Synthesis of dihydro-2*H*-pyran-3(4*H*)-one

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Abstract
A practical synthetic procedure for the synthesis of dihydro-2*H*-pyran-3(4*H*)-one is reported. The method commenced from the readily available α-ketoglutaric acid and allowed preparation of the title compound in four steps in 31% overall yield.

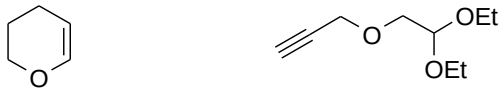
Keywords: Oxygen compounds, heterocycles, cyclization, ketones, pyran

Introduction

A careful choice of the chemotype used as the starting point of drug discovery seems to gain momentum in recent medicinal chemistry studies. A number of papers have appeared which address the question of the properties desirable in potential biologically active substances through comparative analysis with launched drugs and natural compounds.[1–5] Apart from the widely accepted physicochemical parameters such as molecular weight or calculated LogP,[6] there is an enhanced interest in such properties as conformational restriction (measured as number of rotatable bonds), fractional sp^3 character (Fsp^3) and distribution of different heteroatom types.[3-5,7] In particular, it was shown by Fecher and Schmidt[5] that current combinatorial collections suffer from a low ratio of oxygen atoms to all heavy atoms compared with both drugs and natural compounds. In this view, saturated conformationally restricted oxygen-enriched building blocks of low molecular weight and lipophilicity are of particular interest.

Implementation of these ideas leads to saturated oxygen heterocycles such as tetrahydropyran as key structural motifs. Dihydro-2*H*-pyran-3(4*H*)-one (**1**) is an appropriate example which has already proven its utility as a building block in the synthesis of α-amino acids,[8] histamine H3 receptor antagonists,[9] modulators of the AMPA receptor,[10] thrombin inhibitors,[11] and 5-lipoxygenase inhibitors.[12]

To date, most of the approaches to the synthesis of **1** reported in the literature have relied on the functionalization of the double bond in dihydropyran (**2**) (Figure 1).[13] Their major drawback was moderate regioselectivity which led to low yields and problems with purification of the product. Another method which also suffered from low yield and tedious purification of the product commenced from the alkyne **3**.[14]

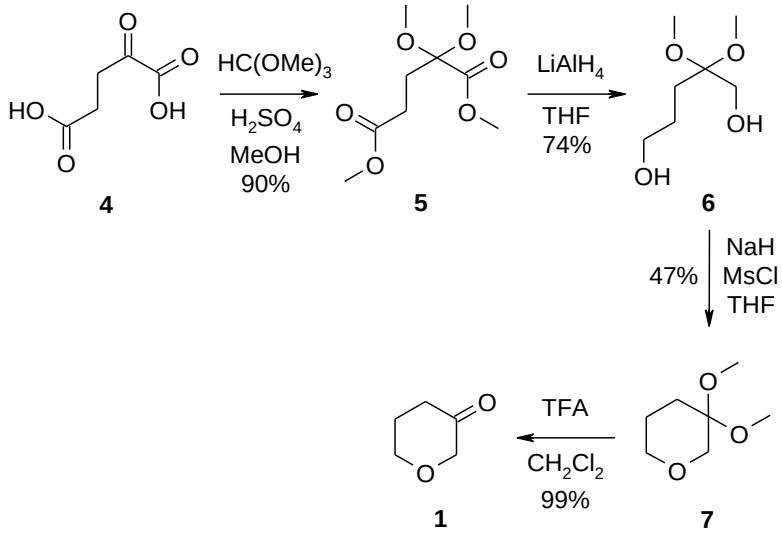


2 **3**

Figure 1. Synthetic precursors of **1** reported in the literature.

Results and Discussion

In this work we describe a different reaction sequence which starts from the readily available α-ketoglutaric acid (**4**) (Scheme 1). In the first step, compound **4** is transformed into the ketal ester **5** in 90% yield by the action of trimethyl orthoformate and sulfuric acid in absolute methanol. The compound **5** was reduced with $LiAlH_4$ to give the diol **6** in 74% yield. The pyran ring was then closed by mesylation of the dianion obtained from **6** to give the tetrahydropyran derivative **7** (47%). Acidic hydrolysis of **7** led to the formation of dihydro-2*H*-pyran-3(4*H*)-one (**1**) in 99% yield. The overall reaction sequence included four steps and gave the target compound in 31% yield starting from **4**. It should be noted that only distillation was used for the purification of the products in all the steps. Hence the method reported herein is suitable for the multigram preparation of **1**.



4 **5** **6** **7** **1**

Scheme 1. Synthesis of dihydro-2*H*-pyran-3(4*H*)-one (**1**).

