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Solventless synthesis of triazoles and bistriazoles through Copper-catalyzed alkyne-azide cycloaddition

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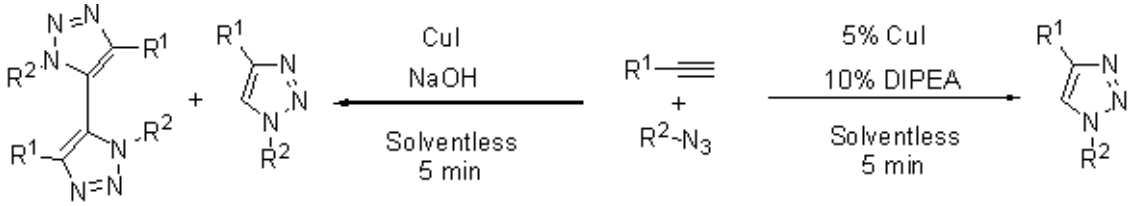

A library of 1,2,3-triazoles, including a series of triazolyl styrenes which have a structural relationship with resveratrol, was synthesized through a novel solventless method that involves the straightforward treatment by grinding of several azides and alkynes in the presence of catalytic amounts of copper iodide and *N*,*N*-diisopropylethylamine. On the other hand, when sodium hydroxide was used as the base, a mixture of bistriazoles and triazoles was formed where 1,2,3-triazoles were the major products. This new solvent-free synthesis protocol is carried out under mild conditions for short times, affording the 1,4-regioisomers in high yields.

Keywords: Triazole, Bistriazole, Alkyne, Azide, Solventless.

INTRODUCTION

Copper-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) is the best known example of an ideal reaction for Click Chemistry and one of the most important methods for molecular assembly [1], as well as a significant source of potentially active compounds [2-4]. Therefore, the development of new procedures for this reaction is highly desirable. Although several groups have thoroughly studied this reaction, designing catalysts and optimizing conditions, the research of this topic is far from complete.

One of the challenges of this reaction, sustainable by itself, is the exploration of the reaction conditions close to the principles of Green Chemistry, avoiding as far as possible, the generation of dangerous products. In this context, the development of solvent-free chemical processes is important and many examples of solventless chemical reactions are reported in the literature [5,6].

These reasons inspired us to start an investigation with the aim of exploring the possibility to obtain 1,2,3-triazoles and bistriazoles in high yields through CuAAC using solvent free conditions. This work summarizes our recent successful efforts in this area.

EXPERIMENTAL

Instrument and chemical materials

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. The solvents were distilled before use. Silica plates of 0.20 mm thickness were used for thin layer chromatography. The melting points were determined with a Fisher-Johns melting point apparatus and they are not corrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Advance 300; the chemical shifts (δ) are given in ppm relative to TMS as an internal standard (0.00). For analytical purposes the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200 °C via a direct inlet probe. Only the molecular and parent ions (m/z) are reported. The IR spectra were recorded on a Bruker Tensor 27 equipment.

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Solventless copper-catalyzed cycloaddition of alkynes and azides.

Typical procedure. Successively added in a mortar were the corresponding alkyne (1 mmol), azide (1 mmol), DIPEA (0.01 mL, 0.1 mmol) and CuI (0.0095 g, 0.05 mmol). The mixture was homogenized in a mortar during 5 minutes using a pestle. The mixture was collected and the final product was purified by crystallization.

1-Benzyl-4-phenyl-1,2,3-triazole (3). White solid; mp 130°C (lit. 130-130.9ºC) [7] ; IR (ATR): v = 3128, 2927, 1461, 1269 cm^{-1}; ^{1}H NMR (CDCl3, 300 MHz) δ 7.67-7.60 (m, 2H), 7.55 (dd, J= 5.7, 3.3 Hz, 1H), 7.50 (s, 1H), 7.28-7.21 (m, 4H), 7.19-7.13 (m, 3H), 5.43 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz)δ 147.7 (C), 134.3 (C), 132.0 (C), 130.4 (CH), 130.1 (C), 128.7 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 125.3 (CH), 119.0 (CH), 53.8 (CH_2); MS [EI^+] m/z (%)235 $[M]^+$ (20), 206 $[M-HN_2]^+$ (50), 116 $[M - C_6H_5N_3]^+$ (90), 91 $[C_6H_5CH_2]^+$ (100).

