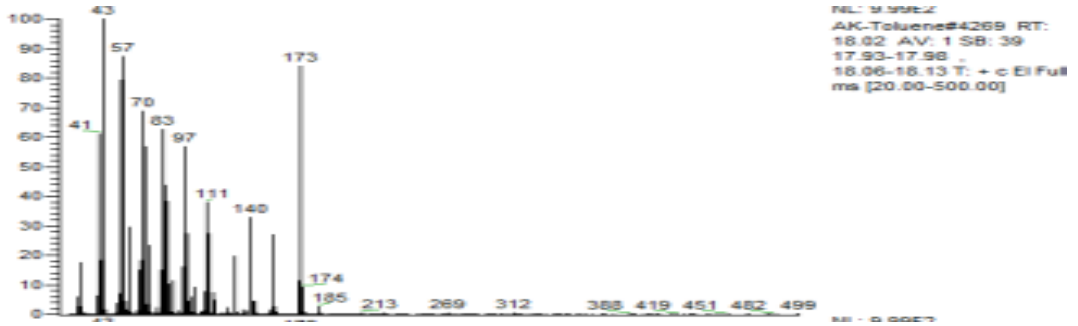






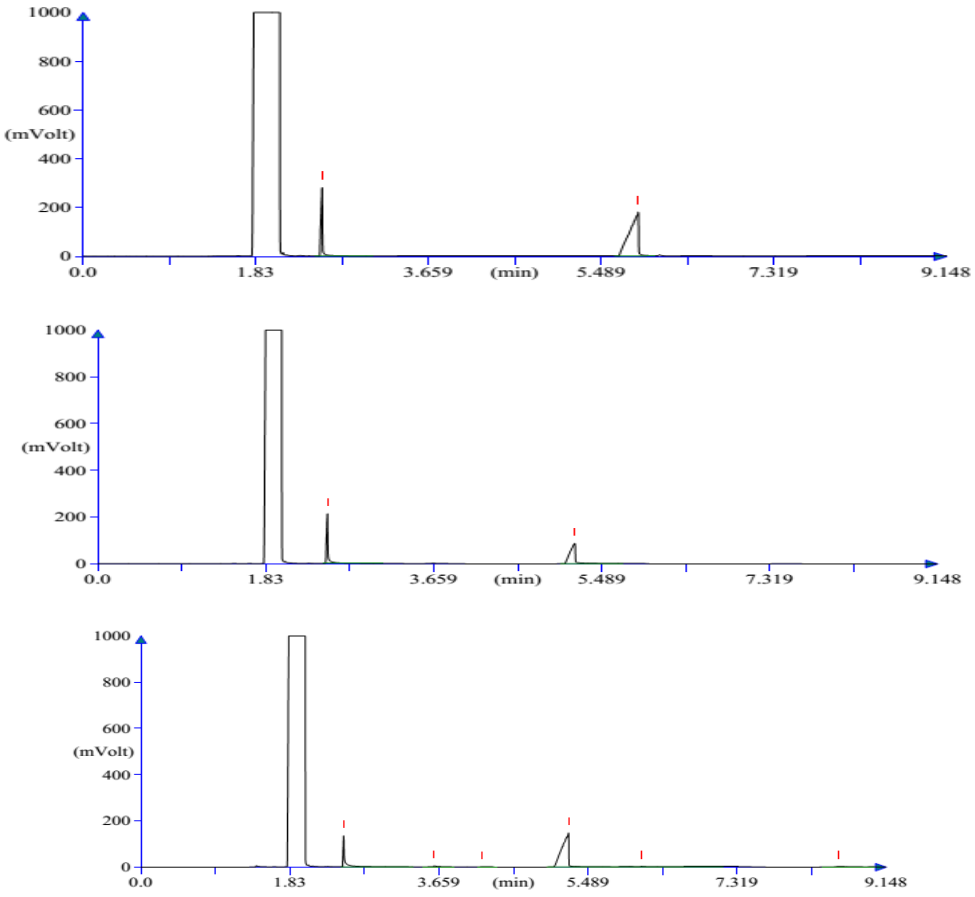






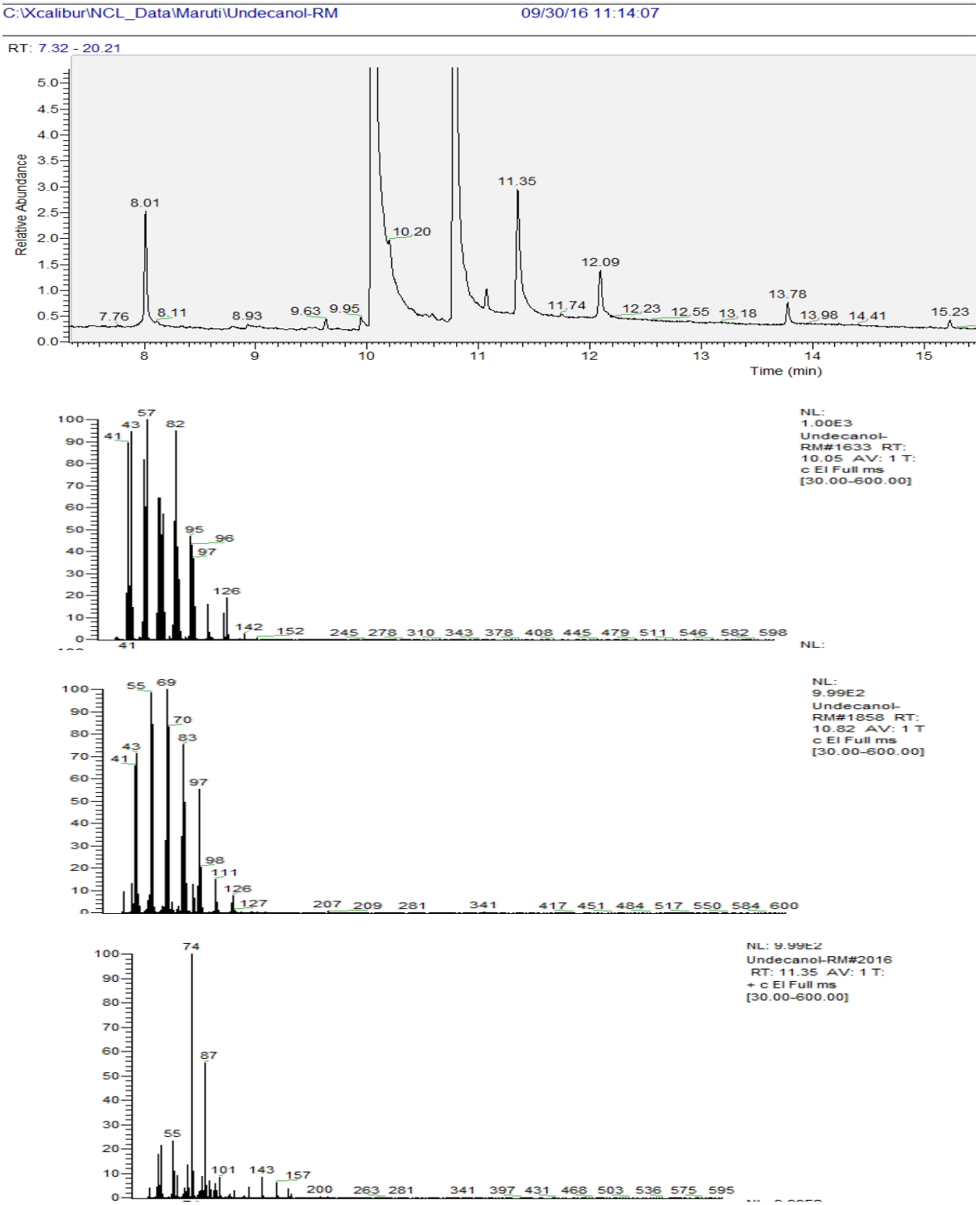
7. Undecanol: GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ºC and hold for 1 min, with ramp 35 ºC/min.

	GC retention time	GCMS retention time
Undecanol	4.1	10.82
Undecanal	5.1	10.05
Impurity (undecanoic acid methyl ester)	6.1	11.35



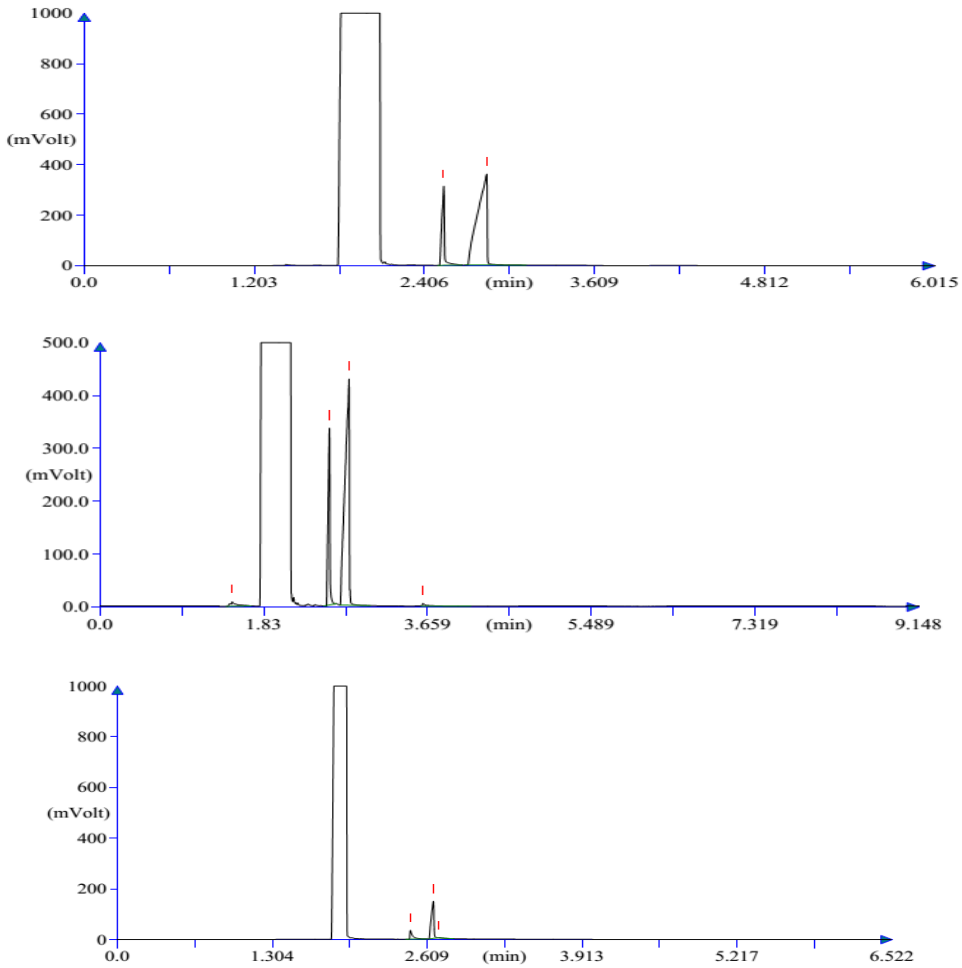
GC spectra of a) Decanol, b) Decanal, and c) Undecanol oxidation reaction mixture

GCMS spectra of Undecanol oxidation reaction mixture



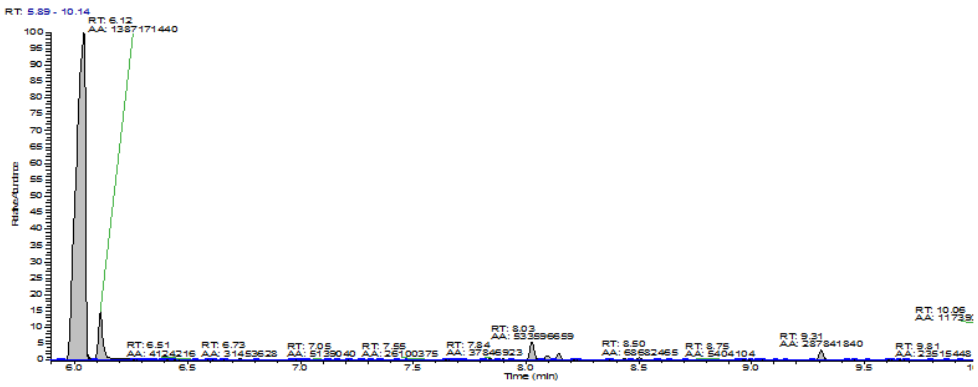
8. **3-Octanol:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ºC and hold for 1 min, with ramp 35 ºC/min.

