Efficient One-Pot Synthesis of 1,2,3-Triazoles from Benzyl and Alkyl Halides

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Abstract: An efficient one-pot method for the preparation of 1,2,3-triazoles by 1,3-dipolar cycloaddition of in situ generated azides and alkynes is presented. This facile method can be applied to benzyl or alkyl halides and pure products are isolated by simple filtration.

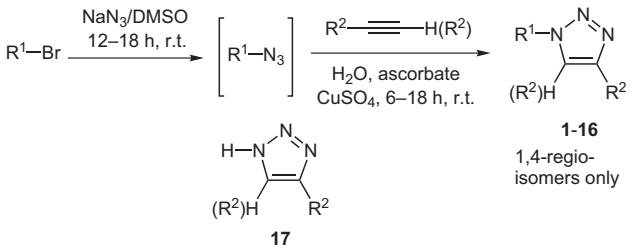
Key words: 1,3-dipolar cycloadditon, click chemistry, 1,2,3-triazoles, one-pot synthesis

1,2,3-Triazoles are an important class of heterocycles due to their range of applications as pharmaceuticals and their synthetic intermediates, in agrochemicals, as optical brighteners, or as corrosion inhibitors.[1] Their formation by the 1,3-dipolar cycloaddition of azides and alkynes has recently been recognized as one of the most powerful methods for linking molecules (click chemistry)[2] and has resulted in a number of excellent applications in the field of medicinal chemistry, e.g. in discovering acetylcholinesterase, 1,3-fucosyl transferase VI and HIV protease inhibitors, as well as in biochemistry and molecular biology for bioconjugation and labeling.[3]

Although organic azides are generally stable at room temperature and the danger of their explosive decomposition decreases with increasing molecular weight (it is believed that five carbon atoms per one azide group makes the molecule safe[2]), isolation or purification of lower organic azides or polyazides can be problematic. In situ generation of azides from suitable precursors followed by addition of an alkyne in a one-pot procedure, to form the desired 1,2,3-triazole would allow the difficulties associated with the explosive nature of the azide to be avoided. Such a one-pot strategy was reported by Maksikova, however, in this procedure low yields of 1,4- and 1,5-regioisomeric products were obtained.[4] In the course of the preparation of this manuscript Fokin demonstrated a very elegant, one-pot approach to the synthesis of 1,4-disubstituted 1,2,3-triazoles from mainly aryl and a few activated alkyl halides[5] as well as a microwave accelerated one-pot synthesis of various 1,2,3-triazoles.[6] The latter, however, required the use of forcing conditions (10 min at 125 °C) which may be not compatible with sensitive substrates, also special sealed pressure-resistant vials were utilized, which makes scale-up difficult. Another procedure for a one-pot synthesis of 1,2,3-triazoles has been reported by Blass who used polymer-supported azides for azidation of organic halides.[7]

We report herein an alternative simple one-pot procedure for the regioselective preparation of 1,2,3-triazoles (**1**–**16**) from a number of benzyl and alkyl halides as azide precursors. The reaction can be carried out at room temperature and without any special equipment (Table 1). We assumed that to ensure a high yield of the *N*-alkyltriazole and eliminate the formation of the undesired NH triazole (the product of the cycloaddition of inorganic azide with alkyne, **17**) the procedure should involve two separate steps, carried out in one flask. It should start with an efficient in situ generation of the benzyl or the alkyl azide, followed by 1,3-dipolar cycloaddition with an alkyne (Scheme 1).

Although there are a number of methods for the formation of azides from halides (by nucleophilic substitution), most of these require the use of a large excess of inorganic azides and result in medium to low yields.[8] These methods are unsuitable for the present synthesis due to the competitive NH-triazole (**17**) formation from the remaining inorganic azide. Detailed inspection of the literature turned our attention to the work of Alvarez, where a very efficient azidation of various halides with only a slight excess (1.1 equiv) of NaN_3 in anhydrous DMSO at room temperature was described.[9]



Scheme 1 One-pot synthesis of 1,2,3-triazoles by click chemistry.

