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A Simple and Effective Synthesis of Aryl Azides via Arenediazonium Tosylates

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Abstract: Aromatic azides are formed in high yield from arenediazonium tosylates and sodium azide in water at room temperature or from aromatic amines via diazotization in the presence of *p*-TsOH. Besides being experimentally simple, these methods do not require any metal catalysis and provide clean products without purification.

Key words: diazotization, sodium azide, aromatic amines, *p*-TsOH, aqueous medium

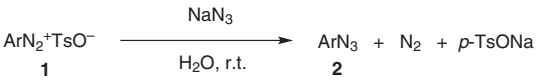
Organic azides are valuable compounds for many fields in organic and bioorganic chemistry.[1] They are used as equivalents of primary amines in the Staudinger reaction and the Staudinger ligation (using phosphine, phosphite, and phosphonite intermediates).[2] In spite of the complexity of their photolytic properties[3] aromatic azides (as sources of intermediate nitrenes) are of particular interest as photoaffinity labeling reagents in structural proteomics when combined with mass spectrometry analyses.[4]

Dipolar cycloaddition reactions of organic azides with alkynes and nitriles in the presence of copper salts that lead to 1,4- or 1,5-disubstituted 1,2,3-triazoles and tetrazoles, appear of the highest relevance in organic synthesis[5] and in the labeling of biomolecules[2] (including the efficient detection of DNA synthesis in vivo by click chemistry using 5-ethynyl-2′-deoxyuridine[6]), as well as to surface modification and in polymer science.[7,8]

These properties have elicited various methods for preparing aromatic azides.[1] Typically, these compounds are prepared through nucleophilic substitution of halides in activated arenes by the azide anion, or by azido-demetalation of arylmagnesium halides and aryllithium reagents (alkali azides, trimethylsilyl azide, or *p*-toluenesulfonyl azide are the most frequent azide sources); through diazotization of hydrazines; or using reactions of aromatic and heteroaromatic amines with TfN_3 or 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (the diazo-transfer reactions[9]) and of nitrosoarenes with hydrogen azide; as well as through base-induced cleavage of triazenes and copper-catalyzed reactions of boronic acids with TfN_3 or NaN_3.[10] More recently a method has been reported for the direct azidation of arenes by $NaICl_2$ and NaN_3.[11] The most general method for the preparation of aromatic azides is based on the reaction of diazonium salts with suitable azide sources,[1,12] including continuous-flow synthesis.[13] However, it is well known that traditional diazonium salts have certain disadvantages – poor thermal stability and explosive properties (including the more commonly used tetrafluoroborates[14]). It should be noted that the diazonium tetrafluoroborates display a poor solubility in water thus requiring use of mixtures of water and an organic solvent.[15]

A few years ago we reported the synthesis of aryldiazonium tosylates $ArN_2^+TsO^-$ (ADT) (**1**), which possess high diazonium reactivity but in contrast to usual diazonium salts have good thermal and storage stabilities and are soluble in water and many organic solvents.[16] The aim of this work was to assess the scope (and limitations) of ADTs as precursors for the synthesis of aromatic azides.

Selected ADTs (up to ten; see Table 1) in aqueous solution and at room temperature instantly reacted with an equivalent quantity of sodium azide (click reaction) resulting in emission of nitrogen and insolubilization of the corresponding aryl azides **2b**,**c**,**e**,**i**–**l**,**n**–**q**, which were obtained in quantitative yields (method A) (Scheme 1, Table 1).



Scheme 1 Click reaction of arenediazonium tosylates with sodium azide (method A)

Table 1 Preparation of Aryl Azides **2** from Arenediazonium Tosylates **1** and NaN_3 by Methods A and B

Entry	Product	Method A, yield (%)[a,b]	Method B[c] Time (min)	Yield (%)
1	PhN_3 (**2a**)	quant	40[d]	67
2	4-$O_2NC_6H_4N_3$ (**2b**)	quant	20	99
3	2-$O_2NC_6H_4N_3$ (**2c**)	quant	20	94
4	3-$O_2NC_6H_4N_3$ (**2d**)		20	93
5	4-$MeOC_6H_4N_3$ (**2e**)	quant	70	95
6	4-$MeC_6H_4N_3$ (**2f**)		20	72
7	4-$C_6H_{13}C_6H_4N_3$ (**2g**)		30	61
8	4-$C_{10}H_{21}C_6H_4N_3$ (**2h**)		40	89
9	4-$HO_2CC_6H_4N_3$ (**2i**)	quant	20	98

