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SYNTHESIS AND CHARACTERIZATION OF *P-* NITRO BENZYL BROMIDE FROM *P-* NITRO TOLUENE

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ABSTRACT

The raw material *p-* Nitro Toluene (PNT) was synthesized successfully using two different routes. In the second route, we obtained *p-* Nitro Toluene (PNT) clear oily yellow-coloured liquid with a boiling point of 230^{0}C, yield of 54.67% and was confirmed by TLC analysis. This was then used for the production of *p-* p-nitro benzyl Bromide **(**PNBBr) in one of the batches placed. The final product *p-* Nitro Benzyl Bromide **(**PNBBr) was also successfully synthesized in 3 batches kept as pale yellow to white coloured solid crystalline powder with a melting point ranging from 90-97^{0}C of crude, washed, crystallized and recrystallized product. The yield obtained was also in sufficient quantity of about 75%.

Keywords: p- Nitro Toluene, p- Nitro Benzyl Bromide, Nitration, Halogenation

INTRODUCTION

Nitration is the process of introduction of one or more nitro groups in a reacting molecule. Nitration is an electrophilic substitution reaction i.e. NO_2^+ is an electrophile. Therefore the substituent which raises the electron density on the ring carbon towards the nitration reaction forms o-, p-nitro products **[1]**.

Nitration is important for two reasons one is for the preparation of aromatic nitro compounds and many important basic molecules having the nitro group. It is of interest because of its characteristics as an electrophilic substitution. The first nitration to be reported was that of benzene itself. Mitscherlich in 1834 prepared nitrobenzene by treating benzene with fuming nitric acid. An important method of effecting nitration with a mixture of nitric and sulfuric acids ('mixed acid') was introduced, evidently in a patent by Mansfield; the poor quality of early nitric acid was probably the reason why the method was developed. Since these beginnings, nitration has been the subject of continuous study **[2]**. Nitronium salts in solution in inert organic solvents have been used in recent years to nitrate a wide range of aromatic compounds.

A variety of nitrating agents can be used depending upon the compound to be nitrated: Dilute, concentrated or fuming nitric acid, HNO_3 dissolved in various solvents like acetic acid, H_2SO_4, acetic anhydride, $CHCl_3$, H_3PO_4. The mixture of HNO_3 and H_2SO_4 is considered a strong nitrating reagent the same way as N_2O_5 and N_2O_4. H_2SO_4 removes the water produced during nitration. Being a stronger acid than nitric acid, it Protonates nitric acid to form a nitryl ion which is a strong nitrating agent.

Nitro toluene are important intermediate in the chemical industry, industrially produced by liquid phase nitration of toluene using a mixture of nitric and sulfuric acid as a nitrating agent having several downstream product **[3]**. The typical product distribution of ortho, meta and para isomers in the conventional nitration is about 58:4:38, whereas the thermodynamic equilibrium concentration is 29:33:38 respectively **[4]**. The para isomer has better commercial value as the pharmaceutical intermediate and is sold at about three times the cost of the o-isomer **[5]**. A large quantity of dilute sulfuric acid is generated as waste in the conventional process and its disposal or recycling is very expensive; this makes the toluene nitration one of the most environmentally harmful processes. The replacement of sulfuric acid with solid acid catalysts with high selectivity for para isomer would be an attractive environmentally benign route for the production of nitro-toluene **[6, 7]**.

p- nitro toluene is a yellow liquid with a weak aromatic odour, Toxic, and Insoluble in water. Combustible but may take some effort to ignite. It produces toxic oxides of nitrogen when burned. In a spill, immediate steps should be taken to limit its spread to the environment. It can easily penetrate the soil and contaminate groundwater or nearby streams.

p- nitro benzyl bromide, is one of the important compounds from the benzyl bromide family due to its class of applications in organics and pharmaceuticals fields and also has many warfare applications **[8-10]**. *p*-nitro benzyl bromide is used for the introduction of the benzyl bromide group to other substrates. It is an important industrial intermediate to produce a variety of compounds. Due to its properties, it falls under the class of analgesics, so it is used in combination with other pharmaceutically active compounds that act as anti-migraine agents. It is also used in organic chemistry confirmative tests to identify the alcohols and carboxylic acids group and is also used in chemical warfare because of its lachrymator and irritating properties. The benzyl group serves as a protecting group for alcohols and carboxylic acids. *p*- nitro benzyl bromide is used in the synthesis of di and tri-substituted azoles. It is also used in the preparation of N-6-Benzyladenosine-5'-uronamides as selective A3 adenosine agonists **[11-13]**.

