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A Facile Synthesis of 2,2-Disubstituted 5-Carbethoxy-2,3-dihydro-4*H*-pyran-4-ones

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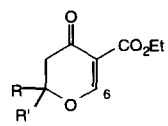
Abstract: A facile synthesis of 5-carbethoxy-2,3-dihydropyran-4-ones is described via the condensation of ethyl 2-formyl-3-oxobutanoate with various ketones.

As part of a program aimed at the synthesis of functionalized 1-oxadecalin systems, we required access to 2,3-dihydro-4*H*-pyran-4-one derivatives of types **1** and **2** that contain an anion stabilizing function at C5. While syntheses of compounds of type **2** have previously been reported by a number of researchers,[1] we were surprised to find that the related systems **1**, having no substituent at C6, were less readily available.[2] Herein, we report an expedient method for the synthesis of this class of compounds.



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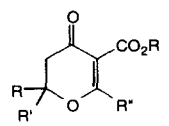
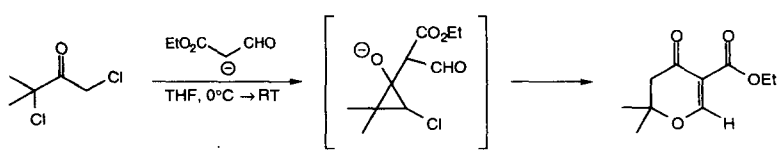


2

To the best of our knowledge, a single preparation of dihydropyrones of type **1** (**1a**: R = R' = Me) has been reported via the Favorskii-type rearrangement of an α,α'-dihaloketone **3** as induced by the enolate of formylacetic ester.[1c] Although the dihydropyrone **1a** is obtained in 53% yield by this method, the considerable instability of the requisite β-formyl esters[3] make this process inconvenient for the routine synthesis of these compounds.



3 **4** **1a**

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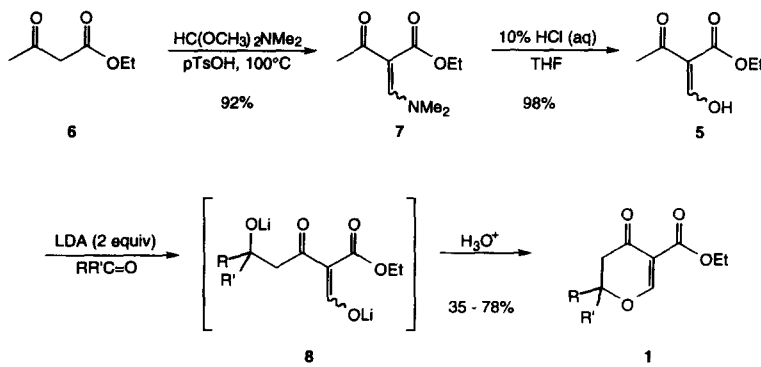
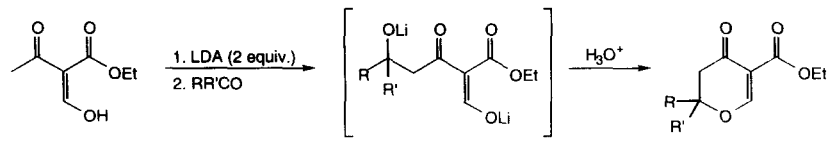
As an alternative strategy, we chose to explore the condensation of various ketones with ethyl 2-formyl-3-oxobutanoate **5**. By this process, we anticipated that the initially formed condensation product would cyclize to provide the desired 2,2-disubstituted dihydropyran-4-one derivatives directly upon acidic workup. Toward this end, ethyl acetoacetate was formylated in a two step process involving aminomethylenation[4] (**7**) and subsequent hydrolysis (aqueous HCl, THF, RT) to the corresponding tricarbonyl derivative **5**. Deprotonation of this intermediate **5** with 2 equivalents of lithium diisopropyl amide (LDA), followed by condensation of the resulting dianion with an appropriate ketone then provided, upon acidic workup, dihydropyrones of type **1**.[5]

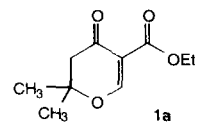
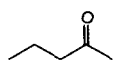
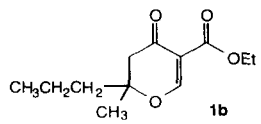
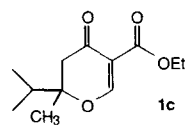
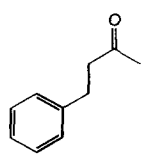
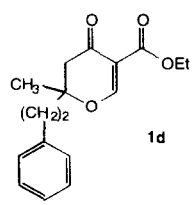
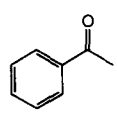
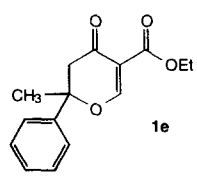
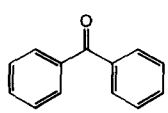
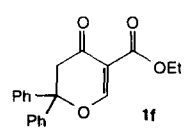


