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Simple Conversion of Aromatic Amines into Azides

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ABSTRACT

$$\mathrm{ArNH_2} \xrightarrow[\mathrm{Et_3N,\ CH_2Cl_2/MeOH}]{\mathrm{TfN_3,\ aq.\ CuSO_4}} \mathrm{ArN_3}$$

A straightforward and highly efficient synthesis of aromatic azides from the corresponding amines is accomplished using triflyl azide under mild conditions.

Aromatic azides have found unique applications in synthetic organic chemistry,[1] although their most common use is probably as photoaffinity labeling reagents for biomolecules.[2] The preparation of aryl azides relies on a rather limited selection of transformations.[1] They can be prepared from the corresponding amines via their diazonium salts.[1,3] While useful for rather simple substrates, this chemistry is not always tolerant of other functional groups. Alternative methods have been explored where, for example, *p*-tosyl azide reacts with aryl Grignard or lithium reagents derived from the corresponding aryl halides.[4] Similarly, aryl amide salts (generated from the amine and strong carbon-based bases) have been shown to react with *p*-tosyl azide to yield the desired azides.[5] The relatively harsh conditions have limited the general use of this transformation. In contrast to aromatic azides, numerous methods are accessible for the synthesis of aliphatic azides.[1,6] In addition to simple substitution reactions using the azide ion and various electrophiles, aliphatic amines can easily be converted to the corresponding azides via a high-yielding reaction with triflyl azide **1** (TfN_3).[7] This reaction, recently popularized by Wong,[8] has found numerous applications[9] and triggered our interest. In this contribution, we disclose the application of this reagent to the simple conversion of aromatic amines into the corresponding azides. Mild reaction conditions and very high yields make this transformation a method of choice for the straightforward preparation of numerous aromatic azides.

In a typical reaction (Scheme 1), a freshly prepared triflyl azide **1**[10,11] is reacted with 8-aminoquinoline in dichloromethane/methanol at room temperature in the presence of

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(1) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368.

(2) For reviews on aryl azides as photoaffinity labels and references therein, see: (a) Bayley, H.; Staros, J. V. In *Azides and Nitrenes*, Scriven, E. F. V., Ed.; Academic Press: Orlando, 1984; pp 433−490. (b) *Annals of the New York Academy of Sciences*; Tometsko, A. M., Richards, F. M., Eds.; New York Academy of Sciences, New York, 1980; Applications of Photochemistry in Probing Biological Targets, Vol. 346. (c) Radominska, A.; Drake, R. R. *Methods Enzymol.* **1994**, *230*, 330−339. (d) Fedan, J. S.; Hogaboom, G. K.; O'Donnell, J. P. *Biochem. Pharmacol.* **1984**, *33*, 1167−1180.

(3) For a review, see: (a) Biffin, M. E. C.; Miller, J.; Paul, D. B. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971; pp 147−176. See also: (b) Kauer, J. C.; Carboni, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 2633−2637. (c) Takahashi, M.; Suga, D. *Synthesis* **1998**, *7*, 986−990.

(4) See for example: (a) Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *J. Org. Chem.* **1969**, *34*, 3430−3433. (b) Smith, P. A. S.; Budde, G. F.; Chou, S.-S. P. *J. Org. Chem.* **1985**, *50*, 2062−2064. (c) Gavenonis, J.; Tilley, T. D. *J. Am. Chem. Soc.* **2002**, *124*, 8536−8537. (d) Gavenonis, J.; Tilley, T. D. *Organometallics* **2002**, *21*, 5549−5563.

(5) (a) Fisher, W.; Anselme, J.-P. *J. Am. Chem. Soc.* **1967**, *89*, 5284−5285. (b) Nielsen, P. E. *Tetrahedron Lett.* **1979**, *20*, 2705−2706.

(6) Sandler, S.; Karo, W. *Organic Functional Group Preparations*; Academic Press: New York, 1971; pp 268−284.

(7) For early examples, see: (a) Ruff, J. K. *Inorg. Chem.* **1965**, *4*, 567−570. (b) Caveander, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567−3569. (c) Zaloom, J. R.; David C. *J. Org. Chem.* **1981**, *46*, 5173−5176. (d) Eaton, P. E.; Fisher, A. M.; Hormann, R. E. *Synlett* **1990**, 737−738.

(8) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032.

(9) See, for example: (a) Ding, Y.; Swayze, E. E.; Hofstadler, S. A.; Griffey, R. H. *Tetrahedron Lett.* **2000**, *41*, 4049−4052. (b) Greenberg, W. A.; Priestley, E. S.; Sears, P. S.; Alper, P. B.; Rosenbohm, C.; Hendrix, M.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 6527−6541.

