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Efficient synthesis of triazole-containing spiro dilactones

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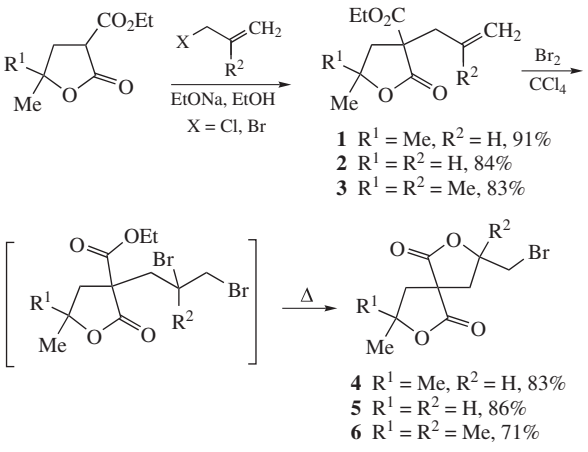
3-Bromomethyl-2,8-dioxaspiro[4.4]nonane-1,6-diones were efficiently prepared from 3-ethoxycarbonyltetrahydrofuran-2-ones. Subsequent conversion of the bromomethyl group into azidomethyl one followed by click reaction with alkynes afforded the multifunctional triazole-containing spiro dilactones in almost quantitative yields.

Molecules bearing sterically-constrained spiro fragment represent many natural products and drugs. Spiro compounds belong to privileged structures which are widely used to increase the success rate of the drug discovery process.[1] New approaches to the synthesis of spiro compounds appeared last time including enantioselective methodologies (see, *e.g.*, the recent reviews[2]). Among these compounds spiro lactones attract significant attention. For example, Spironolactone, Cantrenone and Mexrenone are used in medicine as potassium-sparing diuretics for edema associated with impaired cardia activity, liver cirrhosis, nephrotic syndrome and edema of different origin. Obviously, search and development of new methods of synthesis of spiro cyclic fragments with different structures[3] and in particular, access to such derivatives bearing an additonal functional group[4(a)–(c)] are challenging and important tasks.

This study is devoted to the synthesis of 3-bromomethyl substituted spiro lactones based on simple starting materials. We anticipated that bromomethyl group can be further converted into azidomethyl one which is a good candidate for copper-catalyzed cycloaddition with alkynes.[5]

To prepare the target compounds, we performed allylation of α-ethoxycarbonyl lactones in the presence of sodium ethoxide in ethanol (Scheme 1).[†] Bromination of prepared compounds **1**–**3** in carbon tetrachloride followed by thermal cyclization selectively gave the target spiro lactones **4**–**6** bearing bromomethyl group in high yield, with 5-membered ring only being formed. Products **4**–**6** were obtained as mixtures of diastereomers in 1:1–1.5:1 ratio. These results are in good agreement with Baldwin rules for ring formation. In the case of nucleophilic cyclizations, both 5-*exo-tet* and 6-*exo-tet* cyclizations are favourable.[6] However, it was shown by Houk that γ-butyrolactone is less strained than



Scheme 1

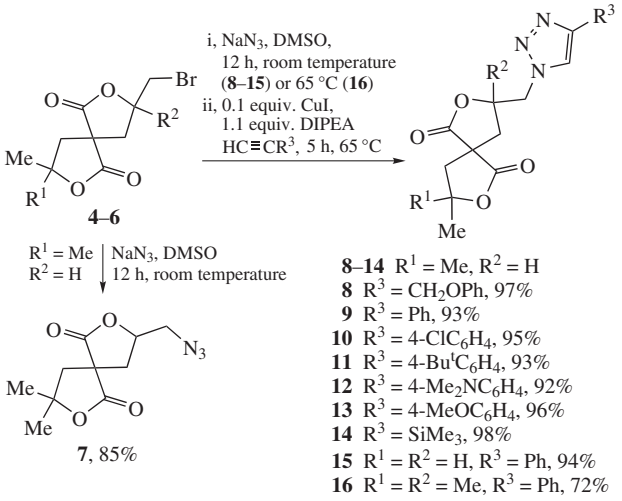
[†] Starting ethyl tetrahydro-2-oxofuran-3-carboxylates were prepared as previously reported.[4(c),(d)]

