



## Synthesis of Novel $\gamma$ -Ketoesters from Succinic Anhydride

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Four alkyl  $\gamma$ -keto hexanoates (**3a-3d**) have been prepared from succinic anhydride employing a three step reaction strategy. In the first step using *p*-toluene sulfonic acid as catalyst, the ring of succinic anhydride was opened with isopropyl, isobutyl, isopentyl and benzyl alcohols, respectively to form alkyl hydrogen succinates (**1a-1d**). In the 2nd step these alkyl hydrogen succinates on treatment with  $\text{SOCl}_2$  yielded 4-alkoxy-4-ketobutanoyl chlorides (**2a-2d**). The acid halides thus obtained, on reaction with diethyl cadmium led to require  $\gamma$ -ketoesters. All the synthesised compounds were characterized by recording and analyzing  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, IR spectra and mass measurements.

**Key Words:**  $\gamma$ -Ketoesters, Isopentyl  $\gamma$ -keto hexanoate, Succinic anhydride, Isobutyl alcohol.

### INTRODUCTION

$\gamma$ -Keto-esters are used in the preparation of lactam antibiotics<sup>1</sup>, isoquinolines<sup>1</sup>, lactonic sex pheromones<sup>1,2</sup>, furans<sup>1,3</sup>, benzotropolones<sup>4</sup>, alkoxythiophenes<sup>5</sup> and other heterocycles<sup>6</sup>. They are used as intermediates in the preparation of cyclopentenone<sup>3</sup>, natural flavor<sup>2</sup> and useful building blocks of pharmaceutical interest<sup>3</sup>. Moreover, they are converted to butyrolactone, its dimer<sup>7</sup>, chiral  $\gamma$ -hydroxyester<sup>8,9</sup>,  $\gamma$ -hydroxycarboxylic acids<sup>6</sup> and chiral auxiliaries in asymmetric synthesis<sup>10,11</sup>. Although many methods have been developed for  $\gamma$ -ketoesters synthesis<sup>12-24</sup>, they often have disadvantages, such as poor yields, expensive starting materials, sensitivity of the esters to hydrolysis in acidic or basic medium and use of expensive catalysts like  $\text{NaAuCl}_4$ <sup>23</sup>,  $\text{Co}(\text{OAc})_2$ <sup>1</sup> and  $\text{Rh}_2(\text{OAc})_4$ <sup>2</sup>. Our objective was thus to develop a new route for the syntheses of  $\gamma$ -ketoesters (**3a-3d**) using inexpensive substrates, solvents and catalysts and to optimize the yield of the products.

### EXPERIMENTAL

All the chemicals were of analytical grade, purchased from E. Merck, Darmstadt, Germany and used as acquired; toluene was dried and stored over sodium metal before use. The purity of the alcohols and succinic anhydride was checked by NMR and IR whereas the purity of thionyl chloride was checked by IR. All the reactions were carried out in an efficient fume hood under dry nitrogen. The chemical splash goggles, Nomex gloves and lab coat were used to minimize the exposure to diethyl cadmium. Melting points were determined using a Gallenkamp digital melting point apparatus and are uncor-

rected. The UV spectrum was recorded in absolute methanol on a IRMECO UV/VIS Model U-2020 spectrophotometer. IR spectra were obtained on a TENSOR 27 FT-IR spectrophotometer supplied by Bruker, Ettlingen, Germany.  $^1\text{H}$  and  $^{13}\text{C}$  NMR (1D, 2D, homo/heteronuclear) spectra were acquired in  $\text{CDCl}_3$  on a Bruker Biospin, AMX 300 MHz FT NMR (300 MHz for  $^1\text{H}$ , 75 MHz for  $^{13}\text{C}$ ) spectrometer. EI-MS were determined with a direct insertion probe on a double-focusing Finnigan MAT 112 at 70 eV. HR-EI-MS measurements were carried out on a JEOL HX 110 spectrometer. Elemental analyses were obtained by Midwest Microlab, Indianapolis, IN. Column chromatography was performed using silica gel (PF<sub>254</sub>, mesh size 60-70), E. Merck, Darmstadt, Germany and thin layer chromatography on pre-coated silica gel plates (20 cm  $\times$  20 cm, 0.2 mm thickness) with UV fluorescence (PF<sub>254</sub>), E. Merck, Darmstadt, Germany; eluting with hexane-EtOAc.

**Alkyl hydrogen succinates (1a-1d). General procedure:** To a single-necked round-bottom flask (100 mL), fitted with a Dean-Stark trap and a reflux condenser and containing a stir bar, succinic anhydride (3.0 g, 30 mmol), anhydrous *p*-toluenesulfonic acid (25 mg) and toluene (15 mL) under nitrogen were added 30 mmol of the alcohols. After 24 h at reflux, the solution was left to cool at 25 °C then poured into a saturated aqueous  $\text{NaHCO}_3$  solution (25 mL) and the aqueous layer was extracted with hexane (3  $\times$  25 mL). The combined organic (toluene and hexane) layers were washed with brine (20 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was removed under vacuum to give a resinous product, which was subjected to column chromatography to afford the pure monoesters.

