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Highly Efficient Nitration of Phenolic Compounds in Solid Phase or Solution Using $Bi(NO_3)_3\cdot 5H_2O$ as Nitrating Reagent

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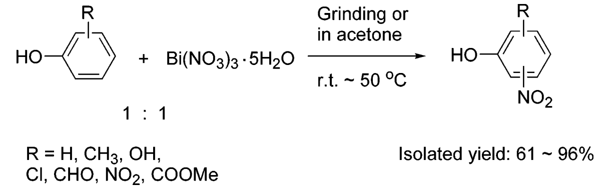
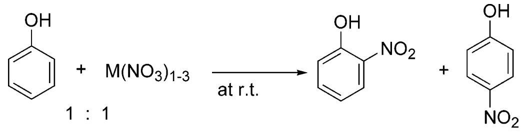
Received July 15, 2005



$Bi(NO_3)_3\cdot 5H_2O$ was used as an efficient nitrating reagent in the nitration of phenolic compounds to give nitrated phenols in good to high yields. The nitration reaction proceeded smoothly by grinding 1 equiv of phenol, 2-methylphenol, 4-methylphenol, or 4-chlorophenol and $Bi(NO_3)_3\cdot 5H_2O$, and the nitration of other phenolic compounds could be performed in acetone at ambient temperature (22−30 °C).

Nitroaromatic compounds are one of the most important classes of organic compounds, and they can be prepared from the nitration of relative aromatic compounds. A mixture of concentrated nitric acid and sulfuric acid has been used as the most common nitrating reagent for the nitration of benzene, alkylbenzene, and less reactive aromatic compounds,[1] but highly reactive aromatic compounds, particularly easily oxidized substrates such as aniline, phenols, pyrroles, etc., require mild nitration conditions; thus, a wide variety of nitrating reactions have been developed.[2] Because nitrophenols are very important organic synthetic intermediates, it is still an interesting subject of organic synthesis to develop the nitrating procedures of phenolic compounds under mild conditions. The recent development of nitration of phenolic compounds using nitrate salts such as $VO(NO_3)_3$,[3] $Fe(NO_3)_3\cdot 9H_2O$,[4] $(Me_4N)NO_3$,[5] $Mg(NO_3)_2\cdot 6H_2O$,[6] and $NaNO_3$,[7] as the nitrating reagents has been reported. However, the reported nitration procedure by using nitrate salts as nitrating reagents required either special solvents or co-reagents.

TABLE 1. Nitration of Phenol with an Equivalent of Nitrate Salts[a]



1a **2a** **2a'**

entry	$M(NO_3)_{2-3}$	reaction conditions	**2a**[b] (%)	**2a'**[b] (%)
1	$Bi(NO_3)_3\cdot 5H_2O$	grinding, <5 min	34	37
2	$Bi(NO_3)_3\cdot 5H_2O$	in acetone, <5 min	46	47
3	$Fe(NO_3)_3\cdot 9H_2O$	grinding, <5 min	29	31
4	$Ni(NO_3)_3\cdot 9H_2O$	grinding, >10 min	no reaction	
5	$Ba(NO_3)_2$	grinding, >10 min		
6	$Ca(NO_3)_2\cdot 4H_2O$	grinding, >10 min		
7	$Cu(NO_3)_2\cdot 3H_2O$	grinding, >10 min		
8	KNO_3	grinding, >10 min		
9	$AgNO_3$	grinding, >10 min		

[a] The reactions were carried out using 1.0 mmol of phenol and 1.0 mmol of nitrate salts. [b] Isolated yield based on the amount of phenol used.

$Bi(NO_3)_3$ had been employed as a co-catalyst in the nitration of phenolic compounds with 65% nitric acid[8] and as a nitrating reagent of aromatic compounds catalyzed by montmorillonite KSF.[9] In this paper, we report the results of our investigation on the nitration of phenolic compounds using $Bi(NO_3)_3\cdot 5H_2O$ as a nitrating reagent in the solid phase or in solution at ambient temperature (22−30 °C), and this nitrating reaction could proceed without catalyst and co-reagent.

Table 1 summarized the results of nitration of phenol **1a** with a number of nitrate salts. When 1 equiv of **1a**

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(8) $Bi(NO_3)_3$ used as co-catalyst in the nitration of phenolic compounds by 65% nitric acid has been reported; see: Shi, M.; Cui, S.-C. *Adv. Synth. Catal.* **2003**, *345*, 1197−1202.

