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Graphical Abstract

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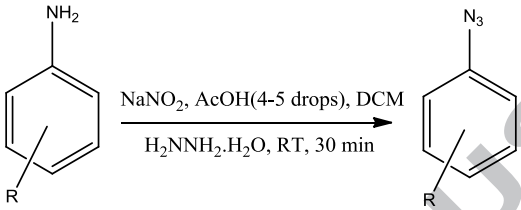

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One pot synthesis of aromatic azide using sodium nitrite and hydrazine hydrate

Afsar Ali Siddiki, Balaram S. Takale, Vikas N. Telvekar*
Department of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Matunga, Mumbai-400 019, India

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ABSTRACT

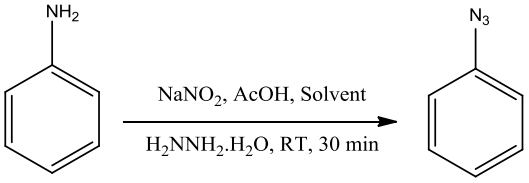
Simple, rapid and efficient protocol for the synthesis of aryl azide using sodium nitrite and hydrazine hydrate at room temperature is discussed. The short reaction time, simple work-up procedure and use of inexpensive reagents are advantages of this method.

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

Aryl azides are found to be prepared from organoboron compounds using copper (II) catalyst,[12] Reaction of $[ArN_2][BF_4]$ salts immobilized in $[BMIM][PF_6]$ ionic liquid with $TMSN_3$ represents an efficient method for the preparation of azido-derivatives via diazotization.[13] However, the synthesis of aryl azides relies upon a more limited selection of transformations.[14] They are commonly prepared from the corresponding amines via their diazonium salts.[15] 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.[16]More recently, Liu and Tor has applied Wong's (TfN_3) methodology toward the efficient preparation of aryl azides.[17] Although powerful, this procedure presents some drawbacks. First, toxic and potentially explosive NaN_3, and the highly reactive Tf_2O are used in excess. Second, TfN_3 has been reported to be explosive when not in solvent.[18] Recently, Das *et al.* reported the use of *tert*-butyl nitrite (*t*-BuONO) in combination with NaN_3 in the synthesis of aromatic azides.[19] This procedure requires a large excess of reagents (12 equiv of *t*-BuONO, 3 equiv of NaN_3), which is undesirable considering the hazards associated with NaN_3. As most of the methods involves multistep reaction and explosive reagent such as NaN_3, the method which avoid use of NaN_3 for aromatic azidation will be very much important from economical point. There are other methods where phenyl hydrazine derivatives act as a starting material for the synthesis of aromatic azides[20a] which involves no. of methods such as using Br_2/PPh_3 in ACN solvent at 273K[20b], N_2O_4/CCl_4 in ACN solvent[20c] and O_2/NO in dichloromethane solvent.[20d] Dutt *et al.*, reported the synthesis of aryl azide by using diazonium salt and sulphonamide, however formation of sulphonic acid as byproduct is a major drawback of this method. [20f]

We are continuously working on the development of new efficient methodologies; recently we explored application of sodium nitrite for decarboxylative bromination.[21] Here in we have developed a simple, single step procedure for azidation from aromatic amines.

For our initially study we have taken aniline as a model substrate. When aniline is treated with $NaNO_2$ 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).



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

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.

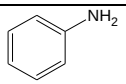
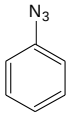
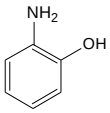
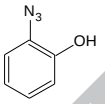
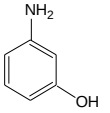
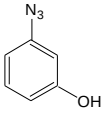
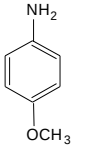
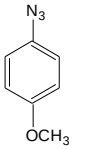
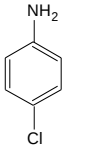
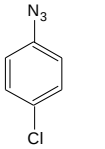
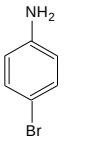
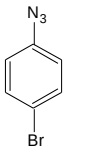
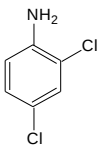
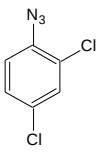
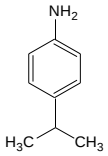
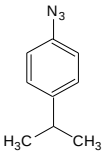
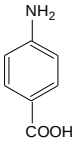
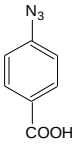
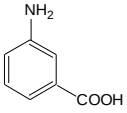
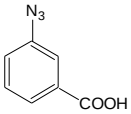
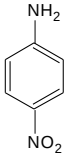
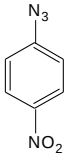
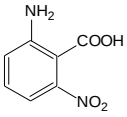
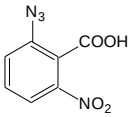
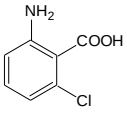
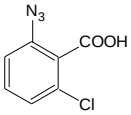
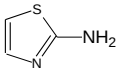
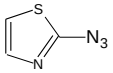
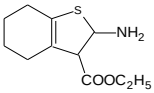
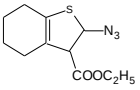
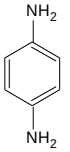
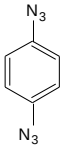
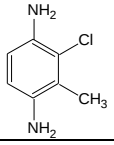
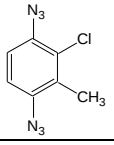
Table 1. Conversion of aniline to azide in presence of various solvents.