1,4-diphenyl-1,2,3-triazole (4). Yellow solid; mp 65.0 ºC; IR (ATR): v= 2958, 1598, 1462, 1272; ^{1}H NMR (CDCl3, 300 MHz) δ 8.22 (s, 1H), 7.95-7.90 (m, 2H), 7.70 (dd, J= 5.9, 3.8 Hz, 1H), 7.63-7.59 (m, 1H), 7.50-7.45 (m, 5H), 7.41-7.33 (m, 1H); ^{13}C NMR (CDCl3, 75 MHz) δ145.8 (CH), 130.6 (C), 128.9 (CH), 128.3 (CH), 127.9 (C), 126.7 (CH), 126.5 (CH), 126.1 (CH), 125.9 (CH), 119.7 (CH)); MS [EI^+] m/z (%) 221 $[M]^+$ (35), 116 $[M - C_6H_5N_2]^+$ (100), 104 $[M - C_7H_5N_2]^+$ (50), 77 $[C_6H_5]^+$ (90).

1-benzyl-4-[(4-bromophenoxy)methyl]-1,2,3-triazole (5). White solid; mp 111.0 ºC; IR (ATR): v= 3138, 2873, 1687, 1581, 1486; ^{1}H NMR (CDCl3, 300 MHz) δ7.51 (s, 1H), 7.37 (dt, J=5.7, 2.9 Hz), 7.28 (d, J= 3.3 Hz), 6.85 (d, J= 8.9 Hz), 5.53 (s, 2H), 5.15 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ156.24 (C), 143.14 (C), 133.33 (C), 131.28 (CH), 128.11 (CH) 127.81(CH), 127.06 (CH), 121.54 (CH), 115.61 (CH), 112.45 (C), 61.22 (CH_2), 53.23 (CH_2); MS [EI^+] m/z (%)343 $[M]^+$ (35), 314 $[M-HN_2]^+$ (3), 226 $[M - C_8H_8N]^+$ (3), 184 $[C_7H_6BrO]^+$(4), 91 $[C_6H_5CH_2]^+$ (100), 77 $[C_6H_5]^+$ (35).

4-[(4-bromophenoxy)methyl]-1-phenyl-1,2,3-triazole (6). White solid; mp 60.0 °C; IR (ATR): v= 3138, 2955, 1584, 1485; ^{1}H NMR (CDCl3, 300 MHz) δ8.05 (s, 1H), 7.68-7.31 (m, 5H), 7.40 (d, *J*= 8.9 Hz, 2H), 6.92 (d, *J*= 8.9 Hz, 2H), 5.29 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ156.4 (C), 142.7 (C), 133.9 (C), 130.0 (CH), 129.9 (CH), 128.9 (CH), 127.7 (C), 127.1 (CH) 126.9 (CH), 119.7 (CH), 61.3 (CH_2); MS [EI^+] m/z (%) 329 $[M]^+$ (10), 164 $[C_9H_9BrN_3O]^+$ (100). Elemental analysis calculated: C, 54.56; H, 3.66; N, 12.73, found: C, 55.01; H, 3.75; N, 12.80.

4-[(4-bromophenoxy)methyl]-1-p-tolyl-1,2,3-triazole (7). White solid; mp 98.0 °C; IR (ATR): v= 3139, 2958, 1589, 1518; ^{1}H NMR (CDCl3, 300 MHz) δ8.00 (s, 1H), 7.60 (d, *J*= 8.4 Hz, 2H), 7.40 (d, *J*= 9.0 Hz, 2H), 7.32 (d, *J*= 8.5 Hz, 2H), 6.91 (d, *J*= 9.0, 2H), 5.27 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ156.1 (C), 142.1 (C), 137.9 (C), 133.4 (C), 131.2 (CH), 129.0 (CH), 119.7 (CH), 119.3 (CH), 115.4 (CH), 112.3 (C), 61.0 (CH_2), 19.8 (CH_3); MS [EI^+] m/z (%) 343 $[M]^+$ (40), 314 $[M-HN_2]^+$ (10), 211 $[M - C7H7N3]^+$ (100), 172 $[M - C6H4BrO]^+$ (70). Elemental analysis calculated: C, 55.83; H, 4.10; N, 12.21, found: C, 56.13; H, 4.50; N, 12.30.

