Improved Protocol for Mononitration of Phenols with Bismuth(III) and Iron(III) Nitrates

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IMPROVED PROTOCOL FOR MONONITRATION OF PHENOLS WITH BISMUTH(III) AND IRON(III) NITRATES

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GRAPHICAL ABSTRACT

0.5 equiv. $Bi(NO_3)_3 \cdot 5H_2O$ or $Fe(NO_3)_3 \cdot 9H_2O$

acetone, r.t. or reflux, 6-20h
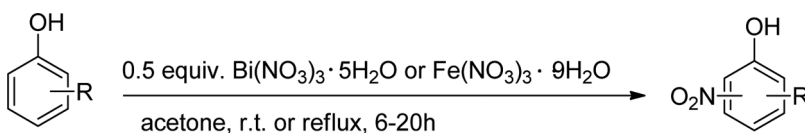
12 examples: R = Cl, Br, OMe, alkyl, benzyl, phenyl   62–93 %

Abstract *A simple and efficient multigram procedure was developed for the selective mononitration of various activated phenols. The reaction proceeded smoothly with 0.5 equivalents of $Bi(NO_3)_3 \cdot 5H_2O$ or $Fe(NO_3)_3 \cdot 9H_2O$ in acetone at ambient temperature or at reflux. The desired products were isolated in 62–93% total yield and essentially no overnitrated compounds were detected.*

INTRODUCTION

Electrophilic aromatic nitration is one of the most widely used reactions[1] for the synthesis of important intermediates for drugs and fine chemicals.[2] The nitrations of less reactive aromatic compounds are usually carried out with an excess of concentrated nitric acid or its mixture with sulfuric acid.[1,2] However, highly reactive, electron-rich aromatic systems such as aniline and phenols require much milder nitration conditions. Otherwise, the unwanted oxidized products and multi-nitro compounds are formed.[3] Numerous useful reagents for the preparation of nitrophenols that are substituted have already been developed, for example, $AgNO_3/I_2/Ph_2PCl$,[4] $NaNO_3/Mg(HSO_4)_2$ or $NaNO_3/NaHSO_4$,[5] $Ca(NO_3)_2$,[6] $NaNO_3$,[7] or $PEG-N_2O_4$.[8] The nitration procedures often require special media or additional activators.[9] Moreover, many of these methods still suffer from

drawbacks, including tedious workup, poor selectivity, poor yields, overnitration, and overoxidation, wasting valuable starting materials.

In the past decade, metal salts including $(NH_4)_2Ce(NO_3)_6$,[10] $ZrO(NO_3)_2 \cdot xH_2O$,[11] $Fe(NO_3)_3 \cdot 9H_2O$,[12] and $Bi(NO_3)_3 \cdot 5H_2O$[13,14] have been introduced as advantageous nitrating agents. In particular, the two last nitrates are cheap, easily available, and nontoxic reagents with LD_{50} of ca. 3–4 g/kg. The use of high-valent metal nitrates exclude a need for strong acids or external promoters. However, even these mild reagents, targeted at the mononitration of phenolic substrates, often gave also the unwanted dinitro derivatives.[13a]

For our ongoing project we needed a series of nitrophenols substituted with electron-donating groups. To choose the most suitable mononitration procedure, we decided to additionally examine the nitrating properties of the metallic nitrates.

RESULTS AND DISCUSSION

Looking for the appropriate mononitration method we tested the reaction of 4-phenylphenol (1a) with iron(III) nitrate and bismuth(III) nitrate. The previously reported procedures[12a,12c,14] were used, applying equimolar amounts of the substituted phenol and the corresponding nitrates, and the desired product was obtained in excellent yield (Table 1, entry 1). Further experiments demonstrated that practically the same yields of 4-phenyl-2-nitrophenol (2a) were obtained using only half the amount of nitrates (Table 1, entries 2 and 5). In this manner the yield based on the nitrate was doubled (cf. entries 1 and 2). When we applied 0.33 equivalent of the nitrates, similarly about two thirds of the anions were consumed in the reaction, leaving one third of the substrate 1a unreacted (entry 3). Even more nitrate from the ferric salt was introduced into 2a and less of the phenol remained (entry 4).

