ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 11, pp. 1701–1704. © Pleiades Publishing, Ltd., 2017.
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# One-Pot Synthesis of 1,2,3-Triazole Derivatives of Maleopimaric and Dihydroquinopimaric Acids

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Received May 31, 2017

**Abstract**—Effective one-pot synthesis of 1,2,3-triazole derivatives of maleopimaric and dihydroquinopimaric acids consists in the reaction of diterpene propargyl esters with organic azides generated *in situ* in the presence of CuI catalyst.

**DOI:** 10.1134/S1070428017110161

Diene adducts of levopimaric acid and products of their further transformations are accessible objects for chemical modification [1–3], applied as synthetic platform for development of pharmacologically active compounds [4]. Maleopimaric and dihydroquinopimaric acids are products of the reaction of levopimaric acid with maleic anhydride and *p*-benzoquinone, and their derivatives possess also antiphlogistic [5], antiviral [6], antitumor [7] properties and may be considered as promising agents for preventing and treating gastric ulcer [8].

Introduction of 1,2,3-triazole fragment into a molecule of diterpenoids is promising because of a wide spectrum of biological activity of compounds, containing this substituent [9, 10]. For compounds of this class antiviral [11], antibacterial [12], antitumor [13], antiphlogistic [14] activity is typical, as well as the ability of selective inhibition of HIV-1 protease [15] and tyrosine kinase [16].

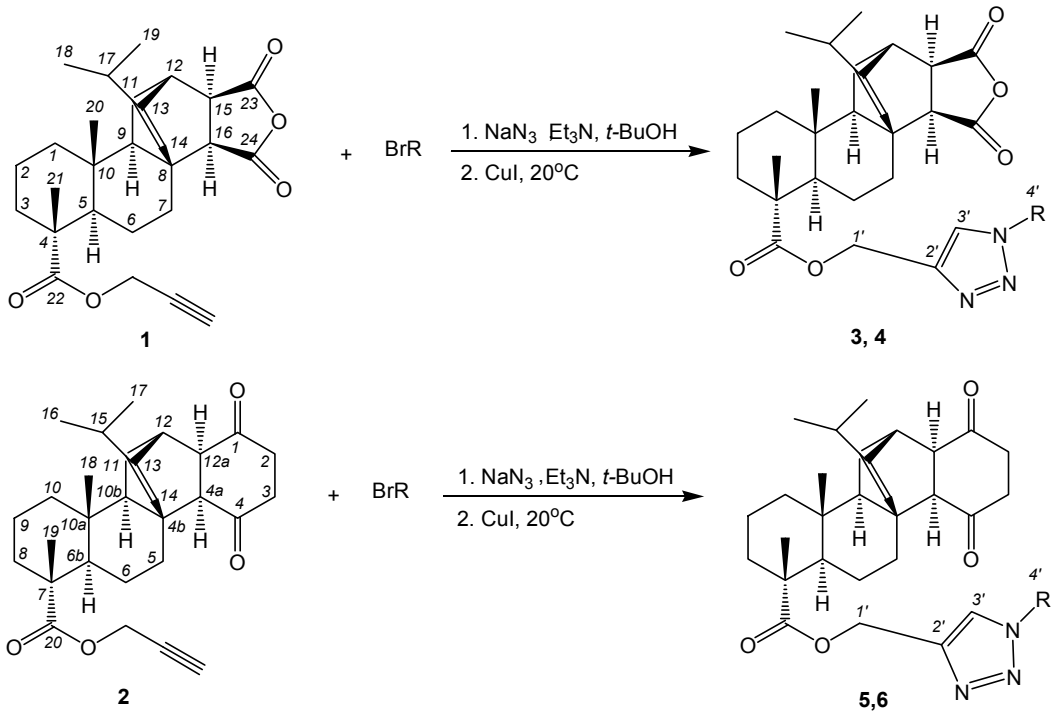
One of the most significant synthetic methods of building up five-membered heterocyclic systems is a 1,3-dipolar cycloaddition, where azide-alkyne cycloaddition (CuAAC) catalyzed by cooper salts (I), with generation of 1,4-disubstituted 1,2,3-triazoles may serve as a classic example [17]. Alkynes are accessible [18], while the preparation of azido derivatives is problematic due to their instability [19], and the exclusion of the stage of azides isolation significantly simplifies the synthesis of triazoles [20].