We adapted this procedure, so as to avoid the use of excess azide, the reaction time was increased to 12–24 hours. After the azidation step was complete, water, alkyne, sodium ascorbate, and $CuSO_4$ solution[10] were added and stirring was continued for 6–18 hours, during which time the products usually precipitated and were collected by simple filtration.

The 1,2,3-triazoles were obtained in both high yield and purity (Table 1). Only 1,4-regioisomers were detected as the products when monosubstituted alkynes were used. This method can be used with a number of mono- and bis-

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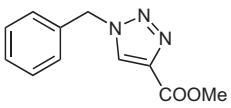
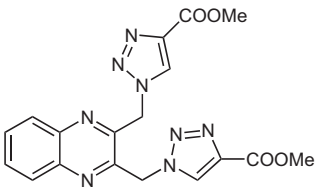
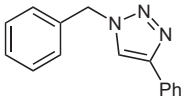
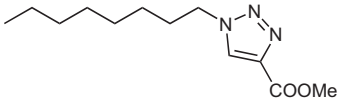
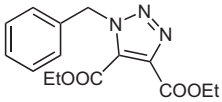
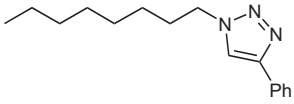
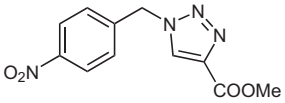
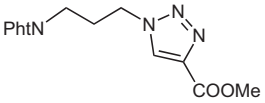
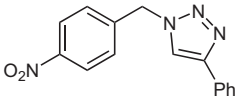
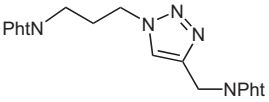
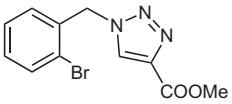
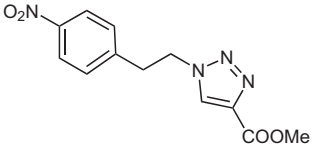
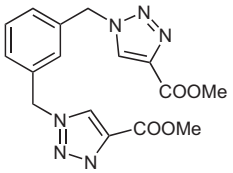
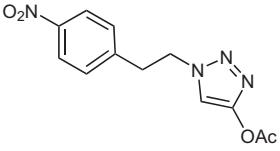
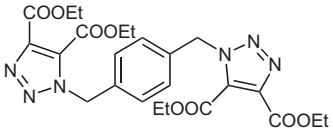
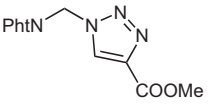
Table 1 One-Pot Preparation of 1,2,3-Triazoles from Benzyl or Alkyl Halides and Alkynes

Compd	Product	Isolated yield (%)	Compd	Product	Isolated yield (%)
1		70	**9**		97
2		86	**10**		76[b]
3		56[a]	**11**		87[b]
4		86	**12**		98
5		94	**13**		96
6		83	**14**		92
7		90	**15**		95
8		60	**16**		89

[a] Reaction with acetylenedicarboxylic acid diethyl ester were carried out at 60 °C for 12–18 h, without copper(I) catalysis. The corresponding 1,2,3-triazole was isolated by extraction with CH_2Cl_2 and purified by column chromatography on silica gel using CH_2Cl_2 as eluent.
[b] A small amount of THF (0.5–1 mL) was added in the azidation step to give a homogenous solution.

benzyl halides as well as with alkyl halides, including those containing various functional groups. This procedure was usually carried out on 0.5 mmol scale but in a few cases we have synthesized the triazoles on 1, 2, and 5 mmol scale, with the same high yields. Functionalized 1,2,3-triazoles can be further elaborated into more diverse compounds.

In conclusion we developed an efficient, simple, and safe one-pot procedure for the formation of 1,2,3-triazoles from benzyl or alkyl halides, sodium azide and alkynes, without isolation of the organic azide.

Experimental

All reagents including organic halides and alkynes were purchased from Aldrich and Fluka and used as received. *N*-propargylphthalimide was obtained by the reaction of phthalimide-DBU salt with propargyl bromide (71%).