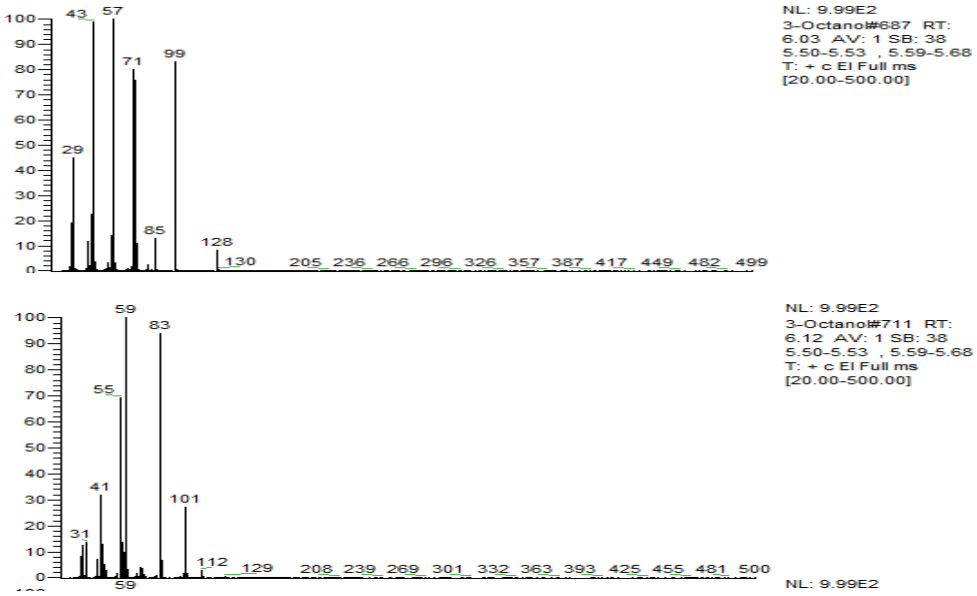
	GC retention time	GCMS retention time
Internal slandered	2.5	
3-Octanol	2.8	6.12
3-Octanone	2.6	6.03



GC spectra of a) 3-Octanol, b)3-Octanone and c) 3-Octanol oxidation reaction mixture

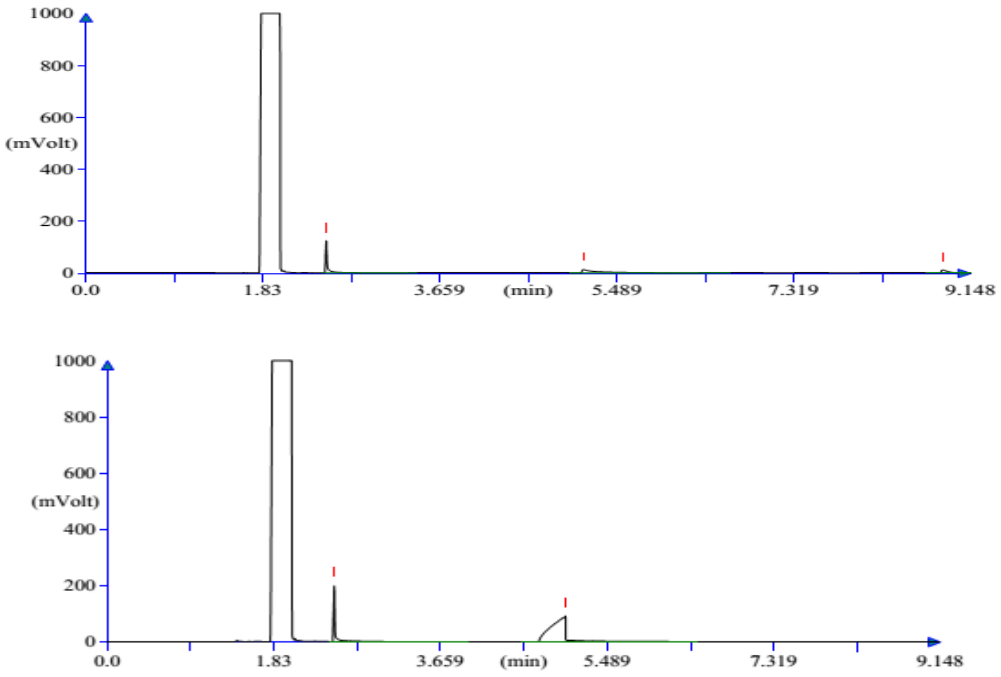
GCMS of 3-octanol oxidation reaction mixture

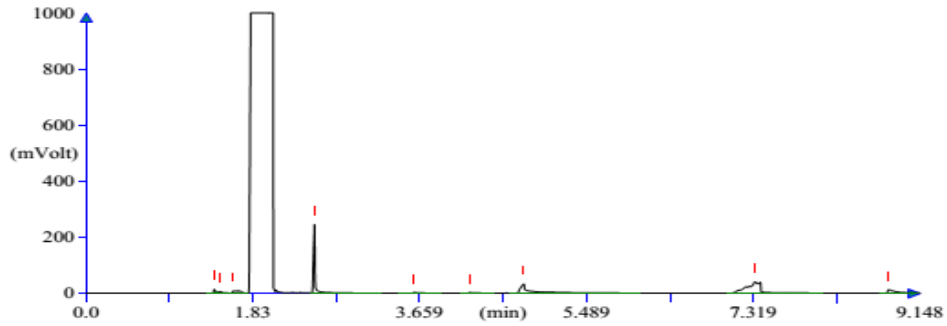




9. **4-methoxybenzyl alcohol:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ºC and hold for 1 min, with ramp 35 ºC/min.

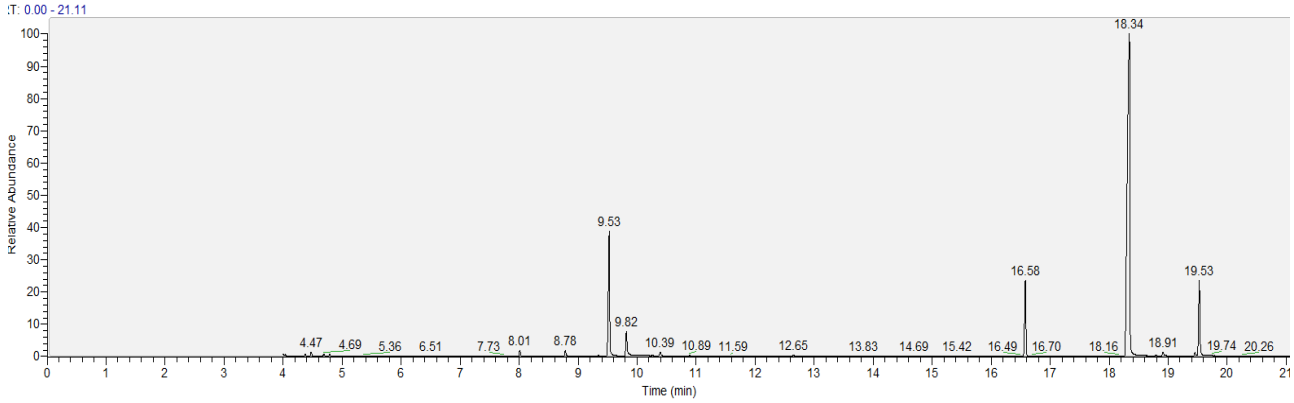
	GC retention time	GCMS retention time
Internal standard	2.4	
4-Methoxybenzyl alcohol	5.1	9.8
4-Methoxybenzeldehyde	5.0	9.5
Impurity(from reactant)	8.8	16.5
Impurity(from reactant)	9.9	18.2, 19.5

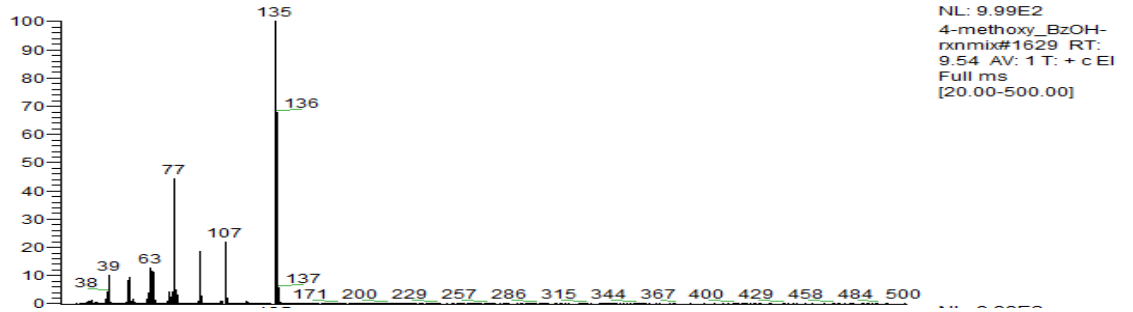


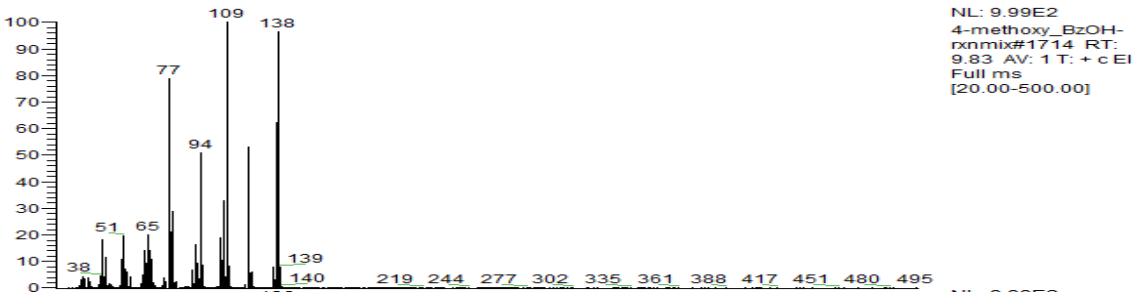


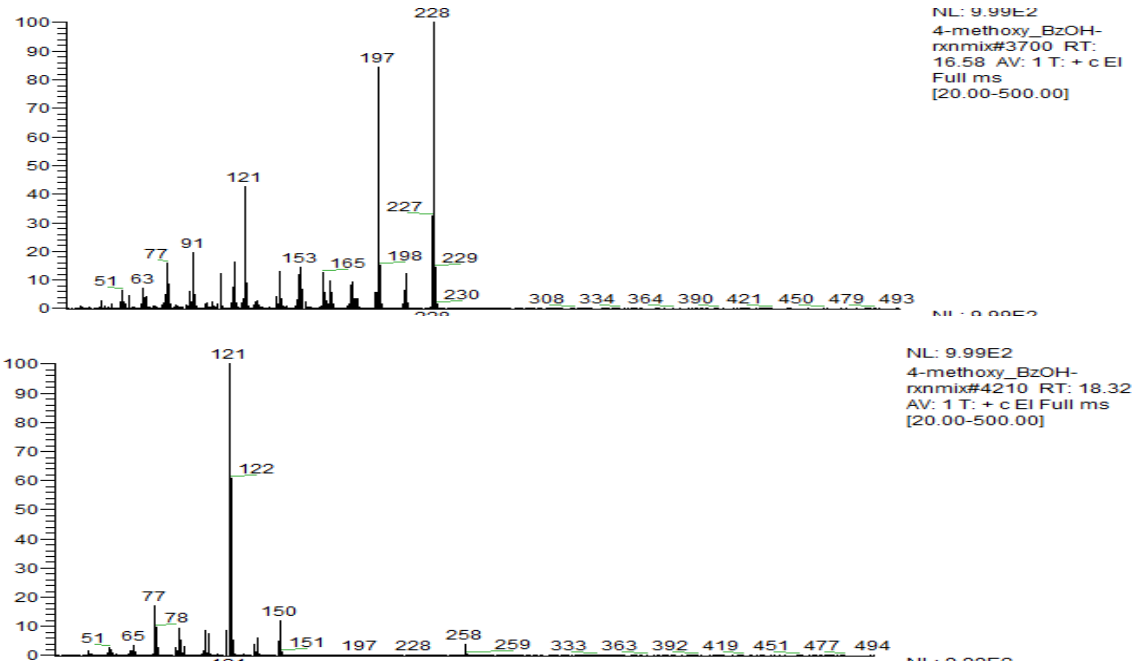
GC spectra of 4-methoxy benzyl alcohol , b) 4-methoxybenzeldehyde and c) 4-methoxy benzyl alcohol oxidation reaction mixture

GCMS of 4-methoxy benzyl alcohol oxidation reaction mixture



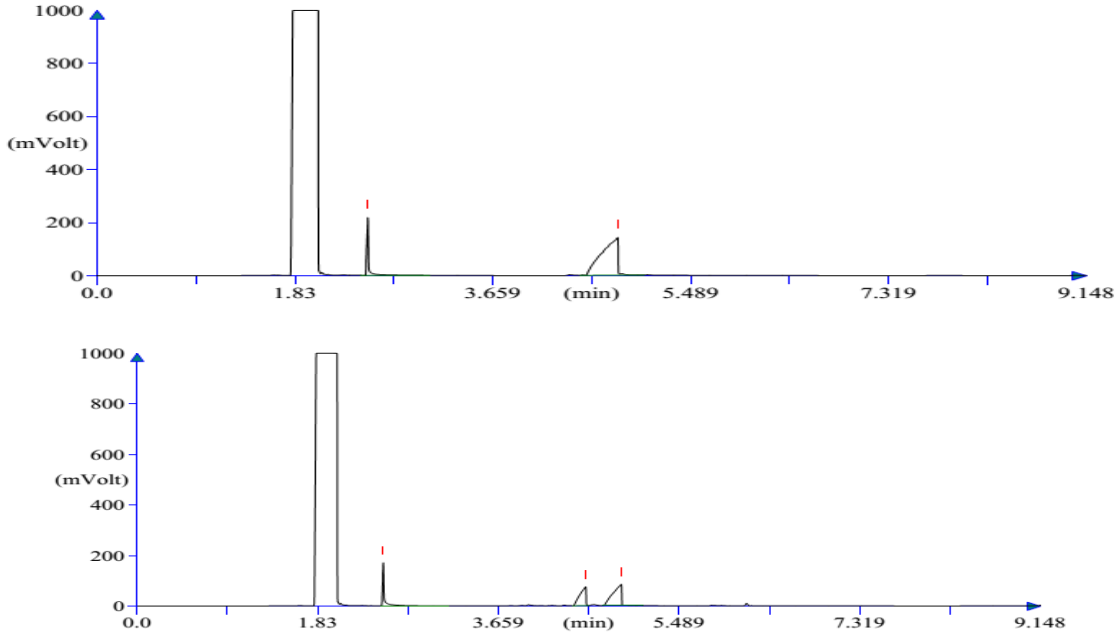


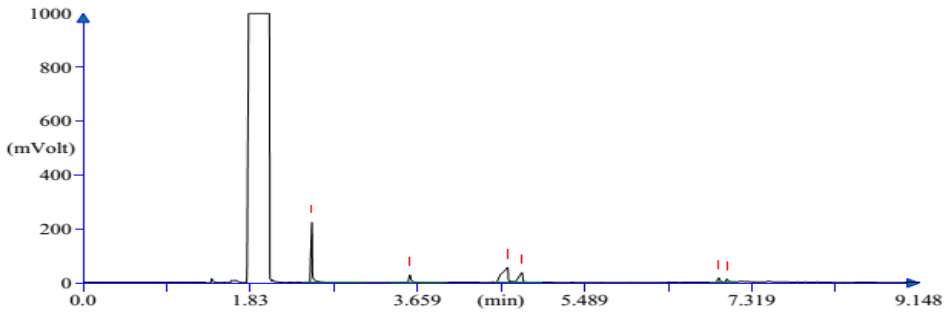




10. Geraniol: GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 30 ºC/min up to 135 ºC temperature, second ramp with 2 ºC/min up to temperature 140 ºC, and finally temperature rose to 250 ºC and hold for 1 min, with ramp 35 ºC/min.

