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Facile and efficient sonochemical synthesis of 1,4-disubstituted 1,2,3-triazole derivatives catalyzed by CuI under mild conditions

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Abstract A facile and highly efficient method for regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles in good to excellent yields from in-situ-generated azides and terminal alkynes by Cu(I)-catalyzed 1,3 dipolar cycloaddition (the so-called click reaction), is described. The reaction proceeds smoothly in a 1:1 mixture of water and ethanol at room temperature without any additive. The method is a convenient means of preparation of a wide range of triazoles in a one-pot operation via a three-component reaction.

Keywords Synthesis · 1,2,3-Triazole · Ultrasound · Catalyst · Click chemistry · 1,3-Dipolar cycloaddition

Introduction

Cycloaddition reactions involving heteroatoms, for example 1,3-dipolar cycloaddition, provide rapid access to a wide variety of interesting five and six-membered heterocycles which have found widespread application in medicinal chemistry and the material sciences [1–4].

In particular, 1,4-disubstituted 1,2,3-triazoles have significant anti-proliferative activity against a wide variety of human cancer cell lines, including those that are multidrug resistant [5–7]. Although organic azides are stable against most reaction conditions, compounds of low molecular weight or those containing several azides tend to be explosive and are difficult to handle [8], hence procedures involving generation of the azides in situ followed by azide alkyne cycloaddition have recently been reported [9–14].

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Copper(I)-catalyzed cycloaddition is normally accomplished with success irrespective of the copper source used, i.e., copper(I) salts, normally in the presence of a base and/or a ligand, in-situ reduction of copper(II) salts (e.g., copper sulfate with sodium ascorbate), or proportionation of copper(0) and copper(II) (generally restricted to biological applications) [3, 15].

Ultrasound has been recognized as an important technique for green and sustainable synthetic processes [16–18]. In sonochemistry, molecules undergo a reaction because of the application of powerful ultrasound irradiation (20 kHz–10 MHz) [19]. Ultrasound induces chemical or physical changes during cavitation, a phenomenon involving the formation, growth, and instantaneous implosive collapse of bubbles in a liquid, which can generate local hot spots at temperatures of approximately 5000 °C, pressures of approximately 500 atm, and a lifetime of a few microseconds [20, 21]. In 1984, Priebe [22] described synthesis of organic azides from the corresponding activated primary halides and aqueous sodium azide under ultrasonic irradiation.

In this paper we describe a simple synthetic sonochemical preparation of 1-*H*-1,2,3-triazoles in the presence of CuI as heterogeneous catalyst at room temperature. The products were identified and confirmed by use of physical and spectroscopic data, for example from IR, ^{1}H NMR, ^{13}C NMR, and CHN analysis.

Experimental

Materials

High-purity chemicals were purchased from Merck, Fluka, and Aldrich. All materials were of commercial reagent grade. Alkyl halides and solvents were purified by use of standard procedures.

Apparatus

IR spectra were recorded as KBr pellets on a Perkin–Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ as solvents on a Bruker DRX-400 spectrometer, with tetramethylsilane as internal reference. A Bandelin ultrasonic HD 3200 with 6 mm diameter model KE 76 probe was used to generate ultrasonic irradiation and homogenize the reaction mixture. The piezoelectric crystals in this kind of probe normally work at approximately 700 kHz; by use of appropriate clamps, however, the output frequency of piezoelectric crystals was controlled and reduced to 20 kHz in the reaction mixture. Melting points obtained with a Thermo scientific 9300 melting point apparatus. Determination of the substrate purity and monitoring of reactions were accomplished by use of thin-layer chromatography (TLC) on Polygram SILG/UV 254 silica gel plates (Merck).

General procedure for synthesis of 1,2,3-triazoles

Alkyne (1.2 mmol), alkyl halide (1 mmol), NaN_3 (1.5 mmol), and 3 mol % CuI were added to a mixture of deionized water and EtOH (1:1) (6 mL) and this reaction mixture was treated by ultrasound irradiation at room temperature for several minutes. After completion of the reaction (as monitored by TLC), the catalyst was isolated by filtration through Celite and the product was extracted with EtOAc (3 × 10 mL). The product was obtained after removal of the solvent. Melting points of all the known compounds were compared with melting points obtained by literature survey. Also, the structures of products were confirmed by comparison of IR, ^1H NMR, and ^{13}C NMR data with those from authentic samples prepared by use of literature methods [23, 24].

