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Copper catalyzed alkyne–azide cycloaddition with 3-propargyl-γ-butyrolactones

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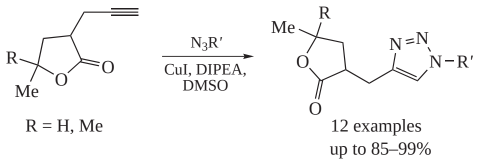
Copper catalyzed [2+3] cycloaddition of 3-propargyl-γ-butyrolactones with azides affords the corresponding 1,2,3-triazoles connected with lactone moiety in high yields. In the presence of air and copper(I) halides, the starting propargylated lactones are prone to dimerize to form bis-lactone diynes.



γ-Butyrolactone is known to be important structural unit of various molecules of natural origin of both animal and plant world. Significant interest towards lactone containing compounds is explained by their high biological activity. The chemistry of lactones counts more than a century of history, nevertheless the isolation of such substances from natural sources and identification of their structures are intensively studied up to now. For example, lactone derived glycoside **1** isolated from the aerial part of *Sibrae angustate* RCHD has the effect of weight loss,[1] Penicillactone isolated from marine fungus *Penicillinum sp.* PSU-F44 displays a stable antimicrobial activity against *Staphylococcus aureus*,[2] sesquiterpene lactone Zawadckiinolid F **3** inhibits LPS,[3] and Paramignyosides A–E (having general skeleton **4**) isolated from *Paramignya scandens* exhibits a pronounced anti-inflammatory effect[4] (Figure 1). In recent years, synthetic modifications of lactone containing compounds have been actively investigated in view of practical interest in pharmacology and medicine.[5–8]

Previously, we obtained some functionally substituted butyrolactones and studied their antibacterial and anti-inflammatory activities.[10–12] Continuing research in this area, we selected 3-propargylated lactones **5**, **6** as valuable starting compounds.[10] The presence of the terminal triple bond in their molecules should enable to extend our knowledge in the field of γ-lactone chemistry and move to new chemotypes of lactone-containing compounds. According to published data, lactone derived heterocycles are very attractive molecules, for example, 1,2,4-triazolylbutanolides exhibit both antifungal and hypotensive effects.[13] On the other hand, click reaction is very powerful method to prepare conjugates connected *via* triazole ring.[14] Moreover, 1,4-disubstituted triazole ring mimics *trans*-amide bond.[15]

Herein, we performed the click reaction of 3-propargyl-γ-butyrolactones **5**, **6** with organic azides (Scheme 1). In fact, the cycloaddition efficiently proceeded in DMSO in the presence of diisopropylethylamine (DIPEA) and copper(I) iodide in argon atmosphere to afford triazoles connected with lactone ring **9–16**

