ORGANIC LETTERS

2007
Vol. 9, No. 9
1809−1811

Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages

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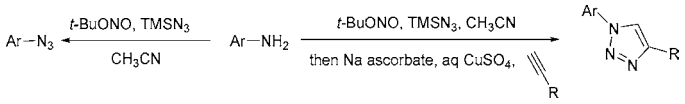
Received March 2, 2007

ABSTRACT



An efficient and improved procedure for the preparation of aromatic azides and their application in the Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition ("click reaction") is described. The synthesis of aromatic azides from the corresponding amines is accomplished under mild conditions with *tert*-butyl nitrite and azidotrimethylsilane. 1,4-Disubstituted 1,2,3-triazoles were obtained in excellent yields from a variety of aromatic amines without the need for isolation of the azide intermediates.

Aromatic azides are versatile intermediates with a diverse range of applications in organic and bioorganic chemistry,[1] with their use as photoaffinity labeling reagents for biomolecules being particularly important.[2]

Recently, organic azides have been somewhat popularized due to their pivitol role in the emerging field of "click chemistry",[3] and in particular since the discovery of the Cu(I)-catalyzed (stepwise) Huisgen[4] cycloaddition between organic azides and terminal alkynes.[5]

This powerful and reliable bond-forming process has found widespread application, e.g., in combinatorial drug discovery,[6] material science,[7] and bioconjugation.[8,9] This has stimulated a demand for readily accessible azide building blocks, and consequently, a need for reliable and efficient methods for installing this functional group.

The preparation of alkyl azides is relatively straightforward,[1,10] and can be achieved by simple subsitution using azide ion and various electrophiles, or by reaction of the corresponding aliphatic amine with triflyl azide (TfN_3).[11] A

(1) For example see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240. (b) 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, FL, 1984; pp 433−490. (b) Radominska, A.; Drake, R. R. *Methods Enzymol.* **1994**, *230*, 330−339. (c) Fedan, J. S.; Hogaboom, G. K.; O'Donnell, J. P. *Biochem. Pharmacol.* **1984**, *33*, 1167−1180.

(3) For recent reviews on click chemistry and references therein see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137. (c) Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147−1149. (d) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *1*, 51−68.

(4) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565−598.

(5) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(6) For example see: (a) Moorhouse, A. D.; Santos, A. M.; Gunaratnam, M.; Moore, M.; Neidle, S.; Moses, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 15972−15973. (b) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588−9589.

(7) For example see: (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Harpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928−3932. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, *48*, 5775−5777. (c) Rozkiewicz, D. I.; Jańczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 5292−5296.

(8) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192−3193.

(9) For example see: (a) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686−4687. (b) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535−546. (c) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398−1399.

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

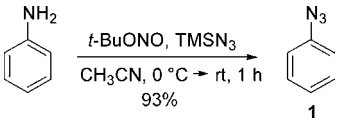
(11) For example see: (a) Ruff, J. K. *Inorg. Chem.* **1965**, *4*, 567−570. (b) Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567−3569. (c) Eaton, P. E.; Fisher, A. M.; Hormann, R. E. *Synlett* **1990**, 737−738.

10.1021/ol070527h CCC: $37.00
Published on Web 03/29/2007

recent modification of the latter method, popularized by Wong,[12] has found numerous applications,[13] due to the high yields and relatively mild conditions of the adapted procedure. However, the synthesis of aryl azides relies upon a more limited selection of transformations.[1b] They are commonly prepared from the corresponding amines via their diazonium salts,[14] which 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.[15] More recently, Liu and Tor have applied Wong's (TfN_3) methodology toward the efficient preparation of aryl azides.[16] 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, thus presenting further potential hazards.[17] Recently, Das et al. reported the use of *tert*-butyl nitrite (*t*-BuONO) in combination with NaN_3 in the synthesis of aromatic azides.[18] 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.

In this contribution, we disclose a less hazardous and practical synthesis of aromatic azides from their corresponding amines using stable and non-explosive reagents: *tert*-butyl nitrite (*t*-BuONO) and azidotrimethylsilane ($TMSN_3$).[19] Mild reaction conditions and very high yields make this transformation an attractive option for the straightforward preparation of numerous aromatic azides.