In continuation of research on synthetic transformations of diene adducts of levopimaric acid [21–24] we performed the functionalization of diterpene terminal alkynes in the conditions of reaction of 1,3-dipolar cycloaddition and carried out the synthesis of 1,2,3-triazole derivatives of maleopimaric and dihydroquinopimaric acids.

Initial diterpene terminal alkynes **1** and **2** were obtained by the reaction of maleopimaric and dihydroquinopimaric acids chlorides with propargyl alcohol in anhydrous chloroform at room temperature [24]. The one-pot synthesis of 1,2,3-triazole derivatives of diterpenoids **3**–**6** was performed in two steps. First the reaction of equimolar amounts of benzyl or hexyl bromide, triethylamine, and sodium azide at room temperature in aqueous solution of 1-butanol ($H_2O$–BuOH, 1 : 1) resulted in the formation of the corresponding organic azide that was without isolation brought into the reaction with propargyl ester of maleopimaric acid **1** or dihydroquinopimaric acid **2** in the presence of CuI as catalyst. As a result we obtained 1,2,3-triazole derivatives of maleopimaric (**3** and **4**) and dihydroquinopimaric (**5** and **6**) acids in 80–89% yields respectively (Scheme 1).

In $^1$H NMR spectra of compounds **3**–**6** signals of protons of the acetylene group are absent, and broadened signals were observed of the proton of triazole ring at 7.60–7.61 ppm that in the HSQC and HMBC spectra was correlated with the signals of atoms $C^{2'}$ and $C^{3'}$ of heterocycle in the region 143.44–146.80 and 123.54–123.71 ppm. In $^{13}$C NMR spectra of compounds **3** and **5** with benzyl residue resonance peaks were present from the carbon atoms of the

**Scheme 1.**




R = Bn (**3**, **5**), $C_6H_{13}$ (**4**, **6**).

aromatic ring in the region 128.07–135.46 ppm, in $^1$H NMR spectra the signals of aromatic protons were observed at 7.21–7.40 ppm. For hexyl-substituted compounds **4** and **6** the signals of protons of methylene groups were registered in the region 1.21–1.78, 1.95–2.00, and 5.10–5.30 ppm, the signals of protons of methyl group appeared as a broadened signal at 0.85 ppm.

Simple and convenient one-pot synthesis of new 1,2,3-triazole derivatives of diene adducts of levopimaric acid from alkyl- or aryl halides, sodium azide, and diterpene terminal acetylenes with copper iodide as catalyst proceeds in mild conditions and includes the formation *in situ* of azides that allows excluding the isolation of unstable organic azides.

## EXPERIMENTAL

$^{13}$C and $^1$H NMR spectra were registered on a pulse spectrometer Bruker Avance III (500.13 and 125.47 MHz respectively), internal reference tetramethylsilane. Melting points were determined on a Boëtius apparatus. For TLC Sorbfil plates were used (Sorbpolymer, Russia), eluent hexane–ethyl acetate, 1 : 1. Spots were visualized by 10% solution of sulfuric acid with subsequent heating at 100–120°C during 2–3 min. For column chromatography neutral $Al_2O_3$ was used (KhromLab, Russia). Propargyl esters of maleopimaric and dihydroquinopimaric acids **1** and **2** were synthesized by method [24].