^{1}H NMR spectra were recorded on a Varian EM-360 or AC-200 spectrometer (300 MHz) in DMSO or $CDCl_3$, with TMS as an internal standard. Mass spectra were recorded on an AMD 604/402, IR spectra (KBr pellets) were recorded on a Brucker ITS 113v spectrometer. Melting points were determined by using a Boetius instrument and are not corrected.

The 0.5 M NaN_3 solution in anhydrous DMSO was prepared according to a known literature procedure.[7]

General Procedure

To a stirred anhydrous DMSO solution of NaN_3 (1 mL, 0.5 M, 0.5 mmol of azide, 1 equiv) organic halide (0.5 mmol, 1 equiv) was added and the mixture was stirred overnight (12–24 hours). Water (2–3 mL) was added followed by solid sodium ascorbate (10% mol), alkyne (0.5 mmol) and aq $CuSO_4$ solution (100 μL; 1 M). The capped flask was stirred for 3–12 h (usually overnight),[11] then more water was added slowly until the product precipitated completely from the solution. The product was collected by filtration, washed with water, and dried in air.

1-Benzyl-4-methoxycarbonyl-1,2,3-triazole (1)

Mp 104–107 °C.

IR: 3111, 1724, 1541, 1496, 1456, 1433, 1365, 1339, 1230, 1048, 1020, 812, 781, 714 cm^{-1}.

^1H NMR (DMSO): δ = 8.90 (s, 1 H), 7.42 (m, 5 H), 5.66 (s, 2 H), 3.82 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}N_3O_2$, 217.0851; found, 217.0851.

1-Benzyl-4-phenyl-1,2,3-triazole (2)

Mp 126–130 °C.

IR: 1494, 1469, 1450, 1361, 1224, 1140, 1076, 1046, 972, 807, 769, 731 cm^{-1}.

^1H NMR (DMSO): δ = 8.64 (s, 1 H), 7.86 (m, 2 H), 7.46–7.30 (m, 8 H), 5.65 (s, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}N_3$, 235.1109; found, 235.1095.

1-Benzyl-4,5-bis(ethoxycarbonyl)-1,2,3-triazole (3)

Oil.

IR (film): 1733, 1552, 1468, 1373, 1267, 1218, 1147, 1095, 1059, 1016, 724 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.37 (m, 5 H), 5.80 (s, 2 H), 4.45 (q, *J* = 7.14 Hz, 2 H), 4.36 (q, *J* = 7.14 Hz, 2 H), 1.42 (t, *J* = 7.14 Hz, 3 H), 1.29 (t, *J* = 7.14 Hz, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}N_3O_4$, 304.1297; found, 304.1292.

1-(4-Nitrobenzyl)-4-methoxycarbonyl-1,2,3-triazole (4)

Mp 187–189 °C.

IR: 1720, 1602, 1516, 1434, 1370, 1353, 1232, 1050, 860, 815, 783, 727 cm^{-1}.

^1H NMR (DMSO): δ = 8.97 (s, 1 H), 8.26 (dd, *J* = 8.8, 4.8 Hz, 2 H), 7.58 (dd, *J* = 8.4, 4.8 Hz, 2 H), 5.85 (s, 2 H), 3.84 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}N_4O_4$, 262.0701; found, 262.0721.

1-(4-Nitrobenzyl)-4-phenyl-1,2,3-triazole (5)

Mp 157–159 °C.

IR: 1608, 1601, 1581, 1518, 1465, 1442, 1426, 1351, 1223, 1111, 1079, 1046, 1016, 862, 802, 764 cm^{-1}.

^1H NMR (DMSO): δ = 8.70 (s, 1 H), 8.28 (dd, *J* = 8.8, 1.9 Hz, 2 H), 7.87 (dd, *J* = 8.5, 1.4 Hz, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 7.48 (m, 2 H), 7.37 (m, 1 H), 5.85 (s, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}N_4O_2$, 280.0960; found, 280.0979.

1-(2-Bromobenzyl)-4-methoxycarbonyl-1,2,3-triazole (6)

Mp 115–118 °C.

IR: 1721, 1527, 1439, 1368, 1218, 1047, 812, 783, 747 cm^{-1}.