4-phenyl-1-p-tolyl-1H-1,2,3-triazole (8). White solid; mp 121.0 °C; IR (ATR): v= 3124, 2956, 1605, 1482; ^{1}H NMR (CDCl3, 300 MHz) δ 8.16 (s, 1H), 7.67 (d, *J*= 8.4 Hz, 2H), 7.60-7.42 (m, 5H), 7.34 (d, *J*= 8.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ148.1 (C), 138.9 (C), 134.6 (C), 132.4 (C), 130.85 (CH), 130.2 (CH), 128.9 (CH), 128.3 (CH), 125.9 (CH), 120.1 (CH), 22.6 (CH_3); MS [EI^+] m/z (%) 235 $[M]^+$ (20), 130 $[M-C_7H_7N]^+$ (20), 91 $[C_6H_5CH_2]^+$ (100).

[1-(4-methoxyphenoxy)-1,2,3-triazole-4-yl]methanol (9). Yellow solid; 80 °C; IR (ATR): v= 2956, 2855, 1594, 1485; ^{1}H NMR (CDCl3, 300 MHz) δ8.03 (s, 1H), 7.40 (d, *J*= 9.0 Hz, 2H), 6.91 (d, *J*= 8.9 Hz, 2H), 5.27 (s, 2H), 4.89 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ157.40 (C), 154.70 (C), 142.36 (C), 119.77 (CH), 118.11 (CH), 113.98 (CH), 54.30 (CH_3), 53.31 (CH_2); MS [EI^+] m/z (%)205 $[M]^+$ (20), 149 $[M - C_3H_4O]^+$ (95), 57 $[M - C_8H_8N_2O]^+$ (100). Elemental analysis calculated: C, 53.35; H, 3.92; N, 11.67, found: C, 53.85; H, 4.10; N, 12.02.

4-[(4-bromophenoxy)methyl]-1-(4-methoxyphenyl)-1H-1,2,3-triazole (10). White solid; mp 109 °C; IR (ATR): v= 2958, 2854, 1590, 1485; ^{1}H NMR (CDCl3, 300 MHz) δδ 7.96 (s, 1H), 7.63 (d, *J*= 9.0 Hz, 2H), 7.40 (d, *J*= 9.0 Hz), 7.02 (d, *J*= 9.0 Hz, 2H), 6.91 (d, *J*= 9.0 Hz, 2H), 5.26 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ158.7 (C), 156.1 (C), 143.0 (C), 131.2 (CH), 129.1 (C), 121.0 (CH), 119.9 (CH), 115.4 (CH), 113.6 (CH), 112.3 (C), 61.0 (CH_2), 54.4 (CH_3); MS [EI^+] m/z (%)359 $[M]^+$ (5), 280 $[M - Br]^+$ (100).

4-[(4-bromophenoxy)methyl]-1p-tolyl-1,2,3-triazole (11). White solid; mp 155°C; IR (ATR): v= 3123, 2921, 1608, 1460; ^{1}H NMR (CDCl3, 300 MHz) δ8.11 (s, 1H), 7.94-7.86 (m, 2 H), 7.69 (d, J= 9.0 Hz, 2H), 7.52-7.31 (m, 5H), 7.05 (d, J= 9.0 Hz, 2 H), 3.89 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz)

δ157.40 (C), 154.70 (C), 142.36 (C), 119.58 (CH), 114.19 (CH), 54.39 (CH_3), 53.23 (CH_2); MS [EI^+] m/z (%) 251 $[M]^+$ (10), 149 $[M - C_8H_6]^+$ (80), 116 $[M - C_7H_7N_2O]^+$ (35), 102 $[M - C_7H_7N_3O]^+$ (15), 77 $[C_6H_5]^+$ (100).

[1-(4-methoxyphenyl)-1,2,3-triazole-4-yl]methyl butylcarbamate (12). White solid; mp 100 °C; IR (ATR): v= 3153, 2928, 1580, 1484; ^{1}H NMR (CDCl3, 300 MHz) δ7.99 (s, 1H), 7.62 (d, J= 8.9 Hz, 2H), 7.02 (d, J= 9.0 Hz, 2H), 5.26 (s, 2H), 3.87 (s, 3H), 3.19 (m, 2H), 1.53-1.43 (m, 2H), 1.37-1.29 (m, 2H), 0.91 (t, J= 7.1 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ159.87 (C), 156.25 (C), 144.06 (C), 130.38 (C), 125.00 (C), 122.20 (CH), 114.76 (CH), 57.57 (CH_2) , 55.61 (CH_3), 40.82 (CH_2), 31.94 (CH_2), 19.85 (CH_2), 13.68 (CH_3);); MS [EI^+] m/z (%) 304 $[M]^+$ (20), 266 (100). Elemental analysis calculated: C, 59.20; H, 6.62; N, 18.41, found: C, 60.05; H, 6.87; N, 18.10.