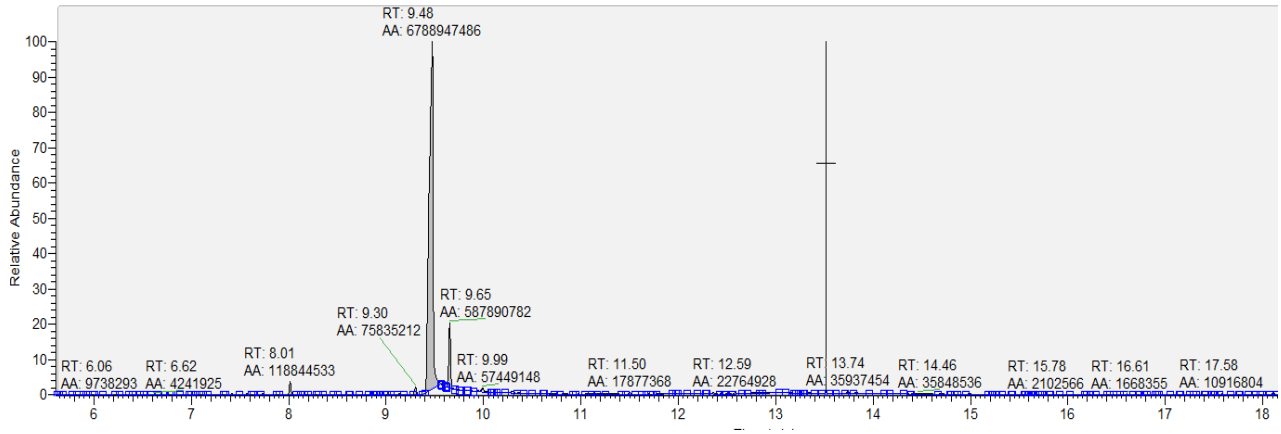
	GC retention time	GCMS retention time
Gereniol	4.8	9.4
Citratl	4.9	9.6
Neral	4.6	9.3
Impurity	6.9	
Impurity	7.0	

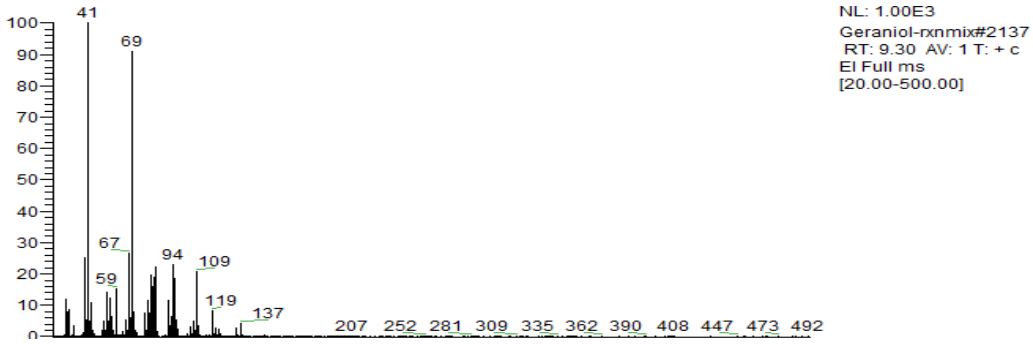


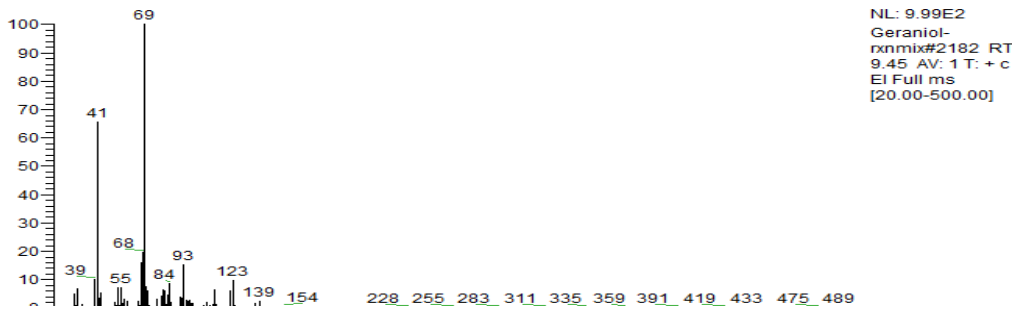


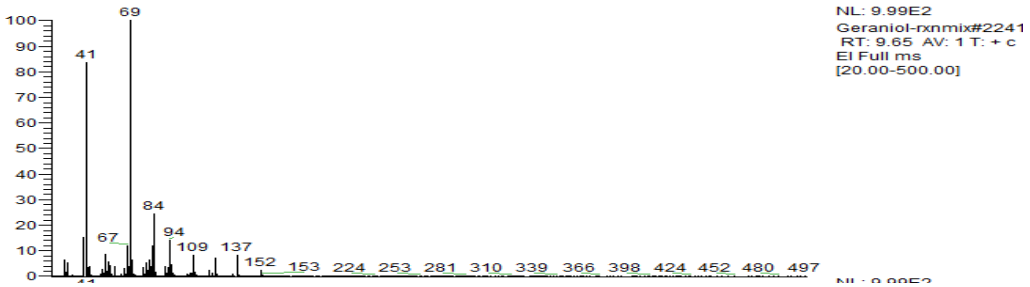
GC spectra of a) Gereniol, b) Gerenial, and c) Gerenioll oxidation reaction mixture

GCMS spectra of geraniol oxidation reaction mixture



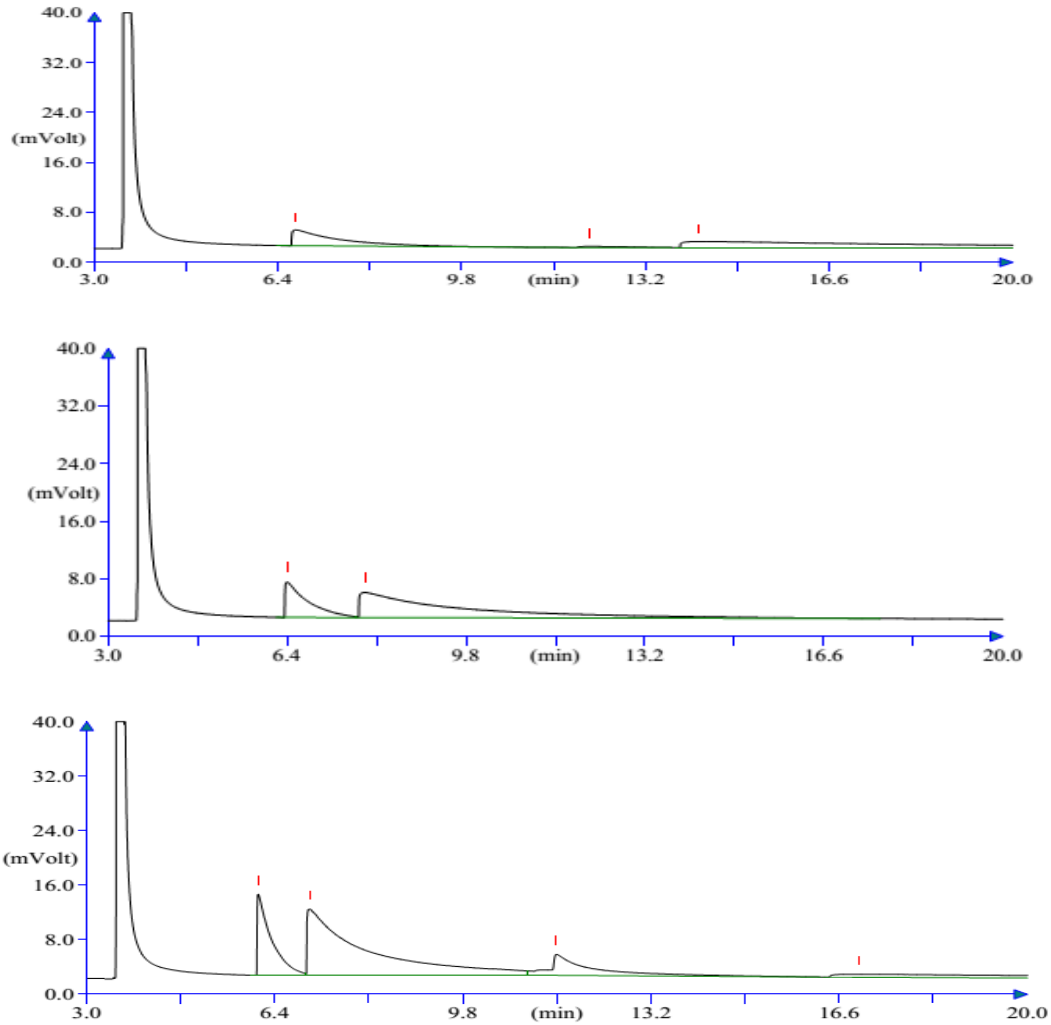






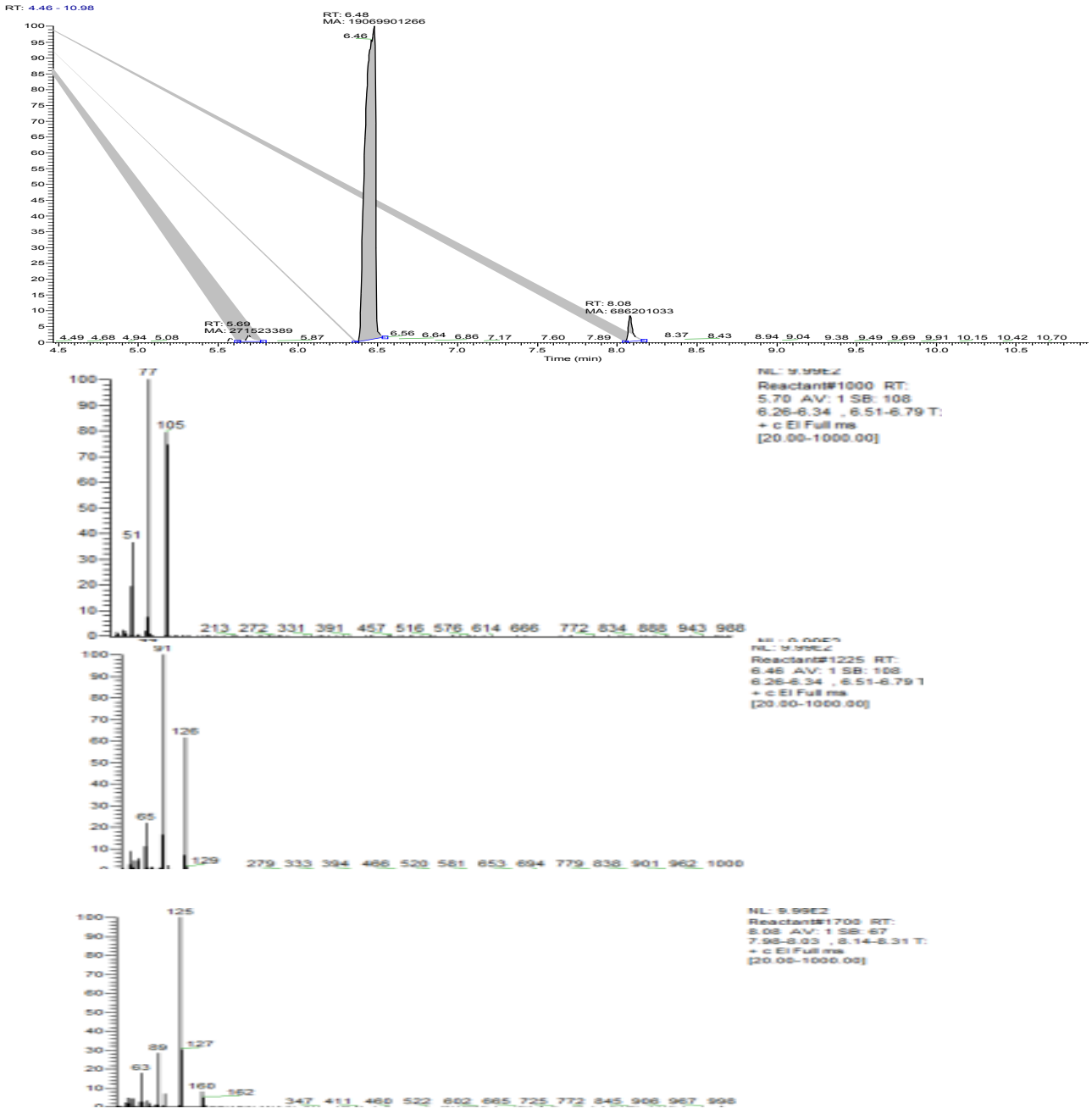
11. Benzyl alcohol: GC method: Initial oven temperature kept 120 ºC and after 15 minutes temperature rose to 250 ºC with ramp 35 ºC/min.

	GC retention time	GCMS retention time
Internal slandered	6. 6	
Benzyl alcohol	14.1	
Benzeldehyde	8.4	5.7
Impurity (from reactant –benzyl chloride)	11.9	6.4
Impurity (benzyl(dichloromethyl)		8.0



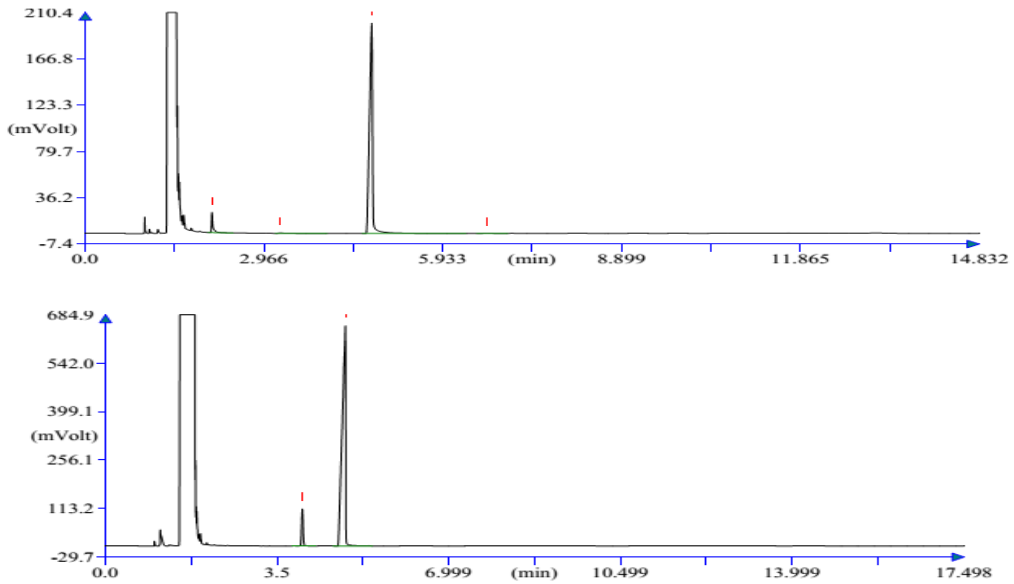
GC spectra of a) Benzyl alcohol, b) Benzeldehyde, and c) Benzyl alcohol oxidation reaction mixture

GCMS of benzyl alcohol oxidation reaction mixture



12. **Bromobenzyl alcohol:** GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 20 ºC/min up to 100 ºC temperature, second ramp with 5 ºC/min up to temperature 135 ºC, and finally temperature rose to 250 ºC and hold for 2 min, with ramp 30 ºC/min.

