



## One pot synthesis of aromatic azide using sodium nitrite and hydrazine hydrate

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### ABSTRACT

A simple, rapid, and efficient protocol for the synthesis of aryl azide using sodium nitrite and hydrazine hydrate at room temperature is discussed. The short reaction time, simple work-up procedure, and use of inexpensive reagents are advantages of this method.

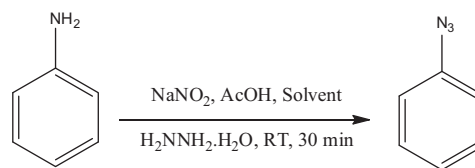
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Aromatic azides are versatile intermediates with a diverse range of applications in organic and bioorganic chemistry.<sup>1</sup> Organic azides are important components in click chemistry.<sup>2</sup> Cycloaddition between organic azides and terminal alkynes has found a widespread application,<sup>3</sup> for example, in combinatorial drug discovery,<sup>4</sup> material science,<sup>5</sup> and bio conjugation.<sup>6,7</sup> Among various types of 1,3-dipoles, organic azides are particularly important as they provide an entry into the synthesis of triazoles and tetrazoles.<sup>8</sup> These heterocyclic derivatives have found use in important applications such as pharmaceuticals, chemical biology,<sup>9</sup> or energetic material.<sup>10</sup> Diazo compounds can also be coupled with arylboronic acids to form C–C bonds without the use of metal catalysts.<sup>11</sup>

Aryl azides are found to be prepared from organoboron compounds using copper(II) catalyst,<sup>12</sup> the reaction of  $[\text{ArN}_2][\text{BF}_4]$  salts immobilized in  $[\text{BMIM}][\text{PF}_6]$  ionic liquid with  $\text{TMSN}_3$  represents an efficient method for the preparation of azido-derivatives via diazotization.<sup>13</sup> However, the synthesis of aryl azides relies upon a more limited selection of transformations.<sup>14</sup> They are commonly prepared from the corresponding amines via their diazonium salts.<sup>15</sup> This may sometimes be problematic with respect to the presence of incompatible functional groups. Alternative methods have been investigated, for example, reactions of organometallic aryls (derived from the corresponding aryl halide) with *p*-tosyl azide.<sup>16</sup> More recently, Liu and Tor has applied Wong's ( $\text{TfN}_3$ ) methodology toward the efficient preparation of aryl azides.<sup>17</sup> Although powerful, this procedure presents some drawbacks. First, toxic and potentially explosive  $\text{NaN}_3$  and the highly reactive  $\text{Tf}_2\text{O}$

are used in excess. Second,  $\text{TfN}_3$  has been reported to be explosive when not in solvent.<sup>18</sup> Recently, Das et al. reported the use of *tert*-butyl nitrite (*t*-BuONO) in combination with  $\text{NaN}_3$  in the synthesis of aromatic azides.<sup>19</sup> This procedure requires a large excess of reagents (12 equiv of *t*-BuONO, 3 equiv of  $\text{NaN}_3$ ), which is undesirable considering the hazards associated with  $\text{NaN}_3$ . As most of the methods involve a multistep reaction and explosive reagent such as  $\text{NaN}_3$ , the method which avoids the use of  $\text{NaN}_3$  for aromatic azidation will be very much important from an economical point. There are other methods where phenyl hydrazine derivatives act as a starting material for the synthesis of aromatic azides<sup>20a</sup> which involves a number of methods such as using  $\text{Br}_2/\text{PPh}_3$  in ACN solvent at 273 K,<sup>20b</sup>  $\text{N}_2\text{O}_4/\text{CCl}_4$  in ACN solvent,<sup>20c</sup> and  $\text{O}_2/\text{NO}$  in dichloromethane solvent.<sup>20d</sup> Dutt et al., reported the synthesis of aryl azide by using diazonium salt and sulfonamide, however the formation of sulfonic acid as byproduct is a major drawback of this method.<sup>20f</sup>

We are continuously working on the development of new efficient methodologies; recently we explored the application of sodium nitrite for decarboxylative bromination.<sup>21</sup> Herein we have developed a simple, single step procedure for azidation from aromatic amines.