4-[(4-bromophenoxy)methyl]-1-(4-bromophenyl)-1,2,3-triazole (13). White solid; mp 127 °C; IR (ATR): v= 3123, 2921, 1516, 1460; ^{1}H NMR (CDCl3, 300 MHz) δ8.02 (s, 1H), 7.71-7.60 (m, 4H), 7.40 (d, J= 8.9 Hz, 2H), 6.91 (d, J= 8.9 Hz), 5.27 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ157.0 (C), 144.7 (C), 135.73(C), 132.8 (CH), 132.3 (CH), 122.5 (C), 121.8 (CH), 120.6 (CH), 116.4 (CH), 113.5 (C), 61.9 (CH_2); MS [EI^+] m/z (%) 406 $[M]^+$ (10), 239 $[M - C_6H_4BrN]^+$ (4), 211 $[M - C_6H_4BrN_3]^+$ (100), 156 $[C_6H_4Br]^+$ (40), 184 $[C_7H_6BrO]^+$ (80). Elemental analysis calculated: C, 44.04; H, 2.71; N, 10.27, found: C, 43.90; H, 2.81; N, 10.90.

Ethyl 3-(4-chlorophenyl)-2-[4-phenyl-1,2,3-triazole-1-yl]acrylate (14). White solid; mp 127 ^{0}C; IR (ATR): v= 3137, 2925, 1725, 1645; ^{1}H NMR (CDCl3, 300 MHz) δ7.98 (s, 1H), 7.93-7.88 (m, 3H), 7.84 (s, 1H), 7.48-7.33 (m, 4H), 6.87-6.82 (m, 2H), 4.34 (q, J= 7.1 Hz, 2H), 1.32 (t, J= 7.1 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ162.7 (C), 148.2 (C), 137.7 (C), 131.5 (CH), 130.8 (C), 130.0 (C), 129.4 (CH), 129.3 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 125.8 (CH), 125.6 (C), 121.2 (CH), 62.5 (CH_2), 14.1 (CH_3); MS [EI^+] m/z (%) 354 $[M+1]^+$ (2), 324 $[M - HN_2]^+$ (30), 251 $[M\text{-}C_8H_6]^+$ (40), 102 $[M\text{-}C_{11}H_{10}ClN_3O_2]^+$ (80). Elemental analysis calculated: C, 64.50; H, 4.56;N, 11.88, found: C, 64.00; H, 4.86; N, 10.90.

Ethyl (2-[4-((4-bromophenoxy)methyl)-1,2,3-triazole-1-yl]-3-(4-chlorophenyl) acrylate (15). White solid; mp 99 ^{0}C; IR (ATR): v= 3144, 1722, 1644, 1590; ^{1}H NMR (CDCl3, 300 MHz) δ7.94 (s, 1H), 7.64 (s, 1H), 7.39 (d, J= 9.0 Hz, 2H), 7.16 (d, J= 8.5 Hz, 2H), 6.88 (d, J= 8.9 Hz, 2H,), 6.70 (d, J= 8.5 Hz, 2H), 5.30 (s, 2H), 4.30 (q, J= 7.1 Hz, 2H), 1.29 (t, J= 7.1 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ162.6 (C), 157.0 (C), 144.4 (C), 139.2 (CH), 137.7 (C), 132.3 (CH), 131.3 (CH), 129.3 (CH), 129.1 (C), 125.4 (C), 124.6 (CH), 116.8 (CH), 113.6 (C), 62.5 (CH_2), 62.0 (CH_2), 14.1 (CH_3); MS [EI^+] m/z (%) 461 $[M]^+$ (5), 251 $[M - C_{11}H_{10}ClO_2]^+$ (4), 154 $[M - C_{14}H_{13}ClN_3O_3]^+$ (100).Elemental analysis calculated: C, 51.91; H, 3.70; N, 9.08, found: C, 52.19; H, 3.79; N, 9.90.

