

## Highly chemoselective nitration of aromatic amines using the $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3$ system

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**Abstract**—The use of  $\text{PPh}_3/\text{Br}_2/\text{AgNO}_3$  provides a new reagent system for the novel and highly chemoselective nitration of aromatic amines under mild reaction conditions.

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The introduction of a nitrogen functionality onto aromatic rings by electrophilic substitution is an important synthetic procedure. Nitro compounds are important building blocks in organic synthesis and their reduction to amino derivatives provides access to diazonium ions as important intermediates.<sup>1</sup> Nitro aromatic compounds are widely studied because of their applications as solvents, dyes, pharmaceuticals, perfumes, agrochemicals, explosives and plastics in the industry.<sup>2</sup>

There are many useful reagents for nitration such as concentrated nitric acid,<sup>3</sup> mixtures of nitric acid with sulfuric acid,<sup>4</sup> nitric acid in acetic anhydride,<sup>5</sup> nitrate salts in trifluoroacetic anhydride,<sup>6</sup> ozone and nitrogen dioxide,<sup>7</sup>  $\text{N}_2\text{O}_5$  and  $\text{Fe}(\text{acac})_3$ ,<sup>8</sup> *N*-nitropyridinium- and quinolinium salts,<sup>9</sup> nitric acid and trifluoromethanesulfonic acid<sup>10</sup> or trifluoromethanesulfonic anhydride,<sup>11</sup> metal nitrates in sulfuric acid,<sup>12</sup> lanthanide(III) nosylates,<sup>13</sup> guanidinium nitrate,<sup>14</sup> potassium nitrate or nitric acid and boron trifluoride monohydrate mixtures<sup>15</sup> and sodium nitrate/chlorotrimethyl silane and aluminium chloride mixtures.<sup>16</sup> Many of these reactions have been carried out in the presence of protic or Lewis acids. Despite the widespread interest in this area of research, as far as we know, there are very limited reports on the nitration of aromatic amines in the literature.<sup>14,17</sup> Using these methods which are not selective, nitration of a

wide range of deactivated and activated aromatic rings is reported, usually in long reaction times and in strongly acidic conditions, for example, the nitration of aniline with guanidinium nitrate in 85% sulfuric acid as solvent occurs in only 51% yield.<sup>14</sup> In continuation of our recent work on aromatic nitration<sup>18</sup> and the use of  $\text{Ph}_3\text{P}$  in conjunction with electron-deficient reagents,<sup>19–22</sup> we report the application of  $\text{PPh}_3/\text{Br}_2/\text{AgNO}_3$  as a novel reagent system for the efficient and highly selective nitration of aromatic amines.

Triphenylphosphine is a fairly general reducing agent and its reactions with selected oxidants can lead to the formation of phosphonium intermediates. Phosphorus in these intermediates is positively charged and its reaction as a strong oxophilic reagent in most cases is driven by the formation of thermodynamically favoured triphenylphosphine oxide.

In this study, we initially reacted *N,N*-dimethylaniline with  $\text{Ph}_3\text{P}/\text{AgNO}_3$  in the presence of different sources of halogen such as molecular bromine or *N*-bromosuccinimide (NBS) and also electron-deficient reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), 2,3,5,6-tetrachlorobenzoquinone (*p*-chloranil) and diethyl azodicarboxylate (DEAD). These latter compounds can react with  $\text{PPh}_3$  to produce the reactive phosphonium intermediates.<sup>19–22</sup> The results of this study (Table 1) show the much greater efficiency of  $\text{Ph}_3\text{P}/\text{Br}_2$  (Table 1, entry 1) compared with the other reagents (Table 1, entries 2–5). The use of DDQ also led to complete reaction but required a longer reaction time (2 h) as compared with the use of  $\text{Br}_2$  (5 min); other reagent

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**Table 1.** Conversion of *N,N*-dimethylaniline to *N,N*-dimethyl-nitroaniline using  $\text{Ph}_3\text{P}$  in the presence of  $\text{AgNO}_3$  and different reagents (X) in acetonitrile at room temperature

