# A practical approach for regioselective mono-nitration of phenols under mild conditions

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**Abstract**

$Cu(NO_3)_2.3H_2O$ was demonstrated to be an efficient, regioselective and inexpensive nitrating reagent for the synthesis of mono-nitro substituted phenolic compounds. 12 examples of different phenols were examined. Good yields (67-90%) have been achieved.

**Keywords:** Nitration, regioselective, metal nitrates, phenolic compounds

## Introduction

Nitration of aromatic compounds is one of the most important reactions in organic synthesis, since the nitro compounds are very useful in many industrial processes.[1-5] They often are critical materials for pharmaceuticals, perfumes, plastics and so on.[6-8] Usually, nitration reactions suffer from low regioselectivity and over nitration.[9-12] The typical process usually requires using mixture of concentrated or fuming nitric acid and concentrated sulfuric acid. The disposal of strong acid waste and generation of nitrogen oxide are environmental concerns. Therefore, traditional nitration method seems uneconomical and hazardous.

Nitrophenols, among these useful nitro compounds, present similar problems during synthesis. And as phenols are highly reactive, the nitration of phenols using strong acids is always unselective and leads to side products such as dinitro compounds, oxidized products, and so on. In the last decade, much effort has been made on nitration of phenols.[13-20] A variety of acidic nitrating agents, including concentrated nitric acid, nitrogen oxides, anhydrides or triflates, and solid acids have been employed. Also many methods have been reported using metal nitrates as source of nitronium ion.[21-30] However, these metal nitrates often need extra co-reagents such as phase transfer catalysts or expensive ionic liquids achieve desirable outcomes. Therefore, it is worthwhile to seek for alternative methods that could overcome these problems.

Recently, we have reported efficient chlorination and bromination of unprotected anilines using copper halides in ionic liquids.[31] Herein, we report our results on highly regioselective mono-nitration of phenols and their derivatives using a metal nitrate without any catalyst or co-reagent.

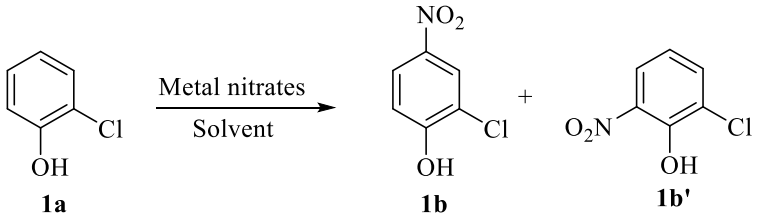
## Results and Discussion

We chose **1a** as the substrate for initial study. The nitration reactions can be readily carried out by mixing the phenol, nitrating reagent and solvent in a vessel and stirring the resultant heterogeneous mixture. Various metal nitrates were screened and the results are summarized in Table 1. The reaction did not show good regioselectivity when using $Fe(NO_3)_3.9H_2O$ and $Bi(NO_3)_3.5H_2O$ as the nitrating reagent. The ratio of the p-nitro and o-nitro products were about 1:1(Table 1, entries 1 and 3) and the temperature needed to reach above 50 $^oC$ to obtain reasonable yield. The o-nitro product **1b**' was obtained as the major product in 36% yield using $Ni(NO_3)_2.6H_2O$. For $Cu(NO_3)_2.3H_2O$, it showed the best performance and resulted in o-nitro product **1b** as the major product in 85% yield (Table 1, entry 10). The progress of the reaction could be monitored by a visible change in the color of the reaction mixture and also by TLC. When 1 equiv of 1a and $Cu(NO_3)_2.3H_2O$ (1.5 equiv) were mixed in THF and was heated to 50 $^oC$, the color was deepened to green and turbid, it then turned brown and finally blue. However, no nitrated phenols were formed by using other nitrate salts such as $Ba(NO_3)_2$, $Ca(NO_3)_2.4H_2O$, $KNO_3$, $AgNO_3$ (Table 1, entries 6-9). Besides, we also investigated the effect of different solvents on the reaction. Among the solvents used such as THF, $CH_3CN$, $CH_2Cl_2$ and chloroform, THF was proved to be the best solvent.

