Annexure-II

Nitration of Phenols using $Cu(NO_3)_2$: Green Chemistry Laboratory Experiment

Abstract:

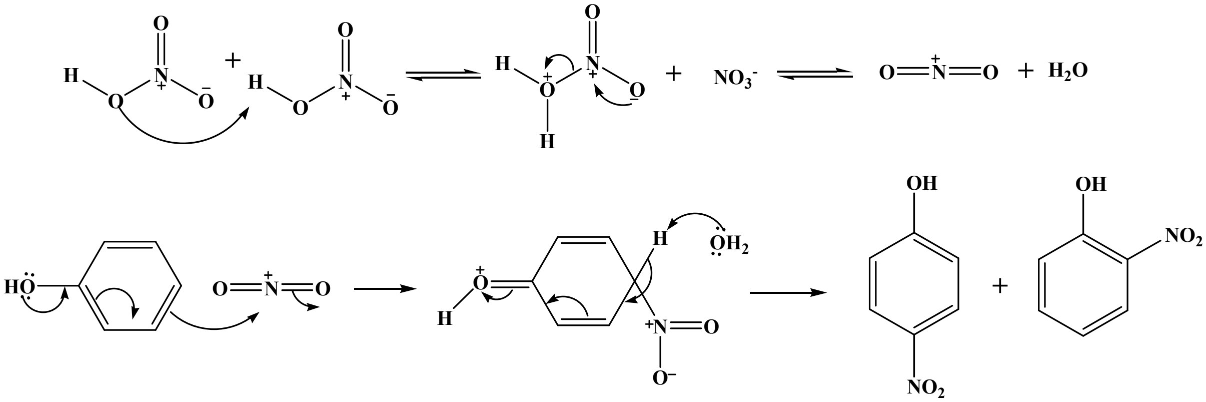
The nitration of phenol with copper nitrate has been achieved in high regio-selectivity in 1-min using microwave irradiation. $Cu(NO_3)_2$ in glacial acetic acid dissociates to give HNO_3 which further produces NO_2^+. In particular, excellent para selectivity of the 70-80% for phenol. Compounds purified using column chromatography/steam distillation in laboratory.

II.1 Introduction

One of the absolutely messiest experiments to be found in organic chemistry laboratories is the nitration of phenol [1]. The immediate result of the mixing of the reactants is a black and sticky mass that adheres perversely to the stirring rod, flask, and fingers. The majority of the methods reported for nitration [2] of aromatic compounds require a mixture of nitric and sulphuric acid. The use of such corrosive reagents (usually in excess) creates serious environmental issues and the treatment and disposal of the used mixed acid is expensive. The method also suffers from disadvantages such as over-nitration, strongly acidic medium, tedious workup, and safety issues.

In order to overcome these problems, alternative procedures for the nitration have been developed [3]. Some of these methods include $AcONO_2$, $TfONO_2$, $NaNO_3$/HCl with catalytic amounts of $La(NO_3)_3$, $Bi(NO_3)_3$/montmorillonite KSF, $NaNO_3$/wet SiO_2, $NaNO_2$/silica sulfuric acid, $Mg(NO_3)_2.6H_2O$, $Cu(NO_3)_2$/clay, $Fe(NO_3)_3.9H_2O$/ionic liquid, $VO(NO_3)_3$[4]. Some other metal nitrate/clay combinations activated by acetic anhydride [18], and more recently, calcium nitrate/microwave, zirconyl nitrate and PTSA/$Ni(NO_3)_3$ [5].

Electrophilic nitration of aromatic compounds is mediated by nitronium ion (NO_2^+) according to the current theory about the mechanism of nitration [6]. In these reactions, NO_2^+ interacts with the aromatic ring so as to give desired product. Nitration of phenolic compounds is very important chemical process which has wide applications in dyes, pharmaceuticals, agrochemicals, explosives, and plastic industry. In the case of nitration of phenol, NO_2^+ ion can attack at two possible sites *ortho*- or *para*- to the -OH group of phenol. This makes reaction very interesting from the mechanistic/regioselectivity point of view, as shown in Scheme II.1.



Scheme II.1: Mechanism of nitration reaction.