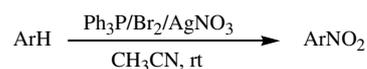
Entry	X	Yield <sup>a</sup> (%)	<i>para</i> + <i>ortho</i> <sup>b</sup> (%)	Time
1	$\text{Br}_2$	100	80+15	5 min
2	NBS	60	35+10	24 h
3	DDQ	100	75+17	2 h
4	<i>p</i> -Chloranil	70	48+9	24 h
5	DEAD	0	—	24 h

<sup>a</sup> Conversion yield.<sup>b</sup> Isolated yield.

systems did not give complete reaction even after 24 h. *n*- $\text{Bu}_4\text{NNO}_3$  can also be used instead of  $\text{AgNO}_3$  for this conversion, but the reaction time was longer (5 h).

Our study showed that employing  $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3/\text{ArNH}_2$  in a ratio of 1.2/1.2/1.2/1 at room temperature in acetonitrile was the optimized condition for the nitration of an aromatic ring (Scheme 1).

We decided to apply this new mixed reagent system ( $\text{Ph}_3\text{P}/\text{Br}_2/\text{AgNO}_3$ ) for the nitration of other aromatic amines. The results of this study are summarized in Table 2, which show that different aromatic amines are



ArH = Aromatic amines

**Scheme 1.**

nitrated in short reaction times (5 min) and in quantitative yields.

This reagent system was found to be highly chemoselective for the nitration of functionalized aromatic amines (Table 2, entries 7–9) and also for nitration of aromatic amines in the presence of other aromatic compounds. The excellent chemoselectivity obtained for the nitration of *N*-methylaniline versus anisole, naphthalene, anthracene and also acetanilide is shown in Table 3.

The enthalpies of formation of triphenylphosphine and triphenylphosphine oxide are  $\Delta_f H_m^\circ = +207.02 \text{ kJ mol}^{-1}$  and  $\Delta_f H_m^\circ = -116.41 \text{ kJ mol}^{-1}$ , respectively.<sup>23</sup> On the basis of this fact, the formation of  $\text{Ph}_3\text{P}=\text{O}$  is the major driving force in the proposed mechanism. Treatment of  $\text{Ph}_3\text{P}$  with  $\text{Br}_2$  forms the intermediate **I**. Addition of  $\text{AgNO}_3$  to **I** produces the intermediate **II** which is accompanied by the precipitation of  $\text{AgBr}$ . This intermediate can then be converted to a product by the formation of triphenylphosphine oxide after addition of the aromatic amine (Scheme 2). The precipitation of  $\text{AgBr}$  and the formation of  $\text{HBr}$  (pH of the reaction is approximately between 3 and 4 during the reaction) are considered to be strong evidence for the proposed mechanism.

In this reaction, the silver salt is recovered as  $\text{AgBr}$  by filtration of the reaction mixture. In a typical experiment, to a flask containing a stirring mixture of  $\text{Ph}_3\text{P}$  (1.2 mmol, 0.314 g) and  $\text{Br}_2$  (1.2 mmol, 0.07 ml) in dry acetonitrile (5 ml), was added silver nitrate (1.2 mmol, 0.2 g) at room temperature. *N*-Methylaniline (1 mmol, 0.1 ml) was then added to the reaction mixture. After 5 min, the reaction mixture was filtered to remove the