After choosing the best nitrating reagent and solvent, nitration of a variety of phenolic compounds by using $Cu(NO_3)_2.3H_2O$ as the nitrating reagent in THF were examined. The results are summarized in Table 2. Phenols with electron donating groups were very active and smoothly afforded the p-nitro and o-nitro phenols at around 50 $^oC$ in very short time (Table 2, entries 5 and 6). Although the p-nitro phenols were the major products, they would afford dinitro-product if the reaction time was longer. Phenols with stronger electron withdrawing groups gave similar results, they yielded the p-nitro products as the major product at reflux for longer time without any dinitro-products (Table 2, entries7, 9 and 11). For phenols with Cl on 2 or 3 positions, they showed better regiospecificity and resulted in p-nitro phenols as the exclusive product, although Cl was also an electron withdrawing group (Table 2, entries 1 and 2). Moreover, the nitration reactions occurred regioselectively at the ortho position relative to the OH group, when there was either an electron donating group or an electron withdrawing group at the para position (Table 2, entries 3, 8, 10 and 12).

**Table 1**. Nitration of phenol compound **1a** with different nitrate salts and solvents[a]




| Entry | Metal Nitrates | Solvent | Time (h), Temp.(°C) | Yield[b] (%) | |
|---|---|---|---|---|---|
| | | | | **1b** | **1b**' |
| 1 | $Fe(NO_3)_3.9H_2O$ | THF | 4, 50 | 31 | 33 |
| 2 | $Ni(NO_3)_2.6H_2O$ | THF | 4, 50 | 28 | 36 |
| 3 | $Bi(NO_3)_3.5H_2O$ | THF | 4, 50 | 42 | 35 |
| 4 | $Ba(NO_3)_2$ | THF | 4, reflux | - | - |
| 5 | $Ca(NO_3)_2.4H_2O$ | THF | 4, reflux | - | - |
| 6 | $KNO_3$ | THF | 4, reflux | - | - |
| 7 | $AgNO_3$ | THF | 4, reflux | - | - |
| 8 | $Cu(NO_3)_2.3H_2O$ | THF | 4, 50 | 85 | 5 |
| 9 | $Cu(NO_3)_2.3H_2O$ | MeCN | 4, 50 | 45 | 10 |
| 10 | $Cu(NO_3)_2.3H_2O$ | Acetone | 4, 50 | 60 | 11 |
| 11 | $Cu(NO_3)_2.3H_2O$ | $CH_2Cl_2$ | 4, 50 | 32 | 15 |
| 12 | $Cu(NO_3)_2.3H_2O$ | $CHCl_3$ | 4, 50 | 33 | 12 |

[a] The reactions were carried out using 1.0 mmol of **1a** and 1.5 mmol of nitrate salts. [b] Isolated yield.

**Table 2.** Nitration of phenolic compounds with $Cu(NO_3)_2.3H_2O$ in THF[a]

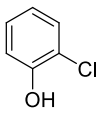
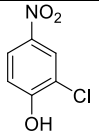
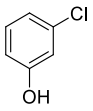
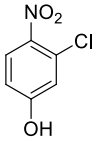
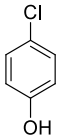
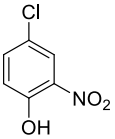
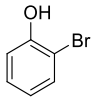
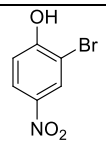
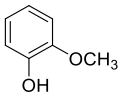
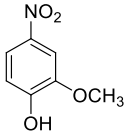
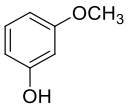
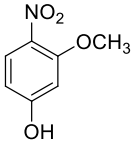
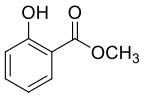
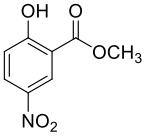
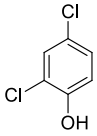
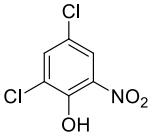
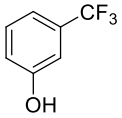
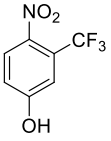
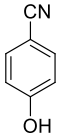
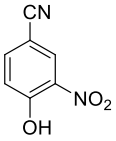
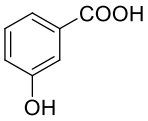
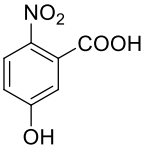
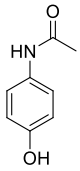
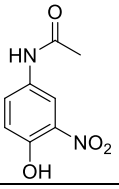
| Entry | Substrates | Reaction conditions | Major Product[b] | Yield[c](%) |
|---|---|---|---|---|
| 1 |  | 50 °C, 4 h |  | 85 |
| 2 |  | 50 °C, 4 h |  | 90 |
| 3 |  | 50 °C, 4 h |  | 87 |

