

An Efficient and Regioselective Nitration of Phenols Using NH_4NO_3 , KHSO_4

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ABSTRACT

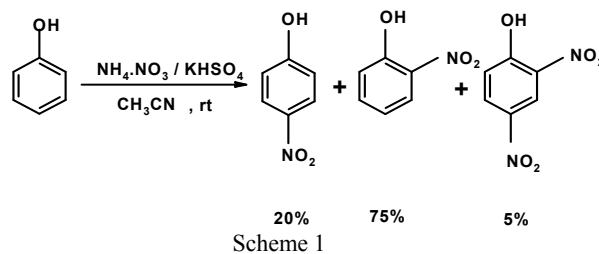
Phenols were nitrated regioselectivity with NH_4NO_3 in the presence of KHSO_4 as a catalyst in high yields.

Key Words: Nitration, Phenols, NH_4NO_3 , KHSO_4 .

1. INTRODUCTION

Electrophilic aromatic substitution reactions are of considerable importance in the production of fine chemicals. Nitration of organic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature. Extensive and well-documented reviews have been published by Ingold, [1] Olah and co-workers, [2,3] Schofield and co-workers, [4,5] and Ione.[6] Nitration in manufacturing process require the use of potent mixtures of concentrated or fuming nitric acid with sulfuric acid leading to excessive acid waste. Nitration of phenol as a special case has been studied using various nitrating agents under different conditions.[7-25] The distribution of the *ortho:para* isomer ratio in electrophilic aromatic substitution of activated monosubstituted benzenes continues to challenge organic chemists. The regioselectivity is governed by steric hindrance, interaction between the substituent and the reagent, electronic effects, and solvent effects.[26] Nitration of benzene derivatives with electron donating substituent leads to substitution at the *o*- and *p*-positions according to a statistical distribution. Steric bulkiness of reagent and/or substrate usually provides high concentrations of the *p*-products.[27] The use of supported reagents [28] and catalysts are known to favor the *para* substitution.[6,7] *o*-Nitrophenol is an important starting material used in multiple step syntheses of valuable compounds.[29] They are also valuable precursors to a variety of biologically important heterocycles such as 2,3-dihydro-2H-1,4-benzoxin-3(4H)-ones,[30] and benzoxazoles.[31]

Thus, a convenient method for the regioselective introduction of an *ortho* nitro group onto phenols is desirable. Herein, we report our results on the regiospecific nitration of phenols and their derivatives using NH_4NO_3 , KHSO_4 . (Scheme 1) Our goal in undertaking this line of work was three fold, a) to overcome the limitation and draw-back of the reported methods such as: tedious work up,[12-14] strongly acidic media,[7b] oxidation ability of the reagent and safety problems (storage, handling) [32,33] ;b) to reach high yielding one pot synthesis of mono nitro phenol using a combination of reagent and c) to consider the rules of green chemistry to implement nitration in eco-friendly conditions.



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2. EXPERIMENTAL

Nitration of phenols with NH₄NO₃, KHSO₄. Typical procedure: 4-Bromo phenol (0.14g, 1 mmol), NH₄NO₃ (0.14g, 2 mmol) and KHSO₄ (0.05 mmol) in acetonitrile (5ml) was magnetically stirred at reflux temperature. After the completion of reaction, the reaction mixture was filtered (the progress of the reaction was monitored by TLC). The residue was washed with acetonitrile (2x3mL). Anhydrous Na₂SO₄ (4 g) was added to the combined filtrate. The mixture was filtered. The solvent was removed by distillation using a water bath (35-40 °C) to obtain the product.

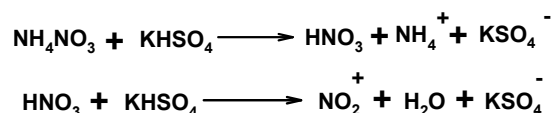
2-Nitrophenol (2a). mp 46 °C (lit. [34] 44.9 °C); IR (KBr) (ν_{\max} , cm⁻¹): 3572, 3050, 1538, 1340; ¹H NMR (CDCl₃, 300 MHz) δ_{H} (ppm): 7.03-7.83 (m, 4H, arom), 10.12 (brs, OH). GC/MS: 139 (M⁺).