Experimental Section

General. The solvents were purified according to standard procedures. All starting materials were purchased from Acros, Merck and Fluka. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons and 124.9 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University. Mass spectra were recorded on an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

Dimethyl 2,2-dimethoxypentanedioate (**5**). The procedure for the preparation of **5** is updated from the literature data.[15] Ketoglutaric acid (**4**) (150 g, 1.03 mol) and trimethyl orthoformate (400 mL) were dissolved in MeOH (1.2 L), and H_2SO_4 (25 mL) was added. The reaction mixture was refluxed with stirring for 15–20 h and then cooled. Saturated aqueous $NaHCO_3$ was added carefully until the gas evolution ceased. The reaction mixture was evaporated *in vacuo*, and the residue was extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was distilled *in vacuo*. Yield 205 g (90%). Colourless oil. Bp 111–112 °C / 1 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H), 3.48 (s, 3H), 3.08 (s, 6H), 2.10–2.13 (m, 2H), 2.00–2.03 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.5, 168.7, 101.2, 52.1, 51.3, 49.6, 28.6, 27.7. Anal. calc. for $C_9H_{16}O_6$ C 49.09, H 7.32. Found C 49.35, H 7.03. MS (EI): 189 (M^+–OCH_3), 161, 129, 101. For spectral and physical data, see also ref. 15.

2,2-Dimethoxypentane-1,5-diol (**6**). To a suspension of $LiAlH_4$ (73 g) in dry THF (1.4 L), a solution of **5** (205 g, 0.93 mol) in dry THF (450 mL) was added dropwise with effective stirring. The reaction mixture was refluxed for additional 2 h, and then cooled. 10% aq KOH (90 mL) was added dropwise upon effective stirring, followed by water (140 mL). The mixture was refluxed for 0.5 h, then cooled and filtered. The precipitate was washed thoroughly with hot THF (1 L). The combined filtrates were evaporated *in vacuo*. The residue was dissolved in dichloromethane, dried over Na_2SO_4 and evaporated again. The crude product was distilled *in vacuo*. Yield 114 g (74%). Colourless oil. Bp 115–117 °C / 1 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.57–3.60 (m, 2H), 3.51 (d, *J* 5.1 Hz, 2H), 3.36 (br s, 2H), 3.18 (s, 6H), 1.70–1.74 (m, 2H), 1.49–1.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 102.3, 62.3, 60.4, 48.0, 27.9, 26.4. Anal. calc. for $C_7H_{16}O_4$ C 51.20, H 9.82. Found C 51.57, H 9.94. MS (EI): 164 (M^+), 133 (M^+–OCH_3).

3,3-Dimethoxytetrahydro-2*H*-pyran (**7**). The compound **6** (96.8 g, 0.590 mol) was dissolved in absolute THF (450 mL). The resulting solution was slowly added to a suspension of NaH (47.5 g, 60% in mineral oil) in absolute THF (2.8 L) with effective stirring. The resulting mixture was refluxed and stirring for 8 h and left overnight. A solution of mesyl chloride (69 g, 0.602 mol) in THF (450 mL) was added dropwise at rt over 5 h. The reaction mixture was stirred at rt for additional 24 h and then carefully quenched with water (100 mL). The solvent was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (200 mL) and filtered. The filtrate was dried over

Na_2SO_4 and evaporated. The residue was carefully distilled *in vacuo*. Yield 40 g (47%). Colourless liquid. Bp 54–56°C / 3 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.48–3.50 (m, 2H), 3.40 (s, 2H), 3.10 (s, 6H), 1.65–1.68 (m, 2H), 1.54–1.59 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 96.0, 69.4, 67.9, 47.6, 30.6, 23.2. Anal. calc. for $C_7H_{14}O_3$ C 57.51, H 9.65. Found C 57.85, H 9.79. MS (APCI): 146 (M^+), 115 (M^+–OCH_3), 101, 88.

Dihydro-2*H*-pyran-3(4*H*)-one (**1**). Compound **7** (23.5 g, 0.161 mol) was dissolved in dry CH_2Cl_2 (80 mL). The solution was added to a solution of trifluoroacetic acid (40 mL) in dry dichloromethane (40 mL). The resulting mixture was stirred overnight and evaporated *in vacuo*. The residue was triturated with saturated aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined extracts were dried over Na_2SO_4, evaporated and distilled *in vacuo*. Yield 16 g (99%). Colourless liquid. Bp 39–40 °C /3 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 2H), 3.77 (t, *J* 5.2 Hz, 2H), 2.45 (t, *J* 6.8 Hz, 2H), 2.02 (quint, *J* 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 207.5, 74.5, 65.9, 37.4, 24.8. Anal. calc. for $C_5H_8O_2$ C 59.98, H 8.05. Found C 59.71, H 7.72. MS (EI): 100 (M^+), 71, 42. For spectral and physical data, see also ref. 13.

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