

Nitration of Substituted Phenols by Different Efficient Heterogeneous Systems

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ABSTRACT

Nitration of substituted phenols were carried out by the mixture of sodium nitrite and wet SiO₂ (50% w/w) in the presence of four different efficient heterogeneous systems: 1) oxalic acid dihydrate (I), 2) sodium hydrogen sulphate (II), 3) aluminum hydrogen sulphate (III) and 4) silica sulphuric acid (IV) in CH₂Cl₂ at room temperature and high yields. Optimum conditions for these systems and the regioselectivities of the reactions are reported.

KEYWORDS

Nitration, nitrophenols, sodium nitrate, oxalic acid dihydrate, sodium hydrogen sulphate, aluminum hydrogen sulphate, silica sulphuric acid, wet SiO₂.

1. Introduction

Nitration of aromatic compounds is an industrially relevant reaction since the nitrated products are important intermediates for fine chemicals and pharmaceuticals.¹ There are various old and new methods for this purpose such as HNO₃/H₂SO₄,² NaNO₂/HNO₃,³ N-nitro-pyrazole/BF₃.Et₂O/CH₂Cl₂,⁴ Ca(NO₃)₂,⁵ metallic nitrates,⁶ NaNO₃/H₂SO₄/NaNO₂,⁷ NaNO₃/HCl/La(NO₃)₃/Et₂O.H₂O,⁸ AgNO₃/BF₃/CH₃CN,⁹ graphite nitrates,¹⁰ tetranitromethane,¹¹ clay supported nitrates,¹² AcONO₂,¹³ BzONO₂,¹⁴ CF₃CO₂NO₂,¹⁵ HNO₃/SiO₂,¹⁶ pyridine derivatives carrying transferable nitro groups,¹⁷ Fe(NO₃)₃.9H₂O, Cr(NO₃)₃.9H₂O and Co(NO₃)₃.3H₂O,¹⁸ Cu(NO₃)₂.N₂O₄, Fe(NO₃)₃.2N₂O₄ and Cr(NO₃)₃.2N₂O₄,¹⁹ Zn(NO₃)₂.2N₂O₄ and Zn(NO₃)₂.2N₂O₄ charcoal supported,²⁰ nitrogen oxide,²¹ and dilute HNO₃/TBAB.²² Nitration reactions are not selective, especially nitration of the phenolic compounds which is always associated with the formation of ortho and para nitro compounds, di-nitro compounds, oxidized products and unspecified residual tarry materials. Recent developments of nitration of phenolic compounds involve nitrate salts such as VO(NO₃)₃,²³ Fe(NO₃)₃.9H₂O,²⁴ (Me₄N)NO₃,²⁵ NaNO₃,²⁶ Ce(NH₄)₂(NO₃)₆,²⁷ Bi(NO₃)₃.5H₂O,²⁸ zirconyl nitrate,²⁹ the ultrasound promoted regioselective nitration of phenols using dilute nitric acid in the presence of phase transfer catalyst,³⁰ and some other methods.^{31–37}

2. Results and Discussion

From our previous research results³⁸ (nitration of *p*-substituted phenols), we knew exactly that what the products are (mono- or di-nitrated compounds where the nitro groups are *ortho* to the hydroxyl group), but we were interested to find more efficient catalytic systems. It was found that the NaNO₂/wet SiO₂/solid acid system is a mild, heterogeneous, cheap and commercially available nitrating agent for the nitration of the *p*-substituted phenols.³⁸

Now, we wish to report nitration of the *ortho*- and *meta*-substituted phenols by application of the same catalytic systems³⁸ [combination of NaNO₂ and wet SiO₂ in the presence of organic

or inorganic solid acids such as oxalic acid dihydrate (I), sodium hydrogen sulphate (II), aluminum hydrogen sulphate (III) and silica sulphuric acid (IV)] at room temperature in CH₂Cl₂ in excellent yields. The project also investigated the regioselectivity of the new reactions (Schemes 1 and 2).

Several experiments were performed with different mole ratios in order to find the best conditions. Different systems (1/1/1, 1/2/2 etc., see Table 1) were investigated and the results were compared to find the optimum conditions. All of the above mentioned solid acids did activate NaNO₂ in the presence of wet SiO₂ and the nitration proceeded smoothly in high yields under the chosen heterogeneous conditions. Nitration by the oxalic acid dihydrate system is faster than the other three solid systems. This observation might be attributed to the slight solubility of oxalic acid in CH₂Cl₂ in comparison with the other three catalytic systems which are not soluble in CH₂Cl₂ at all. Di-nitrated or oxidized compounds were not observed in the course of reactions. All results are tabulated in Tables 1–4.