By this method, a variety of 2,2-disubstituted dihydropyran-4-one derivatives have been prepared in good yield as shown in **Table 1**.[6] Inspection of the crude reaction mixtures by ^{1}H NMR suggests that the limiting step in this process is the initial dianion/ketone condensation as evidenced by the presence of unreacted tricarbonyl **5** (e.g. entries 3, 4, and 6). However, in cases where condensation is facile, high yields of the desired dihydropyrones are observed upon acidic workup. The synthesis of ethyl 2,2-dimethyl-2,3-dihydro-4*H*-pyran-4-one (**9**) is representative: To a stirred solution of dry diisopropylamine (1.80mL, 11.7mmol) in 16mL THF under argon was added 2.5M *n*-butyllithium in hexanes (4.9mL, 11.68mmol) at -78°C. After 15 minutes, a solution of ethyl 2-formyl-3-oxobutanoate **5** (0.922g, 5.84mmol) in 4mL THF was added dropwise via cannula, and the resulting orange solution stirred for 30 minutes at -78°C. Freshly distilled acetone (0.81mL, 11mmol) was then added, and the resulting mixture allowed to warm slowly to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl (aq.), and the reaction mixture acidified to pH 5-6 with 10% HCl (aq.) and stirred at room temperature for 45 minutes. The organics were then extracted with ether, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was

Table 1: Synthesis of 2,3-Dihydropyran-4-one Derivatives



5 8 1

entry	RR'CO	product	yield
1		 1a	78%
2		 1b	51%
3		 1c	35%
4		 1d	45%
5		 1e	71%
6		 1f	45%

purified by flash column chromatography (SiO_2; hexanes:EtOAc, 3:1) to afford the dihydropyrone **1a** as a pale yellow oil (0.755g, 78%).

The route described herein represents an expedient approach to the synthesis of 2,2-disubstituted 5-carbethoxy-2,3-dihydropyran-4-one derivatives. We are currently exploring the use of other doubly activated methylene derivatives in this application.

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1 a) Kidd, D. A. A.; Robins, P. A.; Walker, J. A *J. Chem. Soc.* **1953**, 3244-3246. b) Gelin, S.; Gelin, R. *Bull. Chem. Soc., France* **1968**, 288-298. c) Sakai, T.; Miyata, K.; Ishikawa, M.; Takeda, A. *Tetrahedron Lett.* **1985**, *26*, 4727-4730. d) Graindorge, H.; Roussel, C. *Bull. Chem. Soc., France* **1986**, 454-458. e) Jones, R. C. F.; Bhalay, G.; Carter, P. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1715-1716.

2 A CAS substructure search yielded a single example, dihydropyrone **1a**.

3 Sato, M.; Yoneda, N.; Katagiri, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, 672-674.

4 Beck, J. R.; Lynch, M. R. *J. Het. Chem.* **1987**, *24*, 693-695.

5 For a related approach to 4-pyrones see: McCombie, S. W.; Metz, W. A.; Nazareno, D.; Shankar, B. B.; Tagat, J. *J. Org. Chem.* **1991**, *56*, 4963-4967.

6 All new compounds gave satisfactory spectral and analytical data (^1H NMR, ^{13}C NMR, IR, HRMS). Selected spectral data: **1b**: ^1H NMR (300MHz, $CDCl_3$) δ 8.20 (1H, s), 4.22 (2H, q, *J* = 7.1 Hz), 2.41-2.67 (2H, m), 1.68 (2H, m), 1.38 (3H, s), 1.28 (3H, t, *J* = 7.1 Hz), 1.18-1.43 (2H, m), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 187.14, 169.31, 163.29, 109.02, 86.17, 60.21, 46.35, 41.14, 23.09, 16.56, 14.05, 13.93; IR (neat) ν_{max} 1742, 1702, 1586 cm^{-1}. **1c**: ^1H NMR (300MHz, $CDCl_3$) δ 8.16 (1H, s), 4.17 (2H, q, J = 7.1 Hz), 2.30-2.64 (2H, m), 2.00 (1H, m), 1.25 (3H, s), 1.23 (3H, t, *J* = 7.1 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 187.38, 169.38, 163.35, 109.04, 88.95, 60.27, 43.99, 35.71, 19.05, 16.84, 16.49, 14.11; IR (neat) ν_{max} 1742, 1702, 1586 cm^{-1}. **1d**: ^1H NMR (300MHz, $CDCl_3$) δ 8.22 (1H, s), 7.20 (5H, m), 4.24 (2H, q, *J* = 7.1 Hz), 2.69 (3H, m), 2.50 (1H, d, *J* = 16.0 Hz), 2.02 (2H, m), 1.45 (3H, s), 1.29 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 187.00, 169.28, 163.38, 140.49, 128.51 (2C), 128.14 (2C), 126.18, 109.36, 85.81, 60.47, 46.51, 40.95, 29.65, 23.19, 14.20; IR (neat) ν_{max} 1740, 1700, 1586 cm^{-1}. **1e**: ^1H NMR (300MHz, $CDCl_3$) δ 8.28 (1H, s), 7.28 (5H, m), 4.16 (2H, q, *J* = 7.0 Hz), 3.03 (1H, d, *J* = 16.2 Hz), 2.83 (1H, d, *J* = 16.0 Hz), 1.68 (3H, s), 1.22 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 186.24, 169.12, 163.00, 141.16, 128.57 (2C), 128.13, 124.30 (2C), 110.26, 86.48, 60.30, 47.35, 27.84, 14.01; IR (neat) ν_{max} 1740, 1702, 1579 cm^{-1}. **1f**: ^1H NMR (300MHz, $CDCl_3$) δ 8.36 (1H, s), 7.32 (10H, m), 4.18 (2H, q, *J* = 7.0 Hz), 3.31 (2H, s), 1.25 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 186.10, 169.18, 163.02, 141.06 (2C), 128.58 (4C), 128.43 (2C), 126.0 (4C), 111.13, 89.67, 60.54, 47.63, 14.12; IR (neat) ν_{max} 1740, 1702, 1578 cm^{-1}.