MATERIALS

Nitric acid, Sulphuric acid, Toluene, Bromine, Cyclohexane, Petroleum ether, Diethyl ether, Sodium hydrogen carbonate and Sodium sulphate were laboratory-grade reagents. All other chemicals and materials were laboratory-grade reagents and used without any modification.

Methods

Synthesis of p-nitrotoluene (PNT) (Route: 1)

Preparation of the nitrating acid: Concentrated H_2SO_4 is slowly added under constant shaking and ice cooling to ice-cold concentrated HNO_3, which was placed in a 250 mL wide-necked flask. Using an ice-salt cooling bath, cool the nitrating acid subsequently to -5^0C.

The reaction apparatus consists of a 250 mL three-neck flask with a magnetic stirring bar, and a thermometer. Connect the remaining opening of the flask to a gas trap. Charge the reaction flask with toluene, which was freshly distilled. Cool the toluene in the reaction flask to -10^0C with an ice-salt cooling mixture. The cooled nitrating acid is placed in small portions (to avoid its warming up) into the reaction set-up and is added dropwise under cooling to keep the internal temperature of the reaction mixture below 5^0C. It takes approx. 1.5 hours to add the entire nitrating acid. After complete addition, the reaction mixture, still placed in an ice water cooling bath, is allowed to slowly warm up to room temperature. Warming up must be so slow to avoid the formation of nitrous gases. After reaching room temperature, stir the reaction mixture for an additional 2 hours. Pour the reaction mixture into a 250 mL beaker containing ice. Then place the mixture into a separating funnel, and extract it with cyclohexane. The combined organic phases are washed subsequently with water, saturated aqueous $NaHCO_3$-solution and again with water. The organic phase is dried over Na_2SO_4, the drying agent is removed by filtration and the solvent is removed using the evaporator. The crude product remains as an oily residue. Purify the crude product by distillation. The receiving flasks must be cooled. The desired product distils over in a boiling temperature range of 100–130^0C yielding yellow product as a liquid and other as distillation residue. The liquid product of the distillation crystallizes at -20^0C. Isolate the crystalline material by filtration over a cooled Buchner funnel and recrystallize it **[14, 15]**.