**Scheme 1.** Aniline converted into azide using sodium nitrite and hydrazine hydrate.

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**Table 1**  
Conversion of aniline to azide in the presence of various solvents

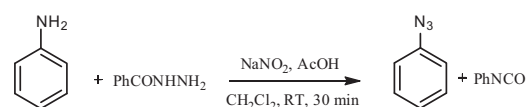
| Entry | Solvents        | Time (min) | Yield <sup>a</sup> (%) |
|-------|-----------------|------------|------------------------|
| 1     | Dichloromethane | 30         | 90                     |
| 2     | Chloroform      | 120        | 85                     |
| 3     | Toluene         | 120        | 80                     |
| 4     | Acetonitrile    | 120        | 80                     |
| 5     | DMSO            | 120        | 40                     |

<sup>a</sup> Isolated yields after silica gel column chromatography.**Table 2**  
Azidation using sodium nitrite<sup>a</sup>

| Entry | Reactant | Product | Time (min) | Yield <sup>b</sup> (%) |
|-------|----------|---------|------------|------------------------|
| 1     |          |         | 30         | 90                     |
| 2     |          |         | 30         | 85                     |
| 3     |          |         | 35         | 80                     |
| 4     |          |         | 30         | 90                     |
| 5     |          |         | 35         | 80                     |
| 6     |          |         | 30         | 80                     |
| 7     |          |         | 30         | 85                     |
| 8     |          |         | 40         | 76                     |
| 9     |          |         | 30         | 80                     |
| 10    |          |         | 35         | 80                     |

**Table 2 (continued)**

| Entry | Reactant | Product | Time (min) | Yield <sup>b</sup> (%) |
|-------|----------|---------|------------|------------------------|
| 11    |          |         | 35         | 75                     |
| 12    |          |         | 9h         | 50                     |
| 13    |          |         | 8h         | 55                     |
| 14    |          |         | 40         | 75                     |
| 15    |          |         | 40         | 75                     |
| 16    |          |         | 40         | 75                     |
| 17    |          |         | 40         | 75                     |

<sup>a</sup> Reaction condition: Substrate (1.45 mmol), NaNO<sub>2</sub> (2.92 mmol), AcOH (11.7 mmol), H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O (7.3 mmol), DCM, rt.<sup>b</sup> Isolated yield after column chromatography and structure was confirmed by comparison of IR, mp/bp, MS, and <sup>1</sup>H NMR with literature reports.**Scheme 2.** Reaction of aniline in the presence of benzhydrazide.

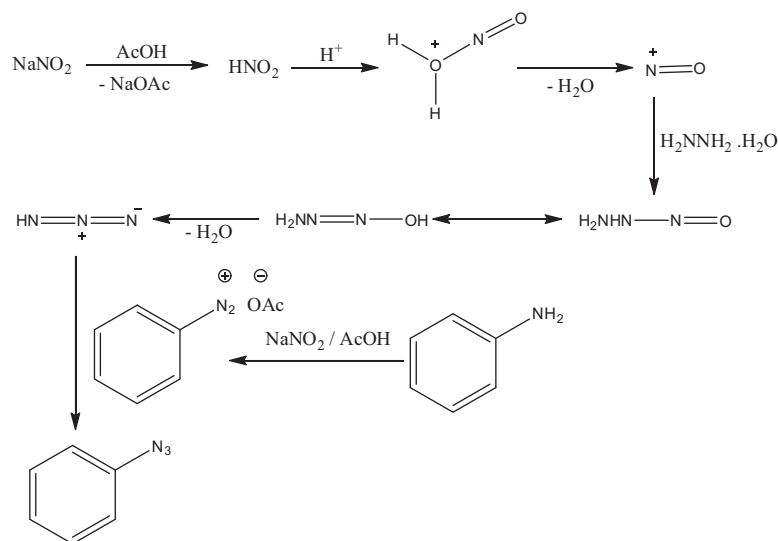
For our initial study we have taken aniline as a model substrate. When aniline is treated with NaNO<sub>2</sub> and hydrazine hydrate in the presence of acetic acid it was found that phenyl azide could be achieved in moderate to good yield (Scheme 1).

Different solvents were screened for this reaction (Table 1) and the dichloromethane was found to be the best solvent. Highly polar solvent like DMSO is found to give low yield of desired product.