4-Methyl-2-nitrophenol (2b). mp 35 °C (lit. [35] 34-35 °C); IR (KBr) (ν_{\max} , cm⁻¹): 3569, 3055, 1539, 1346; ¹H NMR (CDCl₃, 300 MHz) δ_{H} (ppm): 2.49 (s, 3H); 7.11-7.54 (m, 3H, arom), 10.06 (brs, OH). GC/MS: 153 (M⁺).

3. RESULT AND DISCUSSION

As far green chemistry concerns, sulfuric acid in any form is notorious and its safe disposal is one of the problems and concerns of chemical industries and therefore its replacement with safer reagent is desirable. We have recently used, KHSO₄ as a safe and green reagent in synthesis of 1,1-diacetales [36a] and facile synthesis of quinoxallines.[36b] Armed with these experience, it occurred to us, that the replacement of

sulfuric acid with KHSO₄ as a safer reagent might result in more efficient, selective and high yielding nitration with a more reasonable mechanism for generation of NO₂⁺. (Scheme 2) Recently polymers have been nitrated with ammonium nitrate (NH₄NO₃) and trifluoroacetic anhydrid.[37] Thus, we have treated a variety of phenols, having at least one unsubstituted *ortho* position with NH₄NO₃, KHSO₄ and , as shown in Table 1, obtained *o*-nitrophenols in all cases. The yields are good to excellent with high regioselectivity compared with the previous methods (Table 2). The nitration reaction can be carried out by placing the nitrating agents, phenols and the solvent used in a reaction vessel and efficiently stirring the mixture at reflux temperature. The resulting mononitrophenols can be obtained by simple filtration and evaporation of the solvent. The progress of the reaction was monitored by TLC. The percentage of products was obtained by GC/MS analysis. Among the solvents used such as CH₂Cl₂, Ethanol, Ethylacetate, chloroform and CH₃CN, the latter gave the best yields of the *o*-nitro phenols at reflux temperature. The scope of this nitration was widen by nitration of naphтол to give mono-nitrated in high yields (Table 1).



Scheme 2

Table 1. Selective and eco-friendly nitration of phenols.

Entry	Substrates	Products	Time(h)	Yields(%) ^a
1	Phenol	<i>o</i> -nitro phenol	6	75
2	4-nitro phenol	2,4-dinitro phenol	6	98
3	4-bromo phenol	2-nitro-4-bromo phenol	6	97
4	4-methoxy phenol	2-nitro4-methoxy phenol	5	97
5	4-chloro phenol	2-nitro4-chloro phenol	5	96
6	4-methyl phenol	2-nitro4-methyl phenol	5	96
7	3-bromo phenol	2-nitro-5-bromo phenol	5	81
8	3-methyl phenol	2-nitro5-methyl phenol	5	83

9 2-naphtol 1-nitro2-naphtol 5 98

a) All of the isolated products were characterized by GC/MS analysis.

Table 2. Nitration of phenol with different methods.

Entry	Reagent	o-nitro phenol (%)	p-nitro phenol (%)
1	NH ₄ NO ₃ / KHSO ₄	75	20
2	Cu(NO ₃) ₂ . 3H ₂ O[38]	40	60
3	HNO ₃ /Microemulsion[12]	50	50
4	ZrO(NO ₃) ₂ . XH ₂ O[39]	40	60
5	NaNO ₃ /Mg(HSO ₄) ₂ [40]	36	26
6	NaNO ₃ /Silica sulfuric acid[41]	30	20
7	silica sulfuric acid-supported bismuth(III) nitrate[42]	15	85
8	Bi(NO ₃) ₃ .5H ₂ O[43]	34	37
9	iron(III) nitrate[44]	50	50

In conclusion, a regioselective ortho nitration of a various phenols and naphtol using green, available, inexpensive and easy to handle NH₄NO₃/KHSO₄ reagent has been reported. Therefore, the present method is believed to be a suitable method for the synthesis of nitro compounds in organic synthesis.

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