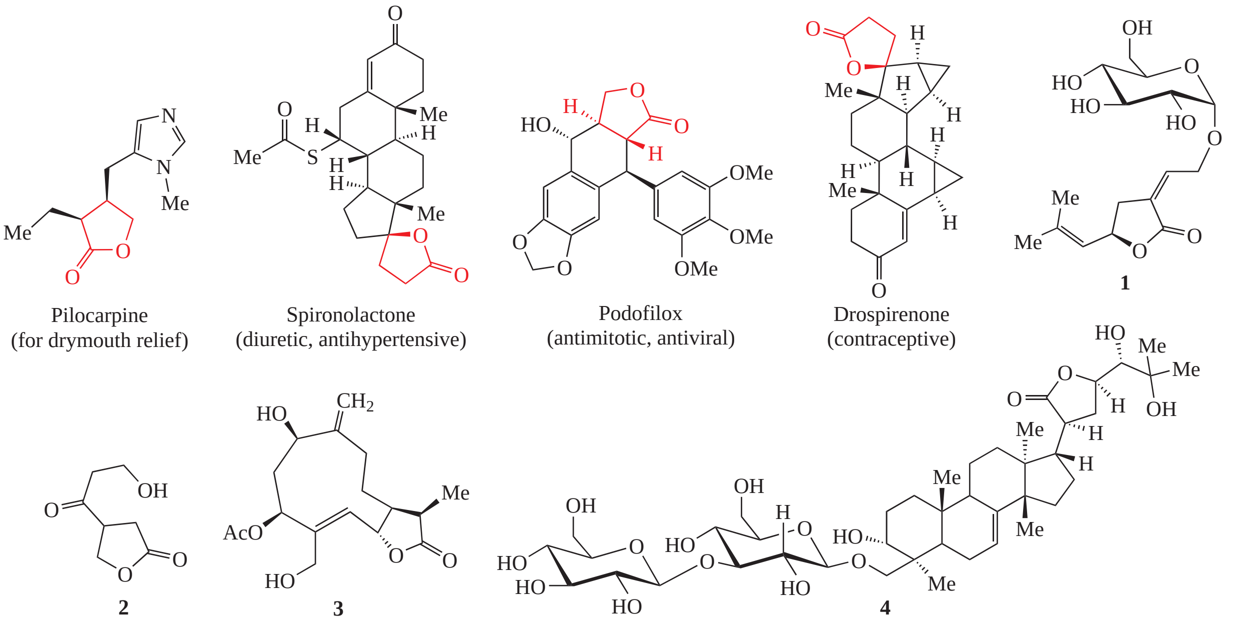
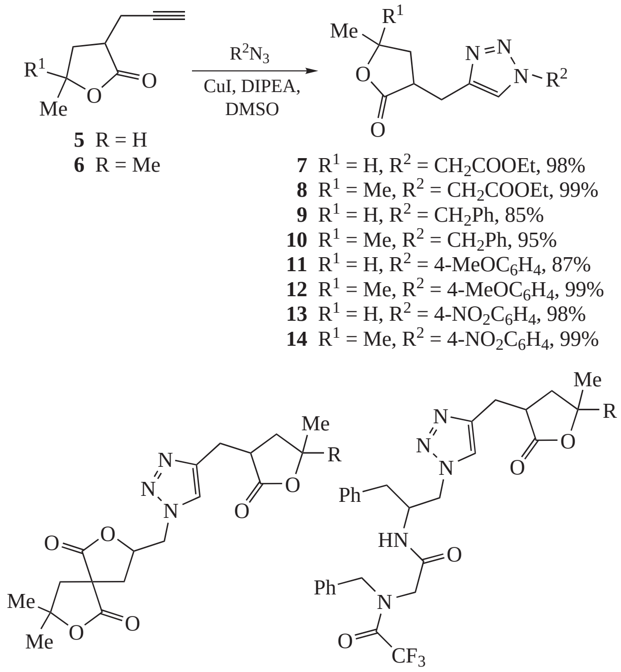

Pilocarpine
(for drymouth relief)
Spironolactone
(diuretic, antihypertensive)
Podofilox
(antimitotic, antiviral)
Drospirenone
(contraceptive)
1
2
3
4

Figure 1 Some examples of lactone derived drugs and bioactive natural compounds.

in 85–99% isolated yields.[†] The reaction has broad synthetic scope allowing one to involve both alkyl- and arylazides into alkyne azide cycloaddition.

Keeping in mind the possibility of preparing more complex conjugates, we also studied the synthesis of triazoles from functionalized azides bearing spirodilactone and peptide fragments.[16–18] In this way, compounds **15–18** were accessed (see Scheme 1).[‡]

During the optimization of this reaction, we found that yields of the target triazoles dropped down significantly when the reaction was performed in contact with air. It was proposed that oxidative dimerization of starting alkynes is a possible reason for this phenomenon. To confirm this suggestion, the Glaser dimerization of alkynes **5**, **6** was carried out in contact with air and copper(I) halides to cleanly obtain diynes **19**, **20** (Scheme 2).[§] Such compounds incorporating lactone fragments connected with diyne are attractive to study their biological activity due



