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REGULAR ARTICLE

Yttrium Nitrate mediated Nitration of Phenols at room temperature in Glacial Acetic acid

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Abstract. Rapid nitration of electron rich phenols using $Y(NO_3)_3.6H_2O$ in glacial acetic acid at room temperature was observed with good yield. The method allows nitration of phenols without oxidation, and isolation of nitration product in a rapid and simple way. The described method is selective for phenols.

Keywords. Nitration; yttrium nitrate; phenols.

1. Introduction

Nitration of aromatic compounds is one of the most important synthetic methods in the design of synthetic strategy of many pharmaceuticals, agrochemicals and fine chemicals. Recent study revealed that nitration is the significant cause of post translational modification that can influence folding and function of proteins, which resulted in many neurological disorders.[1] Thus, the mechanism of nitration in biological system explains how environment and genetic factors induce neurological disorder. Conventional nitration involves use of concentrated H_2SO_4 and HNO_3 mixture as the nitrating agent. Such a method suffers from drawbacks such as poor functional group toleration, poor regioselectivity, excessive nitration, and emission of toxic nitrous fumes into the environment. For activated phenols, oxidation is a common issue. In the last few decades, significant attention was paid on nitration of phenols to overcome such problems. Metal nitrates are among the most important reagents in this regard as they are hazardless and need experimentally simple conditions. Many metal nitrates such as $Ca(NO_3)_2$,.[2] $Bi(NO_3)_3{\cdot}5H_2O$/[bmim][PF_6],[3] $Cu(NO)_3$,[4] $NaNO_3$,[5] $Mg(NO_3)_2$,[6] $VO(NO_3)_3$, $Fe(NO_3)_3$, $(Me_4N)NO_3$, $Ph_2PCl/I_2/AgNO_3$,[7] and Zirconyl Nitrate[8] were used as the source of nitronium ion. However, these methods need extra reagents such as solid acid or ionic liquids and heating condition. Therefore, finding a green nitration method at ambient temperature is highly desirable.

In continuation of our present interest of finding yttrium metal complexes-promoted organic transformation, we found $Y(NO_3)_3.6H_2O$ as an efficient nitrating reagent for phenols at room temperature in acetic acid medium.

2. Experimental

All reagents were commercially purchased and used without further purification. The nitration products were identified by comparing observed and reported ^{1}H-NMR spectra and melting point. Progress of the reaction was checked by thin layer chromatography (Merck TLC Silica Gel 60 F254). Developed TLC plates were seen under UV light (254 nm). Yields mentioned in the Table 2 are isolated yield without column chromatographic purification.

2.1 *Procedure for Nitration of Phenol*

Phenol (94 mg, 1 mmol) dissolved in 3 mL glacial acetic acid in a 50 mL test tube was treated with solid $Y(NO_3)_3.6H_2O$ (383 mg, 1 mmol) with constant shaking at RT for 10 min. The reaction was monitored by TLC at 10% EtOAc in Petroleum benzene. Ice-cold water (30 mL) was added to the reaction mixture after completion of reaction and left for 15 min. Solid was collected by filtration and washed with water. Solid product isolated in this way was used for analysis without further purification. Experimental procedure for the synthesis of compounds **2a–2e** is mentioned in the Supporting Information.

3. Results and Discussion

For the initial study of nitration, we have selected phenol as substrate. When stoichiometric amount of yttrium nitrate was used in acetic acid, nitration was completed within 10 min at room temperature. Analysis of the crude mixture showed (by HPLC, Figure 1) that

