ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 11, pp. 1785–1790. © Pleiades Publishing, Ltd., 2019.

A Simple Efficient Click Synthesis of Novel Crown Ethers Containing 1,2,3-Triazole Moieties

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Received June 30, 2019; revised August 25, 2019; accepted September 3, 2019

Abstract—Novel crown ether derivative containing 1,4-disubstituted-1,2,3-triazole moieties were synthesized. At the first step of the synthesis 4,13-diaza-18-crown-6 and 4-aminobenzo-15-crown-5 were converted into terminal alkynes, which were then subjected to copper(I)-catalyzed alkyne–azide coupling (CuAAC) in methylene chloride. This coupling reaction was performed according to the concept of click chemistry, using an Amberlyst A-21–supported copper(I) iodide catalyst.

Keywords: terminal alkynes, crown ethers, click chemistry, CuAAC, copper(I) catalysis, 1,2,3-triazoles

DOI: 10.1134/S1070428019110228

Heterocyclic compounds containing a triazole motif play an important role in therapeutics [1]. These compounds have several interesting biological applications due to their antimicrobial [2–6], anti-inflammatory [7], antifungal [8, 9] and antitumor activity [10–12]. On the other hand, substituted 1,2,3-triazoles are molecules for organic synthesis, because they present as key structural units in many pharmaceuticals. It is for this reason, heterocyclic compounds containing triazole units are important in several areas [13–17].

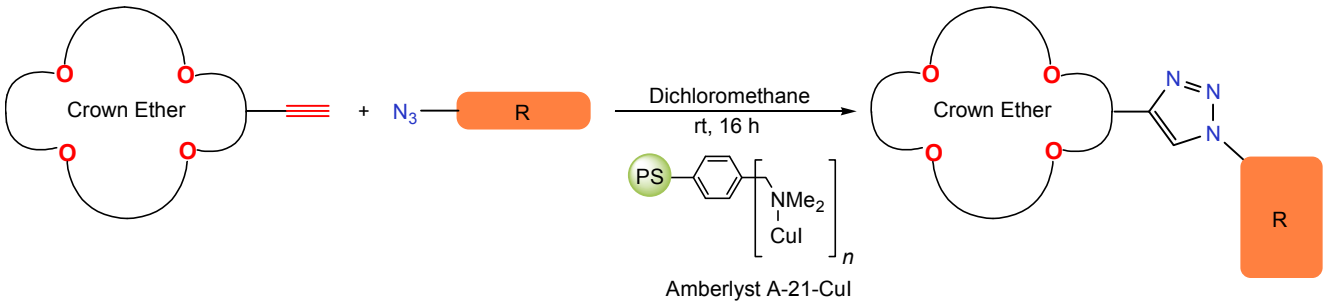
The present paper reports the synthesis of novel 1,4-disubstituted-1,2,3-triazole derivatives of 4-aminobenzo-15-crown-5 and 4,13-diaza-18-crown-6 (Scheme 1). The CuAAC method used in this synthesis was based on the concept of click chemistry [18, 19].

As the a first step, we converted 4,13-diaza-18-crown-6 and benzo-15-crown-5 into terminal alkynes. The second step involved a coupling reaction between the synthesized alkynes with azides prepared by known procedures [15, 20, 23–25]. The coupling reaction was carried out at room temperature in the presence of an Amberlyst A-21-supported copper(I) catalyst (Amberlyst A-21·CuI) prepared as described in [26]. The use of Amberlyst A-21·CuI in this organic synthesis was motivated by that our aim was to obtain 1,4-disubstituted-1,2,3-triazole derivatives but not their mixtures with 1,5-isomers [15, 20] and the copper(I) catalyst could be easily removed, not applying organic solvents or nitrogen compounds [21]. Thus, using Amberlyst A-21·CuI allows minimization of a loss of the synthesized triazole derivatives and ensures high synthetic yields [15, 22].

According to the LC/MS-ELSD data, 1,2,3-triazole-containing crown ethers **2a–2f** and **4a–4d** (Schemes 2 and 3) had a good purity ranging from 94 to 100%. These results are consistent with those obtained by Jlalia et al. [15]. The efficiency of the synthesis varied from 84 to 97%, which is better than in the work of Tilliet et al. [18], where a macrocycle derived from 4,13-diaza-18-crown-6 and containing 1,2,3-triazole moieties was synthesized in a yield not exceeding 21%.