Ethyl 3-(4-chlorophenyl)-2-[4-((4-methoxyphenoxy)methyl)-1,2,3-triazole-1-yl] acrylate (16). Yellow oil; IR (ATR): v= 2957, 2121, 1721, 823; ^{1}H NMR (CDCl3, 300 MHz) δ7.94 (s, 1H), 7.63 (s, 1H), 7.16 (d, *J*= 8.5 Hz, 2H), 6.93 (d, *J*= 9.1 Hz, 2H), 6.83 (d, *J*= 9.2 Hz, 2H), 6.69 (d, *J*= 8.5 Hz, 2H), 5.28 (s, 2H), 4.31 (q, J= 7.1 Hz, 2H), 3.78 (s, 3H), 0.92 (t, *J*= 7.1 Hz, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ162.7 (C), 154.3 (C), 151.9 (C), 145.2 (C), 139.1 (CH), 137.6 (C), 131.4 (CH), 130.8 (C), 129.3 (CH), 129.1 (C), 124.4 (CH), 116.1 (CH), 114.6 (CH), 62.6 (CH_2), 62.5 (CH_2), 55.8 (CH_3), 14.1 (CH_3); MS [EI^+] m/z (%) 413 $[M]^+$ (10), 123 $[M - C_{14}H_{13}ClN_3O_2]^+$ (100). Elemental analysis calculated: C, 60.95; H, 4.87; N, 10.15, found: C, 60.98; H, 4.84; N, 10.80.

Ethyl 2-[4-(2-(butylcarbamoyloxy)ethyl)-1,2,3-triazole-1-yl)-3-(4-chlorophenyl] acrylate (17). Yellow solid; mp 129 ^{0}C; IR (ATR): v= 3156, 1642, 1581, 1487, 1197; ^{1}H NMR (CDCl3, 300 MHz) δ7.95 (s, 1H), 7.68 (s, 1H), 7.23 (d, *J*= 8.6 Hz, 2H), 6.75 (d, *J*= 8.5 Hz, 2H), 5.27 (s, 2H), 4.76 (s, 1H), 4.32 (q, *J*= 7.1 Hz, 2H), 3.17 (m, 2H), 1.37-1.21 (m, 6H), 0.91 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ162.7 (C), 156.0 (C), 144.1 (C), 139.1 (CH), 137.6 (C), 135.2 (CH), 131.4 (CH), 130.8 (C), 129.3 (CH), 128.8 (C), 62.5 ($CH_2$8), 57.6 (CH_2), 32.1 (CH_2), 26.3 (CH_2), 23.4 (CH_2), 14.1 (CH_3), 13.6 (CH_3); MS [EI^+] m/z (%) 405 $[M\text{-}1]^+$ (4), 363 $[M\text{-}C_3H_7]^+$ (4), 349 $[M\text{-}C_4H_9]^+$ (3), 250 $[M - C_7H_{11}N_2O_2]^+$ (35), 154 $[M - C_{14}H_{13}ClN_3O_3]^+$ (50), 57 $[M - C_{15}H_{14}ClN_4O_4]^+$ (100). Elemental analysis calculated: C, 56.09; H, 5.70; N, 13.77, found: C, 56.80; H, 5.32; N, 14.01.

Solventless copper-catalyzed cycloaddition of alkynes and azides with NaOH.

Typical procedure. Successively added in a mortar were the corresponding alkyne (1 mmol), the azide (1 mmol), NaOH (0.40 g, 10.0 mmol) and CuI (0.0095 g, 0.05 mmol). The mixture was homogenized in a mortar for 5 minutes using a pestle. The mixture was collected and the final products were purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