In summary, a convenient procedure for the selective mono nitration of substituted phenols by NaNO₂/wet SiO₂ in the presence of four different systems [C₂H₂O₂.2H₂O, NaHSO₄, Al(HSO₄)₃ or SiO₂.H⁺·SO₃H] in CH₂Cl₂ at room temperature is reported. The reaction proceeds smoothly, rapidly and in excellent yields.

3. Experimental

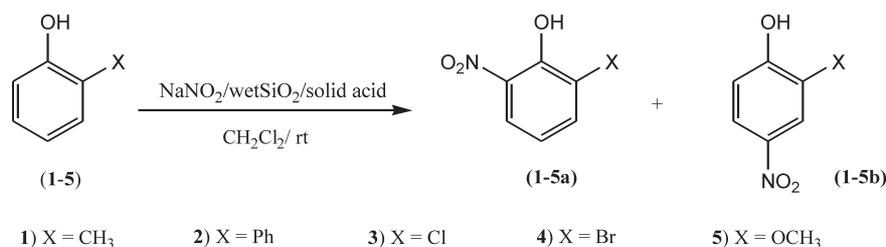
General Procedure

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Wet SiO₂ was prepared by mixing equal gram amounts of SiO₂ (mesh 60-270, Merck) and distilled water. Silica sulphuric acid and aluminum hydrogen sulphate were prepared according to our previous reported procedures.^{39,40}

Yields refer to isolated pure products. The nitration products were characterized by comparison of their spectral (IR, ¹H NMR, TLC) and physical data with authentic samples.

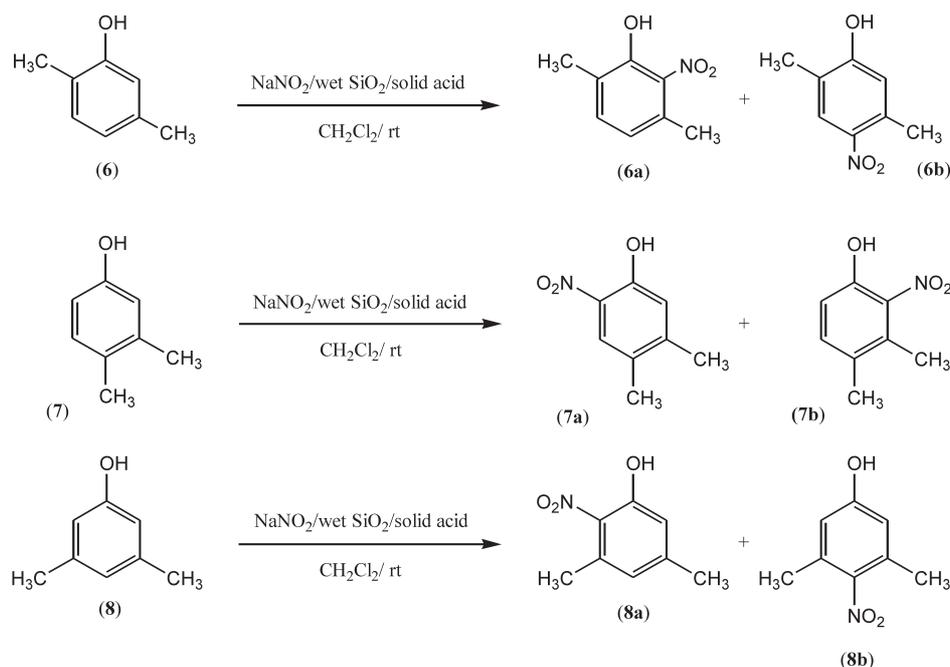
Several experiments were performed with different mole ratios in order to find the best conditions. Different systems (1/1/1, 1/2/2 etc, see Tables 1–4) were investigated and the results were compared to find the optimum conditions. The mole ratios

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Scheme 1

Nitration of different substituted phenols (1–5).



Scheme 2

Nitration of different substituted phenols (6–8).

are varied even within one catalytic system. For example, in the Table 1, mmols of the substrate/NaNO₂/oxalic acid dihydrate (I) are not same in all eight cases and vary from 1/2/2 to 1/3/3, 1/4/4 and 1/6/6.

An example of a typical experimental procedure is presented below.

2-Methyl-6-nitrophenol (1a) and 2-methyl-4-nitrophenol (1b): to a solution of 2-methylphenol (0.24 g, 2.22 mmol) in

CH₂Cl₂ (15 mmol), was added NaNO₂ (0.264 g, 4 mmol), Al(HSO₄)₃ (0.414 g, 1.4 mmol), and wet SiO₂ (50% w/w) (0.44 g) and the resulting mixture stirred. The reaction was completed after 90 min. The products were extracted with CH₂Cl₂ (2 × 15 mL) and dried over anhydrous Na₂SO₄ (5 g). Evaporation of the solvent on a rotary evaporator afforded the crude product (0.312 g, 92%). The nitrated products were purified by preparative TLC (silica gel) using a mixture of ethyl acetate and n-hexane

Table 1 Nitration of different phenols by the mixture of NaNO₂ and wet SiO₂* (50% w/w) in the presence of oxalic acid dihydrate (I) system in CH₂Cl₂ at room temperature.