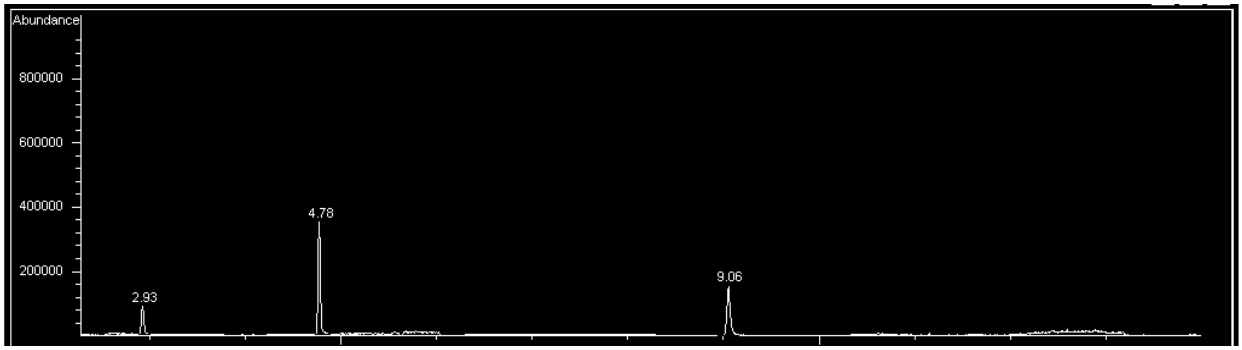
	GC retention time	GCMS retention time
2-Bromobenzzyl alcohol	9.5	9.0
2-Bromobenzeldehyde	4.7	4.7
Internal standard	4.1	

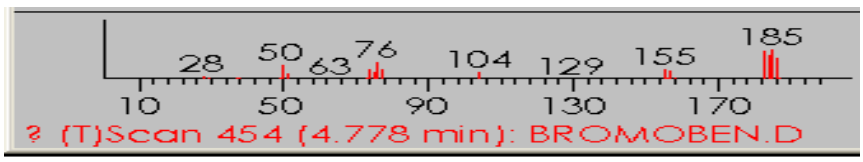


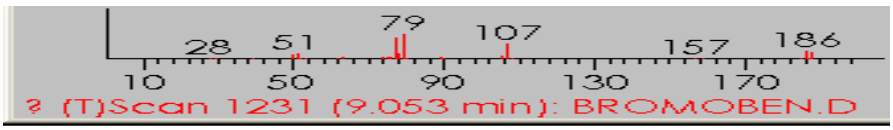
GC spectra of a) 2-Bromobenzyldehyde and b) 2-Bromobenzyl alcohol oxidation reaction mixture

I. GCMS

Wax column with was used for GCMS of this reaction mixture







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Chapter 6

Multistep Flow Synthesis of Isopropyl Phenol

6.1 Introduction

Transformation of the exothermic, multiphase, temperature and selectivity sensitive reaction from batch process to continuous flow synthesis provides a promising technique. It enhances heat & mass transfer, decrease the equipment size, production capacity ratio & energy consumption, with a dramatically decrease in reaction time which is economic. It comes with complete elimination of in-between time and energy consuming laborious isolation and purification steps in case of multistep synthesis A multi-step flow synthesis and purification of Ibuprofen,[1] synthesis of alkaloid natural product oxomaritine,[2] a library of 5-Amino-2-aryl-2*H*-[1,2,3]-triazole-4-carbonitriles,[3] suzuki-miyaura cross coupling reaction,[4] and so many other multistep reactions has been successfully enlarged in flow by academics as well as by industries. Isopropyl phenol is an intermediate for the manufacture of agrochemicals, UV stabilizers, polymerization inhibitors and anti-oxidants etc. It is also used for the production of phosphorus containing plasticizers instead of cresol, as diphenylisopropylphenyl phosphate is less toxic then tricresylphosphate.

6.2 Literature Analysis

Generally isopropyl-phenols are synthesized by either rearrangement of saturated alkylphenylethers or by the selective oxidation of di-isopropylbenzene. In rearrangement approach firstly alkyl phenyl ethers synthesized by reaction of phenol with alkyl bromide in the presence of potassium hydroxide at reflux condition. Rearrangement of this alkylphenylether takes place in sulphuric acid and glacial acetic acid solution which gives ortho as the major product.[5] Second approach oxidation of *p*-di-isopropylbenzene involves two stages,1) liquid phase oxidation of *p*-di-isopropylbenzene to monohydroperoxide by atmospheric oxygen, which follows radical mechanism, followed by 2) acid decomposition of monohydroperoxide into isopropyl phenol in the presence of cation exchange resins. The yield of monohydroperoxide depends on the temperature and rate of distillation. Literature data shows 98% yield at 90 ºC and at a distillation rate of 0.05-0.07 l/hr.[6]

It can also be synthesized by Fe_2O_3 catalyzed rapid oxidation of arylboronic acids in the presence of atmospheric oxygen under solar visible range light irradiation,[7] and via a three step reaction starting from the reduction of nitrocumene followed by diazotization and hydrolysis which involves many separation and purification steps.[8] Highly exothermic nature of a few individual steps, sensitive and reactive intermediates, inbetween separation and

isolation steps and extended reaction time of these reactions raise safety and production concern, especially for the scale-up approach, which has been main outlined asset of flow synthesis.

In this work, isopropylphenol is synthesized in a 4-step continuous flow process with special emphasis on the hydrolysis reaction following a classical approach. Commercially available cumene was chosen as starting material which was nitrated to give nitrocumene followed by reduction, diazotization and hydrolysis with complete elimination of separation and isolation steps. Among these steps, the first three steps are known to be feasible in flow synthesis and a good amount of literature is available in the recent time. For these three reactions, rapid mixing, high interfacial mass transfer rates, excellent temperature control through efficient heat transfer and with adequate residence time, the reactions usually show enhanced yields of the products. However the last step of converting an aniline into a phenol is a classical conversion known as "Phenol-Verkochung". It is a SN1 type reaction of the diazonium salt with water in the presence of concentrated acids at high temperature , which yields respective phenols. Although this reaction is known, here we demonstrate it for the first time in continuous mode under highly acidic conditions. This reaction needs excess water under boiling conditions. The reaction should have relatively higher activation energy as even in the acidic environment, phenol formation happens in a short time only close to boiling conditions.

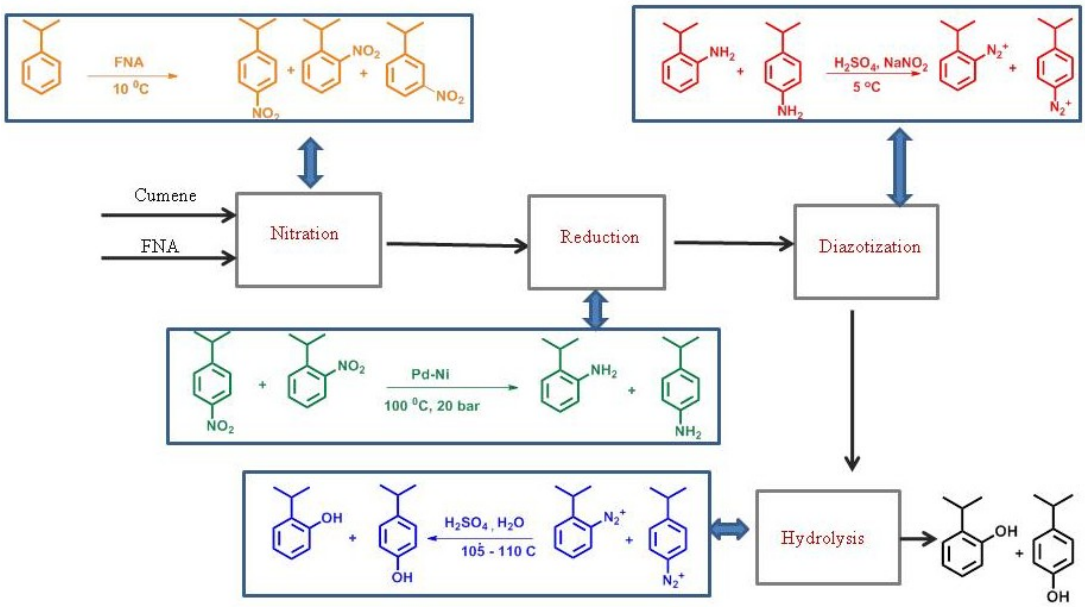


Figure 6. 1: Isopropylphenol synthesis from cumene via multistep approach involving 1) Nitration,2) Reduction, 3) Diazotization and 4) Hydrolysis

6.3 Experiment

6.3.1 SOP for preparing continuous flow setup and experiments

For making a continuous flow set up, first and most important step is to choose a chemistry (reactant, reagent, product, intermediate, solvents etc.) compatible material. During assembling a setup, teflon tape should be warped around the threads of female fitting and all fittings should be tighten enough to prevent leakage, over tightening may harm thread and cause leakage. Leakage check is necessity before performing any experiment to prevent any misshaping, it can be done by passing water at high flow rate, or for gaseous phase reaction, setup can be placed in water and can be done by passing air.

For making multiple outlet setup, volume of each section should be known and calculation of flow rates and residence time will be based on cumulative volume of reactor. Residence time of each section will be calculated on the basis of volume of the section and cumulative flow rate. Sample collection should be done after reaching steady state, which nearly takes twice of residence time, and it should be quenched immediately. Volume of collected sample (reactant) should be constant while collection time may vary with changing flow rates or residence time.

6.3.2 Nitration of cumene: The first step of this approach was nitration of cumene, and the experimental set-up for it consisted of two syringe pumps (Holmarc Optomechatronics, India), loaded with one stainless steel syringe (SS316 syringe of 50 ml volume) containing nitric acid, and a PTFE syringe containing cumene as shown in the Schematic 2. These syringes were connected to SS316 tubes (1/8" o.d.) which were further connected to AMaR1 micromixer (Amar Equipment Pvt. Ltd., India) followed by a residence time section made of a 1/8" helical coil. The entire assembly had four outlets (one immediately after the micromixer and remaining along the length at equal distance.) connected to needle valves for sampling. The reactor assembly was immersed in a constant temperature bath (ME12, Julabo Gmbh, Germany) to maintain the system at the isothermal condition. The flow rates of both reactants and nitric acid were varied to achieve the desired mole ratio as well as the residence time. Known quantity of samples were collected at the different outlets (corresponding to different residence times), in a fixed quantity of ice-cold-water. A known quantity of toluene (Merck Life Science Pvt. Ltd.) was used to extract the organic phase from these samples. The extracted organic phase was washed thrice with water followed by brine and separated by gravity. Trace quantity of water was removed by passing the organic phase through a bed of anhydrous sodium sulphate. Products were confirmed by GCMS and NMR and samples were

analyzed using gas chromatography with an HP5 capillary column and FID detector. Nitrobenzene was used as an internal standard. 19% 2-nitrocumene, 1% 3-nitrocumene and 60% 4-nitrocumene was obtained with > 99% conversion.

6.3.3 Reduction of nitrocumene: Nitrocumene mixture from nitration step was further diluted with toluene and directly used for reduction without any isomer separation steps. H-cube® (ThalesNano GmBH, Austria) with different catalyst Re-Ni and Pd/Ni was used with temperature range of 40 to 100 °C and pressure range of 10 to 50 bar. Internal volume of the catalyst cartridge was 0.3 mL. The nitro-derivatives of cumene were passed through the H-cube® at flow rates over a range of 0.2 mL/min and 2 mL and samples were collected for each experiment. These samples were directly analyzed using GC with HP-5 column and a FID detector. Nitrobenzene was used as internal standard. The analysis showed that the outlet stream contained 15.35% 2-cumidine and 59.73% 4-cumidine (yield are on the basis of cumene).

6.3.4 Diazotization of cumidine: The cumidines collected at the outlet of the reduction step in H-cube were dissolved in toluene. The solution was subsequently converted into hydronium salt by treatment with HCl and water, for which a continuous stirred reactor (also known as CSTR or mixed flow reactor) was used. This hydronium salt is completely soluble in water, and aqueous phase was separated by gravity. Peristaltic pump was used to flow this aqueous phase containing hydronium salt to react with 1.2 equivalent $NaNO_2$ (10%) solution for which syringe pumps with PFE syringe was used. This reaction was carried out at 5 ºC for which constant temperature bath was used. 100% diazotization in 113 seconds was confirmed on titration with β-naphthol.

6.3.5 Hydrolysis of diazonium salt: Diazonium salt from previous step (113 s residence time) was directlty fed to another CSTR placed in a continous microwave oven operated at 210 W, 2.45 GHz (Ragatech Pvt. Ltd. India),, at a the flow rate of 2.35 mL/min (resedence time ~ 4 – 13.4 min depending upon volume of CSTR). HCl was used to provide acidic media for hydrolysis at high temperature. Collected sample was extracted using toluene. Organic layer was separated by gravity. After trice water wash followed by brine wash, sample was directly submitted to GC analysis with HP-5 column and FID detector. On using 16 mol sulfuric acid 5% 2-isopropyl with 4% isopropylphenol was obtained in PFR, while on using 2

mol of HCl in microwave 57.7% 4-isopropyl was achieved with 2% 2-isopropylphenol (yields on the basis of cumene). NMR and GCMS were used for product conformation.

6.4 Analysis

Final products of nitration, reduction, and hydrolysis reactions were analyzed using GC, GCMS and NMR. NMR was done using Bruker AV200 MHz and AV400 MHz, NMR spectrometer in CDCl3 solvent, and GC analysis for nitration and hydrolysis was done with HP-5 capillary column with FID detector, while for analysis of reduction step was done using carbowax column. Formation of diazonium salt was analyzed by titration with *β*–naphthol.

a) 2-nitrocumene, 3-nitrocumene and 4-nitrocumene
b) 2-cumidine, 3-cumidine and 4-cumidine
c) Diazonium salt
d) 2-isopropylphenol and 4-isopropylphenol

Analytical data has been shown at the end of this chapter, before references.