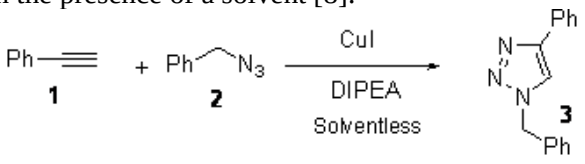
3,3'-dibenzyl-5, 5'-diphenyl -[4,4'] bi [(1,2,3)-triazolyl (Table 4, Entry 1). White solid; mp 65 ^{0}C; IR (ATR): v= 2953, 2852, 1602, 1456; ^{1}H NMR (CDCl3, 300 MHz) δ7.45 (m, 4H), 7.28-7.20 (m, 6H), 7.14 (m, 2H), 7.09 (m, 4H), 6.81 (d, 4H, J = 8.0 Hz), 5.57 (s, 2H,), 5.26 (s, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ147.52 (C), 132.57 (C), 128.93 (C), 128.66 (CH), 128.52 (CH), 128.47 (CH), 128.41 (CH), 127.87 (CH), 125.49 (CH), 119.59 (C), 52.37 (CH_2); MS [EI$^+$] m/z (%) 468 [M]$^+$ (40), 349 [M - $C_7H_7N_2$]$^+$ (35), 321 [M - $C_7H_7N_4$]$^+$ (35), 91 [$C_6H_5CH_2$]$^+$ (100).

3,5,3',5'-tetraphenyl-[4,4']bi[(1,2,3)-triazolyl] (Table 4, Entry 2). White solid; mp 68 ^{0}C; IR (ATR): v= 2957, 2855, 1514, 1461; ^{1}H NMR (CDCl3, 300 MHz) δ8.27 (d, J= 7.2 Hz, 3H), 7.76 (d, J=8.3 Hz, 4H), 7.55-7.42 (m, 11H), 2.47 (s, 6H); ^{13}C NMR (CDCl3, 75 MHz) δ139.12 (C), 133.73 (C), 131.01 (CH), 130.40 (C), 129.82 (CH), 129.34 (CH), 129.12 (CH), 128.25 (CH -35), 123.21 (CH), 121.14 (C), 20.56 (CH_3); MS [EI$^+$] m/z (%) 468 [M]$^+$ (40), 349 [M - $C_7H_7N_2$]$^+$ (35), 321 [M - $C_7H_7N_4$]$^+$ (35), 91 [$C_6H_5CH_2$]$^+$ (100).

3,3'-dibenzyl-5,5'-bis[(4-bromophenoxy)methyl]-4,4'-bi[(1,2,3)-triazolyl] (Table 4, Entry 3). White solid; mp 179 ^{0}C; IR (ATR): v= 3063, 2921, 1581, 1484; ^{1}H NMR (CDCl3, 300 MHz) δ 7.23-7.33 (m, 10H), 6.87-6.89 (d, 4H), 6.44- 6.47 (d, 4H), 5.01 (s, 2H), 4.96 (s, 2H), 4.47 (s, 4H); ^{13}C NMR (CDCl3, 75 MHz) δ156.6, 145.5, 133.6, 132.3, 129.1, 129.0, 128.1, 122.1, 116.1, 113.7, 61.1, 52.6; MS [EI$^+$] m/z (%) 686 [M]$^+$ (2), 92 [$C_6H_5CH_3$]$^+$ (100).

RESULTS AND DISCUSSION

The first studies were carried out using phenylacetylene (**1**) and benzyl azide (**2**) as starting materials (scheme 1). Among many plausible co-reactants to carry out CuAAC under solventless conditions, we decided to use CuI-DIPEA as a catalyst system which represents one of the simplest protocols when this reaction is performed in the presence of a solvent [8].



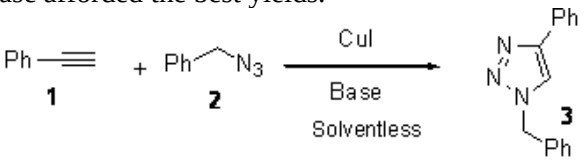
Scheme 1. Solventless cycloaddition between azide **2** and alkyne **1**.

Moreover, we determined to place the alkyne, the azide, the copper salt and the base on a mortar and the resulting reaction mixture was homogenized by grinding with a pestle for a certain time. This procedure was essentially the same during the course of the experiments in solvent-free conditions, and for this case, the direct reaction between alkyne **1** and azide **2** yielded 1-benzyl-4-phenyl-1,2,3-triazole (**3**) as the only reaction product. The effect of the concentration of both CuI and DIPEA was studied, and the results in table 1 show that the reaction is efficient with concentrations of 5 % mol CuI and 10% mol DIPEA.

Table 1. Effect of the concentration of CuI and DIPEA in the synthesis of triazole **3** under solventless conditions.