**Compounds 3–6. General method.** A mixture of 0.7 mL (1 mmol) of triethylamine, 0.07 g (1 mmol) of sodium azide, and 0.25 mL (1 mmol) of benzyl bromide or 0.19 mL (1 mmol) of hexyl bromide in 5 mL of water and 5 mL of 1-butanol was intensively stirred for 30 min at room temperature. To the mixture were added 0.44 g (0.5 mmol) of propargyl ester of maleopimaric acid **1** or 0.45 g (0.5 mmol) of propargyl ester of dihydroquinopimaric acid **2** in 5 mL of 1-butanol and 0.013 g of cooper(I) iodide, and the reaction mixture was stirred for 12 h at room temperature (TLC monitoring). The reaction mixture was poured into 50 mL of water, the reaction products were extracted with chloroform (2 × 50 mL), the extract was washed with water till neutral washings, dried with $CaCl_2$. Solvent was evaporated, the precipitate was chromatographed on a column packed with $Al_2O_3$ eluting with methylene chloride.

**(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl 13-isopropyl-4,10-dimethyl-2,24-dioxotetradecahydro-1*H*-**

**8,12-ethenophenanthro[1,2-*c*]furan-4-carbo-xylate (3).** Yield 0.39 g (89%), mp 102–104°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.60 s (3H, $H^{20}$), 0.65–0.90 m (5H, $H^{1a}$, $H^{2a,e}$, $H^{3a,e}$), 1.00 d (3H, $H^{18}$, *J* 6.9 Hz), 1.15 d (3H, $H^{19}$, *J* 7.0 Hz), 1.21–1.81 m (9H, $H^{1e}$, $H^{5}$, $H^{6a,e}$, $H^{7a,e}$, $H^{9}$, $H^{11a,e}$), 1.30 s (3H, $H^{21}$), 2.25 d (1H, $H^{17}$, *J* 8.4 Hz), 2.40 d.t (1H, $H^{16}$, *J* 3.0, 14.0 Hz), 2.70 d (1H, $H^{15}$, *J* 8.4 Hz), 3.08 d (1H, $H^{12}$, *J* 8.4 Hz), 4.30 br.s (2H, $H^{1'}$), 5.10–5.30 m (2H, $H^{4'}$), 5.50 s (1H, $H^{14}$), 7.21–7.40 m (5$H_{arom}$), 7.61 s (1H, $H^{3'}$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 15.49 ($C^{20}$), 16.70 ($C^{19}$), 16.94 ($C^{2}$), 20.00 ($C^{18}$), 20.58 ($C^{19}$), 21.52 ($C^{6}$), 29.74 ($C^{11}$), 32.77 ($C^{17}$), 34.61 ($C^{7}$), 35.64 ($C^{12}$), 36.42 ($C^{3}$), 37.58 ($C^{10}$), 37.86 ($C^{1}$), 40.33 ($C^{8}$), 45.63 ($C^{15}$), 46.95 ($C^{4}$), 49.19 ($C^{5}$), 53.00 ($C^{16}$), 54.06 ($C^{9}$), 54.71 ($C^{4'}$), 57.70 ($C^{1'}$) 123.71 ($C^{3'}$), 125.14 ($C^{14}$), 128.07 ($C_{arom}$), 128.22 ($C_{arom}$), 128.84 ($C_{arom}$), 129.14 ($C_{arom}$), 134.70 ($C_{arom}$), 135.46 ($C_{arom}$), 143.44 ($C^{2'}$), 148.06 ($C^{13}$), 171.18 ($C^{23}$), 172.90 ($C^{24}$), 178.27 ($C^{22}$). Found, %: C 71.00; H 7.54; N 7.00. $C_{34}H_{41}N_3O_5$. Calculated, %: C 71.43; H 7.23; N 7.35.