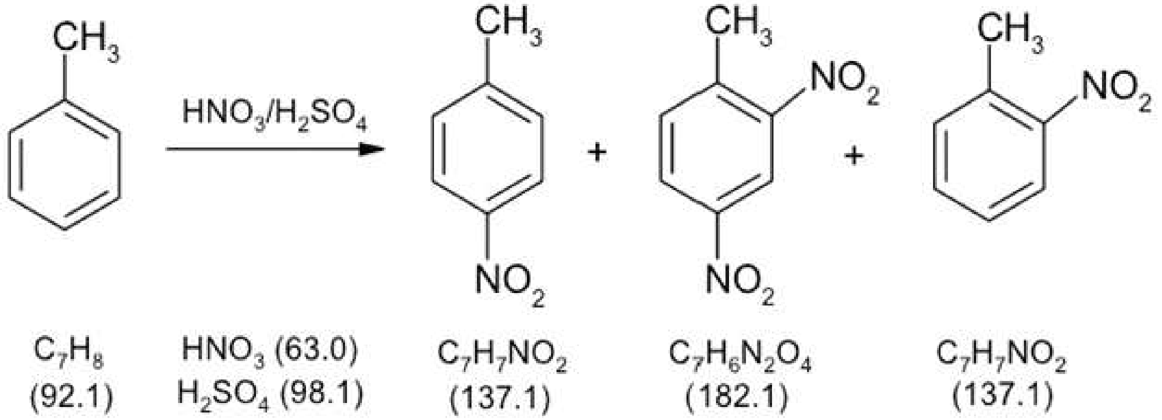


Figure: 1 Nitration of Toluene

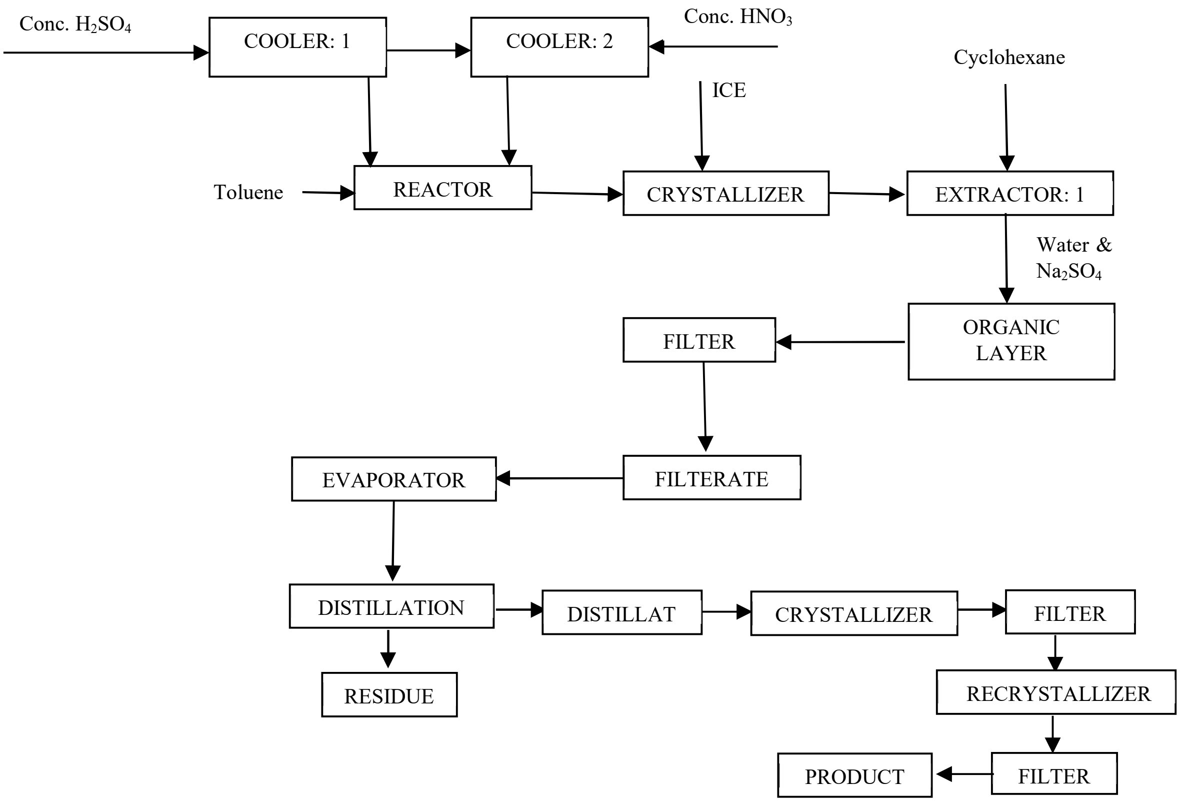


Figure: 2 Flow diagram of synthesis of PNT by Route: 1

Synthesis of *p*-nitro toluene (PNT) (Route: 2)

Place a 5 mL conical vial, equipped with a spin vane, in a crystallizing dish filled with ice water placed on a stirrer. Pour 1.0 mL of concentrated nitric acid into the vial. While stirring, slowly add 1.0 mL of concentrated sulfuric acid. After the addition of sulfuric acid is complete, add 1.0 mL of toluene dropwise and slowly over 5 minutes (slow down if you see boiling. Reaction produces a lot of heat). While stirring, allow the contents of the flask to reach the room temperature. Stir at room temperature for another 5 minutes. Add 10 mL of water into a small separatory funnel. Then transfer the contents of the flask (from step 4) into the funnel. Rinse the contents with 4 mL of diethyl ether and add it to the separatory funnel. Repeat the ether rinsing one more time with a fresh 4 mL portion of ether. Gently shake the contents of the separatory funnel, let them settle, and remove the aqueous layer. Wash the organic layer with a 10 mL portion of 10% sodium bicarbonate (shake and VENT due to the formation of gas), and finally, wash it with 5 mL of water. Discard the aqueous layer, and dry the organic layer using anhydrous sodium sulfate. Evaporate the solvent (critical to keep the temperature as low as possible. Do not overheat.) And obtain the isolated nitrotoluene. The confirmation of PNT was done by TLC.