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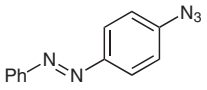
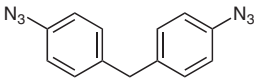
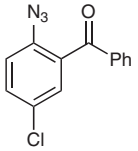
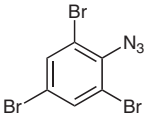
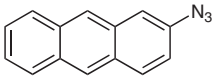
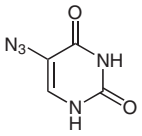
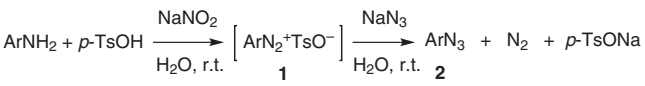
Table 1 Preparation of Aryl Azides **2** from Arenediazonium Tosylates **1** and NaN_3 by Methods A and B (continued)

Entry	Product	Method A, yield (%)[a,b]	Method B[c] Time (min)	Yield (%)
10	2-$HO_2CC_6H_4N_3$ (**2j**)	quant	20	92
11	3-$HO_2CC_6H_4N_3$ (**2k**)	quant	20	87
12	4-$PhC_6H_4N_3$ (**2l**)	quant	20	85
13	4-$IC_6H_4N_3$ (**2m**)		60	80[e]
14	4-$NCC_6H_4N_3$ (**2n**)	quant	20	97
15	 (**2o**)	quant	25	98
16	4-$H_2NC_6H_4N_3$ (**2p**)	69[f]		
17	 (**2q**)	quant	40	96
18	 (**2r**)		45	98
19	4-$BrC_6H_4N_3$ (**2s**)		60	97
20	 (**2t**)		60	93
21	 (**2u**)		60	97
22	 (**2v**)		40	83

[a] GC data.
[b] Reaction conditions: ADT (1 mmol), NaN_3 (1 mmol).
[c] Reaction conditions: $ArNH_2$ (1 mmol), $NaNO_2$ (9 mmol), *p*-TsOH (9 mmol), NaN_3 (1.6 mmol). Time refers to the diazotization step. Yields are for isolated pure products.
[d] At 5 °C.
[e] Reaction conditions: $ArNH_2$ (1 mmol), $NaNO_2$ (27 mmol), *p*-TsOH (27 mmol), NaN_3 (9 mmol).
[f] Reaction conditions: ADT (1 mmol), NaN_3 (3 mmol).

Importantly, method A exclusively yields the targeted aryl azides besides *p*-TsONa. No side-products were detected including phenols and triazenes (as monitored by GC-MS and HPLC), which are often formed in the reactions with diazonium salts. An important advantage of method A is the use of ADT **1** and NaN_3 in equimolar ratios in most cases, thus reducing the risk of toxic hydrazoic acid. The aryl azides **2b**–**d**,**i**–**r**,**t**,**u** were isolated as solid compounds through simple filtration and water washing without any use of organic solvents, while the aryl azides **2a**,**e**–**h**,**s** were isolated as oily products through ethyl acetate extraction and solvent evaporation. One exception is azide **2p**, which was only obtained in 69% yield with the formation of side-products, among them *p*-nitroaniline. In addition, in this case the complete conversion of the starting ADT (*p*-$NH_2C_6H_4N_2^+$ TsO^-) required three equivalents of sodium azide.

We also found that a variety of aromatic amines can be directly converted into the corresponding aromatic azides **2** in high yields by a one-pot mode via diazotization with sodium nitrite in water in the presence of *p*-TsOH followed by the reaction with sodium azide without isolation of the intermediate ADT (method B; Scheme 2, Table 1).