Entry	CuI (mmol/ mmol alkyne)	DIPEA (mmol/ mmol alkyne)	Reaction Time (min)	Yield (%)
1	0.1	1	2	95
2	0.05	1	2	95
3	0.025	1	2	88
4	0.0125	1	2	83
5	0.1	1	5	98
6	0.05	1	5	98
7	0.025	1	5	86
8	0.0125	1	5	82
9	0.1	0.1	5	98
10	0.05	0.1	5	98
11	0.025	0.1	5	85
12	0.0125	0.1	5	84

In addition, other bases were tested and the results are presented in table 2. Although triazole **3** was obtained in all cases, the use of DIPEA as a base afforded the best yields.



Scheme 2. Solventless cycloaddition between azide **2** and alkyne **1** in the presence of a base.

Table 2. Effect of the base in the synthesis of triazole **3** under solventless conditions.

Entry	Base	Yield (%)
1	DIPEA	98
2	Et_3N	88
3	Pyridine	70
4	K_2CO_3	62
5	Na_2CO_3	52
6	$NaHCO_3$	53

In order to explore the reaction scope, we performed solventless CuAAC reactions with diverse alkynes and azides and the results in table 3 demonstrate that this procedure is broad in scope affording the corresponding 1,2,3-triazoles in high yields which were fully characterized by the conventional spectroscopic techniques.

Table 3. Synthesis of 1,2,3-triazoles under solventless conditions.

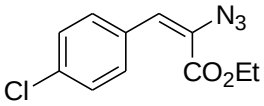
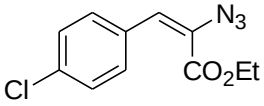
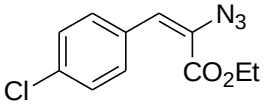
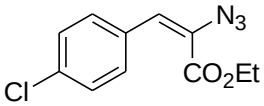
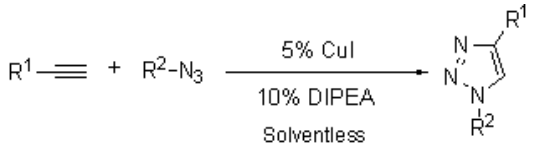
Compound	R^1	R^2	Yield (%)
3	Ph	$PhCH_2$	98
4	Ph	Ph	95
5	4-$BrC_6H_4OCH_2$	$PhCH_2$	57
6	4-$BrC_6H_4OCH_2$	Ph	61
7	4-$BrC_6H_4OCH_2$	4-$CH_3C_6H_4$	75
8	Ph	4-$CH_3C_6H_4$	92
9	CH_2OH	4-$CH_3OC_6H_4$	87
10	4-$BrC_6H_4OCH_2$	4-$CH_3OC_6H_4$	71
11	Ph	4-$CH_3OC_6H_4$	88
12	$nBuNHCO_2CH_2$	4-$CH_3OC_6H_4$	91
13	4-$BrC_6H_4OCH_2$	4-BrC_6H_4	72
14	Ph		87
15	4-$BrC_6H_4OCH_2$		75
16	4-$CH_3C_6H_4OCH_2$		82
17	$nBuNHCO_2CH_2$		80

Table 4. Synthesis of triazoles and bistriazoles using solventless conditions.

Entry	R^1	R^2	% Triazole	% Bistriazole
1	Ph	$PhCH_2$	30	15
2	Ph	4-$CH_3C_6H_4$	35	20
3	4-$BrC_6H_4OCH_2$	$PhCH_2$	27	10

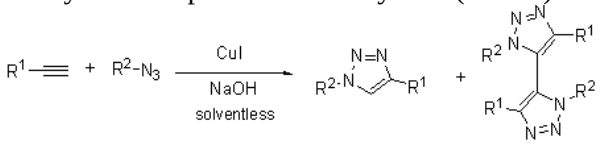
In these examples, triazoles **14**-**17** derived from ethyl 2-azido-3-(4-chlorophenyl)acrylate are similar to other heterocyclic analogs like resveratrol and have an important activity against lung and colon cancer cells.



Scheme 3. Synthesis of 1,2,3-triazoles under solventless conditions.

Other outstanding characteristic of the process is that the reaction times are short, and in the best of the cases these do not exceed 5 minutes. In addition, the purification of the final products is simple, in accordance with the essence of Click Chemistry.