Substrate	Products** (%)	mmol of substrate/NaNO ₂ /(I)***	Time (min)	Isolated yield (%)
1	1a(33), 1b(67)	1/3/3	15	89
2	2a(35), 2b(65)	1/3/3	15	95
3	3a(40), 3b(60)	1/6/6	20	90
4	4a(34), 4b(66)	1/6/6	18	90
5	5a(34), 5b(66)	1/3/3	22	91
6	6a(30), 6b(70)	1/4/4	28	90
7	7a(85), 7b(15)	1/2/2	12	89
8	8a(30), 8b(70)	1/3/3	18	90

* The amount of wet SiO₂ in all cases is 0.2 g per 1 mmol of each substrate.

** All products are known and their spectra as well as physical data have been reported in the literature.

*** Optimum conditions are reported after several ratios were experimented with.

Table 2 Nitration of different phenols by the mixture of NaNO₂ and wet SiO₂* (50% w/w) in the presence of sodium hydrogen sulphate (II) system in CH₂Cl₂ at room temperature.

Substrate	Products** (%)	mmol of substrate/NaNO ₂ /(II)***	Time (min)	Isolated yield (%)
1	1a(36), 1b(64)	1/2/2	20	90
2	2a(35), 2b(65)	1/2/2	20	92
3	3a(39), 3b(61)	1/4/4	30	90
4	4a(40), 4b(60)	1/4/4	28	90
5	5a(34), 5b(66)	1/2/2	31	92
6	6a(34), 6b(66)	1/2/2	90	90
7	7a(80), 7b(20)	1/2/2	50	88
8	8a(30), 8b(70)	1/2/2	55	90

* The amount of wet SiO₂ in all cases is 0.2 g per 1 mmol of each substrate.

** All products are known and their spectra as well as physical data have been reported in the literature.

*** Optimum conditions are reported after several ratios were experimented with.

Table 3 Nitration of different phenols by the mixture of NaNO₂ and wet SiO₂* (50% w/w) in the presence of aluminum hydrogen sulphate (III) system in CH₂Cl₂ at room temperature.

Substrate	Products** (%)	mmol of substrate/NaNO ₂ /(III)***	Time (min)	Isolated yield (%)
1	1a(40), 1b(60)	1/2/0.7	90	92
2	2a(41), 2b(59)	1/2/0.7	90	90
3	3a(40), 3b(60)	1/4/1.4	300	90
4	4a(41), 4b(59)	1/4/1.4	285	90
5	5a(41), 5b(59)	1/2/0.7	60	87
6	6a(44), 6b(56)	1/2/0.7	135	90
7	7a(80), 7b(20)	1/2/0.7	90	89
8	8a(29), 8b(71)	1/2/0.7	90	90

* The amount of wet SiO₂ in all cases is 0.2 g per 1 mmol of each substrate.

** All products are known and their spectra as well as physical data have been reported in the literature.

*** Optimum conditions are reported after several ratios were experimented with.

Table 4 Nitration of different phenols by the mixture of NaNO₂ and wet SiO₂* (50% w/w) in the presence of silica sulphuric acid (IV) system in CH₂Cl₂ at room temperature.

Substrate	Products** (%)	mmol of substrate/NaNO ₂ /(IV)***	Time (min)	Isolated yield (%)
1	1a(39), 1b(61)	1/2/2	130	92
2	2a(37), 2b(63)	1/2/2	130	89
3	3a(36), 3b(64)	1/3.25/3.25	310	90
4	4a(43), 4b(57)	1/3.25/3.25	300	90
5	5a(34), 5b(66)	1/2/2	180	91
6	6a(34), 6b(66)	1/2/2	135	88
7	7a(80), 7b(20)	1/2/2	120	89
8	8a(30), 8b(70)	1/2/2	105	90

* The amount of wet SiO₂ in all cases is 0.2 g per 1 mmol of each substrate.

** All products are known and their spectra as well as physical data have been reported in the literature.

*** Optimum conditions are reported after several ratios were experimented with.

(2:8) as eluent. 2-Methyl-6-nitrophenol (**1a**) and 2-methyl-4-nitrophenol (**1b**) were isolated in 40% (0.125 g, 0.816 mmol) and 60% (0.187 g, 1.22 mmol) to overall yield, respectively.

The IR and NMR spectroscopic data of all nitrated products are available as supplementary material.

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