Ethyl 3-allyl-2-oxotetrahydrofuran-3-carboxylates **1**–**3** *(general procedure)*. Flask was charged with 20 ml of absolute ethanol and sodium (2.3 g, 0.1 mol) was dissolved. Next, the corresponding ethyl 2-oxotetrahydrofuran-3-carboxylate (0.1 mol) was added dropwise with cooling. The mixture was stirred for 15 min and then appropriate allyl halogenide (0.11 mol) was added. Stirring was continued for 2 h at room temperature and then at 75–80 °C until neutral reaction was achieved. Ethanol was evaporated and the residue was acidified by dropwise addition of diluted hydrochloric acid to pH 2–3. The mixture was extracted with diethyl ether, the combined extracts were dried over $MgSO_4$. The volatiles were evaporated and the residue was distilled at reduced pressure.

Ethyl 3-allyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate **1**. Yield 91%, bp 85–86 °C (1 Torr), R_f 0.64 (EtOH–C_6H_6–hexane, 3:3:10); n_D^{20} 1.4550, d_4^{20} 1.0497. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.30 (t, 3H, *Me*CH_2, *J* 7.6 Hz), 1.45 (s, 6H, 2Me), 2.20 and 2.45 (both m, 2H, CH_2 in cycle), 2.56 and 2.82 (both m, 2H, CH_2 non cyclic), 4.22 (m, 2H, Me*C*H_2), 5.05 (m, 1H, C=CH_2), 5.10 (m, 1H, C=CH_2), 5.85 (m, 1H, C*H*=CH_2). IR (ν/cm^{-1}): 1730 (C=O from CO_2Et), 1775, 1755 (C=O from lactone), 1178, 1264 (C–O–C), 1640 (C=C), 3050 (C=CH). Found (%): C, 63.60; H, 8.05. Calc. for $C_{12}H_{18}O_4$ (%): C, 63.70; H, 8.02.

8-Bromomethyl-2,7-dioxaspiro[4.4]nonane-1,6-diones **4**–**6** *(general procedure)*. The corresponding ethyl 3-allyl-2-oxotetrahydrofuran-3-carboxylate **1**–**3** (0.03 mol) was dissolved in 15 ml of CCl_4 and solution of Br_2 (4.8 g, 0.03 mol) in 5 ml of CCl_4 was added dropwise at room temperature keeping the reaction mixture colourless. The mixture was additionally stirred for 15 min, the volatiles were evaporated at reduced pressure. The residue was heated at 15–20 Torr and the cyclization product thus formed was distilled.

8-Bromomethyl-3,3-dimethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione **4**. White powder, yield 83%, bp 170 °C (2 Torr), R_f 0.63 (EtOH–C_6H_6–hexane, 3:3:10), mp 100–101 °C (EtOH–H_2O, 4:1). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ: 1.47 (s, 3H, Me), 1.59 (s, 3H, Me), 2.11–2.24 (m, 1.6H), 2.51 (dd, 0.4H, minor, *J* 13.8 Hz, *J* 7.8 Hz), 2.72–2.83 (m, 1.4H), 2.90 (dd, 0.6H, major, *J* 13.1 Hz, *J* 6.5 Hz), 3.56–3.69 (m, 2H), 4.70–4.78 (m, 0.4H, minor), 5.04–5.09 (m, 0.6H, major). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 28.6 (Me), 29.3 (Me), 33.1, 39.5, 44.6, 54.2 (C_q), 75.6 (CH), 84.3 (C_q), 172.9 (C=O), 173.1 (C=O) (major); 28.5 (Me), 29.4 (Me), 32.0, 38.9, 46.2, 53.3 (C_q), 76.8 (CH), 84.1 (C_q), 173.4 (C=O), 173.7 (C=O) (minor). IR (ν/cm^{-1}): 1775, 1755 (C=O from lactone), 1264, 1178 (C–O–C), 665 (C–Br). Found (%): C, 43.25; H, 4.84; Br, 29.00. Calc. for $C_{10}H_{13}O_4Br$ (%): C, 43.34; H, 4.73; Br, 28.83.



