Efficient synthesis of triazole-containing spiro dilactones

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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 reviews2). 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 cardiac 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 structures3 and in particular, access to such derivatives bearing an additional functional group4–6 is 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-anticipated that bromomethyl group can be further converted into azidomethyl one which is a good candidate for copper-

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3-Bromomethyl-2,8-dioxaspiro[4.4]nonane-1,6-diones were efficiently prepared from 3-ethoxycarbonyl tetrahydrofuran-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.

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δ-valerolactone. Therefore, this cyclization is a thermodynamically controlled process.\(^2\)

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 mixture of diastereomers (Scheme 2).\(^2\) Luckily, subsequent cyclo-

Δ2-Azidomethyl-3,3-dimethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione 7. A 3 ml vial with a screw cap 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\(_2\)Cl\(_2\) (3x10 ml). The combined extracts were dried over Na\(_2\)SO\(_4\), the volatiles were evaporated and the residue was purified by column chromatography with hexane–CH\(_2\)Cl\(_2\) (1:1) to give pure product. White solid (102 mg, 85% yield), mp 45–47°C.

\[\text{IR} (\text{v/cm}^{-1}): 1749 (\text{O–C=O}), 2090 (\text{N≡C})\]

\[\text{1H NMR (400.1 MHz, CDCl}\_3, J = 13.2 \text{Hz,} \text{H}, \text{Me}, 13.7 \text{Hz,} \text{J} = 2.04–2.19 (m, 1H), 2.51–2.69 (m, 1H), 2.64–2.80 (m, 2H), 3.57 (dd, 0.4 Hz, 1H, minor), 4.70–4.77 (m, 1.1H), 4.94–5.01 (m, 0.33 H, 0.57–5.13 (m, 0.3 H, minor), 5.4 Hz, 1H, minor), 4.70–4.77 (m, 1.1H), 4.94–5.01 (m, 0.33 H, 0.57–5.13 (m, 0.3 H, minor), 5.4 Hz, 1H, minor).

\[\text{13C NMR (100.6 MHz, CDCl}\_3, J=13.8 \text{Hz,} \text{C}, 76.5 \text{Hz,} \text{C}, 84.0 \text{Hz,} \text{C}, 73.5 \text{Hz,} \text{C}, 173.8 \text{Hz,} \text{C})\]

\[\text{HRMS (ESI), m/z: 262.0799} \quad \text{(calc. for } \text{C}_9\text{H}_9\text{N}_3\text{O}_4\text{Na}^+ [M+Na]+, m/z: 262.0798)\]

**Triazoles 8-16 (general procedure).** A 3 ml vial with a screw cap 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\(_2\)NEt (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 1 M HCl and extracted with CH\(_2\)Cl\(_2\) (3x10 ml). The combined extracts were dried over Na\(_2\)SO\(_4\), the volatiles were evaporated and the residue was purified by column chromatography on silica gel using mixture of CH\(_2\)Cl\(_2\) and MeOH (9:1) as an eluent.

**Scheme 2**

**References**