6.5 Result and discussion:

Commercially available cumene was chosen as starting material for the multistep flow synthesis of isopropyl phenyl, for which first step is nitration and fuming nitric acid was chosen as nitrating reagent as greener reagent by avoiding use of sulfuric acid[19]. Methyl group in cumene is o/p directing and gives more para-isomer and negligible amount of meta-isomer. The o:p isomer ratio depends on nitrating agent and solvent. Initially, nitration reactions were performed with 1 mole of nitric acid in residence time range of 2.64-10 min, maximum 38% conversion was achieved in residence time of 10 min (see Figure 1). In order to get complete conversion 2 moles of fuming nitric acid was used at 30 ^{0}C and 40 ^{0}C temperature, at both temperatures it gave 65% yield, which clearly shows that nitrating reagent is limiting reagent for this reaction. On using larger quantities of the fuming nitric acid (4 moles) at these temperatures resulted in very rapid reaction and exceedingly rapid heat generation rates. Even the outlet stream was dark in color with several impurities getting formed. Hence further experiments were carried out at lower temperatures (0 ^{0}C and 10 ^{0}C). On using 4 moles of fuming nitric acid 99.6% conversion was achieved with the mononitro mass composition of 19.5%, 1% and 79% for 2-nitrocumene, 3- nitrocumene and 4-nitrocumene, respectively in

residence of 6.4 minutes at 10 ^{0}C. Rest of the mass was impurities. Complete conversion was achieved in 8.5 min. at 0 ^{0}C with almost identical outlet composition. Reaction was quenched inline using ice-cold water and continuous toluene was added to this for extraction of organic compound from aqueous phase.

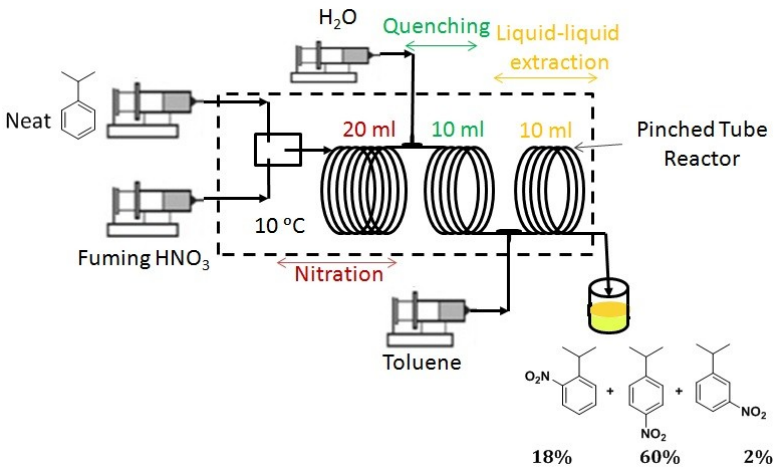


Figure 6. 2: Schematic of cumene nitration followed by in-line quenching and separation

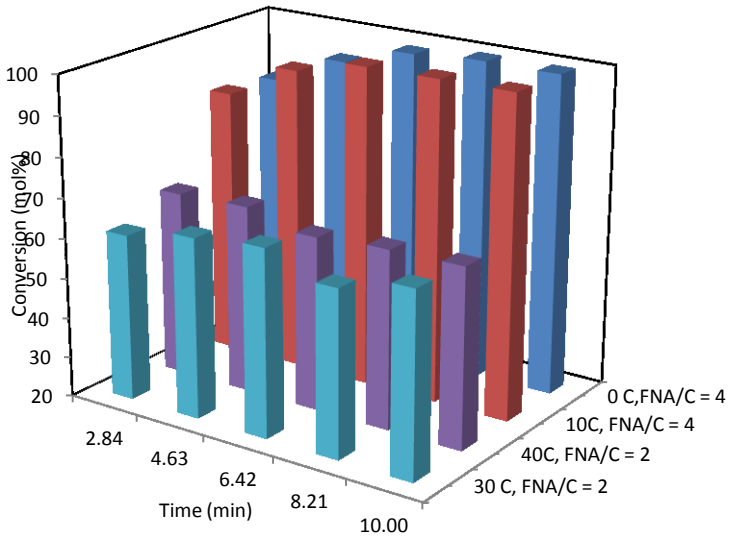


Figure 6. 3: Influene of temperature and residence on conversion of cumene

Higher mass transfer rates for liquid-liquid extraction were achieved using a pinched tube (of 36 mL). Toluene layer containing nitro derivatives was then continuously separated by liquid-liquid separator. The organic stream was subjected to continuous reduction.

Extracted nitrocumene solution exhibits concentration of 0.642 M. First reduction experiment using H-cube® was carried out using Re-Ni catalyst at 100 ^{0}C and at 40 bar with solution of same molarity. However no conversion was achieved at this condition due to much smaller catalyst quantity when compared to the substrate concentration. In view of this nitrocumene solution was diluted to 0.1068 M and 0.0222 M using a suitable solvent and catalytic hydrogenation was carried out at the conditions mentioned before. This resulted in only 10% and 13.83% yield at 40 bar pressure indicating that the catalyst was inappropriate for reduction of nitrocumene and hence for all further experiments Pd-Ni (100mg) was used as the catalyst[20]. Nitrocumene solution (0.018 M) was subjected for its reduction with Pd-Ni catalyst over a temperature range of 40 to 100 ^{0}C and pressure range of 10 to 50 bar with flow rate of 0.2 mL/min. At 100 °C and 40 bar pressure, 76.8% yield was achieved with 16.7% 2-cumidine and 58.6% 4-cumidine. Rest of the components was the reduced forms of impurities from the nitration stage.

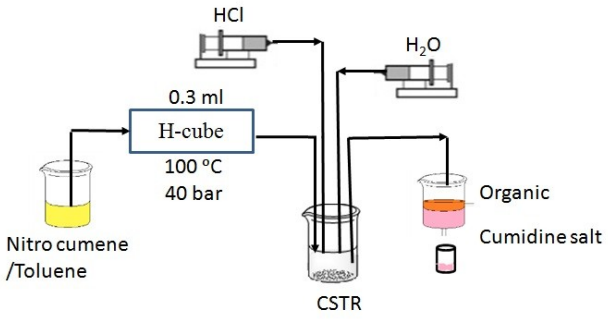


Figure 6. 4: Schematic of nitrocumene reduction using H-cube followed by cumidine salt generation using CSTR

Without any further separation or isolation steps this cumidine mixture was treated with HCl and water to generate hydronium ion in a CSTR. HCl was continuously added with the help of a syringe pump that generated toluene insoluble hydronium ion. Water was also continuously added to dissolve this ionic salt. At room temperature, 30 min residence time was found be sufficient for dissolution. Subsequently, the hydronium ion containing aqueous phase and organic phase separated using a gravity settler. This hydronium ion was treated with 1.2 equivalents $NaNO_2$ (10%). Since the diazonium salt is very unstable intermediate and it decomposes at temperature above 5 ^{0}C or it may go under coupling reaction, reaction time plays an important role. Reaction was carried out in a residence time range of 30 to 120 s at 0

^{0}C. 100% diazotization was achieved with a residence time of 110 s, which was later confirmed via coupling with β-naphthol.

Table 6. 1: Reduction of nitrocumene mixture dissolved in toluene, with flow rate of 0.2 mL/min except in case of 0.642 molar solution, it's 0.3 mL/min. Yields are estimated on the basis of nitrocumene. (H-cube catalyst cartridge: *Re-Ni, ** Pd-Ni)

Nitrocumene (mol/L)	Temp. (°C)	P (bar)	Cumidine isomer		% yield
			2	4	
0.642*	100	40	-	-	-
0.107*		40	4.50	5.88	10.39
		60	1.72	2.72	4.44
0.0445*		20	3.48	4.87	8.35
		40	4.85	6.27	11.12
0.0222*		20	3.27	4.61	7.88
		40	5.79	8.03	13.83
		50	3.42	5.71	9.13
0.01836**	40	20	1.0	7.3	8.43
	60	20	6.6	32.7	39.70
	80	10	9.6	43.5	53.52
		20	13.7	53.1	67.45
	100	10	13.7	53.0	67.32
		20	16.4	58.3	75.35
		30	16.3	58.6	75.62
		40	16.7	59.4	76.79
		50	16.7	58.6	76.02

On hydrolysis at higher temperature, diazonium salts give corresponding phenols. It is known that this hydrolysis follows first order kinetics with water being in far excess only the concentration of diazonium salt governs the rate of reaction. Following this aspect, the mixture of diazonium salts of 2-cumidine and 4-cumidine from the previous steps were directly injected to a tubular reactor (of 9.5 mL volume) having multiple outlets corresponds to

different residence times. This set-up was immerged in constant temperature bath to provide isothermal conditions. Since the reaction is facilitated only at higher temperatures, experiments were carried out at 70 ^{0}C, 80 ^{0}C and 90 ^{0}C. However the maximum yield was only 10% implying that either it needs stronger acidic media or higher temperature or both together along with enhanced interfacial mass transfer between the aqueous and the organic phases. Hence the next set of experiments carried out using sulfuric acid. On using 16 moles of H_2SO_4 at 80 ^{0}C in a residence time of 4.2 min, the highest yield was 39% (see Table 2 section Tubular reactor). Longer residence time resulted in significant loss in the yield due to phenol decomposition. Since this is a two-phase reaction, interfacial mass transfer was enhanced by using a pinched tube PFR reactor which gives better yields than normal PFR.

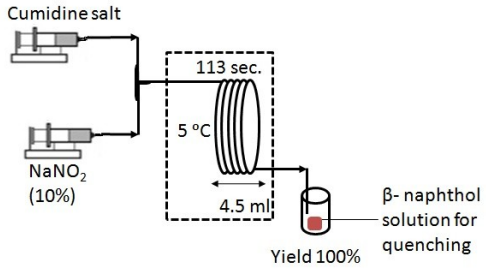


Figure 6. 5: Diazotization of cumidine salt

This approach using sulfuric acid led to generation of water vapors containing nitrophenols. This could be avoided to some extent by using lower number of moles of H_2SO_4 and higher temperature in further experiments. Moreover to avoid the volume of expansion due to evaporation, further experiments were carried out in a continuous stirred tank reactor (CSTR) rather than in a tubular reactor. Hence all further experiments were carried out in a CSTR attached to a condenser was used which helped to release the vapor from the reaction mass and its condensation to at steady state without affecting the residence time.

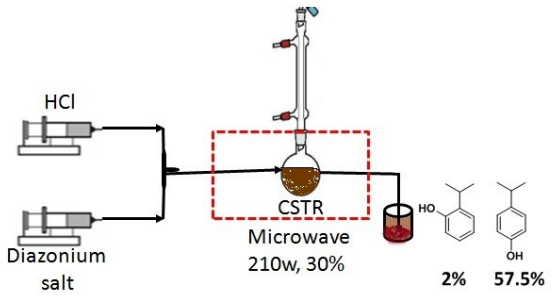


Figure 6. 6: Hydrolysis of diazonium salt

Table 6. 2: Hydrolysis of diazonium salt (yields on the basis of diazonium salt. # Pinched tube tubular reactor, *H_2SO_4 catalyst**,** **HCl catalyst, For the cases without added catalyst, the HCl used in the preparation of diazonium salt got carried forward for hydrolysis reaction.)

	Temp. °C	Catalyst mole	Residence time (min)	Selectivity (%)		Overall yield %
				2-IPP	4-IPP	
Tubular reactor in circulating bath	70	-	4	8.43	0.98	2.5
	80	-	4	11.32	2.6	4.4
	90	-	4	22.84	7.2	10.3
	60	8*	6	5.51	1.91	7.4
	60	16*	6	11.64	0.85	12.5
	70	16*	6	16.15	2.09	18.3
	80	16*	4	32.76	6.27	39.0
	80	16*	9	21.86	3.51	25.4
	70#	-	15	11.36	34.9	30.2
Microwave	140w, 20%	-	7	10.53	31.16	41.7
	210w, 30%	-	13	15.82	39.56	55.4
	240w, 35%	-	13	14.98	29.9	44.9
	210w, 30%	0.8**	13	10.9	47.1	58.0
	210w, 30%	2**	13	3.3	58.4	61.7

In order to achieve rapid heating under stirring the conventional method of circulation of heating fluid through jacket was insufficient to achieve rapid heating when compared to reaction rates, a CSTR without any jacket was used and placed inside a microwave oven with inbuilt magnetic stirring, having inlet and outlet ports and a condenser to condense the

condensable vapors and release non-condensable gases. This also helped to achieve a localized heating in a much shorter time. Initial continuous microwave experiments at 140 W power with 7 minutes residence time resulted in a total 41.7% yield of the phenols (see Table 2, section microwave). At 210 W the yield increased to 55.4%, however at 240 W the yield decreased to 44.9%. Despite circulating ice cold water brown fumes of isopropyl phenol were visible at the outlet of the condenser. Sulfuric acid being a very strong hydrolyzing agent, controlling the reaction rates under rapid heating was relatively difficult. In order to control the rate of hydrolysis further experiments were carried out using 2 mol HCl at 210 W power, which resulted in 61.7% yield with 3.3% 2-isopropylphenol and 58.4% 4-isopropylphenol in 13 minute residence time. This yield of 4-isopropylphenol is close to the observations in the literature. In order to avoid any spark inside the reactor, it was necessary to ensure that no charring happens and no carbon deposition takes place on the surface of reactor or connecting joints. Further increase in residence time or microwave power resulted in rapid generation of brown fumes and lower yield of the phenols. Hence the abovementioned conditions (210 W power, 13 min residence time with 2 mol HCl) were considered as optimum for this step.

Upon integrating the hydrolysis step with the previous steps of continuous nitration, hydrogenation and diazotization, the analysis of reaction mass showed 2% yield of 2-isopropylphenol and 57.9% yield of 4-isopropylphenol. For the isolation of the phenolic isomers, we used column chromatography using 10% ethyl acetate/petroleum ether and also crystallization using methanol/hexane (1:1) mixture. In crystallization protocol, almost quantitative yield of 4-isopropylphenol (melting point 59–60 ºC) was obtained with 2-isopropylphenol remaining in the liquid (melting point ~ 12–16 ºC). Upon further recrystallization, 4-isopropylphenol was isolated in pure form with 52.3% yield.

