

Regioselective nitration of phenols using $\text{Sr}(\text{NO}_3)_2$ or benzyltriphenylphosphonium nitrate in the presence of H_2SO_4 -silica under solvent free conditions

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ABSTRACT

Regioselective nitration of phenols using $\text{Sr}(\text{NO}_3)_2$ or benzyltriphenylphosphonium nitrate in the presence of H_2SO_4 -silica had been realized under solvent free conditions. The reaction proceeds through the formation of nitronium ion, which attack the phenol ring preferential at ortho position in presence of $\text{Sr}(\text{NO}_3)_2$, forming mono nitrophenol. Para-orientation relative to hydroxyl group and mononitration of phenolic compounds was observed in the case of benzyltriphenylphosphonium nitrate. Some of the major advantages of this method are mild reaction conditions, high efficiency and regioselectivity of nitration and complementarity with other reported methods. In addition, benzyltriphenylphosphonium nitrate as nitrating reagent can be easily recycled.

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1. Introduction

Nitration of phenols is an important process, because nitrophenols are important intermediates for the manufacture of drugs and pharmaceuticals. But phenols are highly reactive; therefore the nitration of phenols using the classical method of nitric acid in sulfuric acid generally gives complex mixtures containing o- and p-nitrophenols, dinitrated phenols, plus unextractable tars of phenolic oxidation products.¹ Regioselective nitration of phenol to furnish ortho and para-nitrophenol as special cases has been studied by various nitrating agents under different conditions²⁻¹². However, some of the nitrating reagents are poorly regioselective and uneconomical. On the other hand, considering these concerns, there is still a good scope for research towards finding mild reagents for regioselective nitration of phenols.

Recently, the use of catalysts and reagents supported on solid supports and solvent-free conditions was developed because such reagents not only simplify the purification processes but also help to

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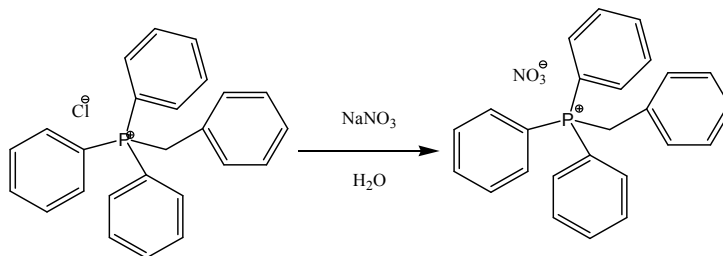
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prevent the releasing of toxic reaction residues such as excess acid or the corresponding salt of acid into the environment.¹³⁻¹⁷

2. Results and Discussion

In this project we wish to report the convenient methods for the regioselective nitration of phenols with benzyltriphenylphosphonium nitrate (BTPPN) or $\text{Sr}(\text{NO}_3)_2$ as the source of nitronium cation in the presence of sulfuric acid adsorbed silica gel (H_2SO_4 -Silica) under solvent-free conditions.

The BTPPN was prepared by mixing an aqueous solution of benzyltriphenylphosphonium chloride with NaNO_3 to obtain a white precipitate (Scheme 1). This reagent is stable and can be kept at room temperature for months without losing its activity.

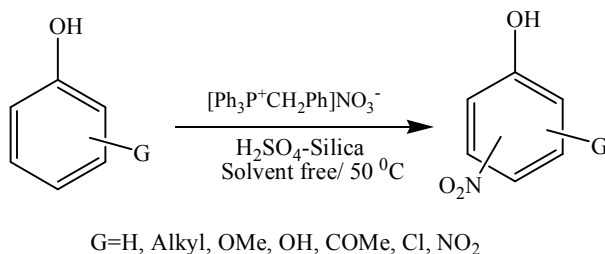


Scheme 1. Preparation of BTPPN

Hajipour et al.¹⁸ reported the application of BTPPN in nitration of aromatic compounds in the presence of methanesulfonic anhydride. However, such a process is less attractive because methanesulfonic anhydride is toxic and expensive. Here we wish to report BTPPN as a regioselective and efficient nitrating agent for the conversion of phenols to mono nitrophenol.