The newly synthesized heterocyclic compounds **2a–2f** and **4a–4d** were characterized by IR and ^{1}H and ^{13}C NMR, elemental analysis, and LCMS.

Scheme 1.



EXPERIMENTAL

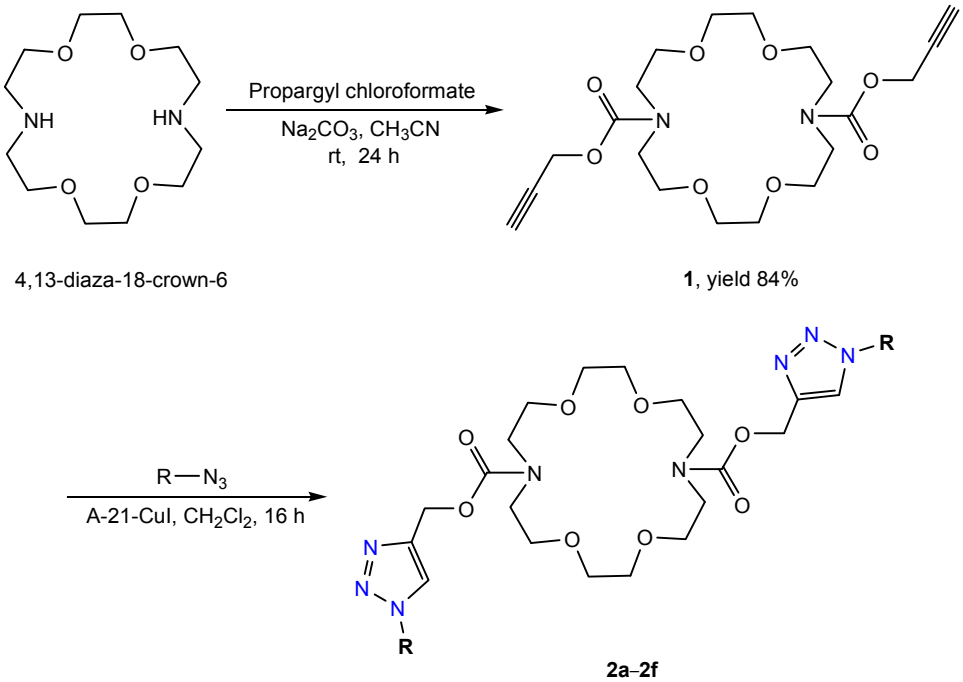
Copper(I) iodide was purchased from Lancaster, 4,13-diaza-18-crown-6, 4-aminobenzo-15-crown-5, propargyl chloroformate, propiolic acid, 1,3-dicyclohexyl carbodiimide, and Amberlyst A21 resin (20–50 mesh) were purchased from Sigma Aldrich.

Azides were prepared from sodium azide, benzyl bromide, 3-chloropropanol, ethyl bromoacetate, phenylboronic acid, *p*-tolylboronic acid, 2-bromoethyl acetate and benzyl bromoacetate (after treatment with ethyl trifluoroacetate) following published procedures [15, 20, 23–25].

Acetonitrile (spectrometric grade, low water) was purchased from SDS France and used as received. Dichloromethane (SDS France) was treated with phosphorus pentoxide under reflux (1 h) and then distilled.

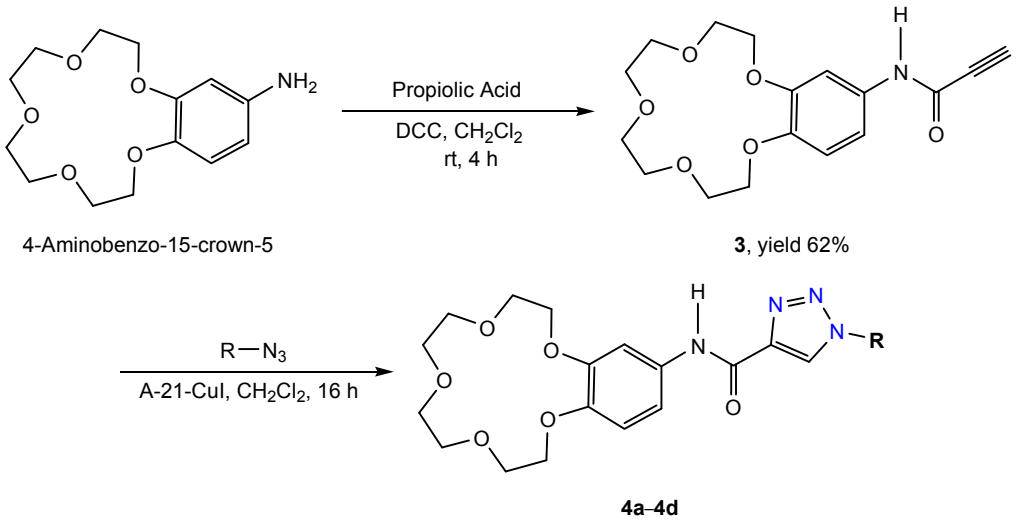
The melting points were determined using a Kofler apparatus in two steps: after initial estimation, the device was calibrated against a reference standard with a melting point close to the estimated value and then a final measurement was made. The IR spectra were recorded neat on a Jasco FT/IR-4100 in the ATR mode (PIKE-MIRacle) between 4000 and 400 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker

Scheme 2.



2, R = $C_2H_5OCOCH_2$ (**a**); $HO(CH_2)_3$ (**b**); $AcOC_2H_4$ (**c**); $PhCH_2$ (**d**); 4-Me-Ph (**e**); Ph (**f**).

Scheme 3.



4, R = $C_2H_5OCOCH_2$ (**a**); $AcOC_2H_4$ (**b**); Ph-CH_2OCOCH_2 (**c**); $PhCH_2$ (**d**).

Avance DRX instrument in $CDCl_3$ (unless otherwise specifies) at 300 (^{1}H) and 75.5 (^{13}C) MHz, respectively, internal reference TMS. Liquid chromatography–mass spectrometry was performed on a Shimadzu LCSM-2010 A instrument equipped with a SPD-M10 A PDA diode array detector (D2, lamp from 190 to 400 nm) and an ELSD-LT light scattering detector. Liquid chromatography was performed on an Alltech Alltima HP C8 3μm reversed-phase HPLC column (53 × 7 mm ID) and a mobile phase comprising MeCN, water, and 0.1% formic acid at a flow rate of 1 mL/min; the MeCN/water gradient was as follows: 0–1 min: 30% MeCN; 1–5 min: ramp from 30% to 100% MeCN; 5–12 min: 100% MeCN; 12–14.99 min: ramp from 100% to 30% MeCN; and 14.99–20 min: 30% MeCN. The ESI mass spectra were recorded in the *m/z* range 100–500 in the positive ion mode (detector 1.5 kV, quadrupole 5 V). Elemental analysis was performed on a Perkin-Elmer 2400 Series II CHN analyzer.

7,16-Bis(prop-2-yn-1-yl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (1). Propargyl chloroformate, 0.47 g (4 mmol) was slowly added to a solution of 0.52 g (2 mmol) of diaza-18-crown-6 in 15 mL of MeCN in the presence of 0.21 g (2 mmol) of Na_2CO_3. The mixture was stirred for 24 h at room temperature. Filtration and evaporation of the solvents under vacuum gave macrocyclic alkyne **1** as a white solid. Yield 0.71 g (84%), mp 108°C. IR spectrum, ν, cm^{-1}: 3053–2945 (CH_2), 1737 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.48 t (1H, C≡CH), 3.59–3.70 m (12H, 6CH_2), 4.72 d (2H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 47.97, 48.04, 48.67, 52.88, 69.84, 69.88, 70.12, 70.16, 70.56, 70.60, 70.65, 70.71, 74.44, 78.51, 155.34. Found, %: C 56.211; H 7.029; N 6.540; O 29.950. $C_{20}H_{30}N_2O_8$. $C_{20}H_{30}N_2O_8$. Calculated, %: C 56.328; H 7.090; N 6.569; O 30.013. Mass spectrum: *m/z* 427 $[M + H]^+$