**(1-Hexyl-1*H*-1,2,3-triazol-4-yl)methyl 13-isopropyl-4,10-dimethyl-23,24-dioxotetradecahydro-1*H*-8,12-ethenophenanthro[1,2-*c*]furan-4-carboxylate (4).** Yield 0.36 g (83%), mp 108–110°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.60 s (3H, $H^{20}$), 0.85 s (3H, $H^{9'}$), 1.05 d (3H, $H^{18}$, *J* 6.9 Hz), 1.10 d (3H, $H^{19}$, *J* 7.0 Hz), 1.20 s (3H, $H^{21}$), 1.21–1.78 m (20H, $H^{1a,e}$, $H^{2a,e}$, $H^{3a,e}$, $H^{5}$, $H^{6a,e}$, $H^{7a,e}$, $H^{9}$, $H^{11a,e}$, $H^{6'}$, $H^{7'}$, $H^{8'}$), 1.95 br.s (2H, $H^{5'}$), 2.25 d (1H, $H^{17}$, *J* 8.4 Hz), 2.40 d.t (1H, $H^{16}$, *J* 3.0, 14.0 Hz), 2.75 d (1H, $H^{15}$, *J* 8.4 Hz), 3.10 d (1H, $H^{12}$, *J* 8.4 Hz), 4.40 br.s (2H, $H^{1'}$), 5.20–5.35 m (2H, $H^{4'}$), 5.50 s (1H, $H^{14}$), 7.60 s (1H, $H^{3'}$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 13.94 ($C^{9'}$), 15.49 ($C^{20}$), 16.75 ($C^{19}$), 16.93 ($C^{2}$), 19.94 ($C^{18}$), 20.56 ($C^{19}$), 21.63 ($C^{6}$), 22.42 ($C^{8'}$), 26.00 ($C^{7'}$), 27.21 ($C^{11}$), 29.84 ($C^{6'}$), 31.11 ($C^{5'}$), 32.74 ($C^{17}$), 34.69 ($C^{7}$), 35.66 ($C^{12}$), 36.49 ($C^{3}$), 37.66 ($C^{10}$), 37.88 ($C^{1}$), 40.40 ($C^{8}$), 45.63 ($C^{15}$), 47.24 ($C^{4}$), 49.27 ($C^{5}$), 50.98 ($C^{4'}$), 53.04 ($C^{16}$), 53.13 ($C^{9}$), 57.80 ($C^{1'}$), 123.54 ($C^{3'}$), 125.17 ($C^{14}$), 146.80 ($C^{2'}$), 148.13 ($C^{13}$), 170.94 ($C^{23}$), 172.75 ($C^{24}$), 178.09 ($C^{22}$). Found, %: C 70.00; H 8.14; N 7.55. $C_{33}H_{47}N_3O_5$. Calculated, %: C 70.06; H 8.37; N 7.43.

**(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl 13-isopropyl-7,10a-dimethyl-1,4-dioxohexadecahydro-1*H*-4b,12-ethenochrysene-7-carboxylate (5).** Yield 0.39 g (87%), mp 98–100°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.55 s (3H, $H^{18}$), 0.75–0.89 m (2H, $H^{6a,e}$), 1.00 d (3H, $H^{16}$, *J* 6.9 Hz), 1.02 d (3H, $H^{17}$, *J* 6.9 Hz), 1.15 s (3H, $H^{19}$), 1.20–1.65 m (12H, $H^{5a,e}$, $H^{6b}$, $H^{8a,e}$, $H^{9a,e}$, $H^{10a,e}$, $H^{10b}$, $H^{11a,e}$), 2.14 s (1H, $H^{4a}$), 2.33 t (1H, $H^{15}$, *J* 6.2 Hz), 2.40–2.50 m (4H, $H^{2}$, $H^{3}$), 2.75 br.s (1H, $H^{1a}$), 3.12 br.s (1H, $H^{12}$), 4.25 br.s (2H, $H^{1'}$), 5.15–5.22 m (2H, $H^{4'}$), 5.55 s (1H, $H^{14}$), 7.18–7.36 m (5$H_{arom}$), 7.60 s (1H, $H^{3'}$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 15.90 ($C^{19}$), 16.60 ($C^{18}$), 17.18 ($C^{9}$), 20.01 ($C^{17}$), 20.55 ($C^{16}$), 21.27 ($C^{6}$), 27.88 ($C^{11}$), 32.89 ($C^{15}$), 34.75 ($C^{3}$), 36.70 ($C^{5}$), 37.14 ($C^{8}$), 37.88 ($C^{12}$), 38.11 ($C^{10}$), 38.18 ($C^{10a}$), 39.87 ($C^{4b}$), 41.28 ($C^{2}$), 46.77 ($C^{7}$), 50.55 ($C^{6a}$), 54.85 ($C^{10b}$), 55.11 ($C^{4'}$), 55.85 ($C^{4a}$), 57.77 ($C^{1'}$), 60.55 ($C^{1a}$), 124.11 ($C^{3'}$), 125.47 ($C^{14}$), 127.00 ($C_{arom}$), 127.11 ($C_{arom}$), 127.14 ($C_{arom}$), 128.02 ($C_{arom}$), 134.00 ($C_{arom}$), 135.16 ($C_{arom}$), 146.84 ($C^{2'}$), 149.11 ($C^{13}$), 178.59 ($C^{20}$), 207.21 ($C^{1}$), 209.00 ($C^{4}$). Found, %: C 74.00; H 7.90; N 7.00. $C_{36}H_{45}N_3O_4$. Calculated, %: C 74.07; H 7.77; N 7.20.