The present experiment is devised to carry out nitration using environmentally friendly nitrating mixture with high regioselectivity. Here we will use $Cu(NO_3)_2$ as a nitrating mixture. $Cu(NO_3)_2$ in glacial acetic acid dissociates to give HNO_3, as shown in Scheme 2.

$$\boxed{Cu(NO_3)_2 + CH_3COOH \longrightarrow Cu(OOC\text{-}CH_3)_2 + HNO_3}$$

Scheme II.2: Green chemical generation of HNO_3

Thus, the present regioselective nitration of phenol is simple, high yield reaction ideally suitable for undergraduate laboratory course. It can be completed in 1 min under microwave irradiation. This will help student to complete purification using column chromatography in laboratory hours. Copper acetate, the byproduct in this nitration reaction, is environmentally benign as is the unreacted excess copper nitrate. The total inorganic material at the end of the reaction therefore need not be chemical waste; it could be suitable for use as an agrochemical since copper nitrate is used as a fertilizer (e.g., in tea gardens). Fungicides and green pigments, reagent for synthesis organic and inorganic compounds.

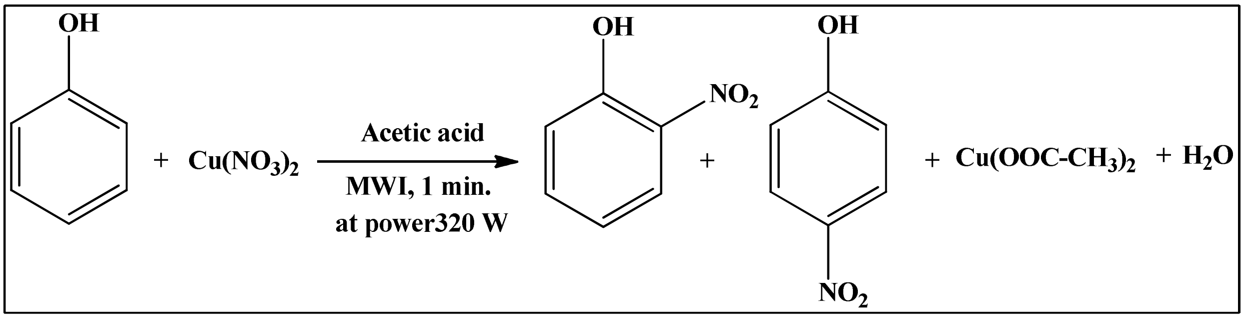
Steam distillation [7] is a means of separating and purifying organic compounds. The operation consists of volatilizing a substance that has a vapour pressure (at least 5-10 mm at 100ºC) by passing steam into a mixture of the compound and water. Present reaction gives two products, *ortho*- and *para*- nitrophenol, which due to their different hydrogen bonding pattern can be separated using steam distillation during lab hours. Steam distillation of reaction mixture gives almost the same yield as obtained from column chromatography.

II.2 Experimental

II.2.1 Materials and Methods:

All chemicals and solvents were of analytical grade reagents. Phenol and copper (II) chloride were from Aldrich; Acetic acid, hexane and ethyl acetate (Qualigens) were used without further purification.

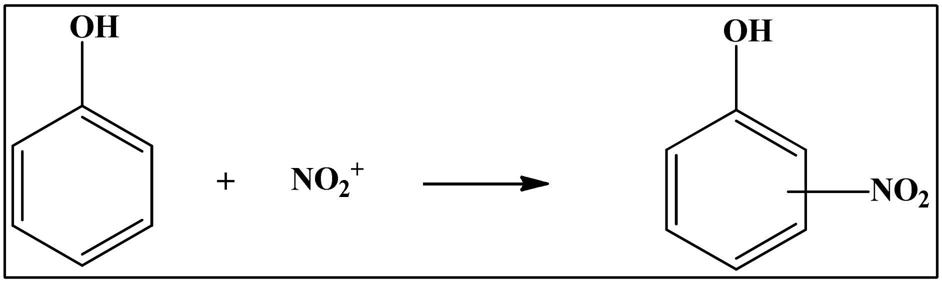
II.2.2 Syntheses of compounds:



Traditional Experiments:

In the conventional method of nitration of phenols, the most common reagent is a mixture of conc. HNO_3 and H_2SO_4 or conc. HNO_3 in acetic acid [8]. Nitration requires long reflux times and gives low yields. The methods for nitration of aromatic compounds suffer from some crucial disadvantages such as over-nitration and strongly acidic media.

$$\boxed{HNO_3 + 2\ H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-}$$



Microwave heating shorten the reaction time in these reactions and perhaps improve yields permitting a scale down of reagents [9]. The time saved would allow for additional chemistry or more in-depth analyses of results. Highly accelerated and safe nitration of phenolic compounds has been found to be feasible with a mixture of copper nitrate and acetic acid as an efficient nitration agent under brief microwave irradiation. This method is compatible as a green chemistry approach. The reagents and byproducts in this reaction are safe and eco-friendly. Selectivity in the site of nitration has been observed.