1-Benzyl-4-phenyl-1H-1,2,3-triazole

White solid, m.p = 125–127 °C (Lit [24]. 128–130 °C); IR (KBr)/ν (cm^{-1}): 3140, 2923, 1609,1449, 1360, 1219, 1072, 1045; ^1H NMR ($CDCl_3$, 400 MHz)/δ ppm: 5.85 (s, 2H), 7.32 (m, 3H), 7.4 (m, 2H), 7.67 (s, 1H), 7.80–7.82 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 54.21, 119.57, 125.71, 128.06, 128.17, 128.78, 128.82, 129.16, 130.58, 134.74, 148.22.

4-Bromobenzyl-4-phenyl-1H-1,2,3-triazole

Colorless solid, m.p = 148–150 °C (Lit [24]. 150–151 °C); IR (KBr)/ν (cm^{-1}): 3082, 2923, 2854, 1590, 1486, 1462, 1352, 1076, 1012, 764, 690; ^1H NMR (DMSO-d_6, 400 MHz)/δ ppm: 5.62 (s, 2H), 7.02–7.41 (m, 5H), 7.57–7.58 (m, 2H), 7.82 (d, 2H), 8.63 (s, 1H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm): 52.79, 121.95, 122.09, 125.67, 128.37, 129.34, 130.62, 131.09, 132.17, 135.81, 147.21.

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

Pale yellow solid, m.p = 140–142 °C (Lit [24]. 140–141 °C); IR (KBr)/ν (cm^{-1}): 3081, 1604, 1348, 1518, 1466, 1220, 1109, 1077, 1044; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.71 (s, 2H), 7.36–7.43 (m, 5H), 7.76–7.82 (m, 3H), 8.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 53.16, 119.82, 124.31, 125.74, 128.56, 128.93, 130.11, 141,82, 148.66.

1-(3-Chlorobenzyl)-4-phenyl-1H-1,2,3-triazole

Green solid, 85–87 °C (Lit. [25] 87–89 °C); IR (KBr)/ν (cm^{-1}): 3082, 2923, 1725, 1577, 1467, 1432, 1344, 1220, 1078, 758, 694; ^1H NMR (Acetone-d_6, 400 MHz) δ (ppm) : 5.71 (s, 2H), 7.41–7.44 (m, 7H), 7.89 (s, 2H), 8.44 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 52.76, 122.15, 125.68, 127.08, 128.33, 128.62, 129.33, 131.14, 131.49, 133.85, 138.78, 147.52.

1-(2-Chlorobenzyl)-4-phenyl-1H-1,2,3-triazole

Green solid, m.p = 95–97 °C (Lit. [26] 96–97 °C); IR (KBr)/*v* (cm^{-1}): 3062, 2926, 1602, 1575, 1478, 1444, 1359, 1319, 1220, 1148, 1100, 1048, 998, 690, 753, 691; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.85 (s, 2H), 7.06–7.08 (d, 1H), 7.22–7.27 (t, 1H), 7.41–7.45 (m, 3H), 7.47–7.49 (m, 3H), 8.24–8.22 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 51.69, 121.37, 126.24, 127.39, 128.23, 128.67, 129.07, 129.67, 130.19, 131.59, 132.60, 132.86, 148,01.

1-(2-Chloro-6-fluorobenzyl)-4-phenyl-1H-1,2,3-triazole

Green solid, m.p = 106–108 °C; IR (KBr) *v* (cm^{-1}): 3072, 2923, 1739, 1604, 1577, 1453, 1351, 764, 691; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.86 (s, 2H) 7.33–7.62 (m, 7H), 8.08 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 49.32, 114.95, 116.04, 118.65, 125.40, 127.10, 127.59, 128.99, 130.07, 133.02, 133.54, 135.08, 143.01, 152.82; CHN analysis: Calcd., C = 62.62, H = 3.85, N = 14.60; Found, C = 62.51, H = 3.67, N = 14.68.