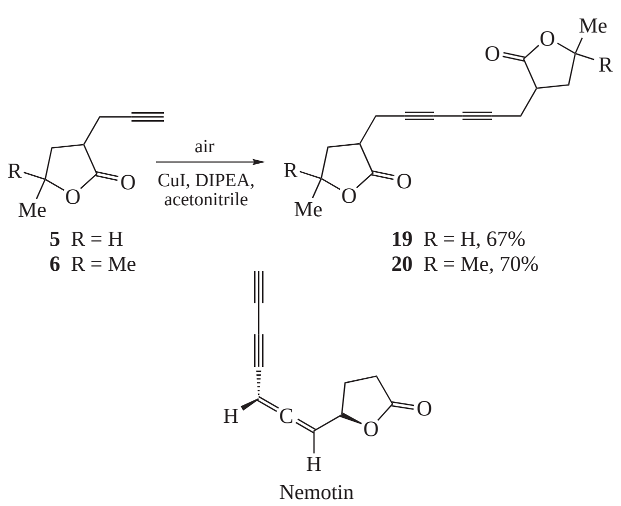
5 R = H
6 R = Me

7 R^1 = H, R^2 = CH_2COOEt, 98%
8 R^1 = Me, R^2 = CH_2COOEt, 99%
9 R^1 = H, R^2 = CH_2Ph, 85%
10 R^1 = Me, R^2 = CH_2Ph, 95%
11 R^1 = H, R^2 = 4-$MeOC_6H_4$, 87%
12 R^1 = Me, R^2 = 4-$MeOC_6H_4$, 99%
13 R^1 = H, R^2 = 4-$NO_2C_6H_4$, 98%
14 R^1 = Me, R^2 = 4-$NO_2C_6H_4$, 99%

15 R = H, 86%
16 R = Me, 82%

17 R = H, 87%
18 R = Me, 93%

Scheme 1



5 R = H
6 R = Me

19 R = H, 67%
20 R = Me, 70%

Nemotin

Scheme 2

[†] *1,2,3-Triazole lactones* **7**–**18** *(general procedure)*. A 3 ml vial with a screw cup was charged with the corresponding azide (1.1 mmol), DMSO (2 ml), DIPEA (0.142 g, 1.1 mmol), CuI (0.019 g, 0.1 mmol) and the corresponding 3-propargyl-γ-butyrolactone (1 mmol) and heated at 65 °C for 5 h. The mixture was poured into 0.1 M HCl (30 ml) and extracted with CH_2Cl_2 (3×10 ml). The combined extracts were dried over Na_2SO_4, the volatiles were evaporated and the residue was purified *via* column chromatography on silica gel using CH_2Cl_2–MeOH mixture (30 : 1) as an eluent.

*Ethyl 2-{4-[(5-methyl-2-oxotetrahydrofuran-3-yl)methyl]-1*H*-1,2,3-triazol-1-yl}acetate* **7** *(mixture of diastereomers)*. White powder, yield 261 mg (98%), mp 87 °C. IR (ν/cm^{-1}) δ: 1742, 1762 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, 3H, *Me*CH_2O, *J* 7.2 Hz), 1.34 (d, 0.9H, *Me*CH, *J* 6.4 Hz, minor), 1.35 (d, 2.1H, *Me*CH, *J* 6.2 Hz, major), 1.64–1.73 (m, 0.7H, major), 2.04–2.11 (m, 0.3H, minor), 2.29–2.36 (m, 0.3H, minor), 2.50–2.56 (m, 0.7H, major), 2.99–3.16 (m, 2H, CH_2Het), 3.19–3.28 (m, 1H, CHC=O), 4.26 (q, 2H, MeC*H*$_2$O, *J* 7.2 Hz), 4.45–4.55 (m, 1H, MeC*H*), 5.13 (s, 2H, NCH_2), 7.56 (s, 1H, Het). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 13.6 (Me), 20.3 (major), 20.7 (minor), 25.2 (major), 25.7 (minor), 33.5 (minor), 35.7 (major), 38.9 (minor), 41.2 (major), 50.4 (CH_2N), 61.9 (CH_2O), 74.7 (O*C*HMe, minor), 75.0 (O*C*HMe, major), 123.2 (C=*C*H–N), 144.2 (*C*=CH–N), 165.9 (C=O), 177.7 (C=O, major), 178.0 (C=O, minor). HRMS (ESI), *m*/*z*: 268.1269 [M + H]$^+$ (calc. for $C_{12}H_{18}N_3O_4^+$, *m*/*z*: 268.1292).