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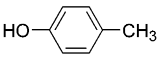
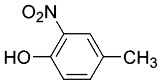
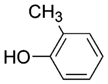
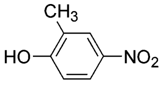
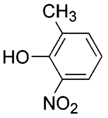
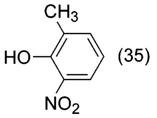
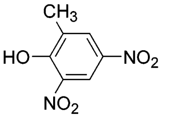
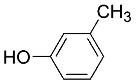
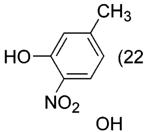
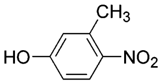
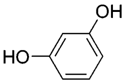
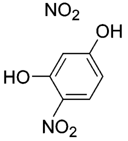
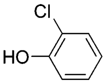
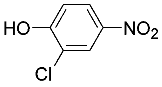
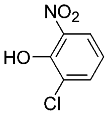
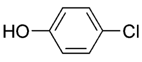
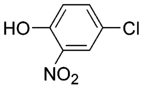
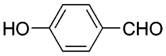
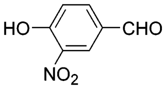
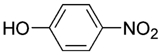
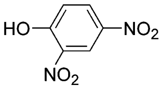
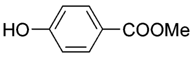
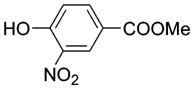
TABLE 2. Nitration of Phenolic Compounds with an Equivalent of $Bi(NO_3)_3·5H_2O$[a]

entry	phenolic compound	reaction conditions	nitrated compound (% isolated yield)[b]
1		r.t., Grinding, < 5 min.	 (63)
2		r.t., in acetone, < 5 min.	(72)
3[c]		r.t., in acetone, < 5 min.	 (51)  (42)
4		r.t., in acetone, < 5 min.	 (35)  (45)
5		r.t., in acetone, < 5 min.	 (22)  (39)
6		50 °C, in acetone, < 5 min.	 (75)
7		r.t., Grinding, < 5 min.	 (42)  (35)
8		r.t., Grinding, < 5 min.	 (88)
9		r.t., in acetone, < 5 min.	(83)
10		r.t., in acetone, 6 h.	 (80)[d]
11		r.t., in acetone, 6 h.	 (99)[d]
12		r.t., in acetone, 15 h.	 (96)

[a] The reactions were carried out using 1.0 mmol of phenol, 1.0 mmol of $Bi(NO_3)_3·5H_2O$, and 1.0 mL of solvent (if required). [b] Isolated yield based on the amount of phenol used. [c] 0.5 mmol of $Bi(NO_3)_3·5H_2O$ was used. [d] Determined by ^1H NMR using 1,2,4,5-tetramethylbenzene as internal standard material.

and $Bi(NO_3)_3·5H_2O$ (1.0 mmol) was quickly ground at ambient temperature for 1−2 min, the solid mixture became warm. After continued grinding for 2−3 min, CH_2Cl_2 (20 mL) was then added to extract the organic compounds immediately. 2-Nitrophenol (34%) and 4-nitrophenol (37%) were easily obtained by separation using preparative TLC (silica, eluent: diethyl ether/cyclohexane = 1/4) (Table 1, entry 1).[10] We also carried out the same reaction in acetone (5 mL), and a higher yield of nitrated phenols could be isolated (Table 1, entry 2). Although $Fe(NO_3)_3·9H_2O$ showed the reactivity with **1a** in the solid phase to give the nitrated products in a total yield of 60% (Table 1, entry 3), no nitrated phenols were formed by using other nitrate salts such as $Ni(NO_3)_2·6H_2O$, $Ba(NO_3)_2$, $Ca(NO_3)_2·4H_2O$, $Cu(NO_3)_2·3H_2O$, KNO_3, and $AgNO_3$.