Scheme 2

δ-valerolactone. Therefore, this cyclization is a thermodynamically controlled process.[7]

The reaction of bromide **4** with NaN_3 cleanly proceeded in DMSO at room temperature to give azide **7** in 85% yield as 1.5:1 mixture of diastereomers (Scheme 2).‡ Luckily, subsequent cycloaddition with terminal acetylenes can be successfully performed without isolation of azide **7** under CuI–DIPEA catalysis. Using this one-pot technique, 1,2,3-triazoles **8**–**16** were thus prepared in 92–98% yields. Spiro lactones **5** and **6** were similarly converted into 1,2,3-triazoles **15** and **16** in 94 and 72% yields, respectively. One can explain the somewhat lower yield of **16** by a bulkiness of spiro lactone **6**, which demanded heating during azidation. It should be also mentioned, that all 1,2,3-triazoles **8**–**16** synthesized are formed as a mixture of diastereomers in 1:1–1.5:1 ratio, which is exactly the same as that in starting compounds **4**–**6**.

Thus, we have demonstrated the possibility of using copper-catalyzed azide–alkyne cycloaddition to prepare spiro lactone-1,2,3-triazole conjugates. All steps of synthetic sequence are very efficient, the products obtained seem promising for medicinal chemistry.

‡ *8-Azidomethyl-3,3-dimethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione* **7**. A 3 ml vial with a screw cup was charged with compound **4** (0.139 g, 0.5 mmol), NaN_3 (0.044 g, 0.6 mmol) and 1 ml of DMSO and stirred for 12 h at room temperature. The mixture was poured into 30 ml of water 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 passed through a short silica pad with hexane–CH_2Cl_2 (1:1) to give pure product. White solid (102 mg, 85% yield), mp 45–47 °C, R_f 0.39 (CH_2Cl_2). IR (ν/cm^{-1}): 1749 (O–C=O), 2090 (N_3). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ: 1.46 (s, 3H, Me), 1.57 (s, 3H, Me), 2.12–2.24 (m, 1.6H), 2.43 (dd, 0.4H, minor, *J* 13.6 Hz, *J* 7.5 Hz), 2.64–2.80 (m, 2H), 3.45 (dd, 0.6H, major, *J* 13.6 Hz, *J* 4.5 Hz), 3.57 (dd, 0.4H, minor, *J* 13.2 Hz, *J* 4.7 Hz), 3.70–3.76 (m, 1H), 4.62–4.68 (m, 0.4H, minor), 4.96–5.00 (m, 0.6H, major). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.5 (Me), 29.1 (Me), 37.2, 44.6, 52.7, 53.9 (C_q), 76.1 (CH), 84.3 (C_q), 173.1 (C=O), 173.2 (C=O) (major); 28.3 (Me), 29.2 (Me), 37.4, 45.8, 53.1 (C_q), 53.5, 76.6 (CH), 84.0 (C_q), 173.5 (C=O), 173.8 (C=O) (minor). HRMS (ESI), *m*/*z*: 262.0799 (calc. for $C_{10}H_{13}N_3O_4Na^+$ [M+Na]$^+$, *m*/*z*: 262.0798).

Triazoles **8**–**16** *(general procedure)*. A 3 ml vial with a screw cup was charged with appropriate 8-bromomethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione **4**–**6** (0.139 g, 0.5 mmol), NaN_3 (0.044 g, 0.6 mmol) and 1 ml of DMSO and stirred for 12 h at room temperature. Next, Pr^i_2NEt (0.071 g, 0.55 mmol), CuI (0.0096 g, 0.05 mmol) and the corresponding alkyne (0.6 mmol) were added and the mixture was heated at 65 °C for 5 h. Then the mixture was poured into 30 ml of 0.1 M HCl 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 by column chromatography on silica gel using mixture of CH_2Cl_2 and MeOH (30:1) as an eluent.