The effect of various reaction conditions on the nitration of phenol was examined first. The reaction was carried out with different molar ratios of phenol/BTPPN and different amounts of H_2SO_4 -Silica. The treatment of 1 equivalent of phenol with 1.3 equivalent of BTPPN in presence of H_2SO_4 -silica (0.58 g) afforded corresponding nitrophenol in a short time in almost quantitative yield, the best results (90 min, 95% conversion) were obtained when the reaction was performed at 50°C under solvent free conditions (Table 1, entry 1).

Different kinds of substituted phenols were also subjected to nitration reaction in the presence of H_2SO_4 -Silica and BTPPN under solvent free conditions (Scheme 2).



Scheme 2. Nitration of substituted phenol by BTPPN

The results of nitration reactions of other phenolic compounds by using BTPPN as nitrating reagent were summarized in Table 1.

Table 1. Nitration of phenols with BTPPN in the presence of H₂SO₄-Silica at 50 °C under solvent free conditions.^a

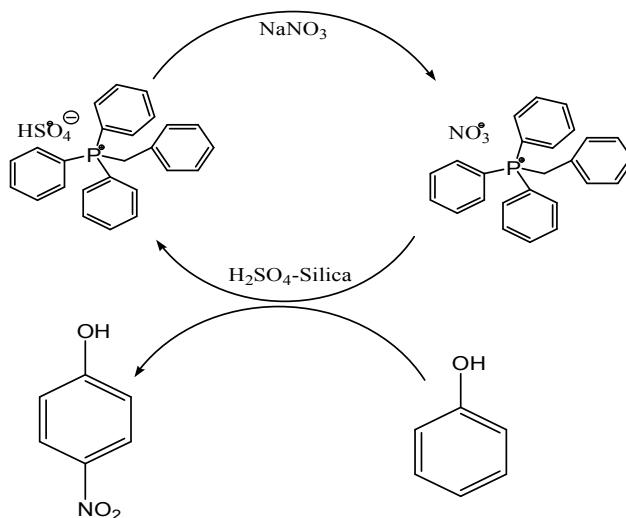
Entry	G	Time (min)	2-nitro (%) ^b	4-nitro (%) ^b
1	H	90	15	80
2	2,4-CH ₃	100	85	-
3	4-COCH ₃	100	75	-
4	4-F	110	65	-
5	2-Cl	60	25	70
6	α-naphtol	130	20	45
7	β-naphtol	130	70	-
8	4-OH	45	90	-
9	4-NO ₂	125	80	-
10	4-CH ₃	35	85	-
11	2-NO ₂	120	25	50
12	2-OCH ₃	40	8	90
13	4-C ₂ H ₅	35	85	-
14	4-Cl	65	75	-
15	3,5-OH	90	65	-
16	2-CH ₃	50	10	85
17	3-CH ₃	35	65	30
18	2-C ₂ H ₅	40	20	70

^a Reaction conditions: Phenol (1 mmol), BTPPN (1.3 mmol) and H₂SO₄-Silica (0.58 g) at 50 °C under solvent free conditions. ^b Yield of isolated pure product.

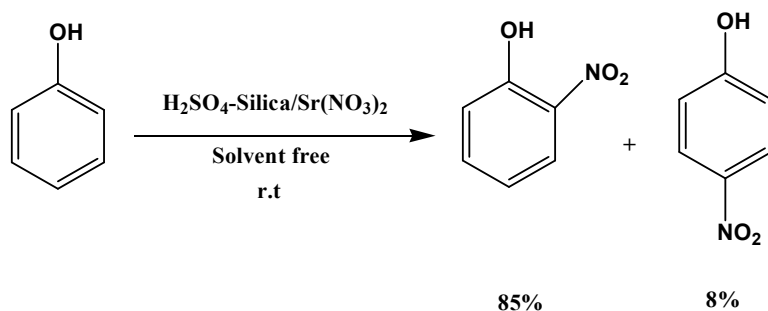
As shown in Table 1 para-orientation relative to hydroxyl group and mononitration of phenolic compounds was preferable. For example, 4-nitrophenol was isolated in 80% yield by the nitration of phenol (Table 1 entry 1).

In the cases of 2-methoxyphenol, 2-ethylphenol and 2-methylphenol, para-nitro relative to the OH group products in excellent yields, was also produced.