(10) Solution of NaN_3 (3.5 g, 54 mmol) in water (8 mL) and CH_2Cl_2 (3 mL) was cooled to 0 °C in an ice−water bath. To the vigorously stirred mixture was added Tf_2O (2.54 g, 1.51 mL, 9 mmol) dropwise. After stirring at 0 °C for an additional 2 h, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (10 mL) and used immediately.

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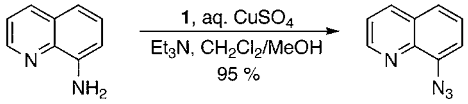
Scheme 1

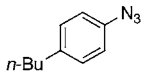
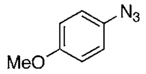
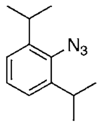
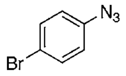
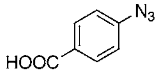
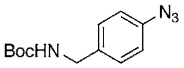
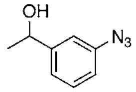
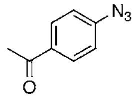
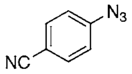
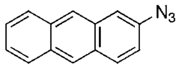


triethylamine and copper(II) sulfate.[12] The reaction proceeds smoothly, rapidly, and quantitatively to yield 8-azidoquinoline in 95% isolated yield.[12,13]

To explore the scope of this reaction, a series of aromatic amines was allowed to react with **1** under similar conditions. Table 1 summarizes the results. Simple anilines containing inert substituents react smoothly and afford the desired product in greater than 90% yield (e.g., entry 1). Electron-rich as well as sterically demanding anilines also react effectively (e.g., entries 2 and 3, respectively). Anilines substituted with strong electron-withdrawing groups such as 4-cyano are weakly nucleophilic and react sluggishly (see entries 8 and 9).[14] Interestingly, 4-aminobenzoic acid yields the desired azide in high yield. Under the basic reaction conditions, the electron-withdrawing carboxylic acid is deprotonated and azidation proceeds well. Importantly, the mild reaction conditions allow one to utilize substrates that contain acidic or acid-labile functional groups. Thus, the Boc-protected 4-amino-benzylamine reacts in excellent yield to give the desired azide (entry 6). Similarly, the presence of a benzylic alcohol does not interfere with the transformation that takes place in 96% yield (entry 7). Other aromatic amines (e.g., 2-aminoanthracene) react effectively (entry 10), although they do require alternative solvents such as THF (Table 1 and Supporting Information).

In summary, a simple and highly effective procedure for the conversion of aromatic amines into their corresponding azides has been described. The easily accessible triflyl azide **1** reacts rapidly under mild conditions with various anilines and related aromatic amines to provide the desired azides.

Table 1. ArN_3 Prepared from $ArNH_2$ and **1**

entry	product[a]	reaction time	yield (%)
1		2 h	93
2		40 min	90
3		1.5 h	92
4		3 h	85
5		3 h	88
6		1.5 h	96
7		1.5 h	96
8		24 h	15[b]
9		24 h	7[c]
10		2 h	78

[a] See Supporting Information for procedures and spectral data. [b] Starting material (75%) was recovered. [c] Starting material (80%) was recovered.

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Supporting Information Available: Detailed experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Although we have not experienced any difficulties in handling tryflyl azide, care should be taken due to the potentially explosive nature of such compounds (see ref 7b).

(12) Aminoquinoline (0.43 g, 3 mmol) was dissolved in CH_2Cl_2 (2 mL) in a 50 mL round-bottomed flask. Et_3N (0.91 g, 1.25 mL, 9 mmol) and a solution of $CuSO_4$ (24 mg, 0.15 mmol in 0.5 mL H_2O) were added to the flask consecutively. Freshly prepared dichloromethane solution of TfN_3 (see ref 10 above) was then added, and the solution was brought to homogeneity by adding MeOH (ca. 2 mL). The resulting solution was stirred at room temperature for 2 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (CH_2Cl_2) to give a brownish solid (0.49 g, 95%). $R_f = 0.33$ (CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, 1H), 8.37 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H), 7.57 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.31 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 148.9, 141.3, 136.4, 135.1, 128.7, 126.5, 124.6, 122.0, 119.0. IR (KBr pellet): 2119 cm^{-1}. GCMS: calcd for $C_9H_6N_4$ 170.06, found 169.9 $[M]^+$, 142 $[M - N_2]^+$.

(13) Mechanism for the metal-catalyzed diazo transfer for the aliphatic amine-to-azide interconversion has been proposed by Wong. See: Nyffeler, P. T.; Liang, C. H.; Koeller, K. M.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778.

(14) Attempts to push the reaction at elevated temperatures have not resulted in any improvement, possibly due to the concomitant decomposition of **1**.