^1H NMR (DMSO): δ = 8.84 (s, 1 H), 7.71 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.43 (m, 1 H), 7.36 (m, 1 H), 7.24 (dd, *J* = 7.4, 1.6 Hz, 1 H), 5.76 (s, 2 H), 3.83 (s, 3 H).

HRMS (FAB): *m*/*z* calcd for $C_{11}H_{11}N_3O_2{}^{79}Br$, 296.0034; found, 296.0028.

Bis(4-methoxycarbonyl-1,2,3-triazolyl)-1,3-methylbenzene (7)

Mp 149–153 °C.

IR: 3130, 1726, 1540, 1438, 1231, 1048, 1020, 812, 777 cm^{-1}.

^1H NMR (DMSO): δ = 8.89 (s, 2 H), 7.43 (m, 4 H), 5.66 (s, 4 H), 3.83 (s, 6 H).

HRMS (FAB): *m*/*z* calcd for $C_{16}H_{17}N_6O_4$, 357.1311; found, 357.1341.

Bis(4,5-ethoxycarbonyl-1,2,3-triazolyl)-1,4-methylbenzene (8)

Mp 73–75 °C.

IR: 1741, 1552, 1478, 1463, 1430, 1380, 1367, 1348, 1311, 1268, 1202, 1140, 1068 cm^{-1}.

^1H NMR (DMSO): δ = 7.25 (s, 4 H), 5.80 (s, 4 H), 4.35 (q, *J* = 7.0, 7.3 Hz, 4 H), 4.31 (q, *J* = 7.0, 7.3 Hz, 4 H), 1.30 (t, *J* = 7.0, 7.3 Hz, 6 H), 1.19 (t, *J* = 7.0, 7.3 Hz, 6 H).

HRMS (FAB): *m*/*z* calcd for $C_{24}H_{29}N_6O_8$, 529.2047; found, 529.2020.

Bis(4-methoxycarbonyl-1,2,3-triazolyl)-1,2-methylquinoxaline (9)

Mp 277–280 °C (dec.).

IR: 2104, 1723, 1546, 1437, 1363, 1238, 1154, 1139, 1054, 1021, 818, 780, 759 cm^{-1}.

^1H NMR (DMSO): δ = 8.91 (s, 2 H), 7.93 (m, 2 H), 7.86 (m, 2 H), 6.29 (s, 4 H), 3.87 (s, 6 H).

HRMS (FAB): *m*/*z* calcd for $C_{18}H_{17}N_8O_4$, 409.1372; found, 409.1355.

4-Methoxycarbonyl-1-octyl-1,2,3-triazole (10)

Mp 78–80 °C.

IR: 3123, 2959, 2916, 1731, 1543, 1471, 1440, 1385, 1349, 1242, 1048, 1020, 946, 881, 816, 778 cm^{-1}.

^1H NMR (DMSO): δ = 8.81 (s, 1 H), 4.43 (t, *J* = 7.14 Hz, 2 H), 3.83 (s, 3 H), 1.88 (m, 2 H), 1.23–1.15 (m, 10 H), 0.87 (t, *J* = 7.14 Hz, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{21}N_3O_2$, 239.1633; found, 239.1616.

1-Octyl-4-phenyl-1,2,3-triazole (11)

Mp 78–79 °C.

IR: 2954, 2918, 2847, 1465, 1216, 1079, 762, 696 cm^{-1}.

^1H NMR (DMSO): δ = 8.59 (s, 1 H), 7.86 (m, 2 H), 7.48 (m, 2 H), 7.35 (m, 1 H), 4.41 (t, *J* = 7.1 Hz, 2 H), 1.88 (t, *J* = 7.1 Hz, 2 H), 1.23–1.15 (m, 10 H), 0.86 (t, *J* = 7.1 Hz, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{23}N_3$, 257.1892; found, 257.1905.

1-(3-Phthalimidopropyl)-4-methoxycarbonyl-1,2,3-triazole (12)

Mp 196–200 °C.

IR: 3122, 1771, 1721, 1697, 1543, 1463, 1438, 1396, 1242, 1048, 1029, 987, 780 cm^{-1}.