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecyn-15-yl)prop-2-ynamide (3).** Propiolic acid, 350 mg (5 mmol), was added to a solution of 1.41g (5 mmol) of 4-aminobenzo-15-crown-5 in 10 mL of CH_2Cl_2. After slow agitation at 0°C for 30 min, 1.28 g of DCC (6.25 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at room temperature for 4 h and then cooled in ice water, filtered through celite, and washed with 20 mL of 1M HCl, 20 mL of saturated aqueous $NaHCO_3$, and 20 mL of water. After drying over $MgSO_4$ and evaporation of the solvent under vacuum, alkyne **3** was purified by column chromatography in heptane–EtOAc, 13 : 7. Yield 1.03 g (62%), beige solid, mp 146°C. IR spectrum, ν, cm^{-1}: 3375 (NH), 3186 (CH), 2895–2857 (CH_2), 2093 (C≡C), 1650 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.99 s (1H, C≡CH), 3.73 s (8H, 4CH_2), 3.86–3.87 m (4H, 2CH_2), 4.07 m (4H, 2CH_2), 6.72 d (1H), 7.01 d.d (1H), 7.29 d (1H), 8.67 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 68.75, 69.31, 69.50, 70.35, 70.39, 70.84, 74.46, 77.78, 107.19, 112.96, 114.36, 131.46, 146.16, 149.05, 149.95. Found, %: C 60.821; H 6.290; N 4.170; O 28.113. $C_{17}H_{21}NO_6$. Calculated, %: C 60.886; H 6.311;

N 4.177; O 28.625. Mass spectrum: *m/z* 358 [*M* + Na]$^+$.

Copper(I)-catalyzed alkyne–azide coupling reaction (*general procedure*). Azide, 2.2 equiv, and 12 mg (0.016 mmol CuI, 8 mol %) of Amberlyst A-21·CuI in 2 mL of CH_2Cl_2 were added to the synthesized terminal alkyne, and the reaction mixture was stirred at room temperature for 16 h, filtered, and washed with 2 mL of CH_2Cl_2. The product was obtained after evaporation of the solvent under vacuum.

7,16-Bis{[1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]methyl}1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2a) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.142 g (1.1 mmol) of ethyl azidoacetate [15, 20, 25]. Yield 0.318 g (93%), white solid, mp 110°C. IR spectrum, ν, cm^{-1}: 3021–2970 (CH_2), 2285 (CH_3), 1741 (C=O), 1699 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23–1.29 m (3H, CH_3), 3.50–3.59 m (12H, 6CH_2), 4.21–4.25 m (2H, CH_2), 5.13 d (2H, CH_2), 5.20 s (2H, CH_2), 7.76 s (1H, C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.61, 47.48, 48.06, 50.42, 57.87, 62, 69.35, 69.50, 69.56, 70.06, 124.64, 124.95, 155.45, 165.70. $C_{28}H_{44}N_8O_{12}$. Calculated, %: C 49.118; H 6.477; N 16.365; O 28.041. Found, %: C 48.987; H 6.234; N 16.118; O 28.029. Mass spectrum: *m/z* 686 [*M* + H]$^+$.

7,16-Bis{[1-(3-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl]methyl}1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2b) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.111 g (1.1 mmol) of 3-azidopropan-1-ol [15, 23]. The product was obtained as a yellow solid. Yield 0.264 g (84%), yellow solid, mp 94°C. IR spectrum, ν, cm^{-1}: 3110–2945 (CH_2), 1746 (C=O), 1704 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.80 s (1H, OH), 2.11 s (2H, CH_2), 3.43–3.73 m (14H, 7CH_2), 4.50 s (2H, CH_2), 5.18 s (2H, CH_2), 7.70 s (1H, C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 31.01, 32.06, 46.57–48.06, 57.95–59.29, 69.24, 70.06, 124.14, 155.56. Found, %: C 49.582; H 7.012; N 17.718; O 25.218. $C_{26}H_{44}N_8O_{10}$. Calculated, %: C 49.673; H 7.054; N 17.824; O 25.449. Mass spectrum: *m/z* 630 [*M* + H]$^+$.

7,16-Bis({1-[2-(acetyloxy)ethyl]-1*H*-1,2,3-triazol-4-yl}methyl)1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2c) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.142 g (1.1 mmol) of 1-azidoethyl acetate [25]. Yield 0.314g (92%), beige liquid. IR spectrum, ν, cm^{-1}: 3100–2954 (CH_2), 1738 (C=O), 1688 (N=N). ^{1}H NMR ($CDCl_3$), δ, ppm: 2.03 s (3H, CH_3), 3.49–3.57 m (12H, 6CH_2), 4.43–4.58 m (4H, 2CH_2), 5.17 s (2H, CH_2), 7.68 s (1H, C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.54, 47.71, 48.29, 48.87, 58.10, 62.15, 69.65, 69.79, 70.31, 124.42, 143.57, 155.77, 170.20. Found, %: C 49.07; H 6.324; N 16.05; O 28.01. $C_{28}H_{44}N_8O_{12}$. Calculated, %: C 49.117; H 6.477; N 16.365; O 28.040. Mass spectrum: *m/z* 686 [*M* + H]$^+$.