Entry	Solvents	Time (min)	% Yield[a]
1	Dichlorormethane	30	90
2	Chloroform	120	85
3	Toluene	120	80
4	Acetonitrile	120	80
5	DMSO	120	40

[a]Isolated yields after silica gel column chromatography

Further screening of the equivalent of sodium nitrite and hydrazine hydrate required for the reaction, it was found that 2 equivalent of sodium nitrite and 5 equivalent 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[22]

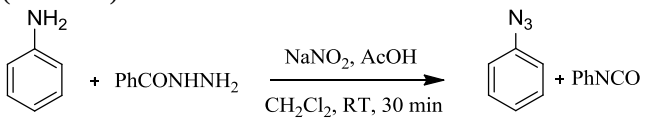
Table 2. Azidation using Sodium nitrite[a]

Entry	Reactant	Product	Time (min)	Yield (%)[b]
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
11			35	75
12			9h	50
13			8h	55
14			40	75
15			40	75
16			40	75
17			40	75

[a]Reaction condition: substrate (1.45 mmol), $NaNO_2$ (2.92 mmol), AcOH (11.7 mmol), $H_2NNH_2.H_2O$ (7.3 mmol), DCM, r.t.
[b]Isolated yield after column chromatography and structure were confirmed by comparison of IR, mp/bp, MS and 1H NMR with literature reports

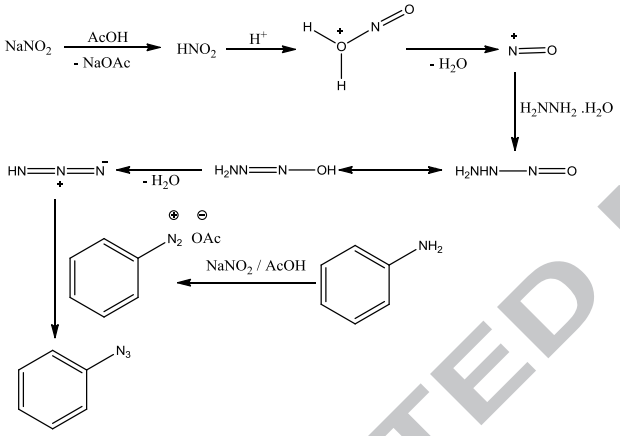
From Table 2 it is clearly seen that both electron donating and electron withdrawing substrates are suitable for this conversion and gave good to moderate yield of desired product in 30-40 min (Table 2, entry 2-11). When the aromatic ring is strongly deactivated, product could be achieved in poor yield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



Scheme 2. Reaction of aniline in the presence of benzhydrazide

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



Scheme 3. Plausible mechanism

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

Acknowledgment

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22. **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 r.t. for 5 min followed by addition of AcOH (8 equiv) and hydrazine hydrate (5 equiv, 99%) at r.t. for 30 min. The reaction mixture was then washed with H_2O (3 × 20 mL) and finally with brine solution (2 × 20 mL). The organic layer dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified using silica gel column chromatography (plane hexane).
Azido benzene (Table 2, Entry 1) [23a]
Yellow liquid, bp 44ºC, IR: 2120, 2091, 1592, 1490, 1292, 1280 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.4 (m, 2H), 7.09 (m, 3H), GC/MS: 120[M] $^+$.
1-azido-2-hydroxybenzene (Table 2, Entry 2) [23b]

Brown red solid, mp 40 ºC, IR (KBr): 3400, 2120, 1610, 1514, 1150, 1092, 860 cm^{-1}, ^1H NMR ($CDCl_3$, 400MHz) δ: 5.3 (s, 1H), 6.9-7.2 (m, 4H), GC/MS: 135$[M]^+$.

1-Azido-4-methoxybenzene (Table 2, Entry 4) [23c]

Yellow oil, IR: 2097, 1501, 1284, 1241 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 3.70 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), GC/MS: 149 $[M]^+$.

1-azido-4-Chlorobenzene (Table 2, Entry 5) [23d]

Yellow liquid bp 54 °C, IR: 3043, 2930, 2094, 1604, 1520, 1340, 1220, 1156, 1096, 822, 768 cm^{-1}, ^1H NMR ($CDCl_3$, 400MHz) δ: 3.70 (s, 3H), 7.3 (d, *J* = 8.6 Hz, 2H), 6.9 (d, *J* = 8.6 Hz, 2H), GC/MS: 153 $[M]^+$.

4-azido benzoic acid (Table 2, Entry 9) [23e]

Off white solid, mp 174 °C: IR (KBr): 2959, 2541, 2101, 1672, 1600, 1577, 1507, 1424, 1330, 1317, 1281, 1177, 1138, 1121, 859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, 8.4 Hz, 2H), 7.09 (d, 8.4 Hz, 2H), GC/MS: 163 $[M]^+$

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