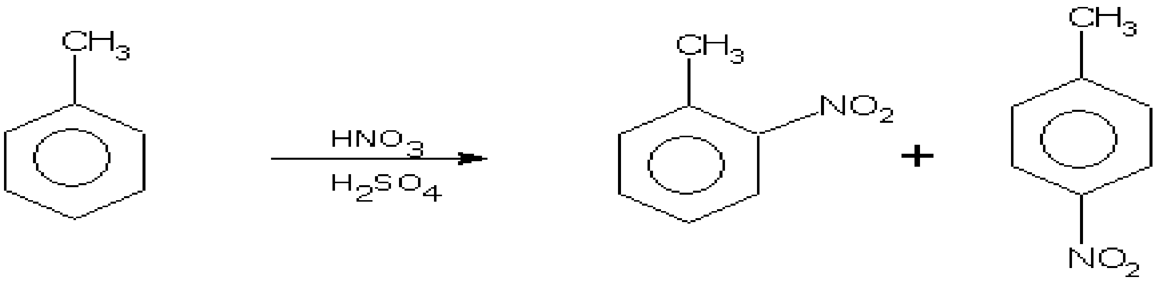


Figure: 3 Nitration of Toluene

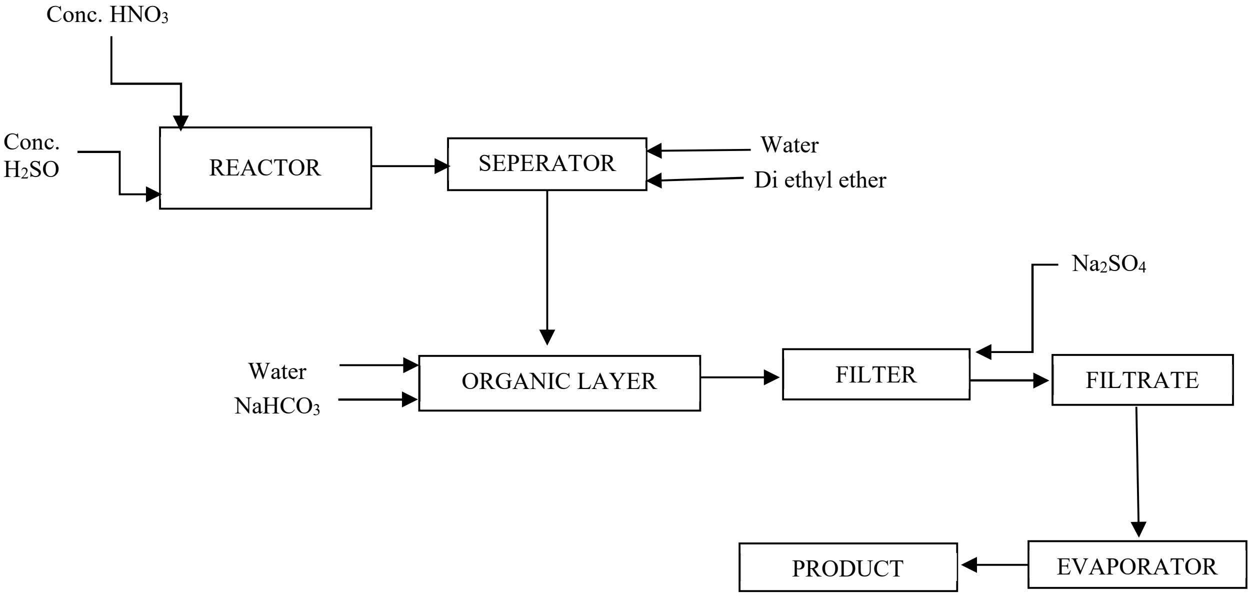


Figure: 4 Flow diagram of synthesis of PNT by Route: 2

Synthesis of *p*- Nitro benzyl bromide (PNBBr)

In a three-necked flask is placed *p*-Nitro toluene (m.p. 51–52^{0}C). The flask is fitted with a reflux condenser, and a separatory funnel arranged so that the stem reaches nearly to the bottom of the flask. The condenser is attached to a gas trap. The flask is heated in an oil bath at 145–150^{0}C, and bromine is added dropwise over two hours. After all the bromine has been added, the heating and stirring are continued for ten minutes. While still liquid, the contents of the flask are poured into a round-bottomed flask containing hot petroleum ether and carbon is added. The material is brought into solution by heating on an electric hot plate, and, after boiling for ten minutes, the solution is filtered rapidly with suction. After cooling to 20^0C, the crystals are filtered with suction.

For purification, this material is dissolved in hot ligroin, boiled with decolorizing carbon, and filtered with suction. After cooling in an ice bath the crystals are collected on a Buchner funnel, pressed, and washed with a cold petroleum ether. The pale yellow product results. Confirmation of PNBBr was done by TLC, FT-IR and NMR.