We have demonstrated that BTPPN is an efficient and moderate para selective nitrating agent for phenols under solvent free condition. Another advantage of this method is that BTPPN can be regenerated. After extraction of the nitrophenols, the aqueous layer was treated with a fresh solution of the aqueous NaNO₃ to regenerate the BTPPN in quantitative yield. (Scheme 3)

**Scheme 3.** Regeneration of BTPPN

The results obtained in the case of nitration using BTPPN and H₂SO₄-Silica prompted us to study the nitration of phenols with Sr(NO₃)₂ in the presence of H₂SO₄-Silica at room temperature. Accordingly, phenol (1 mmol) was reacted with Sr(NO₃)₂ (1.3 mmol) in presence of H₂SO₄-Silica (0.29 g) and it was found that the 2-nitrophenol was obtained in high isolated yields (Table 2 Entry 1, Scheme 4).



Scheme 4. Regioselective nitration of phenol by Sr(NO₃)₂

Table 2 summarizes the nitration experiments of phenolic compounds using Sr(NO₃)₂.

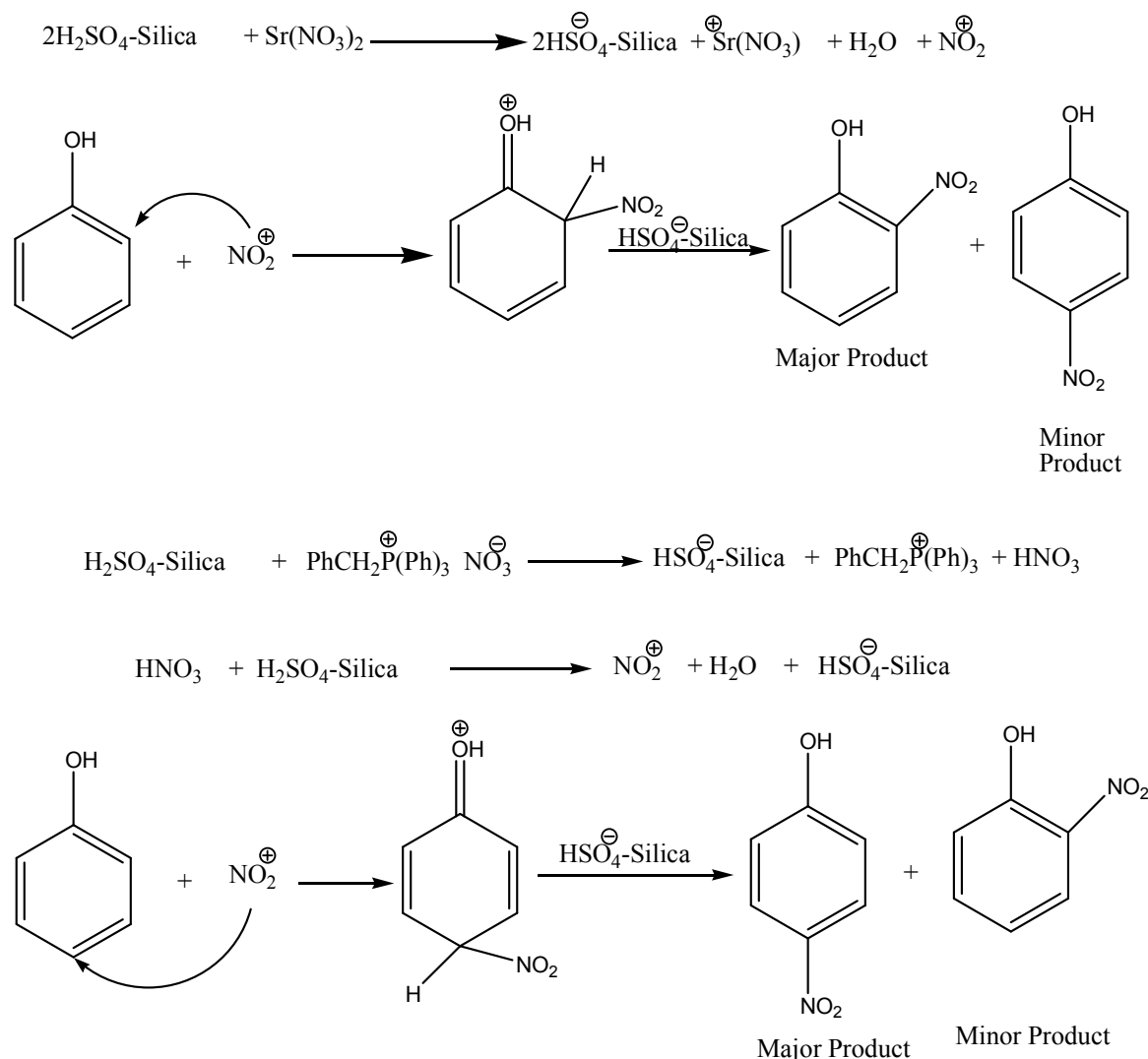
Table 2. Nitration of phenols by Sr(NO₃)₂ in the presence of H₂SO₄-Silica at room temperature under solvent free conditions.