The results of nitration reactions of a variety of phenolic compounds by using $Bi(NO_3)_3·5H_2O$ as nitrating reagent were concluded in Table 2. 4-Methyl-2-nitrophenol was isolated in 63% and 72% yields by the nitration reaction of 4-methylphenol in the solid phase and acetone solution, respectively (Table 2, entries 1 and 2). In the case of 2-methylphenol, the nitration reaction in acetone using 0.5 equiv of $Bi(NO_3)_3·5H_2O$ afforded 4-nitro-2-methylphenol and 6-methyl-2-nitrophenol in 51% and 42% yields, respectively (Table 2, entry 3), but the use of 1 equiv of $Bi(NO_3)_3·5H_2O$ resulted in the formation of the dinitrated product of 6-methyl-2, 4-dinitrophenol, which arose from the nitration of 4-nitro-2-methylphenol and 6-methyl-2-nitrophenol (Table 2, entry 4). 3-Meth-

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(10) All of the obtained nitrated phenolic compounds are known compounds, determined and confirmed by GC−MS and ^1H NMR.

ylphenol was nitrated to give 5-methyl-2-nitrophenol and 3-methyl-4-nitrophenol in 22% and 39% isolated yields (Table 2, entry 5). Although the corresponding 4-nitro-1,3-benzenediol was obtained in 75% yields by the nitration of resorcinol (Table 2, entry 6), under the same reaction conditions, the reactions of 1,4-benzenediol and catechol with $Bi(NO_3)_3 \cdot 5H_2O$ resulted in complicated products containing nitrated and oxidized products.

In the case of 2-chlorophenol, two nitrated products, 2-chloro-4-nitrophenol (42%) and 2-chloro-6-nitrophenol (35%), were obtained by grinding (Table 2, entry 7). However, other phenolic compounds containing an electron-withdrawing group at the para position were obtained when the nitration reactions occurred regioselectively at the ortho position relative to the OH group. Thus, 4-chloro-2-nitrophenol was isolated in 88% and 83% yield from the reaction of 4-chlorophenol with $Bi(NO_3)_3 \cdot 5H_2O$ by grinding or in acetone, respectively (Table 2, entries 8 and 9). The nitration reactions of 4-hydroxybenzaldehyde, 4-nitrophenol, and methyl 4-hydroxybenzoate afforded the corresponding ortho NO_2-substituted compounds in good to high yield after a prolonged reaction time (Table 2, entries 10−12). It should be noted that in the cases of 4-hydroxybenzaldehyde and 4-nitrophenol the nitrated products could not be isolated in satisfactory yield because of the decomposition of products when they were subjected to TLC isolation.

In summary, we have found that $Bi(NO_3)_3 \cdot 5H_2O$ is an efficient and convenient nitrating reagent for the nitration of phenolic compounds in the solid phase or in solution under air at ambient temperature. The present nitrating reaction proceeded to give the nitrated phenols in good to high yields and was easily worked up.

Experimental Section

Typical Experimental Procedures for Phenol Nitration. (1) In the Solid Phase. A solid mixture of phenol (1.0 mmol) and $Bi(NO_3)_3 \cdot 5H_2O$ (1.0 mmol) was ground at ambient temperature for less than 5 min, and then CH_2Cl_2 (20 mL) was added to extract the organic compounds immediately an the insoluble materials were filtered. After the filtrate was concentrated, the nitrated products were purified by preparative TLC (silica) using a solvent mixture of diethyl ether and cyclohexane (1:4) as eluent. 2-Nitrophenol and 4-nitrophenol were isolated in 34% (47.3 mg, 0.43 mmol) and 37% (51.4 mg, 0.37 mmol) yields, respectively. The structures of the nitrated products were confirmed by GC−MS and ^1H NMR.

(2) In Acetone Solution. To a solid mixture of phenol (1.0 mmol) and $Bi(NO_3)_3 \cdot 5H_2O$ (1.0 mmol) was added acetone (5.0 mL), the resulting mixture was then stirred at ambient temperature for ca. 3−4 min. The insoluble materials were filtered out immediately and washed by CH_2Cl_2 (10 mL), and the filtrate was concentrated. The nitrated products were isolated as described above to give 2-nitrophenol and 4-nitrophenol in 46% (64.0 mg, 0.46 mmol) and 47% (65.3 mg, 0.47 mmol) yield, respectively.

The same results could be obtained on a 10 mmol scale in both the solid phase and in solution. In these cases, the highest temperature of the exothermic reaction mixture reached to 43 °C in the solid phase and 45 °C in acetone solution. Therefore, we recommend taking safety precautions when the nitration reaction is performed on a large scale.

Acknowledgment. Financial support from Tsinghua University for Ph.D. Candidate's research is gratefully acknowledged.

Supporting Information Available: MS data and ^1H NMR charts of the nitrated products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0514669