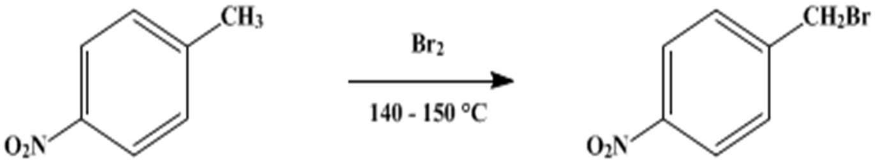


Figure: 5 Synthesis of *p* – Nitro benzyl bromide (PNBBr)

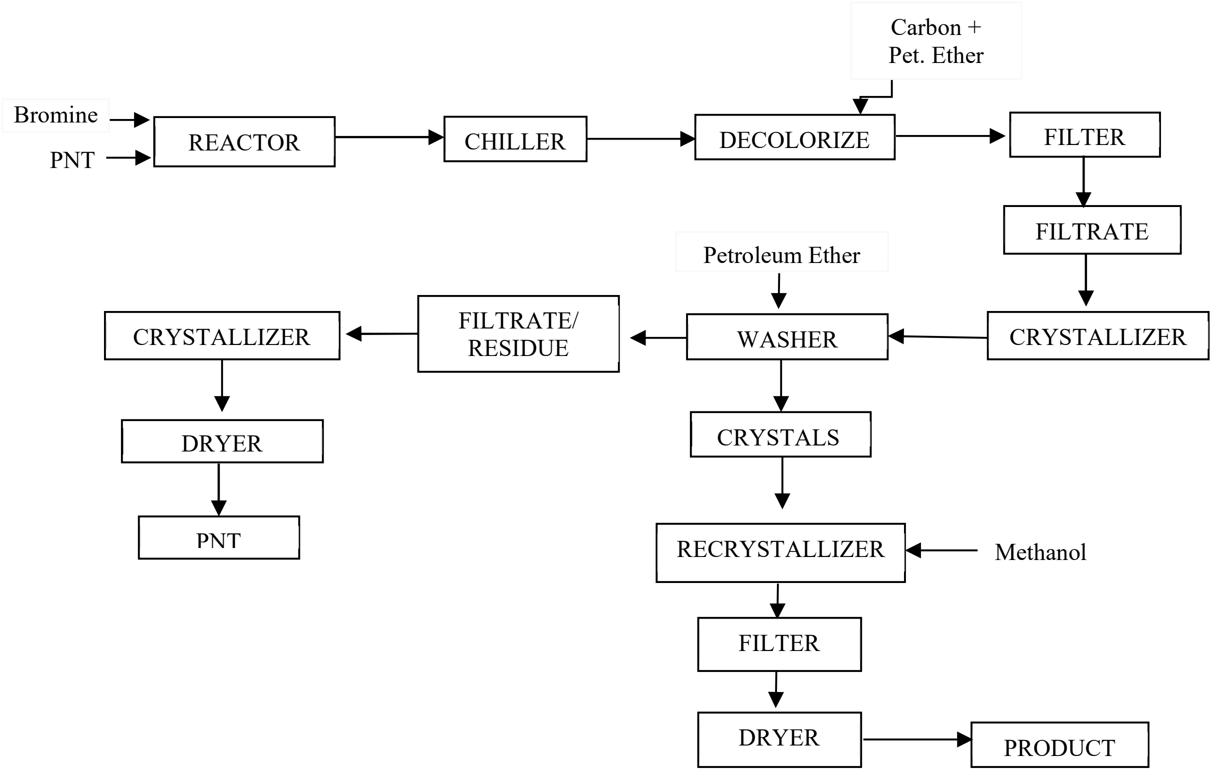


Figure: 6 Flow diagram of synthesis of PNBBr

RESULTS AND DISCUSSION

We have synthesized *p*-nitro toluene using different ratios of mixed acids. Out of which using a higher ratio 6:4 of mixed acids, *p*- Nitro toluene was successfully synthesized as yellow-oily liquid. The yield of *p*- Nitro toluene so obtained was 54% with a boiling point of 230^0C **(Table 1)**. The confirmation of *p*- Nitro toluene was done by TLC with Solvent system, Hexane: Ethyl Acetate: 9:1. *p*- Nitro toluene upon heating with NaOH gives yellow colored fumes indicating the presence of the Nitro group in the product. Primary characterizations of *p*-nitro toluene are shown in **Table 2**.