Entry	G	Time (min)	2-nitro (%) ^b	4-nitro (%) ^b
1	H	90	85	8
2	2,4-CH ₃	80	95	-
3	4-COCH ₃	100	75	-
4	4-F	120	70	-
5	2-Cl	45	60	35
6	α-naphthol	125	60	15
7	β-naphthol	120	70	-
8	4-OH	45	98	-
9	4-NO ₂	120	85	-
10	4-CH ₃	30	90	-
11	2-NO ₂	120	50	25
12	2-OCH ₃	30	80	10
13	4-C ₂ H ₅	25	95	-
14	4-Cl	60	85	-
15	3,5-OH	75	80	-
16	2-CH ₃	45	85	10
17	3-CH ₃	30	85	10
18	2-C ₂ H ₅	35	70	20

^a Reaction conditions: Phenol (1 mmol), Sr(NO₃)₂ (1.3 mmol) and H₂SO₄-Silica (0.29 g) at RT under solvent free conditions. ^b Yield of isolated pure product. It was noticed that only one nitro group was introduced.

The enhanced regioselectivity of nitration with Sr(NO₃)₂ over the classical mixed-acid procedure was best demonstrated by the products obtained with phenol as a substrate. While the latter process produced a mixture of 2-nitrophenol and 4-nitrophenol and 2,4-dinitrophenol, nitration with Sr(NO₃)₂ produced 2-nitrophenol in 85% and 4-nitrophenol only 8% and no dinitrophenol was detected. Similarly, the nitration of α-naphthol, 2-methoxyphenol and 2-alkylphenol produced with high selectivity was the preferred ortho-orientation relative to hydroxyl.

The possible mechanism for nitration of phenol to the corresponding nitrophenol using Sr(NO₃)₂ or BTPPN in the presence of H₂SO₄-Silica under solvent-free conditions is outlined in Scheme 5.



Scheme 5. Mechanism of Nitration

In Table 3, we have compared the results obtained from the nitration of phenol by our method with some of those reported in the literature.

Table 3. Regioselective Nitration of phenol with different methods.

Entry	Reagent	<i>O</i> -Nitro	<i>P</i> -Nitro
1	Sr(NO ₃) ₂ /H ₂ SO ₄ -Silica ^a	85	8
2	BTPPN/H ₂ SO ₄ -Silica ^a	15	85
3	NH ₄ NO ₃ /KHSO ₄ ¹⁹	75	20
4	Cu(NO ₃) ₂ .3H ₂ O ²⁰	40	60
7	NaNO ₃ /Mg(HSO ₄) ₂ ²¹	36	26
8	NaNO ₃ /Silica sulfuric acid ²²	30	20
9	silica sulfuric acid-supported Bi(NO ₃) ₃ ²³	15	85
10	Bi(NO ₃) ₃ .5H ₂ O ²⁴	34	37
11	Bismuth subnitrate ²⁵	42	46
12	Cu(NO ₃) ₂ in acetic acid ²⁶	<20	>80
13	NaNO ₃ /HCl/H ₂ O/Et ₂ O ²⁷	39	26

^aPresent work.

3. Conclusions

In conclusion, we have demonstrated the application of BTPPN and $\text{Sr}(\text{NO}_3)_2$ as an efficient and regioselective nitrating agents used in combination with H_2SO_4 -Silica under solvent free and mild reaction conditions. Utilization of $\text{Sr}(\text{NO}_3)_2$ results in *ortho* selective nitration of phenols. On the other hand *para* selectivity was observed when BTPPN was utilized. In addition, BTPPN can be easily recycled what makes its application in large-scale processes more economically viable.