TABLE-1  
 YIELD, MELTING POINTS AND ELEMENTAL ANALYSIS OF COMPOUNDS 1-2

Compound	Yield (%)	m.p. (°C)	b.p./18 mm (°C)	Elemental analysis (%) found (calcd.)	
				C	H
<b>1a</b>	76	64-65	–	52.49 (52.52)	7.55 (7.56)
<b>1b</b>	77	69-71	–	55.16 (55.10)	8.10 (8.11)
<b>1c</b>	76	75-76	–	57.43 (57.45)	8.57 (8.58)
<b>1d</b>	76	115-116 (Lit.117-119) <sup>25</sup>	–	63.45 (63.47)	5.81 (5.75)
<b>2a</b>	78	–	94-95	–	–
<b>2b</b>	78	–	101-103	–	–
<b>2c</b>	72	–	108-109	–	–
<b>2d</b>	71	–	110-112	–	–

**4-Alkoxy-4-ketobutanoyl Chlorides (2a-2d). Typical procedure:** Compound **1a** (3.6 g, 22.5 mmol) was mixed with thionyl chloride (3.26 mL, 45 mmol) and warmed at 30-40 °C for 3 h. Then the excess of thionyl chloride was removed on a steam bath under reduced pressure to afford a colourless resin (**2a**) which was purified by distillation at reduced pressure and characterized by physical and spectroscopic measurements (Tables 1 and 3).

**Alkyl  $\gamma$ -keto hexanoates (3a-3d). Typical procedure:** Compound **3a** was synthesized by addition of 10 mmol of **2a** (1.78 g) over a period of 10 min to a solution of diethyl cadmium in diethyl ether<sup>27-29</sup>. The mixture was refluxed for six hours and allowed to stand overnight stirring. The reaction mixture was then poured into a beaker (500 mL) containing crushed ice (150 g) and 10 % aqueous H<sub>2</sub>SO<sub>4</sub> (30 mL). It was vigorously stirred using a magnetic stirrer for 5 min. The organic layer was extracted with diethyl ether (3 × 20 mL), washed with 50 % aqueous NaHCO<sub>3</sub> solution (40 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the obtained material was subjected to column chromatography

 TABLE-2  
 YIELD AND BPS OF COMPOUNDS 3a-d FOR COMPARISON

Compound	Yield (%)			b.p./18mm (°C)
	Diethyl cadmium	Gilman reagent	Grignard reagent	
<b>3a</b>	77	29	22	106-107
<b>3b</b>	74	28	21	112-113
<b>3c</b>	72	27	18	118-119
<b>3d</b> <sup>26</sup>	71	23	18	116-117

using an ethyl acetate/hexane [(1:9) → (2:8) → (3:7)] as eluent. The desired product **3a** was obtained after elution with ethyl acetate/hexane (3:7).

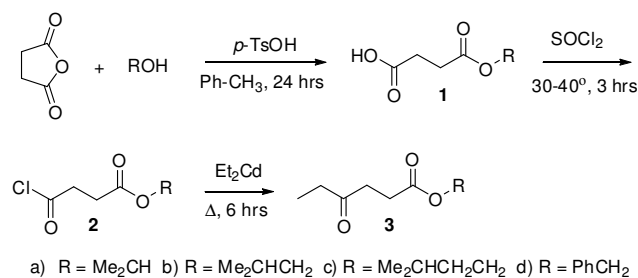
## RESULTS AND DISCUSSION

Reaction of succinic anhydride with alcohols led to alkyl hydrogen succinates **1a-1d** which upon treatment with thionyl chloride afforded the corresponding 4-alkoxy-4-ketobutanoyl chlorides **2a-2d** (Scheme-I). Reaction of **2a-2d** with diethyl cadmium, ethylmagnesium bromide or the corresponding