1-(2,4-Dinitrobenzyl)-4-phenyl-1H-1,2,3-triazole

Pale yellow solid, m.p = 214–215 °C; IR (KBr) *v* (cm^{-1}): 3124, 1610, 1535, 1463, 1402, 1348, 1205, 1152, 1072; ^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 6.16 (s, 2H), 7.2–7.36 (m, 2H), 7.43–7.47 (t, 2H), 7.84–7.86 (d, 2H), 8.53–8.56 (d, 1H), 8.64 (s, 1H,), 8.84 (s,1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 50.47, 122.57, 125.40, 128.55, 129.02, 129.92, 131.02, 132.07, 138.34, 143.39, 146.18, 147.51; CHN analysis: Calcd., C = 55.39, H = 3.41, N = 21.53; Found, C = 55.02, H = 3.50, N = 22.11.

1-Benzyl-4-(4-methylphenyl)-1H-1,2,3-triazole

Pale yellow solid, m.p = 150–152 °C (Lit [23]. 150 °C); IR (KBr) *v* (cm^{-1}): 3058, 1598, 1480, 1445, 1382, 1229, 981, 915; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.159 (s, 3H), 5.36 (s, 2H), 7.17–7.47 (m, 8H), 7.88 (s, 2H).

1-(4-Bromobenzyl)-4-(4-methylphenyl)-1H-1,2,3-triazole

Pale yellow solid, m.p = 202–204 °C; IR (KBr) *v* (cm^{-1}): 3029, 1623, 1592, 1521, 1487, 1442, 1341, 1224, 1071, 1010, 824, 741; ^{1}H NMR (Acetone, 400 MHz) δ (ppm): 2.33 (s, 3H), 5–5.04 (d, 1H), 5.2–5.24 (d, 1H), 6.82–6.84 (d, 2H), 7.01–7.03 (s, 2H), 7.18–7.23 (m, 5H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.34, 52.02, 119.37, 123.02, 125.67, 126.19, 129.65, 129.76, 131.87, 139.26, 148.16; CHN analysis: Calcd., C = 58.55, H = 4.30, N = 12.81; Found, C = 58.41, H = 4.21, N = 12.94.

1-(4-Nitrobenzyl)-4-(4-methylphenyl)-1H-1,2,3-triazole

Green solid, m.p = 243–245 °C; IR (KBr) *v* (cm^{-1}): 2924 (C=C–H), 1607, 1522, 1346, 1446, 1226; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.24 (s, 3H), 4.8 (s, 1H), 5.1 (s, 1H), 6.96 (s, 4H), 7.24 (s, 3H), 7.85 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 29.11, 54.69, 116.74, 124.40, 125.97, 126.70, 131.09, 131.72, 137.11, 143.86, 145.27, 147.64; CHN analysis: Calcd., C = 65.30, H = 4.79, N = 19.04. Found, C = 65.01, H = 4.70, N = 18.88.

1-Benzyl-4-propyl-1H-1,2,3-triazole

Green oil (Lit., [23, 26]); IR (KBr) *v* (cm^{-1}): 2924, 1626, 1449, 1237, 1237, 1158, 1084; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.95 (d, 3H), 1.26 (s, 2H), 2.62 (s, 2H), 5.70 (s, 2H), 7.27–7.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.69, 22.01, 27.33, 53.92, 120.54, 127.83, 128.19, 128.75, 135.03, 150.09.

1-(4-tert-Butylbenzyl)-4-phenyl-1H-1,2,3-triazole

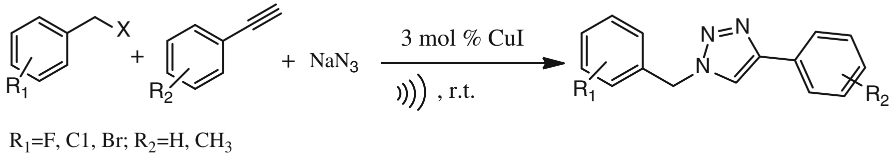
Green solid mp 162–165 °C (Lit., [27] 164-165 °C]; IR (KBr) *v* (cm^{-1}): 2960, 1468, 1350, 1217, 1061, 809, 761, 692; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.78 (m, 2H), 7.67 (s, 1H) 7.38–7.21 (m, 7H), 5.49 (s, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 151.9, 148.1, 131.8, 130.7, 128.2, 127.9, 126.1, 125.8, 119.7, 54.0, 34.7, 31.3.