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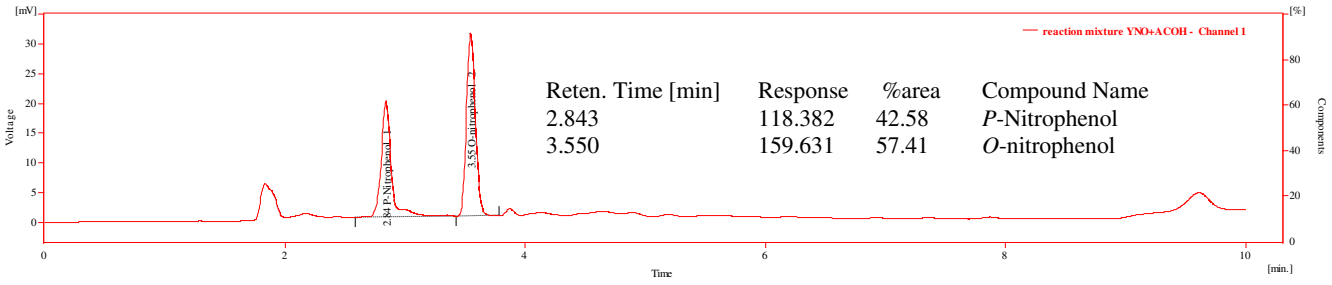
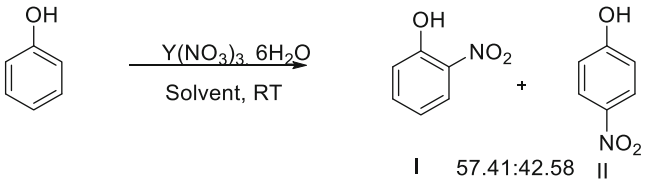


Figure 1. HPLC analysis of the reaction mixture containing phenol and $Y(NO_3)_3.6H_2O$ (1:1) in glacial acetic acid at RT.



Scheme 1. Nitration of phenol at room temperature.

phenol was converted into the nitrophenol I and II in a ratio 57:43 (Scheme 1). Compounds I and II appeared as light yellow precipitate after addition of water to the reaction mixture and simple filtration allowed isolation of the product.

In order make the process catalytic in nature, we used KNO_3 as the source of nitrate and catalytic amount of Yttrium nitrate (10 mol%) in glacial acetic acid (entry 2, Table 1). At room temperature, only 4% of compound I and 11% of compound II was identified by HPLC (Figure 2). About 54% phenol remained unaltered with formation of an unidentified product (Figure 2; fraction at 4.087 min). KNO_3alone in acetic acid at room temperature did not give nitration products of phenol. This suggests that yttrium (III) nitrate is essential. Presumably acyl nitrate is the active nitrating agent like other metal nitrate in acetic acid. Presence of water in the reaction mixture slows down the reaction. Water is not a good solvent of choice. Under anhydrous condition in THF, Lewis acid like LiBF4 (entry 6, Table 1) is needed. Progress of the reaction can be noted visually. Yttrium nitrate in acetic acid did not develop color even after 3 h at room temperature. However, in presence of phenol in the mixture of acetic acid and yttrium nitrate, the color changed from colorless to light yellow and finally deep brown. Deep brown coloration is an indication of the progress of nitration reaction.

Gu *et al.,* in 1997 reported nitration of meta-substituted phenols using $Y(NO_3)_3$ under refluxing in ethyl acetate and found symmetric tri-substituted product (meta-directing).[9] According to the report of Gu *et al.,* 3,5-dinitrophenol as the nitration product *meta*-nitrophenol under refluxing in ethyl acetate. However, we found the nitration of *m*-nitrophenol using $Y(NO_3)_3.6H_2O$ in acetic acid was slow and after two hours LCMS analysis showed that, two mono-nitration products in a ratio 57:33 (Figure 3). These mono-nitration products are presumably 2,4-dintrophenol (*p*-directed product, calculated mono-isotopic mass for $C_6H_4N_2O_5$ is 184.01; found 183.0 and 182.9, for M-H ion)[10] and its isomer 2,3-dinitrophenol (*o*-directed product). All attempts for purification of the isomeric dinitrophenols for further characterization by column chromatography was unsuccessful. This result shows that the nitration in acetic acid using $Y(NO_3)_3.6H_2O$ gives different selectivity. Here, the hydroxyl group acts as *ortho*/*para* directing group.