We have synthesized *p*- Nitro benzyl bromide in 3 different batches using synthesized *p*- Nitro toluene, commercially available *p*- Nitro toluene and recycled *p*- Nitro toluene respectively **(Table 3)**. The basic properties of synthesized *p*- Nitro benzyl bromide are shown in the **Table 4**. The confirmation of the *p*- Nitro benzyl bromide was done by TLC with Solvent system, Hexane: Ethyl Acetate: 7.5:2.5 and characterized by FT-IR and NMR.

The plot of FT-IR confirms the presence of NO_2 by giving two strong bands at 1349.2 cm^{-1} and 1325.19 cm^{-1}. The presence of bromide with the methyl group shows a difference in C-H stretching and bending bands than that observed in PNT which is at 3037.94 cm^{-1}, 2925.06 cm^{-1} with bands of medium appearance. The medium bands of aromatic C=C were also observed at 1598.01 cm^{-1} and 1539.61 cm^{-1} **(Figure 7)**. The ^{1}H –NMR of *p*- Nitro benzyl bromide is shown in **Figure 8**. In ^{1}H –NMR the peaks in the range of 7.723-8.230 ppm are observed due to the presence of benzene ring hydrogen. The chemical shift of the ring hydrogen is shifted to the downfield region because here benzene ring is substituted with an electron-withdrawing group (NO_2). The peak in the range of 2.440-2.551 ppm is observed due to the presence of the benzylic hydrogen which is attached to the carbon atom attached to a benzene ring. The peak at 4.825 ppm is observed due to the presence of the alkyl halides ($R-CH_2-Br$).

We can also recover the unreacted *p*- Nitro toluene by washing the product *p*- Nitro benzyl bromide with petroleum ether because PNT is soluble in petroleum Ether and PNBBr is not, so the unreacted PNT was obtained in the filtrate which upon cooling gave the needle-like crystals of PNT, whose melting point was found as 49^0C. Further the washed product – PNBBr had a melting point of 90^0C, which upon recrystallization with acetone gave the melting point of 93^0C. The recovery of PNT is given in **Table 5**.

Table: 1 Molar ratio of nitrating agents

Batch	Reagents	Ratio and Volume (ml)	% Yield
5	(H_2SO_4: HNO_3) Toluene	1:1 10	NILL
6	(H_2SO_4: HNO_3) Toluene	6:4 10	54.556

Table: 2 Results for *p*- Nitro Toluene (PNT)

Compound	Molecular Formula	Molecular Weight	Colour	B.P. (^{0}C)	Yield (% w/w)	R_f Value
p- Nitro Toluene	$C_7H_7NO_2$	137.138 g/mol	Yellow liquid	230	54.67	0.69

Table: 3 Reaction Scheme for *p*- Nitro Benzyl Bromide (PNBBr)

Batch	Reagents	Weight (gm.)/ Vol.(ml)	% Yield	% Recovery
1	*p*- Nitro Benzyl Bromine	13.71 5.15	Crude: 46% Recrystallize: 65%	PNT: 22%
2	*p*- Nitro Benzyl Bromine	13.71 5.15	Crude: 50% Recrystallize: 72%	PNT: 23%
3	*p*- Nitro Benzyl Bromine	2.74 1.2	Crude: 52% Recrystallize: 55%	PNT: 11%

Table: 4 Results for *p*- Nitro Benzyl Bromide (PNBBr)

Compound *p*- Nitro Benzyl Bromide	Molecular Formula $C_7H_6BrNO_2$	Molecular Weight 216.034 g/mol.	
Colour	M.P. (^{0}C)	% Yield	R_f Value
Crude: Brown Recrystallized: Yellow	88 93	46 65	0.77 0.85
Crude: Light Brown Recrystallized: Light yellow	84 90	50 72	0.82 0.88
Crude: Light brown Recrystallized: White	90 97	52 55	0.82 0.86

Table: 5 Recovery of *p*- Nitro Toluene (PNT)

