

p-Toluenesulfonic acid catalyzed regiospecific nitration of phenols with metal nitrates[☆]

V. Anuradha, P. V. Srinivas, P. Aparna and J. Madhusudana Rao*

Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—Highly regiospecific mononitration of phenols and substituted phenols is accomplished employing a metal nitrate and a catalytic amount of *p*-toluenesulfonic acid in acetone. An exclusive *ortho*-selectivity was observed with excellent yields. A variety of metal nitrates were used to obtain *o*-nitrophenols exclusively in good to excellent yields. The use of *p*-toluenesulfonic acid is key for the selectivity observed.

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Nitration of aromatic compounds is an industrially important reaction¹ as the nitrated products are intermediates for fine chemicals and pharmaceuticals. Usually, nitration reactions are not selective and are the cause of environmental concerns regarding the disposal of large excesses of mixed acids employed in these processes. Thus, the utility of the existing processes^{2,3} are generally low. The nitration of phenol is a fundamental process and there is a need for a regiospecific pollution-free method. A variety of nitrating agents, including concentrated nitric acid, Yb(OTf)₃, and Hf(OTf)₄ in conjunction with HNO₃,⁴ peroxyxynitrite (ONOO⁻),⁵ nitrogen oxides,⁶ and several metal nitrates⁷ have been employed.

With regard to the nitration of phenols, the use of concentrated nitric acid or mixed acids has been associated with the formation of dinitro compounds, oxidized products, and unspecified resinous tarry materials resulting from the over-oxidation of the substrates. The typical yields of direct nitration never exceed 60%² because of the above mentioned side reactions in most cases, making these processes uneconomical. On the other hand, the use of metal nitrates like ferric nitrate, ceric ammonium nitrate,⁸ copper nitrate, and vanadium nitrate have contributed significantly, enhancing the scope of the nitration process, however, there

are concerns regarding achieving efficient regioselectivity. All these methods also suffer from other drawbacks, for example some of the nitrates must be prepared from dinitrogen pentoxide, or they must either be clay supported or absorbed on silica gel prior to their use as nitrating agents. Some even employ the use of expensive ionic liquids as solvents.⁹

Herein, we report our results on the regiospecific nitration of phenols and their derivatives using a metal nitrate and a catalytic amount of *p*-toluenesulfonic acid in acetone.¹⁰ Although nitration of phenols has been reported with several metal nitrates, the observation of regiospecificity is rare.^{8b} Very recently a report appeared describing the use of Bi(NO₃)₃·5H₂O as a nitrating agent for phenols, albeit with no regiospecificity.¹¹ This report also described the use of other metal nitrates, which did not show any reactivity, for example Ni(NO₃)₂·6H₂O, Ba(NO₃)₂, Ca(NO₃)₂·4H₂O, and Cu(NO₃)₂·3H₂O.

Table 1. Nitration of *p*-cresol with different metal nitrates and *p*-TSA to give an *o*-nitro compound

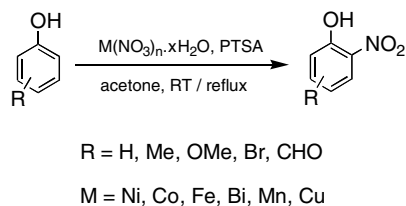
Entry	M(NO ₃) _n ·xH ₂ O	Reaction conditions ^a (min)	<i>o</i> -Nitro compound isolated yield (%)
1	Ni(NO ₃) ₂ ·6H ₂ O	1	85
2	Co(NO ₃) ₂ ·6H ₂ O	2	75
3	Fe(NO ₃) ₃ ·9H ₂ O	15	50
4	Bi(NO ₃) ₃ ·5H ₂ O	2	75
5	Mn(NO ₃) ₂ ·2H ₂ O	3	60
6	Cu(NO ₃) ₂ ·3H ₂ O	3	60

^a 1 mmol *p*-cresol, 1 mmol metal nitrate and 0.012 mmol of *p*-TSA in 15 ml acetone at 25 °C.

Keywords: Nitration; Nickel nitrate; Regiospecific; *p*-TSA.

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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: janaswamy@iict.res.in



Scheme 1.

A variety of metal nitrates were screened and the results are summarized in Table 1. The use of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) is key for the reaction to proceed with high regioselectivity and each of the metal nitrates used afforded *o*-nitrophenols as a single regioisomer in good to excellent yields.

Even though the reaction proceeds with various metal nitrates, the time required for completion of the reaction

Table 2. Nitration of phenol with nickel(II) nitrate and *p*-TSA

Entry	Phenol	Time (min)	Product ^b	Yield ^c (%)
1		30		85
2		30		80
3		5		97
4		1		98
5		30 ^a		75
6		60		78
7		60		72
8		70		71
9		30 ^a		86
10		30 ^a		85
11		30		85
12		5		97
13		720 ^a	No reaction	
14		720 ^a	No reaction	

^a Reaction carried out at 50 °C.

^b All the products were characterized by ¹H NMR and mass spectroscopy.

^c Isolated yields after column chromatography.

was found to be less with $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$. Moreover, the use of nickel(II) nitrate as a nitrating agent for phenols is unprecedented.

The use of a sulfonic acid is preceded in the form of trifluoromethanesulfonic acid and its derivatives¹² but the use of *p*-toluenesulfonic acid in the nitration of phenols has not been reported previously. *p*-Toluenesulfonic acid enjoys other advantages over triflic acid because it is non-corrosive and much cheaper.

Phenol was treated with a metal nitrate and *p*-TSA in acetone either at room temperature or at reflux to afford *o*-nitrophenol as the exclusive product in satisfactory to good yields (Scheme 1).

The scope and generality of the method is illustrated with several examples in Table 2. A variety of phenols were subjected to the standardized conditions of Scheme 1 and all of them yielded the *o*-nitro product exclusively in good to excellent yields.

Phenols with electron donating groups (entries 3, 4, 5, and 10, Table 2) behaved very well to afford the *o*-nitrophenols as the exclusive products in excellent isolated yields. Phenols with moderately deactivating groups (entries 6, 7, and 9) also yielded the *o*-nitrophenols in good yields. A phenol with both an activating and a deactivating group (entry 8) also reacted to afford the desired product in good yield.

Bakuchiol (entry 11), a phenolic natural product also yielded the *o*-nitrophenol as the exclusive product in excellent isolated yield. Phenols with strong deactivating groups failed to react under the given protocol.

In conclusion, the mono-nitration of phenols with a metal nitrate and *p*-TSA has been achieved with high regioselectivity and with excellent isolated yields. In general, exclusive *ortho*-selectivity was observed for all the phenols subjected to this protocol.

The high regioselectivity, with excellent isolated yields and the use of inexpensive and easily accessible *p*-TSA as the catalyst makes this methodology of wide synthetic and commercial utility.

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- Typical Experimental Procedure*: To a stirred solution of the phenol (1 mmol) in acetone (15 ml) was added nickel(II) nitrate (1 mmol) followed by a catalytic amount of *p*-TSA (0.012 mmol) and the reaction mixture was either refluxed or stirred at room temperature until all the phenol was consumed. Acetone was removed under vacuum and the crude mass was partitioned between dichloromethane and water. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (98:2) as eluent.
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