7,16-Bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2d) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.146 g (1.1 mmol) of benzyl azide [15, 24, 25]. Yield 0.311g (90%), green solid, mp 88°C. IR spectrum, ν, cm^{-1}: 3120 (CH), 2941 (CH_2), 1715 (C=O), 1696 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (3H, CH_3), 3.56–3.65 m (12H, 6CH_2), 5.28 s (2H, CH_2), 7.33–7.62 m (4H), 8.07 s (1H, C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.12, 48.02–48.59, 58.40, 69.27, 69.47, 69.97, 120.49, 125.83, 129.19, 130.28, 138.60, 156.04. Found, %: C 58.865; H 6.380; N 15.989; O 18.187. $C_{34}H_{44}N_8O_8$. Calculated, %: C 58.948; H 6.401; N 16.175; O 18.476. Mass spectrum: *m/z* 694 [*M* + H]$^+$.

7,16-Bis{[1-(4-methylphenyl)-1H-1,2,3-triazol-4-yl]methyl}1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2e) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.133 g (1.1 mmol) of 1-azido-4-methylbenzene [24]. Yield 0.304 g (88%), brown liquid. IR spectrum, ν, cm^{-1}: 3055 (CH), 2956 (CH_2), 1720 (C=O), 1676 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.39–3.67 m (12H, 6CH_2), 4.71 d (2H, CH_2), 7.47–7.58 m (3H), 7.75–7.78 m (2H), 8.11 s (1H, C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 48.30, 48.55, 58.64, 70.36, 70.40, 70.37, 120.76, 122.43, 137.26, 146.59, 155.60. Found, %: C 58.889; H 6.390; N 16.080; O 18.351. $C_{34}H_{44}N_8O_8$. Calculated, %: C 58.948; H 6.401; N 16.175; O 18.476. Mass spectrum: *m/z* 694 [*M* + H]$^+$.

7,16-Bis[(1-phenyl-1H-1,2,3-triazol-4-yl)methyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarboxylate (2f) was prepared from 0.213 g (0.5 mmol) of alkyne **1** and 0.131g (1.1mmol) of azidobenzene [24]. Yield 0.311g (90%), brown liquid. IR spectrum, ν, cm^{-1}: 3135 (CH), 3033–2955 (CH_2), 1723 (C=O), 1682 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.49–3.55 m (12H, 6CH_2), 5.18 s (2H, CH_2), 5.28 s (2H, CH_2), 7.25–7.34 m (5H), 7.54 s (1H,

C=CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 47.39, 47.92, 55.30, 57.50, 69.26, 69.96, 127.61, 123.23, 123.30, 128.22, 128.80, 133.95, 138.54, 143.34, 143.39, 155.61. Found, %: C 57.658; H 6.047; N 16.657; O 19.178. $C_{32}H_{40}N_8O_8$. Calculated, %: C 57.822; H 6.065; N 16.857; O 19.255. Mass spectrum: *m/z* 666 $[M + H]^+$.

Ethyl 2-{4-[(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-carbamoyl]-1*H*-1,2,3-triazol-1-yl}acetate (4a) was prepared from 67 mg (0.2 mmol) of alkyne **3** and 28 mg (0.22 mmol) of ethyl azidoacetate [25, 20, 15]. Yield 90.10 mg (97%), brown solid, mp 182°C. IR spectrum, ν, cm^{-1}: 3296 (NH), 2941 (CH), 2875 (CH_2), 1752 (C=O), 1654 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (3H, CH_3), 3.79 s (8H, $4CH_2$), 3.93–3.96 m (4H, $2CH_2$), 4.15–4.22 m (4H, $2CH_2$), 4.32 q (2H, CH_2), 5.26 s (2H, CH_2), 6.89 d (1H), 7.11 d.d (1H), 7.49 d (1H), 8.29 s (1H, C=CH), 8.87 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.09, 51.24, 62.38, 68.35–71.51, 106.79, 112.40, 114.91, 127.14, 131.61, 143.96, 146.05, 149.47, 157.37, 165.60. Found, %: C 54.198; H 6.069; N 12.049; O 27.489. $C_{21}H_{28}N_4O_8$. Calculated, %: C 54.305; H 6.076; N 12.062; O 27.557. Mass spectrum: *m/z* 465 $[M + H]^+$.