For characteristics of compounds **8**–**14**, see Online Supplementary Materials.

[‡] *3,3-Dimethyl-8-({4-[(5-methyl-2-oxotetrahydrofuran-3-yl)methyl]-1*H*-1,2,3-triazol-1-yl}methyl)-2,7-dioxaspiro[4.4]nonane-1,6-dione* **15**. Slightly brown powder, yield 324 mg (86%), mp 115–117 °C, R_F 0.28 (CH_2Cl_2–MeOH, 30 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20–1.28 (m, 3H, Me), 1.34 (s, 2.1H, Me, major), 1.37 (s, 0.9H, Me, minor), 1.44 (s, 2.1H, Me, major), 1.48 (s, 0.9H, Me, minor), 1.49–1.61 (m, 0.6H), 1.94 (dd, 1H, *J* 13.8, 5.2 Hz), 2.04–2.18 (m, 1.4H), 2.23–2.32 (m, 0.2H), 2.33–2.46 (m, 0.7H), 2.50–2.63 (m, 1.7H), 2.76–3.16 (m, 3.6H), 4.35–4.59 (m, 1.8H), 4.63–4.72 (m, 1.2H), 4.87–4.96 (m, 0.3H), 5.08–5.18 (m, 0.7H), 7.53–7.54 (m, 1H, Het). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 20.5 (major), 20.9 (minor), 25.4, 25.5, 25.6, 25.8, 25.9, 28.2 (minor), 28.3 (major), 28.7 (major), 28.9 (minor), 33.8, 33.9, 36.0, 36.1, 36.2, 36.9, 37.0, 38.8, 38.9, 40.6, 41.0, 41.1, 41.2, 43.8, 45.3, 51.6, 51.8, 52.6, 52.7, 53.0, 53.7, 74.82, 74.84, 74.9, 75.1, 75.2, 75.7, 75.8, 76.2, 76.3, 123.3; 144.4 (*C*=CH–N, minor), 144.6 (*C*=CH–N, major), 172.7, 172.8, 173.5, 173.6, 177.7, 177.8, 178.0, 178.1 (C=O). HRMS (ESI), *m*/*z*: 378.1666 [M + H]$^+$ (calc. for $C_{18}H_{24}N_3O_6^+$, *m*/*z*: 378.1660).