*3,3-Dimethyl-8-[(4-phenoxymethyl-1*H*-1,2,3-triazol-1-yl)methyl]-2,7-dioxaspiro[4.4]nonane-1,6-dione* **8**. White powder, yield 180 mg (97%), mp 126–128 °C, R_f 0.25 (CH_2Cl_2–MeOH, 30:1). IR (ν/cm^{-1}): 1749, 1772 (O–C=O). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ: 1.38 (s, 2H, Me, major), 1.43 (s, 1H, Me, minor), 1.49 (s, 2H, Me, major), 1.55 (s, 1H, Me, minor), 1.89 (d, 0.67H, *J* 13.7 Hz), 2.04–2.19 (m, 1H), 2.51–2.69 (m, 1.7H), 2.84 (dd, 0.67H, *J* 13.3 Hz, *J* 6.4 Hz), 4.59 (dd, 0.67H, *J* 14.9 Hz, *J* 5.4 Hz), 4.70–4.77 (m, 1.1H), 4.94–5.01 (m, 0.33H, minor), 5.14 (s, 2H, PhOCH_2), 5.16–5.23 (m, 0.67H, major), 6.91–6.96 (m, 3H, Ph), 7.23–7.27 (m, 2H, Ph), 7.86–7.88 (m, 2H, Ph), 7.77 (s, 0.67H, C_2N_3H, major), 8.62 (s, 0.33H, C_2N_3H, minor). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.4 (Me), 28.8 (Me), 36.9, 43.9, 51.8, 53.1 (C_q), 61.3 (PhO*C*H$_2$), 75.6 (CH), 84.4 (C_q), 114.6, 121.1, 124.3 (C=*C*H–N), 129.4, 144.4 (*C*=CH–N), 157.9 (C_q, Ph), 172.7 (C=O), 172.9 (C=O) (major); 28.3 (Me), 29.0 (Me), 37.1, 45.4, 53.0 (C_q), 53.8, 61.4 (PhO*C*H$_2$), 76.2 (CH), 84.3 (C_q), 144.1 (*C*=CH–N), 158.0 (C_q, Ph), 173.6 (C=O) (minor). Found (%): C, 61.44; H, 5.73; N, 11.15. Calc. for $C_{19}H_{21}N_3O_5$ (%): C, 61.45; H, 5.70; N, 11.31.

*3,3-Dimethyl-8-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-2,7-dioxaspiro[4.4]nonane-1,6-dione* **9**. White powder, yield 158 mg (93%), mp 159–162 °C, R_f 0.29 (CH_2Cl_2–MeOH, 30:1). IR (ν/cm^{-1}): 1751, 1772 (O–C=O). ^{1}H NMR (400.1 MHz, DMSO-d_6) δ: 1.43 (s, 3H, Me), 1.48 (s, 3H, Me), 2.25 (d, 0.67H, *J* 13.8 Hz), 2.36–2.41 (m, 1H), 2.56–2.75 (m, 1.6H), 3.02 (dd, 0.67H, *J* 13.3 Hz, *J* 6.7 Hz), 4.73–4.89 (m, 2H), 5.07–5.13 (m, 0.3H, minor), 5.14–5.21 (m, 0.7H, major), 7.32–7.36 (m, 1H, Ph), 7.43–7.47 (m, 2H, Ph), 7.86–7.88 (m, 2H, Ph), 8.61 (s, 0.3H, C_2N_3H, minor), 8.62 (s, 0.7H, C_2N_3H, major). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 28.3 (Me), 28.4 (Me), 36.5, 43.7, 52.3, 52.4 (C_q), 76.5 (CH), 84.5 (C_q), 122.0 (C=CH–N), 125.2, 127.9, 128.9, 130.5 (C_q, Ph), 146.5 (C=CH–N), 173.4 (C=O), 173.6 (C=O) (major); 28.1 (Me), 28.5 (Me), 36.8, 44.4, 53.5 (C_q), 53.7, 76.8 (CH), 84.2 (C_q), 122.1 (C=CH–N), 125.2, 127.9, 128.9, 130.5 (C_q, Ph), 146.5 (C=CH–N), 173.8 (C=O), 174.5 (C=O) (minor). Found (%): C, 63.57; H, 5.68; N, 12.03. Calc. for $C_{18}H_{19}N_3O_4$ (%): C, 63.33; H, 5.61; N, 12.31.

For more details, see Online Supplementary Materials.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.005.

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