1-(4-Methoxybenzyl)-4-phenyl-1H-1,2,3-triazole

Yellowish Green solid mp 127–129 °C (Lit., [25, 27] 125–128 °C]; IR (KBr) *v* (cm^{-1}): 3068, 3034, 2971, 1446, 1362, 1224, 1080, 768, 605; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.78 (s, 1H), 7.77 (s, 1H) 7.62 (s, 1H), 7.26 (m, 5H), 6.90–6.92 (m, 2H), 5.52 (s, 2H), 3.81 (s, 3H).

Results and discussion

This three-component reaction proceeds via in-situ formation of an alkyl azide from an alkyl halide and sodium azide. The alkyl azide then undergoes 1,3-dipolar cycloaddition reaction with terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles in good to excellent yields. Here we describe a process in which copper iodide



Scheme 1 Synthesis of 1,4-disubstituted 1,2,3-triazoles

Table 1 Effect of solvent on the sonochemical synthesis of 1,2,3-triazole

Entry	Solvent	Time (min)	Yield (%)[a]
1	CH_3CN	25	50
2	Acetone–H_2O (1:1)	12	80
3	H_2O–EtOH (1:1)	5	90
4	H_2O	15	75
5	Acetone	20	45
6	EtOH	20	60

Reaction conditions: 1.2 mmol phenylacetylene, 1 mmol benzyl chloride, 1.5 mmol NaN_3, and 3 mol % CuI were added to the selected solvent (6 mL) under 70 W ultrasound irradiation at room temperature

[a] Isolated product yields

Table 2 Studies of ultrasonic irradiation power in the click reaction

Entry	Power (W)	Time (min)	Yield (%)[a]
1	20	60	35
2	40	35	58
3	50	10	80
4	60	8	85
5	70	5	90
6	80	5	75

Reaction conditions: 1.2 mmol phenylacetylene, 1 mmol benzyl chloride, 1.5 mmol NaN_3, and 3 mol % CuI were added to the 1:1 mixture solvent of EtOH:H_2O as solvent (6 mL) under various ultrasound irradiation power at room temperature

[a] Isolated yields

efficiently catalyzes azide–alkyne cycloaddition under ultrasonic irradiation (Scheme 1).

Initially, the effect of solvents on formation of the triazoles from benzyl chloride, sodium azide, and phenylacetylene in the presence of CuI (3 mol%) as heterogeneous catalyst at room temperature was investigated. The corresponding results are listed in Table 1. Among the solvents used, CH_3CN, acetone, and EtOH required longer reaction times and yields were 50, 45, and 60 %, respectively (Table 1, entries 1, 5, and 6). Reaction in water resulted in high catalytic activity and 75 % yield of the desired product; use of a 1:1 mixture of H_2O and EtOH also gave the product in excellent yield (90 %). Although use of acetone as solvent resulted in moderate yield (45 %), a mixture of acetone and water furnished the product in good yield (Table 1, entries 2 and 5).

In recently reported work we assessed, calorimetrically, the cavitational energy supplied to water by ultrasonication [28]. In continuation of this research, the effect of ultrasonic irradiation of different power was investigated. It was observed that reaction in the presence of CuI (3 mol%) and ultrasonic irradiation power of 70 Watt afforded the best yield of product, with 90 % isolated yield after 5 min (Table 2, entry 3).

Table 3 Preparation of 1,2,3-triazoles by reaction of alkyl halides, acetylenes, and sodium azide