2-{4-[(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-carbamoyl]-1*H*-1,2,3-triazol-1-yl}ethyl acetate (4b) was prepared from 67 mg (0.2 mmol) of alkyne **3** and 28 g (0.22 mmol) of 1-azidoethyl acetate [25]. Yield 87.31 mg (94%), beige solid, mp 182°C. IR spectrum, ν, cm^{-1}: 3385 (NH), 2933 (CH), 2870 (CH_2), 1746 (C=O), 1662 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 s (3H, CH_3), 3.79 s (8H, $4CH_2$), 3.93–3.96 m (4H, $2CH_2$), 4.15–4.23 m (4H, $2CH_2$), 4.52 t (2H, CH_2), 4.72 t (2H, CH_2), 6.89 d (1H), 7.11 d.d (1H), 7.48 d (1H), 8.22 s (1H, C=CH), 8.89 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.98, 49.93, 62.44, 69.14-71.38, 107.04, 112.67, 115.12, 126.53, 131.85, 144.07, 146.33, 149.73, 157.80 170.61. Found, %: C 54.119; H 6.054; N 12.047; O 27.478. $C_{21}H_{28}N_4O_8$. Calculated, %: C 54.305; H 6.076; N 12.062; O 27.557. Mass spectrum: *m/z* 465 $[M + H]^+$.

Benzyl 2-{4-[(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-carbamoyl]-1*H*-1,2,3-triazol-1-yl}acetate (4c) was prepared from 67 mg (0.2 mmol) of alkyne **3** and 42 g (0.22 mmol) of benzyl azidoacetate [25]. Yield 96.88 mg (92%), beige solid, mp 168°C. IR spectrum, ν, cm^{-1}: 3293 (NH), 3003 (CH), 2864 (CH_2), 1753 (C=O), 1650 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.80 s (8H, $4CH_2$), 3.93–3.97 m (4H, $2CH_2$), 4.16–4.23 m (4H, $2CH_2$), 5.30 s, 2H), 6.86–6.92 d.d (1H) 7.38–7.50 m (6H), 8.30 s (1H, C=CH), 8.86 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 50.39, 51.20, 67.58, 68.32, 68.79, 69.46, 69.69, 70.40, 70.56, 71.07, 106.68, 112.34, 114.87, 127.26, 128.59, 128.71, 128.98, 131.65, 134.39, 143.93, 145.95, 149.41, 157.34, 165.67; Found, %: C 59.304; H 5.470; N 10.538; O 24.297. $C_{26}H_{30}N_4O_8$. Calculated, %: C 59.308; H 5.742; N 10.640; O 24.308. Mass spectrum: *m/z* 549 $[M + Na]^+$.

1-Benzyl-*N*-(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-1*H*-1,2,3-triazole-4-carboxamide (4d) was prepared from 67 mg (0.2 mmol) of alkyne **3** and 28.5 mg (0.22 mmol) of benzyl azide [15, 24, 25]. Yield 89.95 mg (96%), yellow solid, mp 200°C. IR spectrum, ν, cm^{-1}: 3299 (NH), 3048 (CH), 2937 (CH_2), 1659 (C=O), 1610 (N=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.74 s (8H, $4CH_2$), 3.93–3.96 m (4H, $2CH_2$), 4.16–4.21 m (4H, $2CH_2$), 5.62 s (2H, CH_2), 6.88–6.91 m (1H), 7.09–7.13 m (1H), 7.32–7.47 m (6H), 8.05 s (1H, C=CH), 8.86 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 54.80, 68.99, 69.62, 69.83, 70.61, 70.77, 71.19, 71.24, 106.93, 112.52, 115.04, 125.65, 128.40, 129.32, 129.47, 131.71, 133.78, 143.95, 146.14, 149.58, 157.68. Found, %: C 61.413; H 5.998; N 11.768; O 20.118. $C_{24}H_{28}N_4O_6$. Calculated, %: C 61.528; H 6.024; N 11.958; O 20.490. Mass spectrum: *m/z* 469 $[M + H]^+$.

CONCLUSIONS

We realized a click synthesis of some novel 1,2,3-triazole derivatives. These heterocyclic compounds were synthesized from 4,13-diaza-18-crown-6 or 4-aminobenzo-15-crown-5 and azides in the presence of an easily prepared Amberlyst A-21-supported copper(I) catalyst with high purities and very good yields. Following the approach of Jlalia et al. [15], developed for the synthesis of 1,2,3-triazole derivatives, starting from small molecules, we found that the same approach is also suitable for supramolecular chemistry.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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