^1H NMR (DMSO): δ = 8.78 (s, 1 H), 7.89 (m, 4 H), 4.52 (t, *J* = 7.1 Hz, 2 H), 3.83 (s, 3 H), 3.63 (t, *J* = 6.6 Hz, 2 H), 2.47 (quintet, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}N_4O_4$, 315.1093; found, 315.1078.

4-(*N*-Phthalimidomethyl)-1-(3-phthalimidopropyl)-1,2,3-triazole (13)

Mp 194–197 °C.

IR: 1768, 1725, 1708, 1613, 1468, 1439, 1430, 1396, 1189, 1095, 1087, 768, 714 cm^{-1}.

^1H NMR (DMSO): δ = 8.08 (s, 1 H), 7.92–7.80 (m, 8 H), 4.80 (s, 2 H), 4.40 (t, *J* = 7.2 Hz, 2 H), 3.62 (t, *J* = 6.7 Hz, 2 H), 2.18 (q, *J* = 6.7, 7.3 Hz, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{17}N_5O_4$ 415.1280 found 415.1312.

1-[2-(4-Nitrophenyl)ethyl]-4-methoxycarbonyl-1,2,3-triazole (14)
Mp 186–190 °C.

IR: 1715, 1604, 1599, 1513, 1346, 1235, 1052, 857, 778 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.18 (dd, *J* = 8.8, 4.8 Hz, 2 H), 8.00 (s, 1 H), 7.31 (dd, J = 8.5, 4.8 Hz, 2 H), 4.75 (t, *J* = 7.1 Hz, 2 H), 3.94 (s, 3 H), 3.43 (t, *J* = 7.1 Hz, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{12}N_4O_4$, 276.0858; found, 276.0871.

1-[2-(4-Nitrophenyl)ethyl]-4-acetoxy-1,2,3-triazole (15)
Mp 187–190 °C.

IR: 1742, 1608, 1600, 1517, 1348, 1219, 1126, 1057, 870, 855, 787 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.17 (dd, *J* = 8.5, 1.6 Hz, 2 H), 7.40 (s, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 4.66 (t, *J* = 7.14 Hz, 2 H), 3.39 (t, *J* = 7.14 Hz, 2 H), 2.06 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}N_4O_4$, 290.1015; found, 290.1005.

1-(*N*-Phthalimidomethyl)-4-methoxycarbonyl-1,2-3-triazole (16)
Mp 176–180 °C.

IR: 1776, 1717, 1611, 1559, 1403, 1359, 1243, 1218, 1038, 952, 776, 760 cm^{-1}.

^1H NMR (DMSO): δ = 8.84 (s, 1 H), 7.98 (m, 5 H), 6.23 (s, 2 H), 3.83 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{11}N_4O_4$, 287.0780; found, 287.0806.

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References

(1) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225; and references cited therein.
(2) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128.
(3) (a) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 1053. (b) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, Ch.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588. (c) Brik, A.; Muldoon, J.; Lin, Y.-Ch.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, Ch.-H. *ChemBioChem* **2003**, *4*, 1246. (d) Link, A. J.; Tirrell, D. *J. Am. Chem. Soc.* **2003**, *125*, 11164. (e) Deiteres, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. Ch.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782. (f) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (g) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (h) Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609.
(4) Maksikova, A. V.; Serebryakova, E. S.; Tikhonova, L. G.; Vereshagin, L. I. *Chem. Heterocycl. Compd.* **1980**, 1284.
(5) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897.
(6) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.
(7) Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Seible, W. L.; Srivastava, A. *Tetrahedron Lett.* **2003**, *44*, 2153.
(8) (a) Grundmann, C. In *Houben–Weyl, Methoden der organischen Chemie*, 4th Ed., Vol. 10/3; Muller, E., Ed.; Thieme: Stuttgart, **1965**, 777. (b) See also references in Ref. 7
(9) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.
(10) Cu(I) formed under this condition is a catalyst for highly regioslective 1,4-triazole formation see: Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
(11) Progress of the reaction can be monitored by TLC.