The method was also extended to various phenols as mentioned in Table 2. Nitration of *ortho*-vanillin resulted mono-nitration product in 92% yield within 10 min and the analytical data was collected without further purification (entry1). Similarly, vanillin was nitrated with 87% isolated yield within 10 min. Nitration of vanillin and *ortho*-vanillin were clean. Perez *et al*., reported 4-hydroxy-3-methoxy-5-nitrobenzaldehyde in a multistep strategy, *viz*., protection of hydroxyl group followed by nitration and deprotection[11] Whereas, $Y(NO_3)_3.6H_2O$ in glacial acetic acid gave exclusively 4-hydroxy-3-methoxy-5-nitrobenzaldehyde. The moderate isolated yield is because of the slight solubility of the product in water diluted reaction mixture. Structure of products was confirmed by ^{1}H-NMR. Phenolphthalein was nitrated into dinitrophenolphthalein (**2e**) smoothly. Fitzgerald and Gherkin in 1998 reported the crystal structure of dinitrophenolphthaleins[12] Nitration of phenolphthalein under controlled condition using sub-stoichiometric amount of $Y(NO_3)_3.6H_2O$ gave complicated mixture of mono and dinitro products. The structure of nitrophenolphthalein was confirmed by ^{1}H-, ^{13}C-NMR and LC-MS. These nitrophenolphthaleins are important materials for the synthesis 3′,3″-*di*-sulphanifylamino-phenolphthalein as potential chemotherapeutics for combating infected bile ducts.[13] Yttrium nitrate reacts rapidly with 2-napthol and the reaction mixture became dark brown to black within 10 minutes. The complex mixture was purified by repeated flash

Table 1. Optimization of reaction conditions of $Y(NO_3)_3.6H_2O$ mediated nitration of phenol.

Entry	Nitrating reagent[a]		Solvent	Temp. & time	Yield[b] (%) I	Yield[b] (%) II	Conv. (%)
1	$Y(NO_3)_3$, 1.0 eq	–	AcOH, glacial	RT, 10 min	57	43	100[c]
2	$Y(NO_3)_3$, 0.10 eq	KNO_3(1.5 eq)	AcOH, glacial	RT, 10 min	4	11	54[c]
3	$Y(NO_3)_3$, 1.0 eq	–	Water	RT, 30 min	0	0	0
4	–	KNO_3 (1.5) Eqv	AcOH, glacial	RT, 4h	–	–	Trace
5	$Y(NO_3)_3$, 0.10 eq	KNO_3 (1.5 eq)	AcOH/H_2O(3:1)	RT, 4h	70	30	20[c]
6	$Y(NO_3)_3$, (1.0 eq)	$LiBF_4$ (0.2 eq)	THF	RT, 30 min	65	35	40[c]

a. The reactions were carried out using 1.0 mmol of phenol and nitrate salts as mentioned in the table.
b. All the products are known and compared with authentic product by TLC, M.p., HPLC.
c. Conversion measured by HPLC (C18, CH_3CN:H_2O=70:30, measured at 254 nm, flow rate 1 mL/min).