On the other hand, we examined the use of sodium hydroxide in solventless CuAAC reactions. Previous reports described the formation of bistriazoles in the presence of inorganic bases [9], in particular, through the use of a high concentration of sodium hydroxide at low temperatures [10]. Thus, the solventless treatment of some alkynes and azides with excess sodium hydroxide and catalytic CuI yielded a mixture of triazoles and bistriazoles (scheme 4). In these processes, the yields of bistriazoles did not exceed 20% and in most cases the triazoles were obtained as only reaction products in low yields (table 4).



Scheme 4. Solventless synthesis of 1,2,3-triazoles and bistriazoles.

Despite these results, this method offers an alternative, direct and rapid protocol for the synthesis of these kinds of compounds with promising applications and the possibility of obtaining bistriazoles as major products of these processes that represent a great motivation to continue the studies in this area.

CONCLUSION

In summary, appropriately constituted alkynes and azides are easily converted to the corresponding 1,2,3-triazoles through a novel method that does not require the use of solvents in the presence of catalytic amounts of both CuI and DIPEA. This process combines short reaction times and high efficiency. In addition, when NaOH is used as the base, bistriazoles could be obtained through a solvent-free process. All the triazoles and bistriazoles described have biological potential activities and promise a broad application.

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REFERENCES

1. M. Meldal, C.W. Tornoe, *Chem. Rev.*, **108**, 2952 (2008).
2. S.G. Agalave, S.R. Maujan, V.P. Pore, *Chem. Asian J.*, **6**, 2696 (2011).
3. H.C. Kolb, K.B. Sharpless, *Drug Discov. Today*, **8,** 1128 (2003*).*
4. Hein, C. D.; Liu, X. M.; Wang, D. *Pharm. Res.* **2008**, *25*, 2216.
5. H. Wang, K. Wen, L. Wang, Y.;Xiang, X. Xu, Y. Shen, Z. Sun, *Molecules*, **17**, 4533 **(**2012).
6. G.T. Tigineh, Y.S. Wen, L.K. Liu, *Tetrahedron*, **71,** 170 **(**2015).
7. H. Gallardo, G. Conte, F. Bryk, M.C.S. Lourenço, M.S. Costac, V.F. Ferreira, *J. Braz. Chem. Soc*., **18,** 1285 (2007).
8. C.W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* , **67**, 3057 (2002).
9. Y. Angell, K. Burgess, *Angew. Chem. Int. Ed.* , **46**, 3649 **(**2007).
10. J. González, V. M. Pérez, D. O. Jiménez, G. Lopez-Valdez, D. Corona, E. Cuevas-Yañez, *Tetrahedron Lett*., **52**, 3514 (2011).

СИНТЕЗА БЕЗ РАЗТВОРИТЕЛ НА ТРИАЗОЛИ И БИС-ТРИАЗОЛИ ЧРЕЗ АЛКИН-АЗИД‘ОВО ЦИКЛО-ПРИТЪКМЯВАНЕ, КАТАЛИЗИРАНО ОТ МЕД

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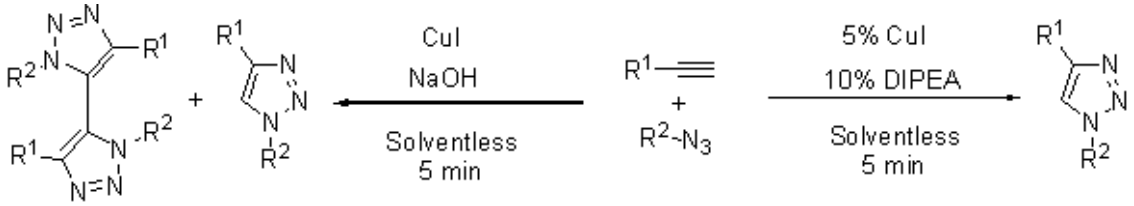
(Резюме)



Синтезирани са 1,2,3-триазоли, включително серия от триазол-стирени, които имат структурна връзка с ресвератрол чрез нов метод без използване на разтворител. Методът включва пряко третиране чрез смилане на няколко азини и алкини в присъствие на катализатор от меден йодид и *N*,*N*-ди-изопропил-етиламин. От друга страна, когато се използва натриева основа като алкален агент се получава смес от бис-триазоли и триазоли, при която 1,2,3-триазолите са главният продукт. Този нов протокол на синтезата се извършва при меки условия за кратко време, допускащ 1,4-позиционни изомери с високи добиви.