**(1-Hexyl-1*H*-1,2,3-triazol-4-yl)methyl 13-isopropyl-7,10a-dimethyl-1,4-dioxohexadecahydro-1*H*-4b,12-ethenochrysene-7-carboxylate (6).** Yield 0.36 g (80%), mp 113–115°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.57 s (3H, $H^{18}$), 0.65–0.80 m (2H, $H^{6a,e}$), 0.85 s (3H, $H^{9'}$), 1.02 d (3H, $H^{16}$, *J* 6.9 Hz), 1.05 d (3H, $H^{17}$, *J* 6.9 Hz), 1.18 s (3H, $H^{19}$), 1.20–1.66 m (12H, $H^{5a,e}$, $H^{6b}$, $H^{8a,e}$, $H^{9a,e}$, $H^{10a,e}$, $H^{10b}$, $H^{11a,e}$), 1.70–1.88 m (6H, $H^{6'}$, $H^{7'}$, $H^{8'}$), 2.00 br.s (2H, $H^{5'}$), 2.20 s (1H, $H^{4a}$), 2.40 t (1H, $H^{15}$, *J* 6.2 Hz), 2.50–2.62 m (4H, $H^{2}$, $H^{3}$), 2.78 br.s (1H, $H^{1a}$), 3.22 br.s (1H, $H^{12}$), 4.42 br.s (2H, $H^{1'}$), 5.20–5.35 m (2H, $H^{4'}$), 5.54 s (1H, $H^{14}$), 7.77 s (1H, $H^{3'}$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 13.94 ($C^{9'}$), 15.88 ($C^{19}$), 16.70 ($C^{18}$), 16.98 ($C^{9}$), 19.89 ($C^{17}$), 20.53 ($C^{16}$), 21.23 ($C^{6}$), 22.42 ($C^{8'}$), 26.00 ($C^{7'}$), 27.75 ($C^{11}$), 29.84 ($C^{6'}$), 31.11 ($C^{5'}$), 32.89 ($C^{15}$), 34.66 ($C^{3}$), 36.76 ($C^{5}$), 36.99 ($C^{8}$), 37.88 ($C^{12}$), 38.12 ($C^{10}$), 38.16 ($C^{10a}$), 38.98 ($C^{4b}$), 41.22 ($C^{2}$), 46.72 ($C^{7}$), 49.92 ($C^{6a}$), 50.98 ($C^{4'}$), 54.85 ($C^{10b}$), 55.85 ($C^{4a}$), 60.58 ($C^{1a}$), 57.80 ($C^{1'}$), 125.54 ($C^{3'}$), 126.92 ($C^{14}$), 146.80 ($C^{2'}$), 148.25 ($C^{13}$), 178.55 ($C^{20}$), 208.01 ($C^{1}$), 209.16 ($C^{4}$). Found, %: C 73.02; H 9.14; N 7.50. $C_{35}H_{51}N_3O_4$. Calculated, %: C 72.75; H 8.99; N 7.27.

## ACKNOWLEDGMENTS

Structural investigations of compounds **3–6** were performed in the Center of joint usage "Agidel" at the Institute of Petrochemistry and Catalysis of the Russian Academy of Sciences. Study was performed under the financial support of the Russian Science Foundation (grant no. 16-13-10051).

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