**Table 2 (continued)**

| | | | | |
|---|---|---|---|---|
| 4 |  | 50 °C, 4 h |  | 75 |
| 5 |  | 50 °C, 1 h |  | 70 |
| 6 |  | 50 °C, 1 h |  | 75 |
| 7 |  | reflux, 1 h |  | 75 |
| 8 |  | reflux, 1 h |  | 88 |
| 9 |  | reflux, 2 h |  | 69 |
| 10 |  | reflux, 3 h |  | 67 |
| 11 |  | reflux, 3 h |  | 70 |
| 12 |  | reflux, 40 min |  | 75 |

[a] The reaction were carried out using 1.0 mmol of **1a** and 1.5 mmol of nitrate salts. [b]All the products were determined by NMR and mass spectroscopy. [c]Isolated yield of the major product.

## Conclusions

In summary, $Cu(NO_3)_2.3H_2O$ was found to be an efficient, safe, and inexpensive nitrating reagent for the synthesis of mono-nitro substituted phenolic compounds either at 50 ºC or at reflux. This methodology offers a suitable alternative for the preparation of nitro phenolic compounds in organic synthesis.

## Experimental Section

**General** Unless otherwise noted, solvents and starting materials were obtained from commercial suppliers. All chemicals used were of reagent grade without further purification before use. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance (400 MHz for $^1$H, and 100 MHz for $^{13}$C) in $CDCl_3$, MeOH-$d_4$, DMSO-$d_6$. Chemical shifts were recorded in ppm (δ) relative to $CHCl_3$ on 7.26 or TMS on 0.00 for $^1$H NMR and 77.0 for $^{13}$C NMR, to MeOH on 3.31 for $^1$H NMR and 49.0 for $^{13}$C NMR, to DMSO on 2.50 for $^1$H NMR and 39.5 for $^{13}$C NMR. High-resolution mass spectra were recorded on an IT-TOF of Shimadzu mass spectrometer.

**General experimental procedure for nitration of phenols** A suspension of 2-methylphenol (18.5 mmol, 1.0 eq) and $Cu(NO_3)_2.3H_2O$ (27.7 mmol, 1.5 eq) in THF was stirred magnetically at 60 ºC or reflux for several hours. Then after the solvent was removed under vacuum, the mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography to afford the product (67-90%).

**2-Chloro-4-nitrophenol.** $^1$H NMR (400 MHz, $CDCl_3$) 8.32 (d, *J* 2.8 Hz, 1H, Ar-H), 8.15 (dd, *J* 9.2, 2.8 Hz, 1H, Ar-H), 7.15 (d, *J* 9.2 Hz, 1H, Ar-H), 6.38 (s, 1H, OH). $^{13}$C NMR (100 MHz, $CDCl_3$) 156.9, 141.6, 125.3, 124.6, 120.3, 116.3.

**3-Chloro-4-nitrophenol.** $^1$H NMR (400 MHz, $CDCl_3$) 8.0 (d, *J* 8.8 Hz, 1H, Ar-H), 7.03 (d, *J* 2.4 Hz, 1H, Ar-H), 6.85 (dd, *J* 8.8, 2.4 Hz, 1H, Ar-H), 6.20 (s, 1H, OH). $^{13}$C NMR (100 MHz, $CDCl_3$) 159.6, 129.9, 128.3, 118.6, 114.4.

**4-Chloro-2-nitrophenol.** $^1$H NMR (400 MHz, $CDCl_3$) 10.5 (s, 1H, OH), 8.13 (d, *J* 2.4 Hz, 1H, Ar-H), 7.56 (dd, *J* 8.8, 2.4 Hz, 1H, Ar-H), 7.16 (d, *J* 8.8 Hz, 1H, Ar-H). $^{13}$C NMR (100 MHz, $CDCl_3$) 153.7, 137.6, 125.2, 124.3, 121.4.

**2-Bromo-4-nitrophenol.** $^1$H NMR (400 MHz, DMSO-*d*6) 11.99 (s, 1H, OH), 8.35 (d, *J* 2.8 Hz, 1H, Ar-H), 8.12 (dd, *J* 8.8, 2.8 Hz, 1H, Ar-H), 7.10 (d, *J* 8.8 Hz, 1H, Ar-H). $^{13}$C NMR (100 MHz, DMSO-*d*6) 161.1, 140.3, 129.2, 125.6, 116.3, 109.8.