The purpose of this work was to not only demonstrate the telescopic 4-step integration of flow synthesis of isopropyl phenols but to also show that the classical approach of transforming an aniline to a phenol still works and can be improved through synergy of flow synthesis and microwave heating. More such examples can be shown where overall reaction time of 21 hours in batch for all 4 steps can be reduced by at least 25 times with no intermittent isolation stages.

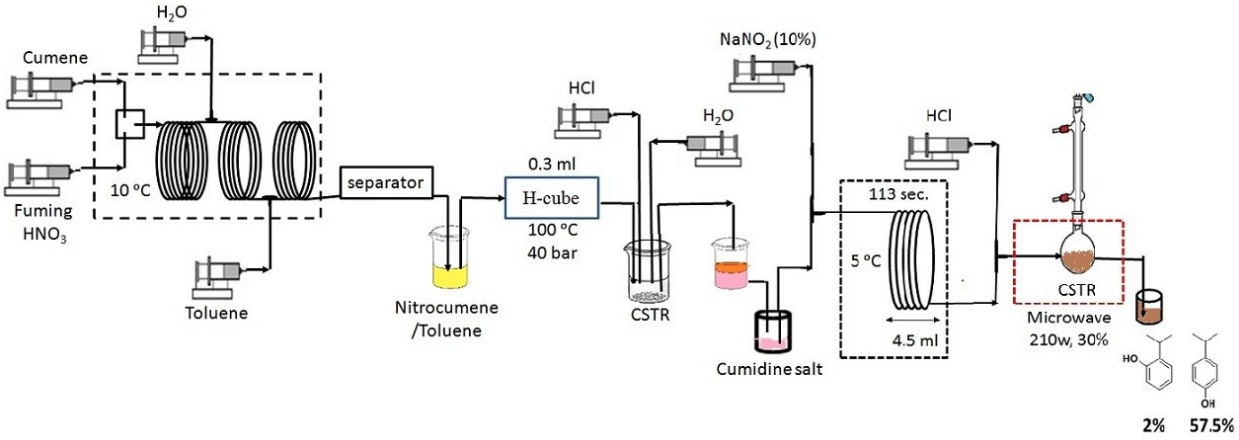


Figure 6. 7: Integrated multistep flow synthesis of isopropylphenol

Table 6. 3: Number of experiments performed

	Batch experiments	Continuous flow experiments
Cumene nitration	4	38
Nitrocumene reduction	4	17
Diazotization	3	5
Hydrolysis	5	13

6.6 Conclusion:

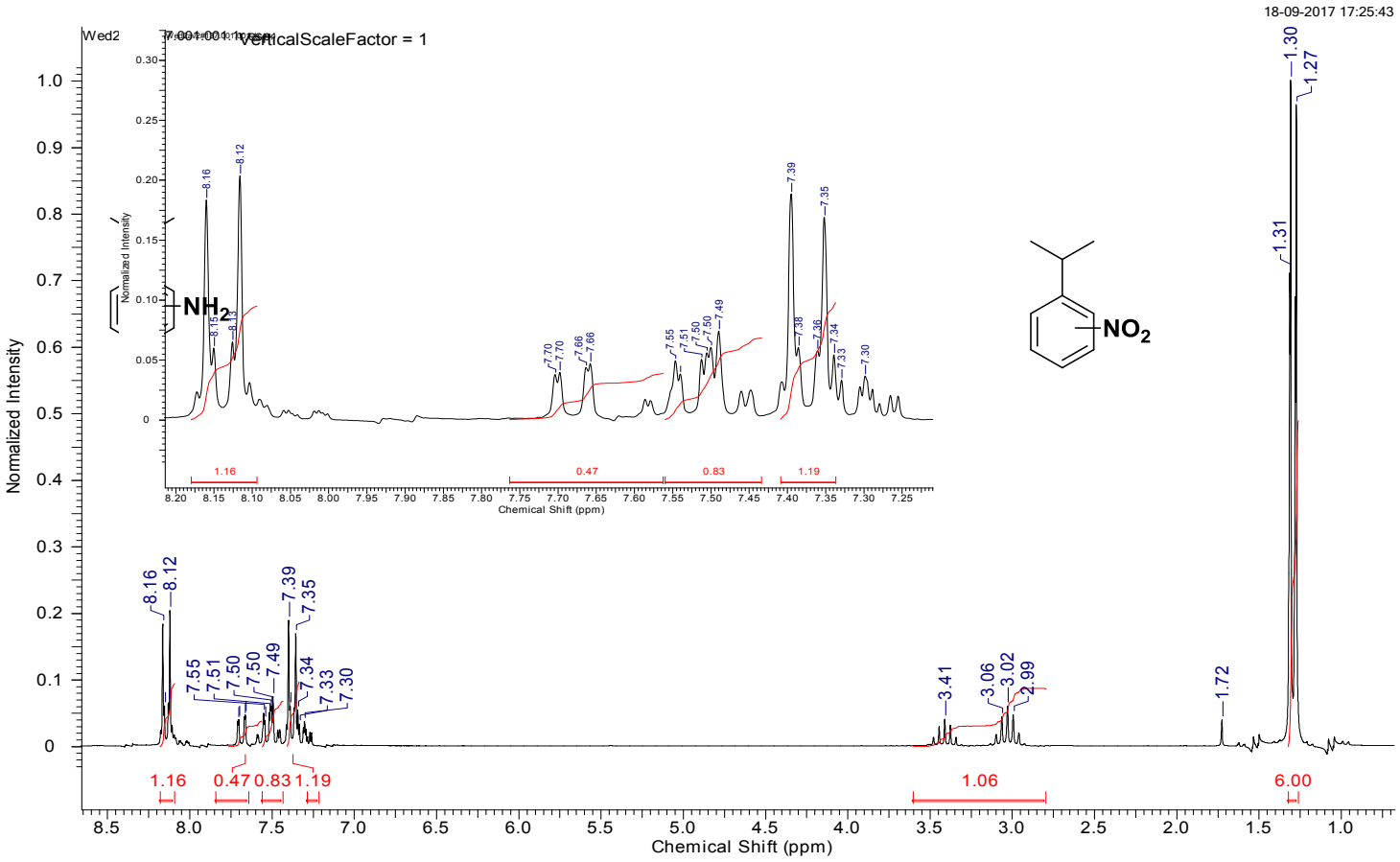
4-step integrated continuous flow synthesis of isopropylphenol has been established with reduction of overall process time from several hours to 50 min with complete elimination of any intermittent isolation, separation, and purification steps. The sequence of reactions includes exothermic reactions like nitration and hydrogenation, temperature sensitive and unstable diazonium intermediate and endothermic continuous hydrolysis. The last stage of hydrolysis follows the classical approach of reacting diazonium salt with water under strong acidic and at boiling conditions. The entire sequence of stages covers a very wide range of experimental conditions with the final stage under microwave to achieve rapid heating. The reaction sequence followed cumene nitration with fuming nitric acid that gives 2 and 4-nitrocumene, which gives respective cumidines upon reduction using H-cube with Pd/Ni catalyst. Upon diazotization of mixture of cumidines in acidic environment followed by high temperature continuous hydrolysis in a microwave gives 2-isopropyl phenol and 4-isopropyl phenol with complete elimination of intermittent separation, isolation and purification steps. The yield of 4-isopropylphenol after purification was 52.3%. The hydrolysis step was seen to

be extremely sensitive to acidic environment as well as microwave power and hence should be optimized for individual anilines separately. The approach can be used for the synthesis of other useful substrates leading to important pharmaceutical or agrochemical intermediates.