Using Microwave

Model: START SYNTH; Serial No.:131568.

Line Voltage: 230V (1200W); Frequency 50 Hz.

Phenol (1.000 g, 0.0106 moles) and 5 mL of acetic acid were mixed in a 50mL glass round bottom flask and placed on a Weflon holder P/N SGL0020 into the centre of the microwave cavity. $Cu(NO_3)_2$ (2.385g, 0.0127 moles) were added to the mixture slowly and closed the smaller neck with stopper. Reaction mixture color changed to red brown and brown fumes were generated. Magnetic stir bar was added and assembly was completed for microwave heating. Slot number was recorded of the microwave heating method: DA320W1MN120C. It indicates that the reaction was performed with the oven at power -320W, heated to 120ºC and held at this temperature for 1 minute. Reaction mixture color darkens and more brown fumes were generated. Once the reaction was complete, the mixture was allowed to cool to room temperature. Then 10 mL of ethyl acetate was added and well stirred. The slurry was filtered. The solid generated was $Cu(OOCCH_3)_2$ and filtrate contained the expected nitration product. 10 mL water was added to it and ethyl acetate layer separated from it. The separated ethyl acetate layer was checked with the thin layer chromatography to determine presence of impurity or byproducts.

TLC system: Hexane: Ethyl Acetate (8:2)

Using Domestic Microwave

Model: CMG 17E 07 WHGX; Serial No.:6D0807.

Line Voltage: 230V (1200W); Frequency 50 Hz.

Phenol (1.000g, 0.0106 moles) and 5 mL of acetic acid were mixed in a 100mL beaker. Then $Cu(NO_3)_2$ (2.385g, 0.0127 moles) were added to the mixture slowly. Brown fumes were generated. Once the reactants were thoroughly mixed, the beaker containing reaction mixture in the microwave oven and covered with a Pyrex watch glass. It was heated for 1 min with a 10 sec pulse at Power-320W. Once the reaction was complete, the mixture was allowed to cool to room temperature. Then 10 mL of ethyl acetate was added and well stirred. The slurry was filtered. The solid generated was $Cu(OOCCH_3)_2$ and filtrate contained the expected nitration product. 10 mL water was added to it and ethyl acetate layer separated from it. The separated ethyl acetate layer was checked with the thin layer chromatography to determine presence of impurity or byproducts.

TLC system: Hexane: Ethyl Acetate (8:2).

II.3 Result and Discussions

II.3.1 FT-IR:

***o*- nitro phenol:**

IR: 3500 cm^{-1}, 1555-1487 cm^{-1}.

***p*-nitro phenol**

IR: 3500 cm^{-1}, 1555-1487 cm^{-1}.

The reaction showed significant result when reaction was performed in a microwave oven set at 320W. Acetic acid, an excellent absorber of microwave energy acts as a solvent as well as reactant and shortened the reaction time to one min. One minute of microwave heating produced yields that ranged from 70.0-80.0 %. The reaction was monitored using TLC and purified using Column chromatography and steam distillation. Various equivalent ratios of metal nitrate were used out of which 1.2 equivalent shows better result. Melting point values were matched with literature values, 113.5 ºC for *para*- and 45.5 ºC for *ortho*- nitrophenol.

With the time saved, the experiment was completed in two to three hours with purification of reaction mixture by column chromatography and steam distillation. The remaining time was used for a discussion of ^{1}H NMR and IR Spectra and to teach literature searching on SciFinder Scholar.

II.3.2 Hazards

Phenol is corrosive if inhaled, ingested, or if comes in contact with the skin may cause burns. Avoid inhalation of acetic acid and silica gel may cause irritation of respiratory tract, characterized by coughing or chocking. Hexanes and ethyl acetate are volatile and flammable organic solvents, hence avoid exposing them to flames and heat sources. All students and the instructor should wear goggles, gloves, and lab coats or aprons. The TLC plate should be handled with tweezers, not by hand.