N^2*-Benzyl-*N^1*-(1-benzyl-2-{4-[(5-methyl-2-oxotetrahydrofuran-3-yl)methyl]-1*H*-1,2,3-triazol-1-yl}ethyl)-*N^2*-(trifluoroacetyl)glycinamide* **17**. Slightly brown powder, yield 484 mg (87%), mp 73–75 °C, R_F 0.26 (CH_2Cl_2–MeOH, 30 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28–1.32 (m, 3H, Me), 1.56–1.66 (m, 0.7H), 1.96–2.06 (m, 0.3H), 2.14–2.25 (m, 0.5H), 2.33 (br. s, 0.3H), 2.38–2.54 (m, 0.7H), 2.72–3.20 (m, 5.5H), 3.61–3.89 (m, 2H), 4.36–4.70 (m, 6H), 6.67–6.69 (m, 0.6H, Ph), 6.93–7.00 (m, 0.4H, Ph), 7.08–7.34 (m, 10H, Ph, Het, NHCO), 7.46–7.58 (m, 1H, Ph). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –69.17 to –69.20 (m, 1.96F, CF_3), –69.97 to –69.99 (m, 1.04F, CF_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 20.5, 21.0, 25.4, 25.5, 25.9, 26.1, 33.9, 34.0, 35.9, 36.0, 36.2, 36.3, 37.4, 37.5, 37.6, 39.1, 39.2, 41.40, 41.43, 41.48, 41.53, 48.2, 48.3, 48.5, 50.6, 50.7, 50.9, 51.0, 51.1, 51.2, 51.4, 51.6, 51.9, 52.1, 75.15, 75.21, 75.3, 75.4, 75.46, 75.52, 75.6, 116.2 (q, CF_3, *J* 288.2 Hz), 116.3 (q, CF_3, *J* 287.5 Hz), 123.3, 123.6, 123.7, 126.9, 127.0, 127.6, 128.1, 128.3, 128.6, 128.8, 128.9, 128.96, 129.04, 133.79, 133.81, 134.46, 136.37, 136.42, 143.9–144.6 (m, *C*=CH–N), 157.0–157.7 [m, *C*(O)CF_3], 166.40, 166.45, 166.49, 166.54, 178.1, 178.2, 178.4, 178.6 (C=O). HRMS (ESI), *m*/*z*: 558.2333 [M + H]$^+$ (calc. for $C_{28}H_{31}F_3N_5O_4^+$, *m*/*z*: 558.2323).

For characteristics of compounds **16**, **18**, see Online Supplementary Materials.

[§] *Diynes* **19** *and* **20** *(general procedure)*. A mixture of the corresponding 3-(prop-2-ynyl)dihydrofuran-2(3*H*)-one **5** or **6** (0.01 mol) triethylamine (0.03 mol) in MeCN (3 ml) was stirred at room temperature for 15 min, then CuI (0.02 mmol) was added. The mixture was stirred at room temperature for 1 h in contact with air and then under reflux for 5 h. The mixture was cooled, diluted with water (20 ml) and extracted with Et_2O (3×10 ml). The combined extracts were dried over $MgSO_4$, the volatiles were evaporated. The resulting crystals were washed with water and recrystallized.

to structural similarity with natural lactone Nemotin exhibiting a broad spectrum of antimicrobial activity.[9,19] The dimerization can be performed in acetonitrile, DMF or DMSO, the best results (yields up to 70%) having been achieved in acetonitrile.

In conclusion, synthesis of triazole–lactone conjugates has been elaborated using copper catalyzed acetylene–azide cycloaddition based on propargylated lactones. These results open an access to a variety of new promising biomolecules.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.007.

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*3,3'-(Hexa-2,4-diyne-1,6-diyl)bis[5-methyldihydrofuran-2(3*H*)-one]* **19**. Light yellow amorphous compound, yield 0.92 g (67%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.26–1.56 (m, 6H, 2Me), 1.64–1.85 (m, 1H, CH), 2.01–2.18 (m, 1H, CH), 2.24–2.43 (m, 2H, CH_2), 2.43–2.66 (m, 4H, 2CH_2), 2.20–3.02 (m, 2H, CH_2), 4.41–4.60 (m, 1H, CH), 4.63–4.80 (m, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.9, 19.5, 20.4, 20.8, 33.4, 35.3, 37.9, 40.2, 69.8, 69.9, 70.2, 74.8, 74.9, 176.6 (C=O), 177.0 (C=O). HRMS (ESI), *m*/*z*: 275.1289 [M + H]$^+$ (calc. for $C_{16}H_{19}O_4^+$, *m*/*z*: 275.1278).

For characteristics of compound **20**, see Online Supplementary Materials.