**2-Methoxy-4-nitrophenol.** $^1$H NMR (400 MHz, $CDCl_3$) 7.91 (dd, *J* 8.8, 2.4 Hz, 1H, Ar-H), 7.79 (d, *J* 2.4 Hz, 1H, Ar-H), 7.01 (d, *J* 8.8 Hz, 1H, Ar-H), 6.22 (s, 1H, OH), 4.01 (s, 3H, $OCH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) 151.6, 146.1, 141.2, 118.6, 114.0, 106.3, 56.5.

**3-Methoxy-4-nitrophenol.** $^{1}$H NMR (400 MHz, $CDCl_3$) 11.05 (s, 1H, OH), 8.03 (d, *J* 2.4 Hz, 1H, Ar-H), 6.55 (d, *J* 2.8 Hz, 1H, Ar-H), 6.53 (d, *J* 5.6 Hz, 1H, Ar-H), 3.9 (s, 3H, $OCH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) 167.1, 158.0, 127.8, 126.9, 109.4, 101.5, 56.1.
**Methyl 2-hydroxy-5-nitro benzoate**. $^{1}$H NMR (400 MHz, DMSO-*d*6) 11.5 (s, 1H, OH), 8.54 (d, *J* 2.8 Hz, 1H, Ar-H), 8.33 (d, *J* 9.2 Hz, 1H, Ar-H), 7.18 (d, *J* 9.2 Hz, 1H, Ar-H), 3.90 (s, 3H, $COOCH_3$). $^{13}$C NMR (100 MHz, DMSO-*d*6) 166.6, 164.5, 139.7, 130.2, 127.3, 119.0, 115.7, 53.2.
**2, 4-Dichloro-6-nitrophenol.** $^{1}$H NMR (400 MHz, $CDCl_3$) 10.9 (s, 1H, OH), 8.09 (s, 1H, Ar-H), 7.70 (s, 1H, Ar-H). $^{13}$C NMR (100 MHz, $CDCl_3$) 150.3, 137.4, 134.3, 125.8, 124.7, 123.1.
**4-Nitro-3-(trifluoromethyl) phenol.** $^{1}$H NMR (400 MHz, $CDCl_3$) 10.6 (s, 1H, OH), 8.25 (d, *J* 8.8 Hz, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 6.87 (dd, *J* 8.8, 1.6 Hz, 1H, Ar-H). $^{13}$C NMR (100 MHz, $CDCl_3$) 154.8, 138.5 (q, *J* 33.0 Hz), 135.3, 126.1, 128.2 (q, *J* 272.0 Hz), 126.1, 117.9, 116.6.
**4-Cyano-2-nitrophenol.** $^{1}$H NMR (400 MHz, $CDCl_3$) 10.9 (s, 1H, OH), 8.5 (s, 1H, Ar-H), 7.85 (d, *J* 8.8 Hz, 1H, Ar-H), 7.32 (d, *J* 8.8 Hz, 1H, Ar-H). $^{13}$C NMR (100 MHz, $CDCl_3$) 157.8, 139.6, 130.1, 121.8, 116.6, 104.6.
**5-Hydroxy-2-nitrobenzoic acid.** $^{1}$H NMR (400 MHz, DMSO-*d*6) 7.75 (d, *J* 8.8 Hz, 1H, Ar-H), 6.91 (d, *J* 2.4 Hz, 1H, Ar-H), 6.85 (dd, *J* 8.8, 2.4 Hz, 1H, Ar-H). $^{13}$C NMR (100 MHz, DMSO-*d*6) 168.9, 162.8, 139.3, 138.7, 126.3, 115.3, 115.2, 49.1.
***N*-(4-Hydroxy-3-nitrophenyl)acetamide.** $^{1}$H NMR (400 MHz, $CDCl_3$) 10.4 (s, 1H, OH), 8.28 (s, 1H, NH), 7.78 (d, *J* 7.2 Hz, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 7.16 (d, *J* 9.2 Hz, 1H, Ar-H), 2.22 (s, 3H, $COCH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) 168.4, 151.8, 133.0, 130.6, 130.5, 120.3, 115.7, 30.9. HRMS m/z calcd for $C_8H_9N_2O_4$ $[M+H]^+$ = 197.0484, found 197.0476.

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