Table 1. Bismuth(III) and iron(III) nitrates reaction with 4-phenylphenol (1a)[a]
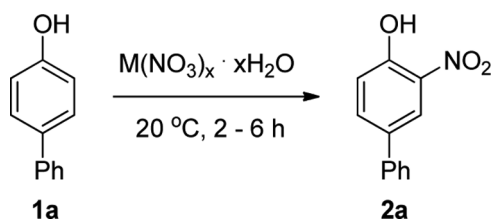
Entry	Ratio 1a/M(NO₃)₃	Nitrate	Time (h)	Conversion of 1a (yield of 2a) (%)[b]	Based on M(NO₃)₃[c]
1	1:1	$Bi(NO_3)_3 \cdot 5H_2O$	2	100 (92)	31
2	1:0.5	$Bi(NO_3)_3 \cdot 5H_2O$	2	97 (92)	62
3	1:0.33	$Bi(NO_3)_3 \cdot 5H_2O$	6	66 (64)	64
4	1:0.33	$Fe(NO_3)_3 \cdot 9H_2O$	6	82 (75)	75
5	1:0.5	$Fe(NO_3)_3 \cdot 9H_2O$	2	100 (93)	62

[a]The reaction was carried out using 10 mmol of the nitrate salt and 10, 20, or 30 mmol of 1a in 100 mL of acetone at 20 °C.

[b]Isolated yield of 2a in parentheses.

[c]Based on the consumed nitrate.

Based on these observations, the stoichiometry of nitration for entries 1–3 leads us to believe that the inorganic product is the well-known bismuth oxynitrate [(Eq. (1)]:

$$Bi(NO_3)_3 + 2 \underset{R}{\overset{OH}{\bigcirc}} = BiO(NO_3) + 2 \underset{R \quad NO_2}{\overset{OH}{\bigcirc}} + H_2O \qquad (1)$$
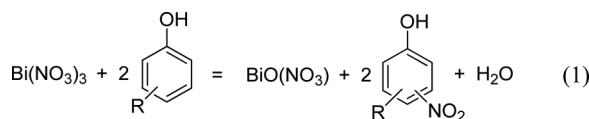
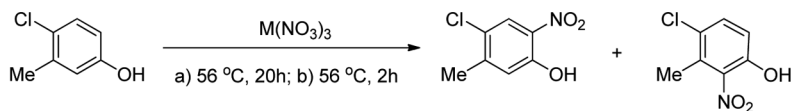It seems that the formation of the exceptionally stable oxo-bismuth species (BiO^+) is responsible for this outcome. Interestingly, bismuth oxynitrate has been used for nitration of phenols, but this compound needed additional activation by thionyl chloride[9e] or trichloroisocyanuric acid.[9f]

Thus we have found that the nitration of 4-phenylphenol (**1a**) with 0.5 equivalent of $Bi(NO_3)_3 \cdot 5H_2O$ or $Fe(NO_3)_3 \cdot 9H_2O$ in acetone at room temperature gave the 2-nitro-4-phenylphenol (**2a**) in excellent yield. It is noteworthy that the method[14] recommended for the nitration of electron-rich phenols with equimolar amount of $Bi(NO_3)_3 \cdot 5H_2O$ was developed for a small laboratory scale only. The authors were aware that extra care would be needed when the procedure was performed on a multigram scale, because the reaction was exothermic. Hence, in the scaled-up procedure, only half of the amounts of the previously used nitrating agents were used, and we smoothly obtained the desired mononitrated product, avoiding the reported difficulties.[14] Moreover, grinding 4-phenylphenol (**1a**) with 0.5 equivalent of bismuth(III) nitrate in the absence of solvent did not yield any product.
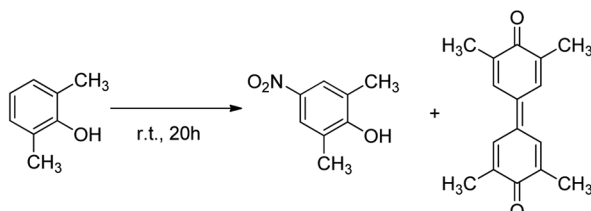
It has been reported that the selective nitration of phenols with cerium(IV) ammonium nitrate (CAN) in the presence NaHCO₃ afforded *o*-nitrophenols in good yields.[10] Among them 3-methoxyphenol (**1e**) was reportedly converted to 3-methoxy-6-nitrophenol (**2e**) in 90% yield.[10a] In our hands this reaction resulted in the formation of isomeric mononitrates: **2e** (18%), **3e** (9%), and **4e** (7%). Also, the attempted nitration of 2-benzylphenol (**1d**) with CAN/NaHCO₃ gave 4.5% of 6-benzyl-2-nitrophenol (**4d**) only.