**Table 2.** Nitration of aromatic amines in  $\text{CH}_3\text{CN}$  at room temperature

Entry	Aromatic amine	Time (min)	Conversion (%)	Isolated yield (%)
1	<i>N,N</i> -Dimethylaniline	5	100	<i>ortho</i> : 15 <i>para</i> : 80
2	<i>N</i> -Methylaniline	5	100	<i>ortho</i> : 15 <i>para</i> : 78
3	<i>N</i> -Ethylaniline	5	100	<i>ortho</i> : 27 <i>para</i> : 66
4 <sup>a</sup>	<i>N,N</i> -Diethylaniline	5	100	<i>ortho</i> : 20 <i>para</i> : 65
5	Aniline	5	100	<i>ortho</i> : 30 <i>para</i> : 61
6	<i>m</i> -Anisidine	5	100	4-Nitro: 55 6-Nitro: 40
7	<i>p</i> -Bromo- <i>N</i> -methylaniline	5	100	2-Nitro: 91
8	<i>p</i> -Bromo- <i>N,N</i> -dimethylaniline	5	100	2-Nitro: 92
9	4-Aminodiphenyl ether	5	100	3-Nitro: 90
10	Pyrrole	5	100	2-Nitro: 75 3-Nitro: 17
11	<i>p</i> -Hydroxyaniline	5	100	2-Nitro: 50 3-Nitro: 40
12	1-Naphthylamine	5	100	2-Nitro: 22 4-Nitro: 71
13 <sup>a</sup>	<i>o</i> -Toluidine	5	100	4-Nitro: 67 6-Nitro: 15

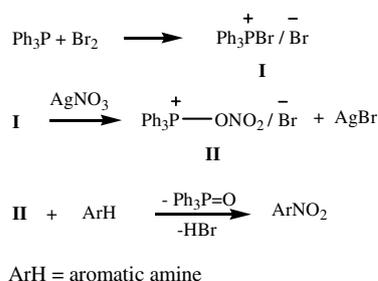
<sup>a</sup> A trace amount of an unidentified product was also produced.

**Table 3.** Selective nitration of *N*-methylaniline with Ph<sub>3</sub>P/Br<sub>2</sub>/AgNO<sub>3</sub> in different binary mixtures in acetonitrile at room temperature<sup>a</sup>

Entry	Binary mixture	Time (min)	Conversion <sup>b</sup> (%)
1	<i>N</i> -Methylaniline	5	100
	Anisole		0
2	<i>N</i> -Methylaniline	5	100
	Naphthalene		0
3	<i>N</i> -Methylaniline	5	100
	Anthracene		0
4	<i>N</i> -Methylaniline	5	100
	Acetanilide		0

<sup>a</sup> The stoichiometry of the binary mixture/Ph<sub>3</sub>P/Br<sub>2</sub>/AgNO<sub>3</sub> is 1/1/1.2/1.2/1.2.

<sup>b</sup> Conversion % was determined by GC and NMR analysis.

**Scheme 2.**

precipitated AgBr. The solvent was evaporated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and washed with 5% aq sodium bicarbonate (2 × 5 ml) followed by water (5 ml) and dried with anhydrous MgSO<sub>4</sub>. Evaporation of the solvent followed by column chromatography of the crude mixture on silica gel using *n*-hexane and ethyl acetate (3:1) as eluent gave *N*-methyl-4-nitroaniline [Reg. No. 100-15-2, (mp 149–150 °C, lit.<sup>24</sup> 152 °C)]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) = 2.8 (3H, s), 4.7 (1H, s), 6.5 (2H, m, AA'XX'), 8.1 (2H, m, AA'XX'); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (ppm) = 30.25, 110.52, 126.40, 138.0, 154.44 and *N*-methyl-2-nitroaniline [Reg. No. 612-28-2, (mp 36–37 °C, lit.<sup>24</sup> 35–38 °C)]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) = 3.0 (3H, s), 6.65–8.15 (4H, m), 8.0 (1H, s, br); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (ppm) = 29.54, 113.0, 115.22, 126.65, 132.0, 136.33, 146.40 in 78% and 15% yields, respectively.

In conclusion, the present investigation has demonstrated the use of the Ph<sub>3</sub>P/Br<sub>2</sub>/AgNO<sub>3</sub> system as a very simple mixed reagent system for the efficient nitration of aromatic amines in high yields and short reaction times. In addition, the method shows excellent chemoselectivity for the nitration of aromatic amines.

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