Further screening of the equivalents of sodium nitrite and hydrazine hydrate required for the reaction, it was found that 2 equiv of sodium nitrite and 5 equiv of 99% hydrazine hydrate were sufficient to provide the desired product in 90% yield.

To establish further scope of the reaction we applied these optimized conditions on activated and deactivated aromatic amines and results are summarized in Table 2.<sup>22</sup>

From Table 2 it is clearly seen that both electron donating and electron withdrawing substrates are suitable for this conversion



Scheme 3. Plausible mechanism.

and gave good to moderate yield of the desired product in 30–40 min (Table 2, entries 2–11). When the aromatic ring is strongly deactivated, the product could be achieved in poor yield (Table 2, entries 12 and 13). Heterocyclic amines were also found to be suitable substrates to give moderate yields (Table 2, entries 14 and 15) and it was interesting to know that free ester group tolerated reaction conditions without the formation of hydrazide. In the case of *p*-phenylenediamines both amine groups were converted into azide through the formation of monoazide and give 1,4-diazides as a major product (Table 2, entries 16 and 17).

To find out the role of reagents we altered the reaction conditions and checked the effect on the reaction by their absence. It was observed that all the three reagents were necessary for the reaction. To check the role of hydrazine hydrate, it was replaced with benzhydrazide and found that the expected product could be achieved in good yield, however there is formation of side product which after characterization, was confirmed as phenylisocyanate (Scheme 2).

Plausible mechanism of the conversion of amine to azide is predicted as shown in Scheme 3. One mole of sodium nitrite reacts with aniline to give diazonium salt followed by the nucleophilic substitution with azide ion which was formed in situ by a reaction between the second mole of sodium nitrite and hydrazine hydrate in the presence of acidic medium.

In summary, we have described a simple, efficient, and single step procedure for the conversion of aromatic amines into corresponding aryl azides using sodium azide and hydrazine hydrate in short reaction time.

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- Typical procedure for the azidation of aromatic amines:* A finely ground mixture (in case of solid) of aromatic amine (1 equiv) and sodium nitrite (2 equiv) was stirred in dichloromethane solvent at rt for 5 min followed by the addition of AcOH (8 equiv) and hydrazine hydrate (5 equiv, 99%) at rt for 30 min. The reaction mixture was then washed with H<sub>2</sub>O (3 × 20 mL) and finally with brine solution (2 × 20 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified using silica gel column chromatography (hexane).  
Azido benzene (Table 2, entry 1)<sup>23a</sup>  
Yellow liquid, bp 44 °C, IR: 2120, 2091, 1592, 1490, 1292, 1280 cm<sup>-1</sup>, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.4 (m, 2H), 7.09 (m, 3H), GC/MS: 120 [M]<sup>+</sup>.  
1-Azido-2-hydroxybenzene (Table 2, entry 2)<sup>23b</sup>

Brown red solid, mp 40 °C, IR (KBr): 3400, 2120, 1610, 1514, 1150, 1092, 860 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 5.3 (s, 1H), 6.9–7.2 (m, 4H), GC/MS: 135 [M]<sup>+</sup>.

*1-Azido-4-methoxybenzene* (Table 2, entry 4)<sup>23c</sup>

Yellow oil, IR: 2097, 1501, 1284, 1241 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 3.70 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), GC/MS: 149 [M]<sup>+</sup>.

*1-Azido-4-chlorobenzene* (Table 2, entry 5)<sup>23d</sup>

Yellow liquid, bp 54 °C, IR: 3043, 2930, 2094, 1604, 1520, 1340, 1220, 1156, 1096, 822, 768 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 3.70 (s, 3H), 7.3 (d, *J* = 8.6 Hz, 2H), 6.9 (d, *J* = 8.6 Hz, 2H), GC/MS: 153 [M]<sup>+</sup>.

*4-Azido benzoic acid* (Table 2, entry 9)<sup>23e</sup>

Off white solid, mp 174 °C: IR (KBr): 2959, 2541, 2101, 1672, 1600, 1577, 1507, 1424, 1330, 1317, 1281, 1177, 1138, 1121, 859 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.09 (d, 8.4 Hz, 2H), 7.09 (d, 8.4 Hz, 2H), GC/MS: 163 [M]<sup>+</sup>.

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