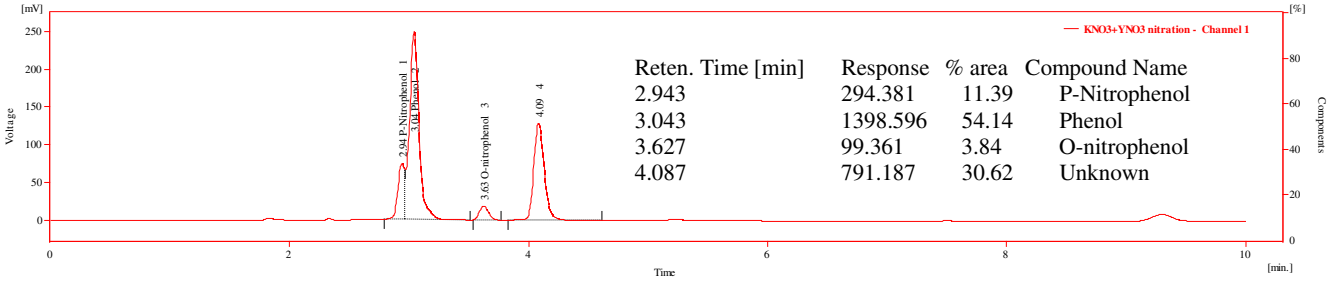


Figure 2. HPLC analysis of the reaction mixture containing phenol, KNO_3 and $Y(NO_3)_3.6H_2O$ (Molar ratio 1:1.5:0.1) in acetic acid at RT.

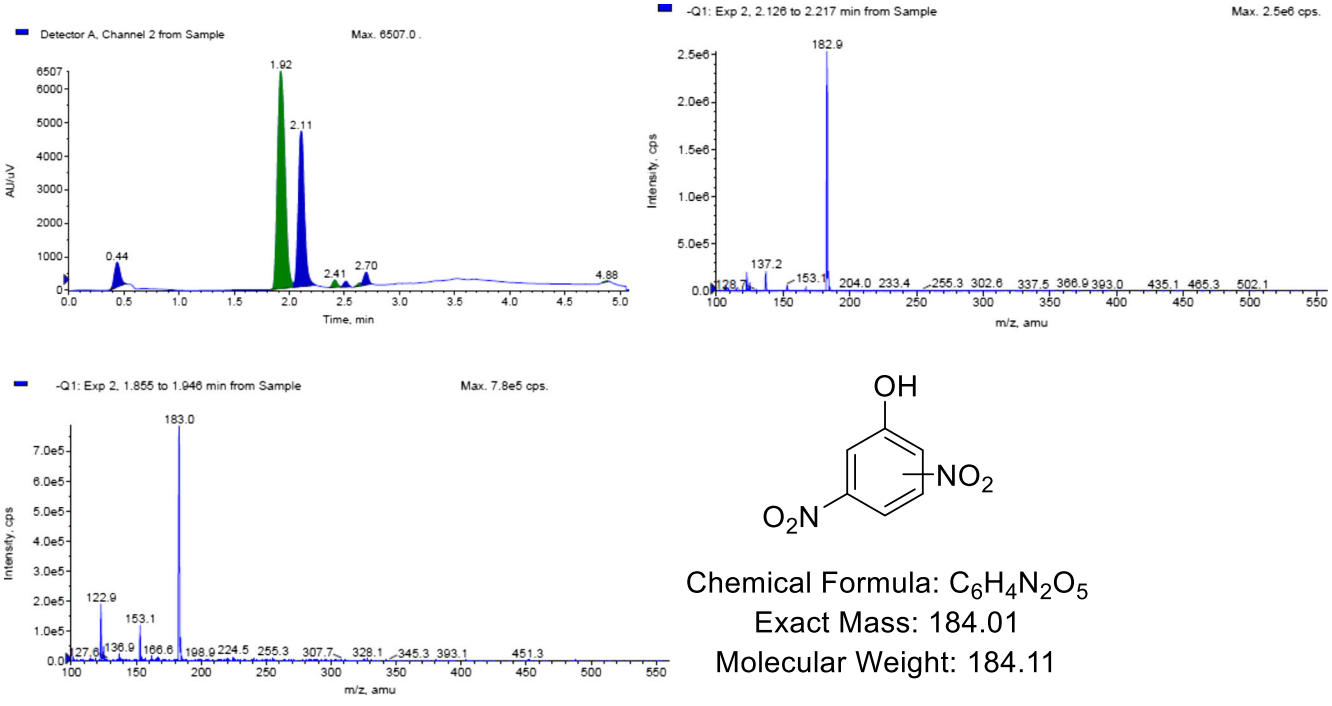
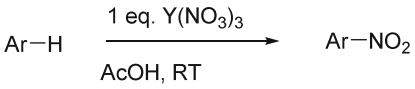
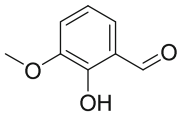
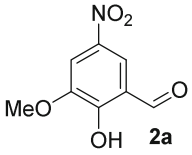
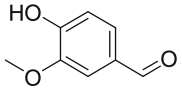
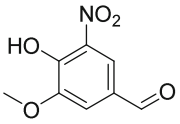
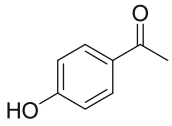
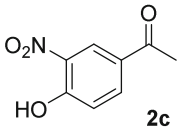
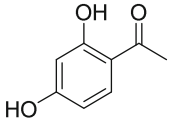
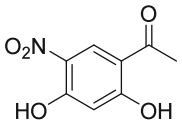
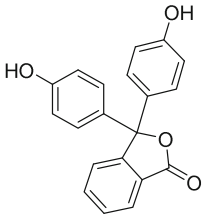
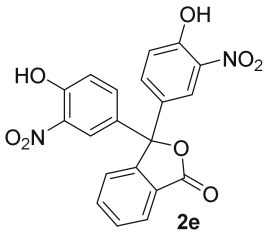
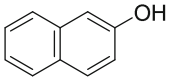
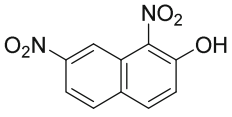
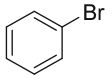
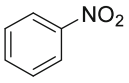
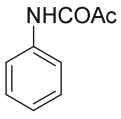