Colour	M.P. (^{0}C)	% Yield
Yellow	49	23
White	43	11
White	52	36

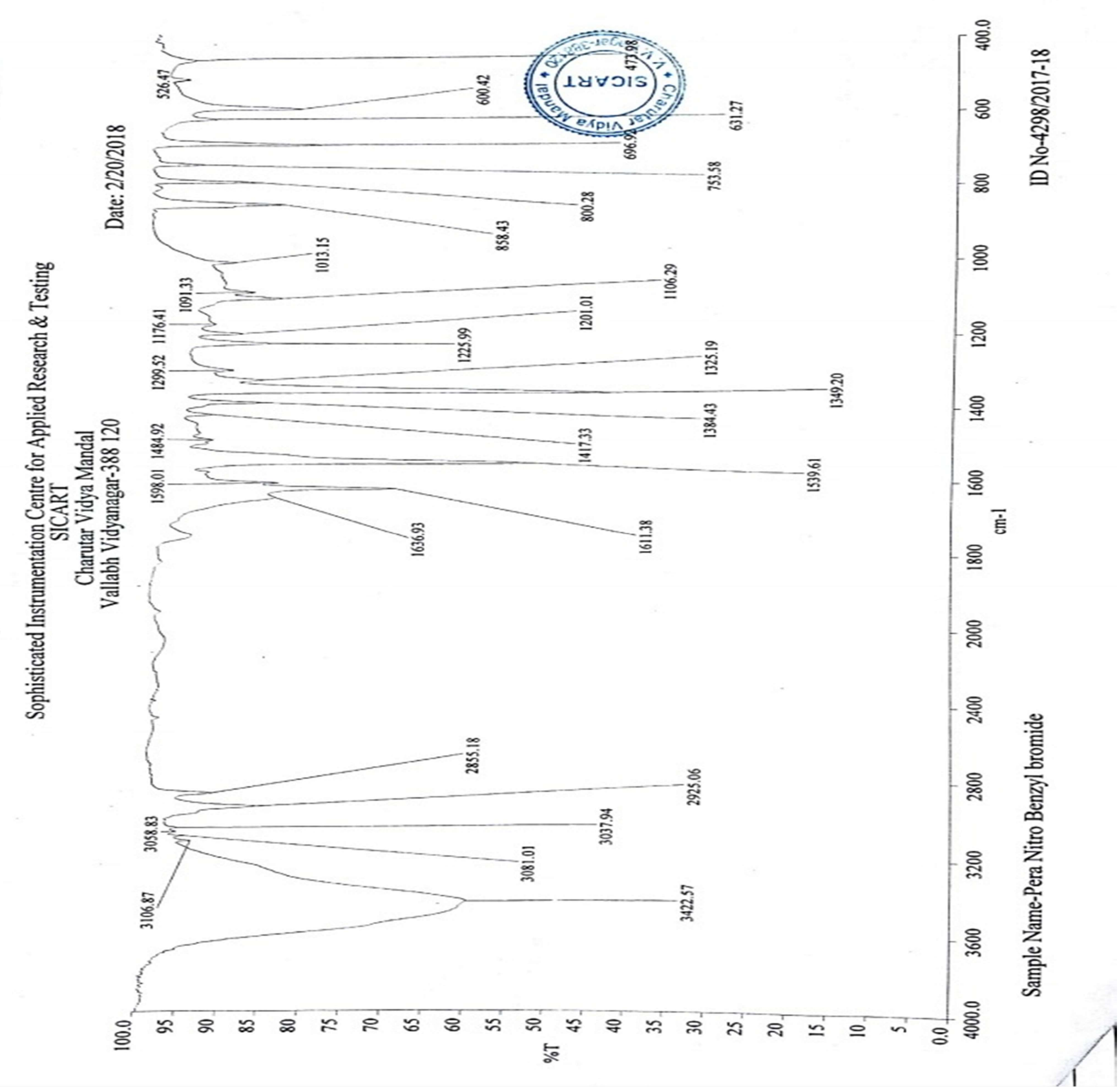
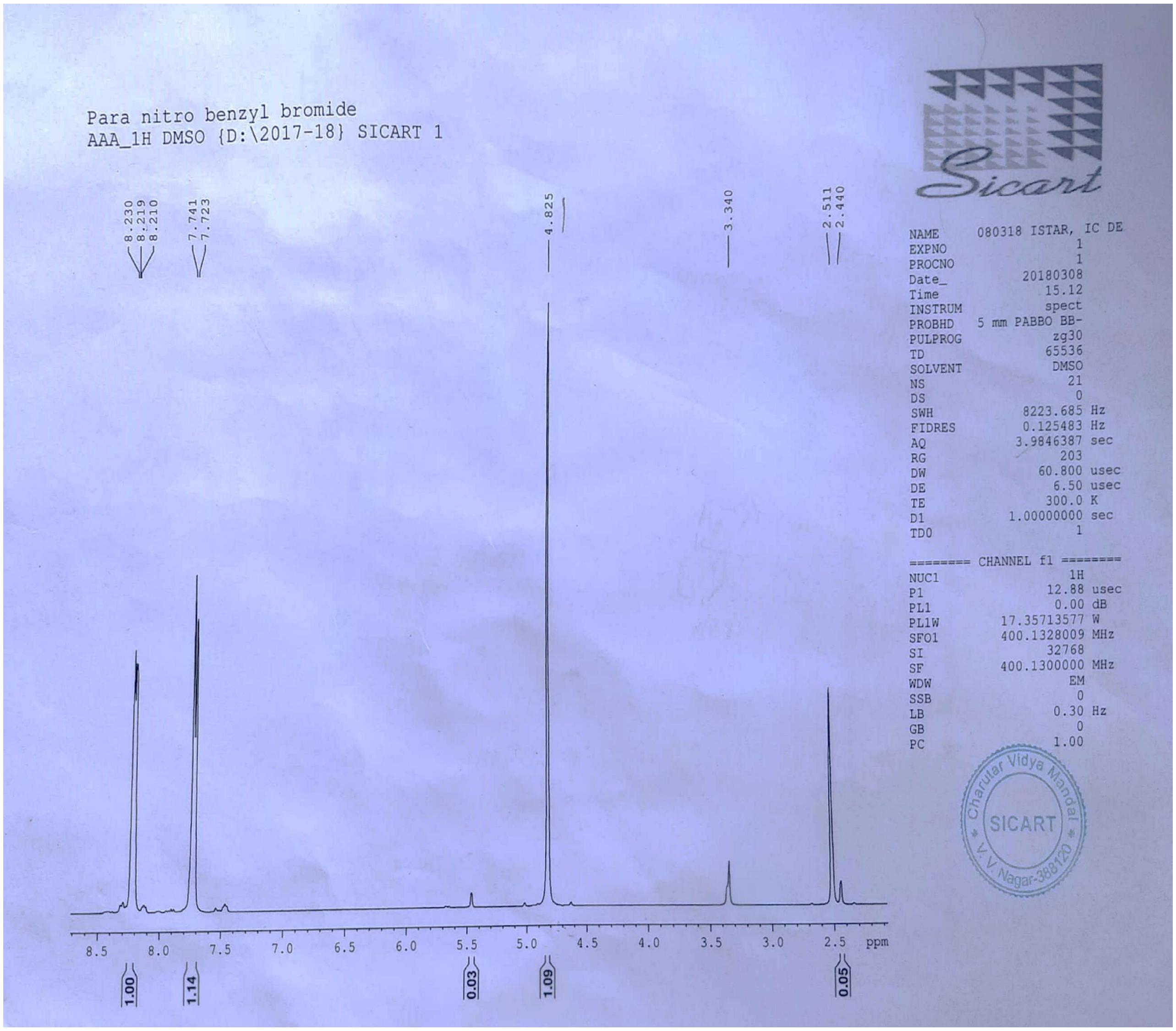