Scheme 2 One-pot preparation of aryl azides **2** from aromatic amines (method B)

Both reactions shown in Scheme 2 proceed smoothly at room temperature. Only aniline diazotization is an exception. In this case the temperature was lowered to 5 °C to afford azide **2a** without the formation of side-products. The resulting solid azides **2b**–**d**,**i**–**r**,**t**–**v** were readily isolated from water by filtration while the oily azides **2a**,**e**–**h**,**s** were isolated after extraction with ethyl acetate and solvent evaporation. In all cases, products **2** are of sufficiently high purity (NMR, GC) and can be further used without any additional purification. Avoiding recrystallization and distillation of the targeted products **2** enhances the safety of the synthetic procedure considering that azides are potentially hazardous substances and explosophores. These points are of crucial relevance to any large-scale azide production.

In contrast to many conventional methods our proposed synthesis of aryl azides **2** displays a general applicability thus including aromatic azides with electron-withdrawing or electron-donating substituents, as well as groups with a marked lipophilic character (compounds **2 g**,**h**). Similarly, polycyclic and heterocyclic azides with different degrees of steric hindrance (**2t**–**v**) are formed in high yields.

One exception is the reaction with 4-iodoaniline, in which an 80% yield of 1-azido-4-iodobenzene (**2m**) was only achieved with a relatively large excess of sodium azide (an optimal ratio of the reactants was found to be 4-iodoaniline/$NaNO_2$/*p*-TsOH/NaN_3 = 1:27:27:9).

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At the same time, method B has its limitations. It appears unusable for the preparation of 4-azidobenzenamine (**2p**), since diazotization of benzene-1,4-diamine leads to significant amounts of by-products including PhN_3, PhOH, $PhNO_2$, 4-$HOC_6H_4NH_2$, 1,4-$(O_2N)_2C_6H_4$, 4-$H_2NC_6H_4NO_2$, and 4-$PhC_6H_4NH_2$ (GC-MS data). Finally, method B is improper to the synthesis of azidopyridines since diazotization of aminopyridines in the presence of *p*-TsOH results in the formation of pyridinyl tosylates instead of pyridinediazonium tosylates.[17]

In summary, we have developed a reliable and efficient approach for the synthesis of aryl azides through the reaction of arenediazonium tosylates with sodium azide in water at room temperature. This procedure offers several advantages over the methods reported so far that include an increased safety and a large chemical applicability (although with some limitations) under metal-free conditions with minimal purification stages.

All starting materials were ACS grade and were used without further purification. Arenediazonium tosylates **1** were prepared by a previously described method.[16] HPLC analyses were conducted with an Agilent 1200 instrument fitted with an Eclipse Plus C18 column (5 μm, 4.6 × 150 mm) and UV detector; 0.1% TFA–H_2O and 0.1% TFA–MeCN were used as eluents. GC-MS measurements were obtained with an Agilent 7890/5975C instrument. ^{1}H, ^{13}C NMR, and IR spectra were recorded on a Bruker Avance 300 and PerkinElmer BXII instruments. Melting points (uncorrected) were obtained with a Melting point system MP50, Mettler, Toledo. Elemental analyses were performed with a Vario MACRO cube CHNS instrument (Elementar Analysensysteme GmbH, Germany). Thermal analyses of some of the starting ADT were performed on an integrated DSC-TGA-DTA instrument STD Q600 in open cells.

Thermal stability for some ADT salts (as assessed by DSC between 0–600 °C under a N_2 atmosphere). Decomposition temperature (°C) and decomposition energy (J/g): Ar = 4-$NO_2C_6H_4$ 137, –339.9; 2-$NO_2C_6H_4$: 144, –323.0; 3-$NO_2C_6H_4$: 141, –389.8; 4-$C_6H_{13}C_6H_4$: 128, –785.0; 4-$CO_2HC_6H_4$: 97, –412.4; 2-$CO_2HC_6H_4$: 121, –840.3; 4-IC_6H_4: 115, –245.5; 4-CNC_6H_4: 113, –332.4; 4-$NH_2C_6H_4$: 148, –298.0; 2,4,6-$Br_3C_6H_2$: 139, –184.7.