Figure 3. LC-MS of the reaction mixture containing equimolar mixture *m*-nitrophenol and yttrium nitrate in acetic acid stirred for 2 hours. (a) Liquid chromatogram using ZORBAX EXT (4.6×50 mm, 5μ) column, NH_4OAc (10 mM):CAN::90:10. (b) Mass spectra of the fraction eluted at 1.92 min. (c) Mass spectra of the fraction eluted at 2.11 min.

column chromatography and 1,6-dinitronaphthalen-2-ol (**2f**) was isolated in 41% yield as the major product. The low yield is because of the formation of all possible mono- and dinitro products along with the unidentified black solid. Isolated product was confirmed by LC-MS, ^{1}H-NMR and comparing them with those of reported

Table 2. Nitration of phenols with $Y(NO_3)_3.6H_2O$ at room temperature.



Entry	Substrates	Products	Time	Yield (%)[a]
1	 ***O*-vanillin**	 **2a**	10 min	92
2	 **vanillin**	 **2b**	10 min	87
3	 **4-hydroxy acetophenone**	 **2c**	4 h	91
4	 **2,4-dihydroxy acetophenone**	 **2d**	3 h	94
5	 **Phenolphthalein**	 **2e**	1 h	87
6	 **β-napthol**	 **2f**	–	41
7		No reaction	2 h	–
8		No reaction	2 h	–
9		No reaction	2 h	–
10	aniline	No reaction	2 h	–

a. Isolated yield without column purification.

NMR data.[14] Further study of this method revealed that aromatic ring without phenolic −OH is not reactive (entry 7–10, Table 2). Presence of electron withdrawing group makes the process slow. Surprisingly, activated ring containing acetanilide and aniline (entry 9 and 10, Table 2) did not react under the described method. This suggests that the nitration reaction is selective to phenols.

4. Conclusions

In summary, $Y(NO_3)_3.6H_2O$ in acetic acid was found to be an efficient nitrating reagent for the synthesis of nitro substituted phenolics at room temperature. The method offers several advantages including rapid nitration, high yield, simple experimental condition, and easy product isolation procedure. The method is selective for nitration of phenols and offers a suitable alternative for synthesizing nitrophenols. $Y(NO_3)_3.6H_2O$ in acetic acid gave different selectivity as compared to the previously reported nitration in ethylacetate under refluxing condition. Detailed mechanistic investigation as well as further scope of the nitration is under investigation.

Supplementary Information (SI)

Experimental details and NMR and LC-MS spectral data for this article can be accessed at www.ias.ac.in/chemsci.

Acknowledgements

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