To compare the reactivity of $Bi(NO_3)_3 \cdot 5H_2O$ and $Fe(NO_3)_3 \cdot 9H_2O$ as the mononitrating agents we ran the reactions with four additional phenols (Scheme 1).
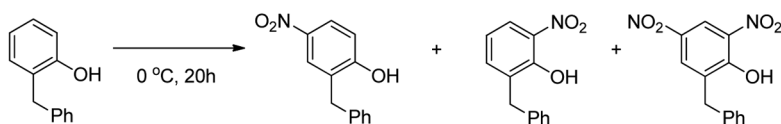
The obtained results demonstrated that both salts performed similarly well, with somewhat greater yields obtained for bismuth nitrate. One can relate this difference to the respective oxidizing abilities (E° for Bi^{3+}/Bi^0, Fe^{3+}/Fe^{2+}, and Ce^{4+}/Ce^{3+} are +0.317,[15a] +0.771,[15b] and +1.61[15c] V, respectively). Thus CAN is known as a strong outer-sphere oxidant, easily generating radical cations, highly reactive intermediates, leading to many different products. The reaction with ferric nitrate supposedly forms ArO-Fe(NO₃)₂ species, where an internal electron transfer may take place, forming a phenoxyl radical and iron(II) salt. In consequence, the obtained phenoxyl radical could reduce nitric acid to (NO₂), initiating a radical nitration pathway.[12d] However, the observed resemblance of the nitration product distribution for bismuth and ferric nitrates (Scheme 1) suggests that a similar mechanism is operating in both cases. When we attempted to react 1-methoxy-2,4-dimethylbenzene (**7k**) with bismuth nitrate, no nitration product could be detected. This supports the formation of ArO-Bi(NO₃)₂ as the first intermediate on the

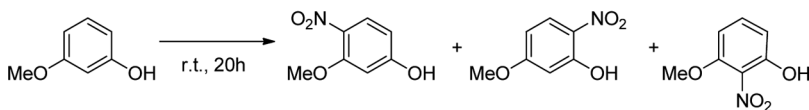**Scheme 1.** Nitration of **1b–d** with 0.5 equiv. and **1e** with 0.33 equiv. of $Bi(NO_3)_3 \cdot 5H_2O$ or $Fe(NO_3)_3 \cdot 9H_2O$ in acetone.[19]

reaction route, as depicted in Scheme 2. It is also consistent with the known large *oxophilicity* of bismuth(III). On the other hand, the less-oxidizing character of Bi^{3+} than Fe^{3+} is reflected in slightly greater selectivity toward *ortho*-nitration and the products observed when the bismuth salt is used are in strict compliance with the stoichiometric equation [Eq. (1)] (Table 1, entries 3 and 4).

Moreover, in the reaction of 2,6-dimethylphenol (**1c**) with both nitrates, along with the expected mononitration product **4c**, we also obtained the respective
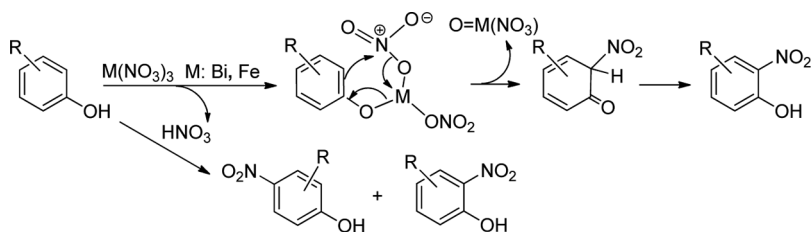
Scheme 2. Nitration mechanism.

oxidation product **5c** (Scheme 1). As has already been noted, the observed carbon–carbon coupling is related to the presence of two methyl substituents in both *ortho*-positions of the phenolic ring.[3a]

Additionally, we examined the nitration of further phenolic compounds **1f–l** with Bi(NO$_3$)$_3$ · 5H$_2$O. The reaction was performed under heterogeneous conditions at room temperature or at solvent boiling point, to give the mononitration products **2–4** in good to excellent yields (Table 2).[16]