Scheme 1



In a typical reaction (Scheme 1), aniline was dissolved in acetonitrile and reacted in the presence of *t*-BuONO (1.5 equiv) and $TMSN_3$ (1.2 equiv) at 0 °C, with warming to room temperature.[20] The reaction proceeds smoothly and rapidly to afford azidobenzene **1** in 93% isolated yield.[20]

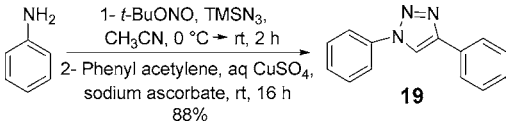
To explore the scope of this reaction, a range of aromatic amines (**2**−**18**) were reacted under the optimized conditions. Table 1 summarizes the results. Simple anilines containing inert substituents reacted smoothly to afford the desired product in high yield (e.g., entry **2**). Electron-rich (e.g., entries **5** and **6**) as well as sterically demanding (e.g., entry **3**) anilines also react effectively. In contrast to the related TfN_3 procedure,[16] anilines substituted with strong electron-withdrawing groups react rapidly and with high yields (e.g., entries **7**, **9**, and **10**). Interestingly, several aminobenzoic acid derivatives afforded the desired azides in good yields and did not require purification (e.g., entries **12**−**18**) (Table 1 and the Supporting Information).

Although organic azides are stable against most reaction conditions, compounds of low molecular weight tend to be explosive and are difficult to handle.[1] Thus, in the context of the "click reaction", procedures which generate azides in situ, followed by azide−alkyne cycloaddition have become an attractive option.[21]

We considered whether our described procedure could be adapted toward a convenient one-pot synthesis of triazole linked structures starting from aromatic amines, thus avoiding the isolation of the azide intermediates. The key to this procedure was the generation of Cu(I) required for the azide−alkyne cycloaddition, which was achieved by adding Cu(II) and a reducing agent after complete diazo transfer.[5b]

The reaction conditions for a sequential one-pot procedure were optimized by using aniline as the chosen substrate (Scheme 2).[22] First, the azide transfer was performed as outlined above. After complete consumption of starting material (TLC), catalytic amount sof $CuSO_4$ (7 mol %),

Scheme 2



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

(13) For example see: (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.

(14) For a review see: 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) Takahashi, M.; Suga, D. *Synthesis* **1998**, *7*, 986−990.

(15) For example see: (a) Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *J. Org. Chem.* **1969**, *34*, 3430−3433. (b) Gavenonis, J.; Tilley, T. D. *Organometallics* **2002**, *21*, 5549−5563.

(16) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571−2572.

(17) Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173−5176.

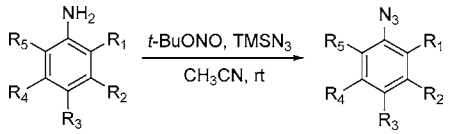
(18) Das, J.; Patil, S. N.; Awasthi, R.; Narasimhulu, C. P.; Trehan, S. *Synthesis* **2005**, *11*, 1801−1806.

(19) This combination of reagents has been previously used in large excess in the synthesis of 2-azidodeoxyadenosine, see: (a) Higashiya, S.; Kaibara, C.; Fukuoka, K.; Suda, F.; Ishikawa, M.; Yoshida, M.; Hata, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 39−42. (b) Wada, T.; Mochizuki, A.; Higashiya, S.; Tsuruoka, H.; Kawahara, S.-I.; Ishikawa, M.; Sekine, M. *Tetrahedron Lett.* **2001**, *42*, 9215−9219.

(20) Aniline (200 mg, 2.14 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (331 mg, 380 μL, 3.21 mmol) followed by $TMSN_3$ (300 mg, 340 μL, 2.56 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the product, **1**, as a pale yellow oil (236 mg, 93%). IR (film) 3062.99, 2124.35, 2093.43, 1593.63, 1491.52, 1294.58 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (dd, J = 7.6 and 0.7 Hz, 2H), 7.06 (td, J = 7.6 and 0.7 Hz, 1H), 7.27 (t, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 119.0, 124. 9, 129.8, 140. 0. EA calcd for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.48; H, 4.27; N, 35.25.

(21) For example see: (a) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1−4. (b) Titz, A.; Radic, Z.; Schwardt, O.; Ernst, B. *Tetrahedron Lett.* **2006**, *47*, 2383−2385. (c) Yan, R.-B.; Yang, F.; Wu, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron Lett.* **2005**, *46*, 8993−8995. (d) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331−2336. (e) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897−3899. (f) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223−4225.