Reaction of ADT 1 with NaN_3 (Method A); General Procedure

To a solution of ADT (1.0 mmol) in H_2O (10 mL) at r.t. was added NaN_3 (65 mg, 1.0 mmol) under stirring. An immediate emission of N_2 was observed. Solid compounds **2b**–**d**,**i**–**r**,**t**,**u** were filtered and washed with H_2O (50 mL) (Table 1).

4-Azidobenzenamine (2p)[18]

Yield: 92.5 mg (69%, 0.69 mmol); brown solid; mp 60 °C.

^{1}H NMR (300 MHz, DMSO): δ = 6.77 (d, *J* = 6.0 Hz, 2 H), 6.59 (d, *J* = 6.0 Hz, 2 H), 5.14 (s, 2 H).

Aryl Azides 2 from Aromatic Amines (Method B); General Procedure

Caution! *Volatile, highly toxic, and explosive HN_3 can occasionally evolve and this operation needs to be conducted in a well-ventilated exhaust hood*.

To a solution of *p*-TsOH·H_2O (1.62 g, 9 mmol) in H_2O (9 mL) was added $ArNH_2$ (1 mmol). After stirring for 1 min, andhydrous $NaNO_2$ (0.621 g, 9 mmol) was added gradually during 5 min. The resulting solution was then stirred for 2–60 min until the starting $ArNH_2$ disappeared as monitored by TLC (eluent: benzene–EtOH, 9:1). To the resulting solution, andhydrous NaN_3 (0.104 g, 1.6 mmol) was added. An immediate emission of N_2 was observed. Solid aryl azides **2b**–**d**,**i**–**r**,**t**–**v** were filtered, washed with H_2O (50 mL) and dried. Oily azides **2a**,**e**–**h**,**s** were extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), filtered, and the solvent was removed in a rotary evaporator under reduced pressure (Table 1).

Azidobenzene (2a)[10a]

Yield: 79.7 mg (67%, 0.67 mmol); pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.39 (m, 2 H), 7.17 (m, 1 H), 7.07 (d, *J* = 7.8 Hz, 2 H).

1-Azido-4-nitrobenzene (2b)[10c]

Yield: 164 mg (quant, 1 mmol); pale yellow solid; 66 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.25 (d, *J* = 9.0 Hz, 2 H), 7.35 (d, *J* = 9.0 Hz, 2 H).

1-Azido-2-nitrobenzene (2c)[19]

Yield: 154 mg (94%, 0.94 mmol); orange solid; 52 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.01 (d, *J* = 9.6 Hz, 1 H), 7.74 (m, 1 H), 7.59 (m, 1 H), 7.36 (d, *J* = 9.6 Hz, 1 H).

1-Azido-3-nitrobenzene (2d)[10b]

Yield: 152.5 mg (93%, 0.93 mmol); orange solid; 52°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.99 (d, *J* = 6.9 Hz, 1 H), 7.82 (s, 1 H), 7.68 (m, 1 H), 7.59 (d, *J* = 6.9 Hz, 1 H).

1-Azido-4-methoxybenzene (2e)[20]

Yield: 141.5 mg (95%, 0.95 mmol); yellow oil.

IR (film): 2106 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.05 (d, *J* = 9.3 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 3.39 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.8, 131.4, 120.9, 115.3, 55.4.

MS (EI): *m*/*z* = 149 ($[M]^+$), 121, 106, 91, 78, 64, 52, 45, 39.

1-Azido-4-methylbenzene (2f)[9c]

Yield: 96 mg (72%, 0.72 mmol); brown oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.22 (d, *J* = 8.4 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 2.28 (s, 3 H).

1-Azido-4-hexylbenzene (2g)[21]

Yield: 124 mg (61%, 0.61 mmol); brown oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.23 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 2.57 (m, 2 H), 1.55 (m, 2 H), 1.25 (m, 6 H), 0.87 (m, 3 H).

1-Azido-4-decylbenzene (2h)

Yield: 231 mg (89%, 0.89 mmol); brown oil.