Accordingly, scope of the reaction is illustrated by 12 examples of the mono-nitrated phenols **1a–l** (Tables 1 and 2, Scheme 1). In all cases, the conversion of the substrates was complete. On the other hand, phenols with electron-withdrawing substituents, such as 3-trifluoromethylphenol, 2-methyl-6-nitrophenol, and both 2- and 4-carboxymethylphenols remained resistant toward nitration. This outcome differs from the reported effective corresponding nitration using 1 equivalent of Bi(NO$_3$)$_3$.[14] We also examined competitive reactions of the equimolar mixture of 2,4-dimethylphenol (**1k**) and its *O*-methyl derivative with bismuth(III) and ferric(III) nitrating salts. It was observed that the nitration of **1k** took place exclusively, whereas 1-methoxy-2,4-dimethylbenzene remained intact in the reaction mixture. These results also suggest that the radical nitration pathway plays for both nitrates a marginal role only.
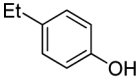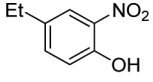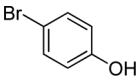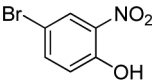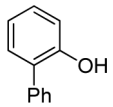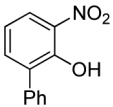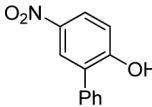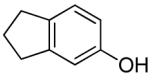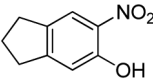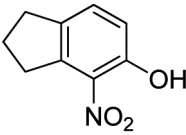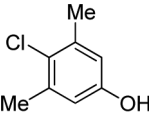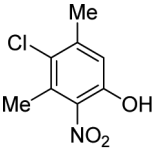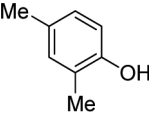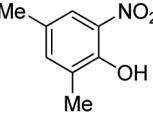
CONCLUSIONS

In conclusion, we have developed simple multigram protocols for the selective mono-nitration of various activated phenols. Based on the observed stoichiometry, the reaction was carried out with 0.5 equivalents of Bi(NO$_3$)$_3$ · 5H$_2$O or Fe(NO$_3$)$_3$ · 9H$_2$O in acetone at ambient temperature or at reflux. The desired mono-nitrophenols were isolated in 62–93% total yield and essentially no overnitrated compounds were detected. The reaction, under the applied conditions, is highly specific for the activated phenols. The readily available, inexpensive, and environmentally acceptable nitrating salts and the simple procedure offer an attractive alternative to the classical nitration methods for the electron-rich phenols.

EXPERIMENTAL
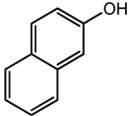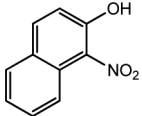
Acetone (100 ml) was added to a solid mixture of the phenol (10.0, 20.0, or 30.0 mmol) and Bi(NO$_3$)$_3$ · 5H$_2$O (10.0 mmol). The resulting mixture was magnetically stirred at room temperature or at reflux for 2–24 h (Tables 1 and 2).

Table 2. Mononitration of phenolic compounds **1f–l** with 0.5 equiv of $Bi(NO_3)_3 \cdot 5H_2O^a$
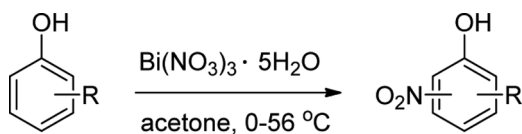
Entry	Phenolic compound	T (°C)	Time (h)	Nitrated compound (% isolated yields)[b]
1	**1f**	20	20	**2f** (80)
2	**1g**	56	6	**2g** (87)
3	**1h**	0	20	**2h** (45) **4h** (42)
4	**1i**	20	6	**2i** $(52)^c$ **3i** $(28)^c$
5	**1j**	56	6	**2j** (80)
6	**1k**	20	6	**2k** (87)

(*Continued*)

Table 2. Continued

Entry	Phenolic compound	T (°C)	Time (h)	Nitrated compound (% isolated yields)[b]
7	**1l**	20	2	**2l** (52)

^{a}Reaction conditions: Phenolic compound (20 mmol), Bi(NO$_3$)$_3$ · 5H$_2$O (10 mmol), and acetone (0.1 L) were stirred at 0–56 °C for 6–20 h.

^{b}Isolated yield based on the amount of phenol used.

^{c}Distribution of isomer determined by ^{1}H NMR.

The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica-coated plates. After the reaction had finished the insoluble materials were filtered off using a Celite pad, which was then additionally washed with acetone (50 ml). The filtrate was treated with solid NaHCO$_3$. The insoluble material was filtered off again, and the solvent was removed under vacuum in a water bath at 25–35 °C. The products were separated and purified by column chromatography using silica gel. All the isolated products are known compounds characterized by ^{1}H and ^{13}C NMR and IR spectroscopy, and were identified by comparison of the spectral data and melting points with those reported in the literature. For the analytical details, see the Supporting Information.

FUNDING

SUPPLEMENTAL MATERIAL

Supplemental date for this article can be accessed on the publisher's website.

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