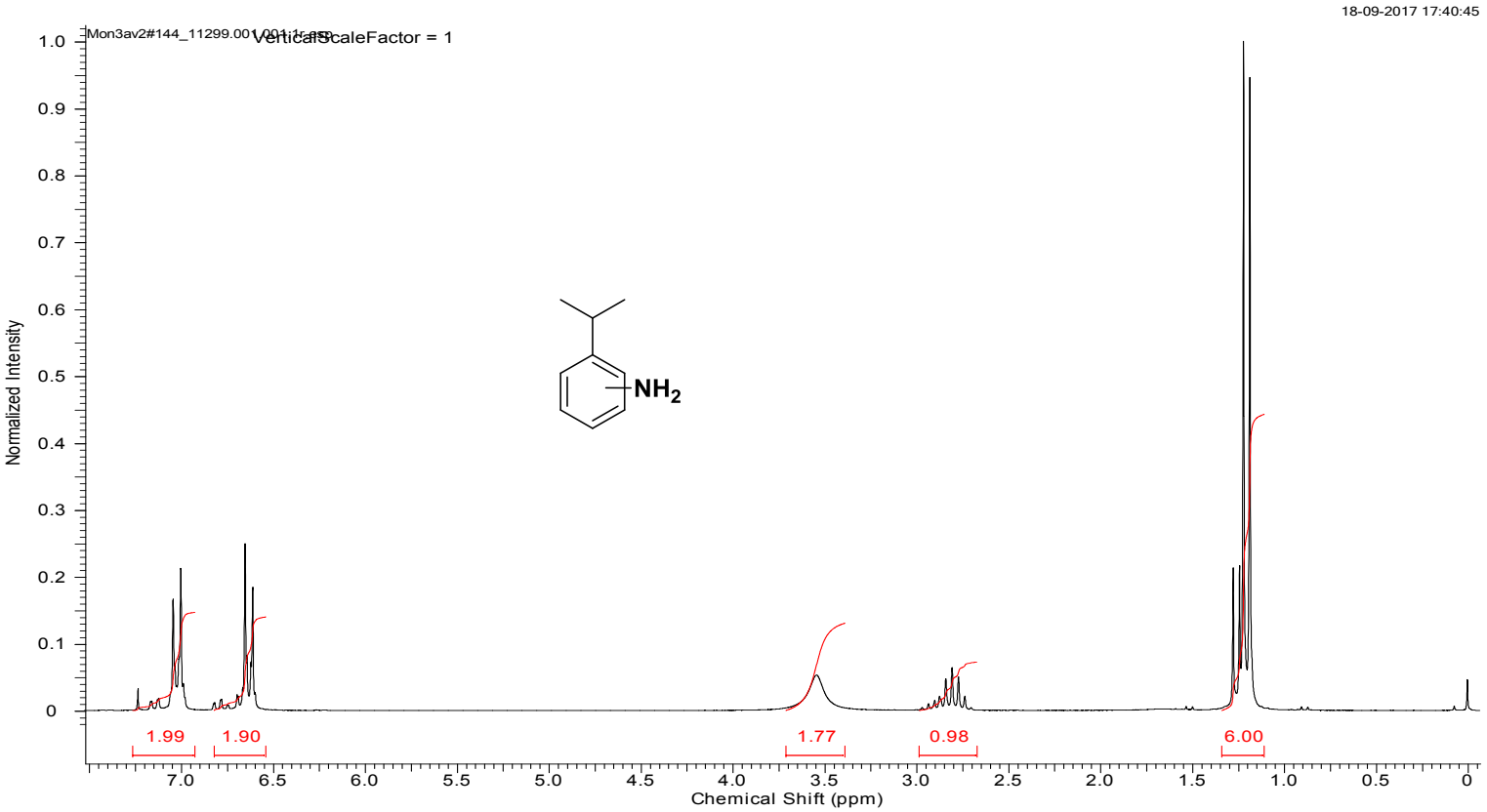
Analysis

NMR

1. Nitrocumene

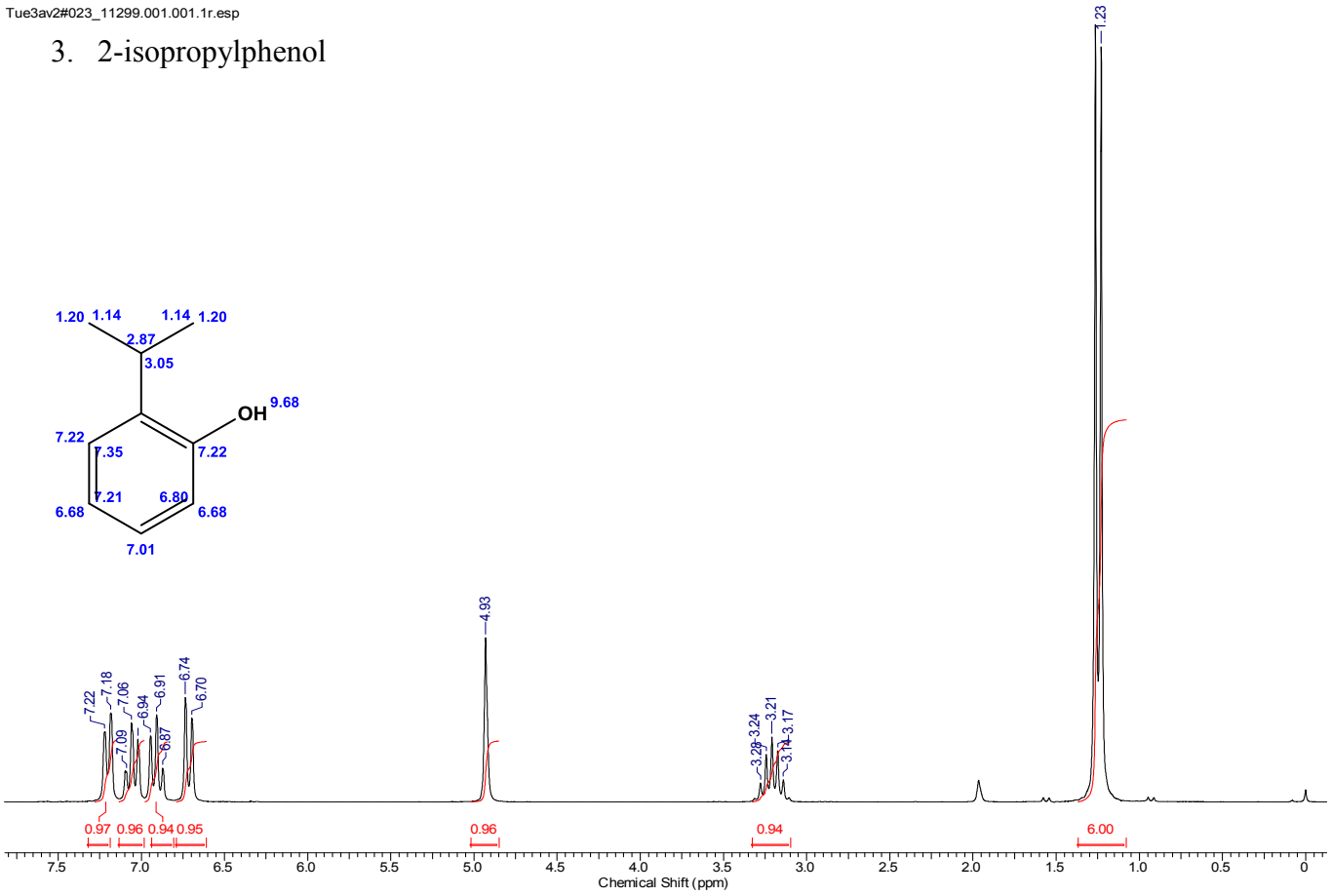


2. Cumidine

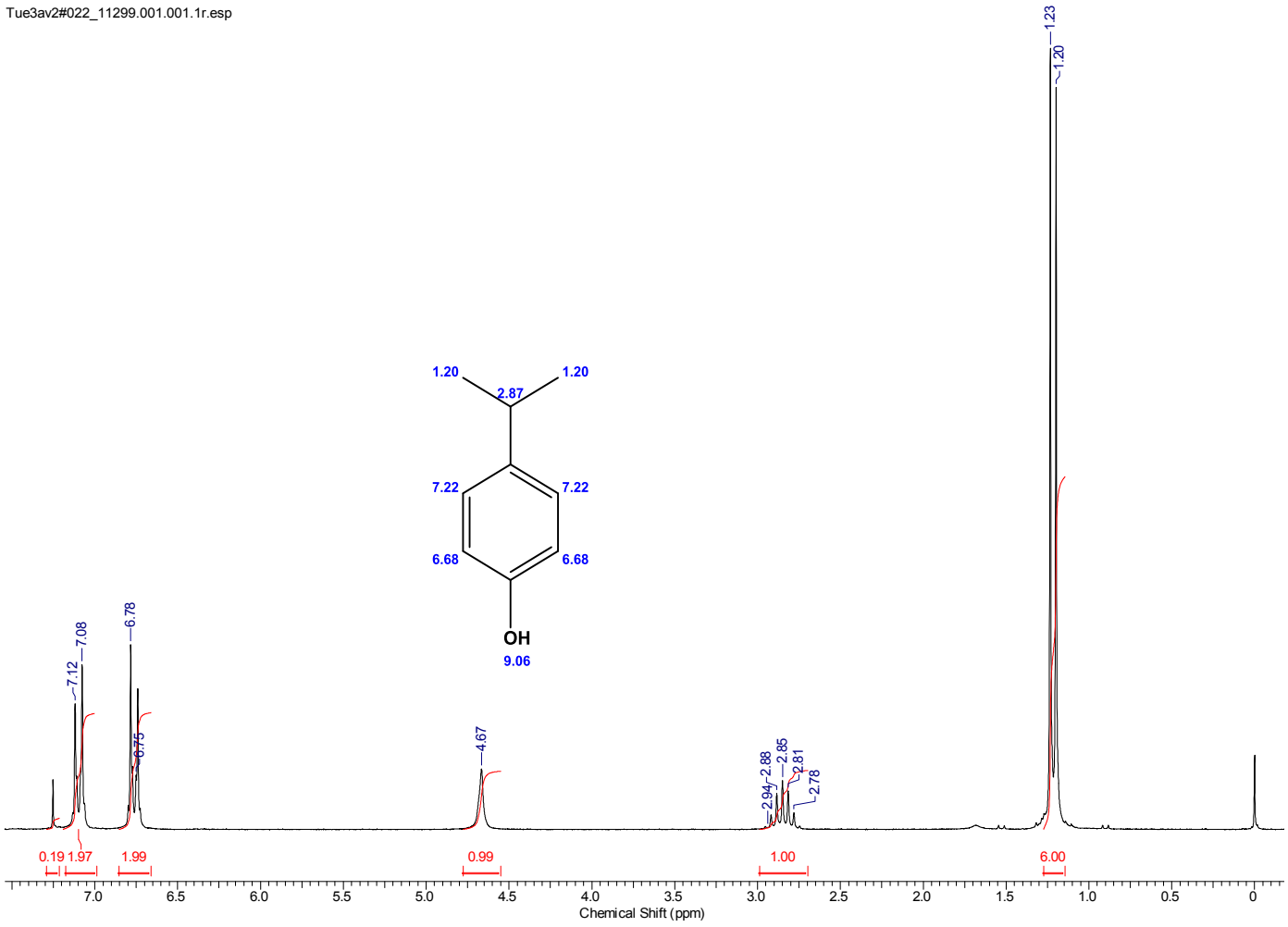

18-09-2017 17:40:45
VerticalScaleFactor = 1
Normalized Intensity
Chemical Shift (ppm)
NH2
1.99
1.90
1.77
0.98
6.00

Tue3av2#023_11299.001.001.1r.esp

3. 2-isopropylphenol



4. 4-isopropylphenol

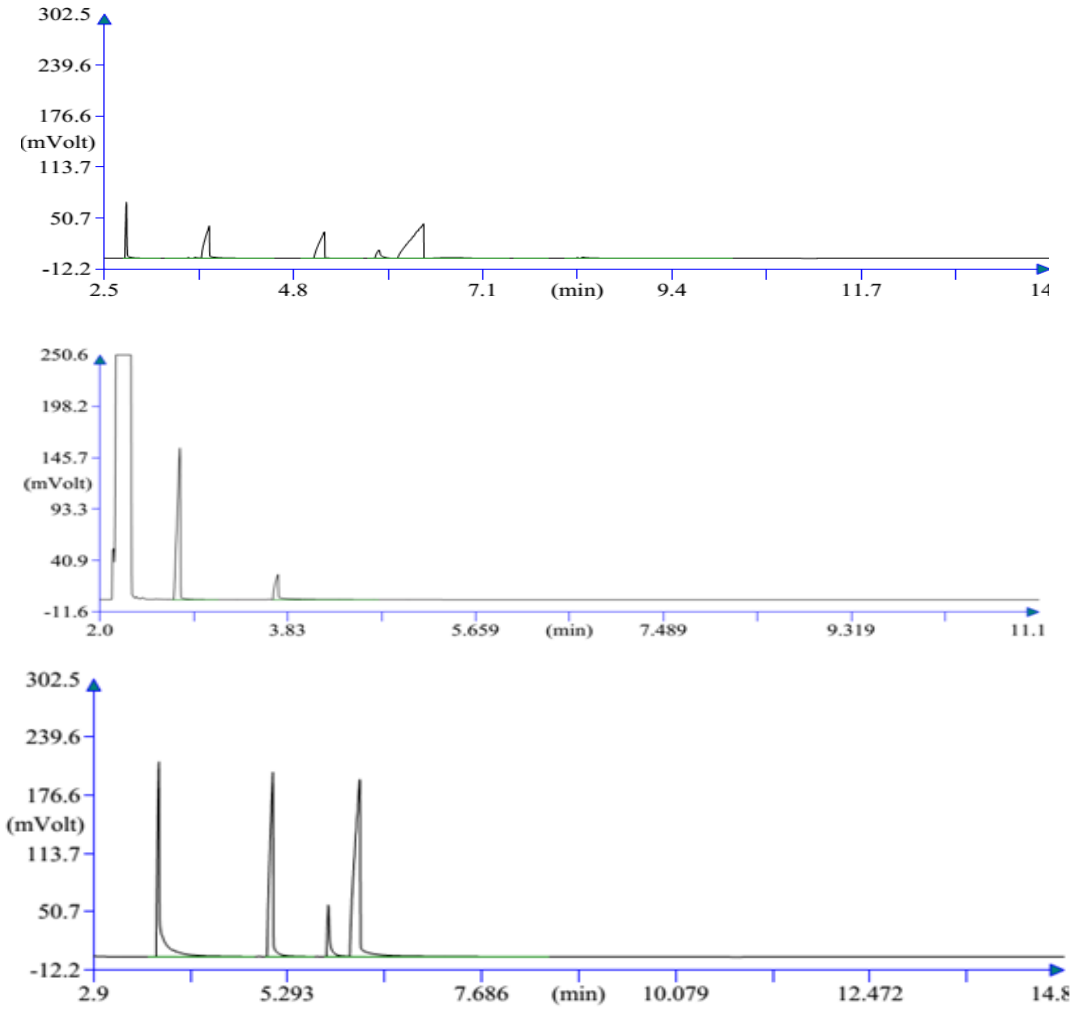


GC and GC-MS

1. Cumene nitration:

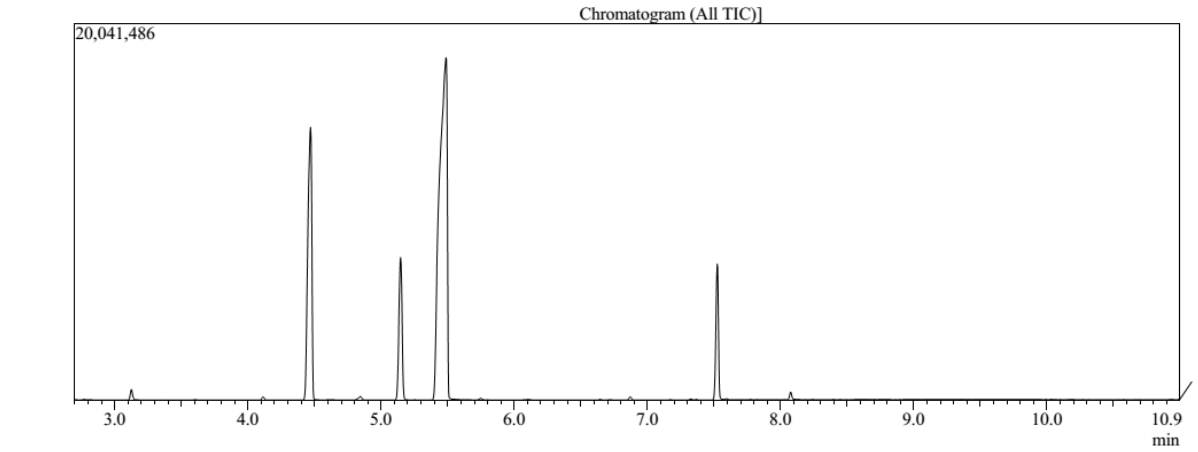
GC method: Initial oven temperature kept 80 ºC and temperature rise with the ramp 40 ºC/min up to 130 ºC temperature, second ramp with 10 ºC/min up to temperature 180 ºC, and finally temperature rose to 250 ºC and hold for 3 min, with ramp 40 ºC/min.

	GC retention time	GCMS retention time
Internal standard	3.70	
Cumene	2.78	
2-Nitrocumene	5.11	4.47
3-Nitrocumene	5.79	5.14
4-Nitrocumene	6.18	5.47



GC spectra of a) reaction mixture b) cumene, and c) 2, 3 and 4-nitrocumene

GCMS



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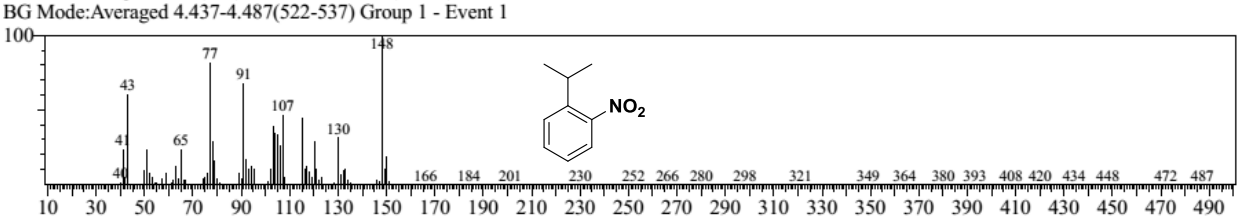
BG Mode:Averaged 4.437-4.487(522-537) Group 1 - Event 1



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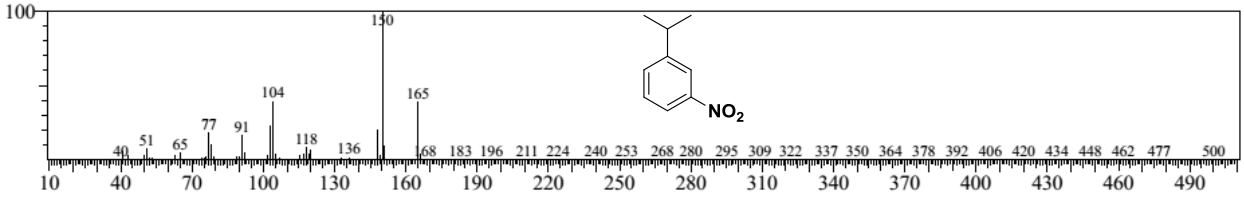
BG Mode:Averaged 5.123-5.163(728-740) Group 1 - Event 1



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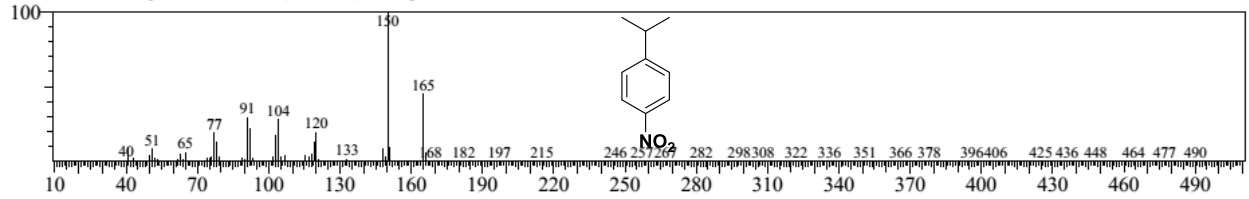