4. Experimental

4.1. Materials and Methods

Yields refer to isolated pure products. All the products were identified by comparison of their spectral data with the well-known compounds.²⁸ The products were characterized by their spectral (^1H -NMR and IR). All ^1H -NMR spectra were recorded at 250 MHz in CDCl_3 relative to TMS (0.00 ppm). IR spectra were recorded on Perkin-Elmer Spectrum RXI FT-IR spectrophotometer. Thin layer chromatography was performed on silica SIL G/UV 254 plates.

4.2. Preparation of benzyltriphenylphosphonium nitrate

A solution of benzyltriphenylphosphonium chloride (1.9 g, 4.9 mmol) in 10 ml of water was prepared, and then KNO_3 (0.495 g, 4.9 mmol) in water (10 ml) was added dropwise to the above solution and stirred for 1 h at room temperature. The resulting precipitate was filtered and washed with cooled, distilled water (5 ml), and dried in a desiccator under vacuum over calcium chloride to afford a white powder (1.9 g, 94% yield), which decomposed at 181–182 °C to a dark-brown material.¹⁸

4.3. Preparation of H_2SO_4 -silica

In a mortar silica gel (0.063–0.2 mm, 2 g) and H_2SO_4 (98% 1 g, 10 mmol) were ground with a pestle and the residue was heated at 100 °C for 12 h to furnish H_2SO_4 -silica as a free flowing powder.²⁹

4.4. General procedure for the nitration of phenols by $\text{Sr}(\text{NO}_3)_2$ and H_2SO_4 -Silica

In a mortar, a mixture of substituted phenol (1 mmol), H_2SO_4 -Silica (0.29 g), $\text{Sr}(\text{NO}_3)_2$ (1.3 mmol) was ground at room temperature with a pestle for the time specified in Table 1. The progress of the reaction was followed by TLC (Ethyl acetate:n-Hexane 1:6). After the completion of reaction ethyl acetate (5 mL) was added to the reaction mixture, and the solid material was separated by filtration. The filter cake was washed with ethyl acetate (2×5 mL), and the filtrates were combined. The combined Organic phases were washed successively with saturated solution of sodium bicarbonate (3×5 mL) and distilled water (5 mL), then dried over anhydrous magnesium sulfate and concentrated. The crude product was purified through preparative TLC plate.

4.5. General procedure for the nitration of phenols by BTPPN and H_2SO_4 -Silica

In a 10 mL round bottom flask, a mixture of H_2SO_4 -Silica (0.58 g), BTPPN (1.3 mmol) and phenol derivative (1 mmol), was ground at 50 °C for the time specified in Table 2. The progress of the reaction was followed by TLC (Ethyl acetate:n-Hexane 1:6). After the completion of reaction the ethyl acetate (5 mL) was added to the reaction mixture, and the solid material was separated by filtration. The filter cake was washed with ethyl acetate (2×5 mL), and the filtrates were combined. The combined organic phases were washed with saturated solution of sodium bicarbonate (3×5 mL) and distilled water (5 mL), then dried over anhydrous magnesium sulfate and concentrated. The crude product was purified through preparative TLC plate.

4.6. General procedure for the regeneration of BTPPTN

After the residue was washed with ethyl acetate and filtered the filter cake was washed with distilled water (3×10 mL) and separated from solid residue by filtration. Then to the combined stirred solution was added a solution of sodium nitrate (1.3 mmol) in water (10 mL) at room temperature until a white precipitate was formed. After being stirred 30 min the mixture was filtered, and washed with water (3×5 mL). The filter cake was dried to afford BTPPN as white powder (0.48 g, 90% recovery).

4.7. Spectral Data

2-Nitrophenol: ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 10.63$ (s, 1H), 8.11-8.13 (d, $J = 9.6$ Hz, 1H), 7.58-7.63 (dd, $J = 1.2$ Hz, $J = 7.2$ Hz, 1H), 7.16-7.19 (d, $J = 9.6$ Hz, 1H), 7.06-7.0 (dd, $J = 1.2$ Hz, $J = 7.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): $\delta_{\text{C}} = 155.23, 137.59, 133.68, 125.08, 120.25, 119.98$.

4-Nitrophenol: ^1H NMR, (400 MHz, CDCl_3) $\delta_{\text{H}} = 6.22$ (s, 1H), 6.98-6.95 (d, $J = 2$ Hz, 2H), 8.20-8.23 (d, $J = 2$ Hz, 2H). ^{13}C NMR, (100 MHz, CDCl_3) $\delta_{\text{C}} = 161.47, 141.59, 126.35, 115.76$.

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