II.4 Conclusion

We describe an easy, quick and inexpensive electrophilic aromatic nitration reaction via green chemistry method using microwave. In this the starting material and final product are analyzed by melting point/boiling point, FT-IR spectroscopy, and TLC. The additional benefit associated with microwave heating instead of the conventional methods of heating is rate enhancement. Prelab and postlab analysis indicates that this activity increased student understanding of this type of chemical reaction.

II.5 References

[1] (a) P. J. Zeegers, *J. Chem. Edu.* **1993**, *70*, 1036; (b) T. McCullough, K. Kubena, *J. Chem. Edu.* **1990**, *67*, 801.

[2] (a) M. J. Wieder, R. Barrows, *J. Chem. Edu.* **2008**, *85*, 549; (b) A. V. Joshi, M. Baidoosi, S. Mukhopadhyay, Y. Sasson, *Org. Process Res. Dev.* **2003**, *7*, 95-97; (c) N. Nandurkar, M. Bhor, S. Samant, B. Bhanage, *Ind. Eng. Chem. Res.*, **2007**, *46*, 8590-8596; (d) A. K. Bose, S. N. Ganguly, *Tet. Lett.* **2006**, 47, 1885-1888.

[3] (a) X. Peng, H. Suzuki, C. Lu, *Tet. Lett.* **2001**, *42*, 4357-4359; (b) S. Hong-Bin, R. Hua, Y.Yin, *J. Org. Chem.*, **2005**, *70*, 9071-9073; (c) M. M. V. Ramana, S. S. Malix, J. A. Parihar, *Tet. Lett.* **2004**, *45*, 8681-8683; (d) P. Strazzolini, A. G. Giumanini, A. Runcio, *Tet. Lett.* **2001**, *42*, 1387-1389; (e) D. Koley, O. C. Coln, S. N. Savinov, *Org. Lett.*, **2009**, *11*, 4172-4175.

[4] (a) S. Nagy, E. Zubkov, V. Shubin, A. Pelmenschikov, E. Paukshts, N. Razdobarova, *Acta Chim Hung* **1992**, *129*, 579; (b) S. Nagy, K. Yarovoy, M. Shakirov, V. Shubin, L. Vostrikova, K. Ione, *J. Mol. Catal.* **1991**, *64*, L31-L34; (c) Outertani, M.; Giraro, P.; Kagan, H. *Tet. Lett,* 1982, *23*, 4215; (d) Samjadar, S.; Becker, B.; Banik, B. *Tet. Lett,* 2000, *41*, 8017; (e) Zolfigol, M.; Madrakian, E.; Ghaemi, E. *Molecules*, 2001, *6,*614; (f) Zolfigol, M.; Madrakian, E.; Ghaemi, E. *Molecules*, 2002, *7,*734; (g) Zolfigol, M.; Madrakian, E.; Ghaemi, E. *Syn. Commun.*, 2000,*30,*1689; (h) Gigantee, B.; Prazeres, A.; Maarcelo, M.; Laszlo, P. *J. Org. Chem.*, 1995,*60,*3445; (i) Rajagopal, R.; Srininasan, K. *Syn. Commun.,*2003, *33*, 961.

[5] (a) A. Bose, S. Ganguly, M. Manhas, S. Rao, J. Speck, *Tet. Lett.,*2006,*47,*1885; (b) J. Selvam, V. Suresh, K. Rajesh, S. Reddy, *Tet. Lett.,*2006, *47*,2507; (c) V. Anuradha, P. Srinivas, P. Aparna, J. Rao, *Tet. Lett.,*2006, *47*, 4933.

[6] P. M. Esteves, J. W. M. Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. Surya Prakash, G. A. Olah *J. Am. Chem. Soc.*, **2003**, *125* (16), 4836-4849.

[7] S. S. Carlson, J. Stewart *Technique in Organic Chemistry*, 2nd edn. Ed. A. Weissberger. New York: Wiley-Interscience, **1965**, *4*, 49.

[8] B. S. Furniss, A.J. Hannaford, P. W. G. Smith, A.R.Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th edn. Pearson. London: pp-375.

[9] Microwave-Enhanced Chemistry-Fundamentals, Sample Preparation, and Applications; Kingston, H. M., Haswell, S. J. Eds.; American Chemical Society: Washington, DC, 1997.