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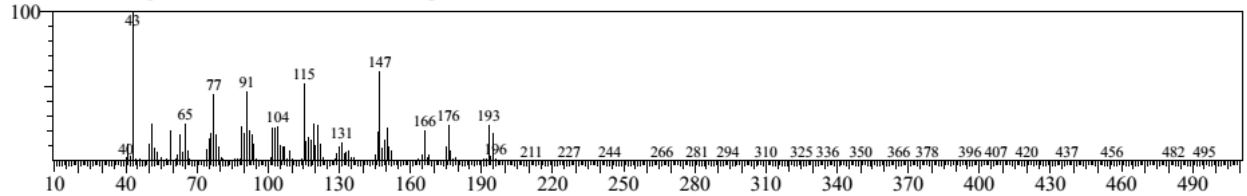
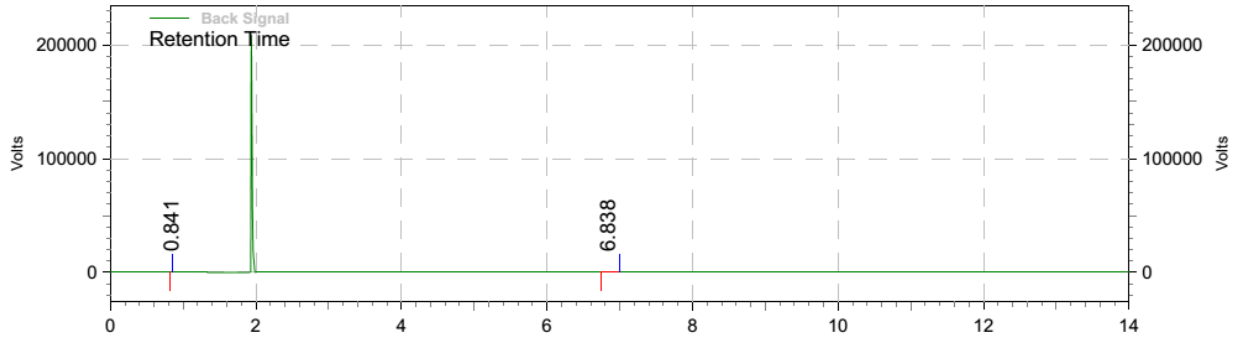
BG Mode:Averaged 7.503-7.540(1442-1453) Group 1 - Event 1



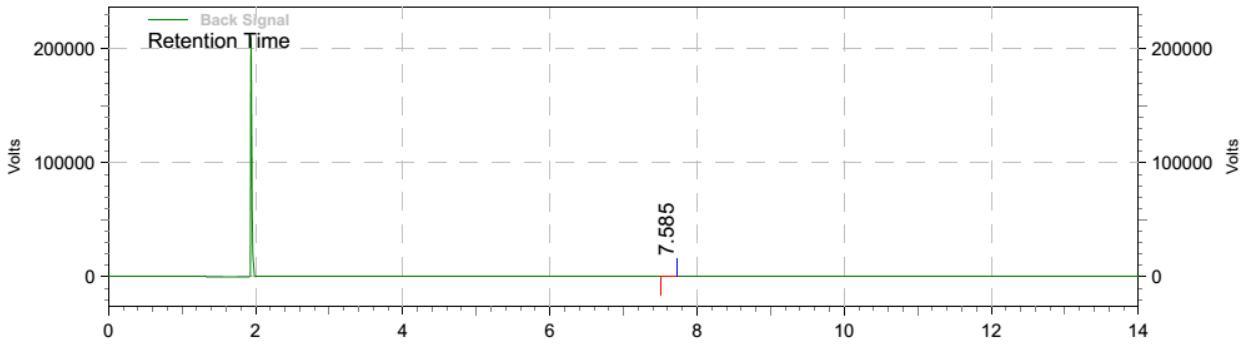
2. Reduction of nitrocumene:

GC method: Carbo-wax column was used for this analysis. Initial oven temperature kept 100 ºC and temperature rise with the ramp 20 ºC/min up to 160 ºC temperature, second ramp with 10 ^{0}C/min up to temperature 200 ^{0}C, and finally temperature rose to 220 ºC and hold for 0 min, with ramp 20 ºC/min.

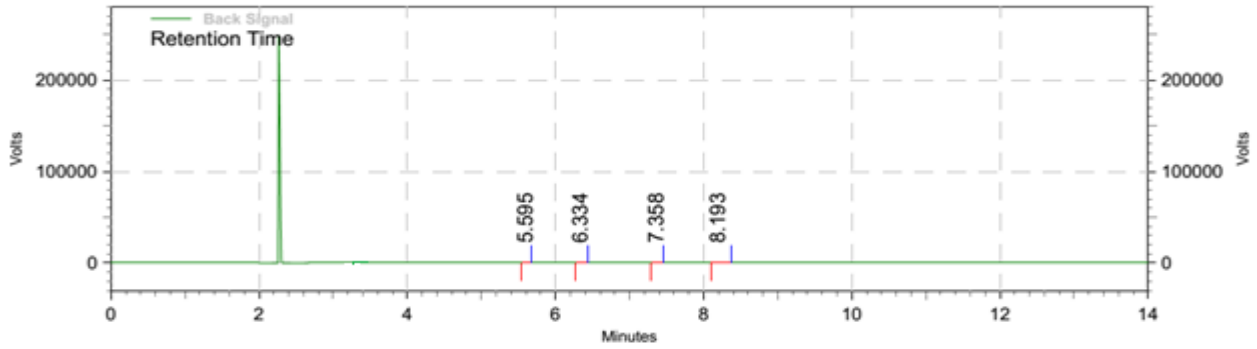
	GC retention time	GCMS retention time
Internal standard (*o*-xylene)	5.59	
2-Nitrocumene	6.33	
3-Nitrocumene	7.35	
4-Nitrocumene	8.19	
2-Cumidine	6.83	
3-Cumidine	7.56	
4-Cumidine	7.58	



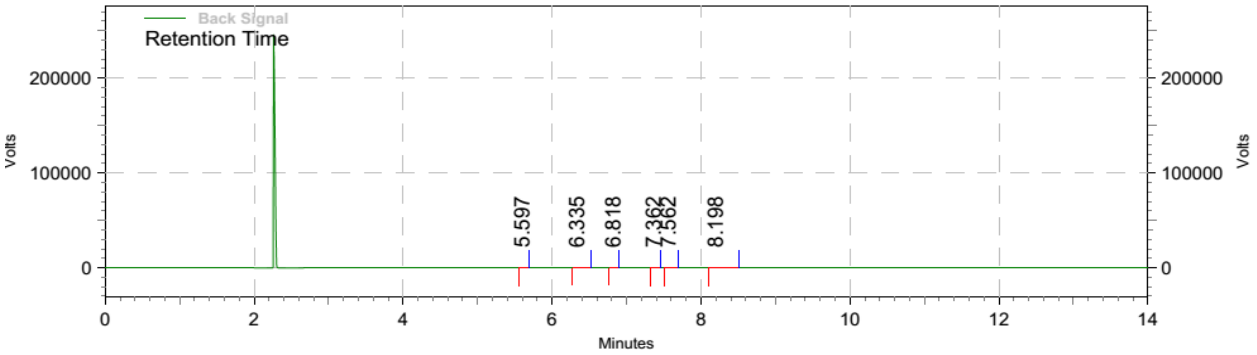
2-cumidine



4-cumidine



Mixture of nitrocumene with internal standerd (*o*-xylene)

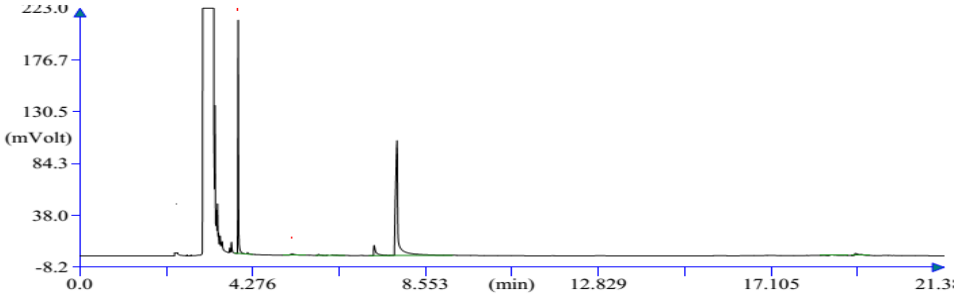


Reaction mixture of nitrocumene reduction

3. Hydrolysis of diazonium salt:

GC method: Initial oven temperature kept 60 ºC and temperature rise with the ramp 15 ºC/min up to 125 ºC temperature, second ramp with 0.5 ºC/min up to temperature 129 ºC, and finally temperature rose to 250 ºC and hold for 3 min, with ramp 20 ºC/min.

	GC retention time	GCMS retention time
Internal standard (*o*-xylene)	3.92	
2-isopropylphenole	7.28	
4-isopropylphenole	7.84	4.47



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Continuous flow nitration of *o*-xylene (1) is studied for different nitrating agents over a wide range of conditions for different parameters such as temperature, residence time and concentrations. The effect on the conversion and yield of 3 has been investigated in detail.

On using 4 molar equivalents of NM (HNO_3:H_2SO_4 ~ 40/60 v/v) at 40 ºC only di-nitro derivatives of *o*-xylene were observed within 10 minutes of reaction time. At a residence time of 20 minutes with an equimolar nitrating mixture (1:FNA:H_2SO_4 = 1:1:1) no complete conversion was achieved even at higher temperatures (50 - 70 ºC) due to the lack of sufficient nitronium ion concentration.

With only fuming nitric acid in excess as nitrating agent at 20 ºC, 99% conversion and only 7.2 % di-nitro impurities were observed in less than 40 s. This also resulted in higher selectivity for 3 when compared to 2, which is a complete contradiction to the observations based on experiments that use sulphuric acid. In the presence of fuming nitric acid, the mono-nitro *o*-xylenes can undergo further nitration to yield different dinitro derivatives of *o*-xylene (viz. 5, 7, 6 and 4) and it also undergoes partial oxidation leading to phenols, and nitrophthalic acid.

An economic analysis of the continuous flow reactor is also presented for continuous production of 100 kg/hr of 3, i.e. about 72 TPM in a jacketed tubular reactor. The analysis showed that having more continuous reactor units running in parallel is always economical as it decreases the OPEX by a few orders of magnitude rather than having a single flow reactor. If the reactor is made only of 3.175 mm diameter tubes, the overall net profit is found to be always lesser than the reactors is made out of 6.3 mm diameter tubes. The choice of suitable tube size needs to be made based on the overall heat transfer coefficient (usually limited by tube size heat transfer coefficient) and the ability to remove the heat efficiently throughout the reactor. Importantly what comes out from the analysis is to have a combination of small size and large size tubes for constructing such a flow reactor, which will be better in terms of safe operation and cost effective than using only small size tubes throughout the reactor. The analysis also showed that numbering-up helps to increase the profit and hence reduces the payback period significantly.

In general, nitric acid is a limiting reagent for benzene nitration. Higher moles of nitric acid or large volume of sulfuric acid are required for achieving complete conversion and high yield. Using fuming nitric acid alone makes this process rapid as well as sustainable. Only for benzene nitration 96% yield of nitrobenzene was achived on using 2 moles of fuming nitric acid with only 2 wt% sulfuric acid at 110 ºC reaction temperature in reaction time of 33 s. On the other hand at 145 ºC with 0.5 mole of fuming nitric acid and 2 wt% sulfuric acid also resulted in complete consumption of nitric acid along with 50% conversion of benzene and 50% yield of nitrobenzene. 87%, 69% and 92% p-selectivity with >99% conversion was achieved for the nitration of fluorobenze, chlorobenzene and bromobenzene using only fuming nitric acid in residence time of 2.34, 3.63 and 4.89 minute respectively, with complete elimination of solvent and catalyst.

Two-step, discontinuous, flow synthesis of m-amino acetophenone is demonstrated using simple tubular reactors (SS316 and silicon tube). The yields from continuous flow reactions were comparable with the batch reactions. The flow synthesis approach for nitration step yields a safer process even at enhanced temperatures with shorter reaction time to achieve consistent performance. Both the steps involved homogeneous solutions (in contrast to typical two phase aromatic nitration). Using a good micromixer is essential to achieve the activated aromatic substrate with the nitrating agent while for the reduction a simple T micromixer was sufficient to achieve the desired mixing. The formation of di-nitro derivative as an impurity was seen to have a strong dependence on temperature, residence time and the internal composition of nitrating mixture. The reduction with sodium sulfide is recommended due to lower costs which makes the process economical. From the simple set-up as described here, both the steps can be scaled to make a few 100 gm quantity of **3** at lab scale in a single day. Since the solutions are homogeneous, scaling up of this process will be relatively easy so far the necessary heat transfer area is made available to control the reaction. Continuous flow nitration of other aromatic ketones using variety of nitrating agents including fuming nitric acid is also reported.

A four step continuous flow oxidation of alcohols is demonstrated with continuous chlorine generation as the first step through the reaction of hydrochloric acid and manganese-di-oxide followed by its use for the flow

synthesis of high strength sodium hypochlorite, with continuous pH adjustment. The solution is subsequently used for oxidation of alcohols in the presence of catalytic amount of nitroxyl radical "TEMPO" which inhibits oxidation at the aldehyde stage. Selective oxidations of eight different aliphatic and aromatic alcohols have been demonstrated with high yield in range of 80 – 99% for aliphatic alcohols and relatively lower yields for aromatic alcohols containing electron withdrawing groups. The approach helps to generate high strength hypochlorite solution that can be used or variety of reactions. It is necessary to note that for specific oxidation reactions using TEMPO one would need to maintain a specific pH of the solution. This implies that just having high strength hypochlorite solution is not sufficient but pH needs to be adjusted in-line to facilitate the subsequent reaction. Since the approach generates pure chlorine in gas phase it can be used for efficient chlorination reactions in flow and relevant work will be reported separately.

4-step integrated synthesis of isopropylphenol has been established with reduction of overall process time from several hours to 50 minutes with complete elimination of in between isolation, separation, and purification steps. It includes exothermic reactions like nitration and hydrogenation, temperature sensitive and unstable diazonium intermediate and endothermic continuous hydrolysis. As a model system cumene was selected as the initial substrate. Cumene upon nitration with fuming nitric acid gives 2 and 4-nitrocumene which gives respective cumidines by the reduction using H-cube with Pd/Ni catalyst. Upon diazotization of cumidines in acidic environment followed by high temperature hydrolysis it gives 2-isopropyl phenol and 4-isopropyl phenol with complete elimination of in between separation, isolation and purification steps. 57.9% 4-isopropyl alcohol was obtained with good yields in all steps.

1. Final products can be further used in subsequent reactions
2. In-line analysis will further reduce the overall process development time
3. Design of experiments (DOE) will help to reduce number of experiments
4. Data can be used for kinetic calculations
5. Pilot plant calculations can be done by proper use of experimental data

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6. Patent: **(WO2015011729 A1)** Continuous flow liquid phase nitration of alkyl benzene compounds