Figure 7: FT-IR



Para nitro benzyl bromide
AAA_1H DMSO {D:\2017-18} SICART 1

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EXPNO                    1
PROCNO                   1
Date_             20180308
Time                 15.12
INSTRUM              spect
PROBHD     5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      21
DS                       0
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ               3.9846387 sec
RG                     203
DW                  60.800 usec
DE                    6.50 usec
TE                   300.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   12.88 usec
PL1                   0.00 dB
PL1W           17.35713577 W
SFO1           400.1328009 MHz
SI                   32768
SF             400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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Figure 8: ^{1}H-NMR

CONCLUSION

The raw material *p*-nitro toluene (PNT) was synthesized successfully as a liquid with a melting point of 230^{0}C and a yield of 54.667%. This was then used for the synthesis of the product *p*- nitro benzyl bromide (PNBBr) as pale yellow to white-coloured solid crystalline powder with a melting point ranging from 90-95^{0}C and a yield of about 75%. We have also recovered the unreacted *p*-p-nitro toluene after the synthesis of *p*-nitro benzyl bromide. The maximum recovery of the unreacted *p*-nitro toluene was 23%. The product PNBBR is found to have pharmacological activities (analgesic) in the presence of other APIs only, so to study its pharmacological activity as an analgesic, it can be combined with the API with similar properties to get maximum efficiency of the product as a drug. Also due to its irritating properties, it can be used in the components of tear gas, as it is required in very small quantities to show its effect.

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