IR (film): 2109 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.23 (d, *J* = 8.1 Hz, 2 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 2.56 (m, 2 H), 1.52 (m, 3 H), 1.22 (m, 7 H), 1.03 (m, 5 H), 0.84 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 139.3, 136.5, 129.8, 118.8, 34.4, 31.2, 30.9, 28.9, 28.6, 28.4, 22.0, 13.9.

Anal. Calcd for $C_{16}H_{25}N_3$: C, 74.09; H, 9.71; N, 16.20. Found: C, 74.22; H, 9.78; N, 16.24.

4-Azidobenzoic Acid (2i)[10c]

Yield: 160 mg (98%, 0.98 mmol); white solid, 113 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H).

2-Azidobenzoic Acid (2j)[22]

Yield: 150 mg (92%, 0.92 mmol); beige solid; 136 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.78 (d, *J* = 7.5 Hz, 1 H), 7.62 (m, 1 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 7.29 (m, 1 H).

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3-Azidobenzoic Acid (2k)[23]
Yield: 150 mg (92%, 0.92 mmol); white solid; 164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.72 (d, J = 7.5 Hz, 1 H), 7.58 (s, 1 H), 7.39 (m, 1 H), 7.14 (d, J = 7.5 Hz, 1 H).

4-Azidobiphenyl (2l)[10c]
Yield: 122.8 mg (63%, 0.63 mmol); pale brown solid; 62 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.69 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 7.2 Hz, 2 H), 7.47–7.42 (m, 2 H), 7.37–7.32 (m, 1 H), 7.19 (d, J = 8.4 Hz, 2 H).

1-Azido-4-iodobenzene (2m)[10c]
Yield: 196 mg (80%, 0.8 mmol); beige solid; 31 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.74 (s, 2 H), 6.95 (s, 2 H).

4-Azidobenzonitrile (2n)[10c]
Yield: 139.6 mg (97%, 0.97 mmol); white solid; 60 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.85 (d, J = 8.4 Hz, 2 H, ArH), 7.29 (d, J = 8.4 Hz, 2 H, ArH).

(*E*)-1-(4-azidophenyl)-2-phenyldiazene (2o)[24]
Yield: 218.5 mg (98%, 0.98 mmol); dark orange solid; 63 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.96 (d, J = 8.7 Hz, 2 H, ArH), 7.89–7.87 (m, 2 H, ArH), 7.62–7.58 (m, 1 H, ArH), 7.50 (d, J = 7.8 Hz, 2 H, ArH), 7.13 (d, J = 7.8 Hz, 2 H, ArH).

Bis(4-azidophenyl)methane (2q)[25]
Yield: 240 mg (96%, 0.96 mmol); dark red solid; 110–113 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.25 (d, J = 5.7 Hz, 4 H), 7.03 (d, J = 6.0 Hz, 4 H), 3.90 (s, 2 H).

(2-Azido-5-chlorophenyl)phenylmethanone (2r)[26]
Yield: 251.8 mg (98%, 0.98 mmol); beige solid; 82 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.74–7.67 (m, 4 H), 7.57–7.48 (m, 4 H).

1-Azido-4-bromobenzene (2s)[10c]
Yield: 191 mg (97%, 0.97 mmol); yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.58 (d, J = 8.7 Hz, 2 H), 7.09 (d, J = 8.7 Hz, 2 H).

2-Azido-1,3,5-tribromobenzene (2t)[27]
Yield: 331 mg (93%, 0.93 mmol); beige solid; 74 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.97 (s, 2 H).

2-Azidoanthracene (2u)[9a]
Yield: 212.4 mg (97%, 0.97 mmol); dark gray solid; 170–172 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.58 (s, 1 H), 8.52 (s, 1 H), 8.17 (d, J = 8.7 Hz, 3 H), 7.79 (s, 1 H), 7.52 (d, J = 6.9 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H).

5-Azidouracil (2v)
Yield: 127 mg (83%, 0.83 mmol); beige solid; 98 °C (dec.).

IR (KBr): 2158, 2116 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.28 (s).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.9, 150.2, 130.2, 112.2.

Anal. Calcd for $C_4H_3N_5O_2$: C, 31.38; H, 1.98; N, 45.74. Found: C, 31.42; H, 1.97; N, 45.79.

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