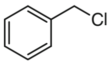
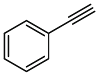
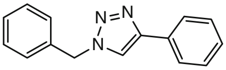
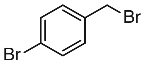
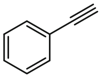
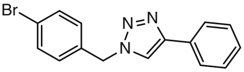
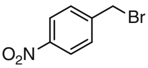
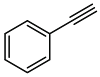
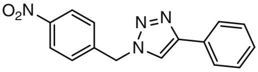
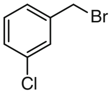
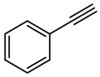
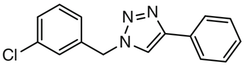
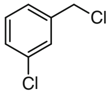
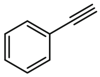
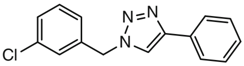
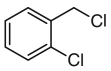
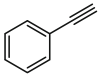
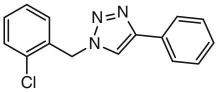
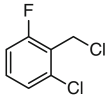
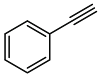
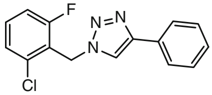
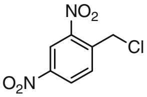
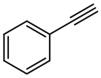
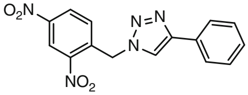
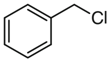
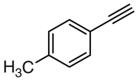
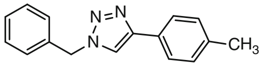
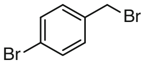
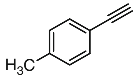
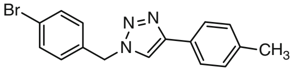
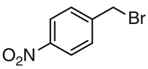
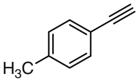
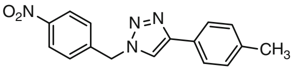
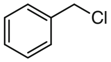
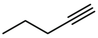
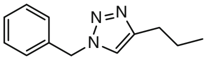
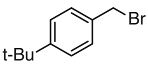
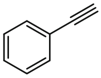
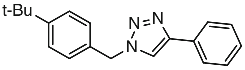
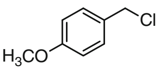
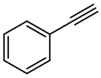
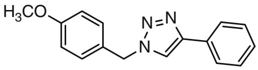
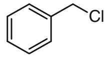
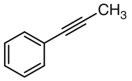
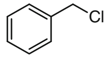
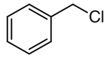
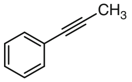
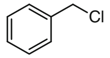
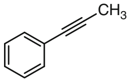
Entry	Alkyl halide	Alkyne	product	Time (min)	Yield[a] (%)
1				5	90
2				6	91
3				8	90
4				8	92
5				9	90
6				12	88
7				14	90
8				15	91
9				10	94
10				12	94
11				14	95
12				16	85
13				14	88
14				18	87

Table 3 continued

Entry	Alkyl halide	Alkyne	product	Time (min)	Yield[a] (%)
15[b]			-	50	-
16[b]		$EtO_2C—≡—CO_2Et$	-	50	-
17[c]			-	50	-
18[d]			-	50	-

[a] Isolated product yields

[b] The reaction was performed under 100 W power as harsh reaction conditions

[c] CH_3CN was used as solvent

[d] Acetone was used as solvent

The observed effects of ultrasonic irradiation during organic reactions can be because of cavitation. Cavities are believed to act as microreactors for volatile molecules—the molecules enter the micro-bubbles and the high temperature and pressure produced during cavitation break their chemical bonds leading to reaction with other species [16, 19, 29].

To ascertain the scope and limitation of this reaction, some aryl halides and acetylenes were reacted with sodium azide in the presence of the optimum amount of CuI (3 mol%) under ultrasonic irradiation (Table 3). The desired 1,4-disubstituted 1,2,3-triazole derivatives were synthesized, then characterized by spectroscopic methods. As shown in Table 3, the corresponding products were obtained in excellent yields and short reaction times under ultrasonic conditions. Reactions with non-terminal alkynes were conducted under harsh reaction condition (100 W power); the results are shown in Table 3, entries 15 and 16. Reaction of these alkynes was also checked in other solvents; the results are shown in Table 3, entries 17 and 18.

Conclusion

In this study we synthesized 1,4-disubstituted 1,2,3-triazole derivatives by reaction of a variety of alkyl halides with acetylene compounds, under the action of ultrasonic irradiation, in the presence of CuI as novel catalyst, in a 1:1 mixture of water and ethanol at room temperature. The corresponding products were obtained in excellent yields and high purity after short reaction times. The identities of the products were confirmed by use of physical and spectroscopic data from IR, ^{1}H NMR, and ^{13}C NMR analysis.

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