Table 1. ArN_3 Prepared from $ArNH_2$



entry[a]	R_1	R_2	R_3	R_4	R_5	reaction time (h)	yield (%)
2	H	H	$CH-(CH_3)_2$	H	H	1	96
3	CH_2-CH_3	H	H	H	CH_2-CH_3	1	95
4	H	C≡CH	H	H	H	1	84
5	H	OCH_3	H	H	H	1	88
6	H	H	OCH_3	H	H	2	83
7	H	H	NO_2	H	H	2	76
8	H	H	I	H	H	2	90
9	H	H	$C(O)CH_3$	H	H	2	95
10	H	H	C≡N	H	H	2	96
11	OH	H	NO_2	H	H	1	74
12	COOH	H	H	H	H	2	81
13	COOH	CH_3	H	H	H	2	83
14	COOH	Cl	H	H	H	2	78
15	COOH	H	I	H	H	2	67
16	COOH	H	H	F	H	2	65
17	COOH	H	OCH_3	OCH_3	H	2	78
18	COOH	H	H	NO_2	H	2	90

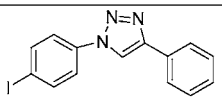
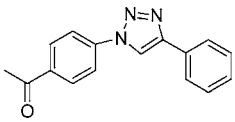
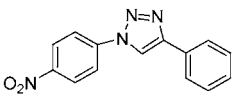
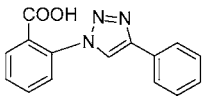
[a] See the Supporting Information for procedures and spectral data.

sodium ascorbate (0.2 equiv), and phenylacetylene (1 equiv) were added directly at room temperature without any workup procedure. The 1,2,3-triazole product, **19**, was obtained in high yield within a reasonable reaction time.

To investigate the scope of this one-pot protocol, a selection of aromatic amines were employed using this methodology (Table 2). In each case, the triazole products **20**−**23** were isolated in very good yields.[22]

In summary, a simple and highly efficient procedure for the conversion of aromatic amines into their corresponding azides, under very mild conditions, has been described. This procedure offers advantages over current methodologies in terms of safety, ease of execution, and efficiency. Moreover, an efficient one-pot "click-reaction" has been described, which enabled access to 1,2,3-triazoles without the need to isolate the corresponding aromatic azide. This procedure should prove especially useful when unstable low molecular weight and polyvalent aromatic azides are needed.

Table 2. One-Pot Synthesis of 1,2,3-Triazoles from Aromatic Amines

entry	product[a]	reaction time (h)	yield (%)
20		16	79
21		16	81
22		16	82
23		16	87

[a] See the Supporting Information for procedures and spectral data.

Acknowledgment. We thank the EPSRC and AICR for funding, our colleagues at The School of Pharmacy, Caterina Lombardo for assistance in synthesis, and Kersti Karu and Sibylle Heidelberger for providing analytical services.

Supporting Information Available: Detailed experimental procedures for all compounds, and spectral data for new compounds **13**, **14**, **16**, and **20**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070527H

(22) For example: Aniline (50 mg, 0.54 mmol) was dissolved in CH_3CN (2 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (83 mg, 96 μL, 0.81 mmol) followed by $TMSN_3$ (75 mg, 86 μL, 0.65 mmol) dropwise. The resulting solution was stirred at room temperature for 2 h. Phenylacetylene (55 mg, 60 μL, 0.54 mmol), an aq solution (0.2 mL) of $CuSO_4$ (9 mg, 0.027 mmol), and sodium ascorbate (24 mg, 0.108 mmol) were then added and the reaction was stirred overnight at room temperature. Most of the solvent was evaporated and the product was then precipitated with methanol to give the product, **19**, as an off-white solid (104 mg, 88%). IR (film) 3062.99, 2372.93, 1597.92, 1502.89, 1480.90 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.03 (m, 1H), 7.39 (m, 3H), 7.48 (t, J = 7.6 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 8.12 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 117.6, 120.6, 125.9, 128.5, 128.8, 128.9, 129.8, 130.3, 137.1, 148.5. HRMS [ES^+] calcd for $C_{14}H_{11}N_3$ 222.1031 $[M + H]^+$, found 222.1029. EA calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.82; H, 4.91; N, 18.72.