 TABLE-3  
 SPECTROSCOPIC DATA OF COMPOUNDS 1-3

Comp.	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR ( $\delta$ )	<sup>13</sup> C NMR (DEPT) ( $\delta$ )	HR-EI-MS (m/z)	
				Calcd.	Found
<b>1a</b>	3417 (OH) 1728 (CO <sub>2</sub> H), 1755 (CO <sub>2</sub> R)	2.55 (t, 6.7), 2.72 (t, 6.7), 4.45 (septet, 7.5), 1.1 (d, 7.5)	173.3 (s), 28.2 (t), 36.6 (t), 180 (s), 68.3 (d) 21.2 (q)	160.17	160.15
<b>1b</b>	3438 (OH) 1725 (CO <sub>2</sub> H), 1759 (CO <sub>2</sub> R)	2.55 (t, 6.7), 2.72 (t, 6.7) 4.01 (d, 7.5), 1.18 (septet, 7.5), 1.1 (d, 7.5)	173.3 (s), 28.2 (t), 36.6 (t), 180 (s), 68.3 (t), 26.7 (d), 21.2 (q)	174.19	174.18
<b>1c</b>	3396 (OH), 1722 (CO <sub>2</sub> H), 1765 (CO <sub>2</sub> R)	2.55 (t, 6.7), 2.72 (t, 6.7) 4.45 (d, 7.5), 1.48 (m), 1.77 (m), 1.1 (d, 7.5)	173.3 (s), 28.2 (t), 36.6 (t), 180 (s), 68.3 (t), 36.7 (t), 23.6 (d), 21.2 (q)	188.22	188.24
<b>1d</b>	3324 (OH), 3014 (Ar-H), 1748 (CO <sub>2</sub> R), 1708 (CO)	2.57 (t, 6.7), 2.69 (t, 6.7) 5.2 (s), 7.2-7.3 (Ph)	171.7 (s), 28.3 (t), 35.5 (t), 203.2 (s), 79.1 (t), 128-137, (1C, s, 5C, d)	208.21	208.19
<b>2a</b>	1810 (COCl), 1755 (CO <sub>2</sub> R), 741 (C-Cl)	2.53 (t, 6.7), 2.73 (t, 6.7) 4.5 (septet, 7.5), 1.12 (d, 7.5)	171.4 (s), 28.4 (t), 37.5 (t), 172.6 (s), 66.2 (d), 20.1 (q)	178.61	178.62
<b>2b</b>	1802 (COCl) 1740 (CO <sub>2</sub> R), 734 (C-Cl)	2.56 (t, 6.7), 2.70 (t, 6.7) 4.05 (d, 7.5), 1.47 (m), 1.16 (d, 7.5)	172.2 (s), 27.0 (t), 37.8 (t), 205.2 (s) 64.5 (t), 31.7 (d), 22.1 (q)	192.64	192.65
<b>2c</b>	1807 (COCl) 1739 (CO <sub>2</sub> R), 739 (C-Cl)	2.58 (t, 6.7), 2.74 (t, 6.7) 4.1 (t, 7.5), 1.6 (dt, 7.5), 1.5 (m), 1.1 (d, 7.5)	171.1 (s), 27.5 (t) 36.9 (t), 172.3 (s), 59.9 (t), 37.2 (t) 25.5 (d), 22.2 (q)	206.67	206.66
<b>2d</b>	3094 (Ar-H), 1787 (COCl), 1748 (CO <sub>2</sub> R) 734 (C-Cl)	2.57 (t, 6.7), 2.69 (t, 6.7), 5.2 (s), 7.2-7.3 (Ph)	171.7 (s), 28.3 (t) 35.5 (t), 176.7 (s), 79.1(t), 128-137 (1C, s, 5C, d)	226.66	226.67
<b>3a</b>	1745 (CO <sub>2</sub> R), 1729 (CO), 1210 (C-O)	2.57 (t, 6.7), 2.71 (t, 6.7) 2.49 (t, 7.3), 1.08 (t, 7.3), 4.52 (septet, 7.5), 1.15 (d, 5)	171.2 (s), 27.9 (t), 35.6 (t), 204.5 (s), 34.7 (t), 7.9 (q) 63.7 (d), 22.6 (q)	172.22	172.21
<b>3b</b>	1740 (CO <sub>2</sub> R), 1722 (C=O), 1220 (C-O)	2.56 (t, 6.7), 2.70 (t, 6.7) 2.47 (t, 7.3), 1.07 (t, 7.3), 4.05 (d, 7.5), 1.47(m), 1.16 (d, 7.5)	172.3 (s), 27.0 (t), 37.8 (t), 205.2 (s), 35.2 (t), 8.3 (q), 64.5 (t), 31.7 (d)	186.23	186.24
<b>3c</b>	1739 (CO <sub>2</sub> R), 1717 (C=O), 1225 (C-O)	2.58 (t, 6.7), 2.74 (t, 6.7), 2.51 (q, 7.3), 1.09 (t, 7.3), 4.1 (t, 7.5), 1.6 (dt, 7.5), 1.5 (septet, 7.5), 1.1 (d, 7.5)	173.2 (s), 27.5 (t), 36.9 (t), 202.3 (s), 35.9 (t), 7.7 (q), 59.9 (t), 37.2 (t), 25.5 (d), 22.2 (q)	200.27	200.26
<b>3d</b> <sup>26</sup>	1736 (CO <sub>2</sub> R), 1718 (C=O), 1230 (C-O)	1.05 (t, J = 7.3 Hz, 3 H), 2.48 (q, J = 7.3 Hz, 2 H), 2.65 (t, J = 6.7 Hz, 2 H), 2.74 (t, J = 6.7 Hz, 2 H), 5.15 (s, 2 H), 7.33-7.35 (m, 5 H)	171.7 (s), 28.3 (t), 35.5 (t), 208.2 (s), 36.1 (t), 7.9 (q), 66.1 (t), 128-137, (1C, s, 5C, d)	220.26	220.24

Gilman reagent converted these compounds to alkyl  $\gamma$ -ketoesters **3a-d** (Scheme-I, Table-1).



Scheme-I: Preparation of compounds 1-3

Comparison of the results with the three organometallic reagents is illustrated in Table-2. The yield was highest utilizing the cadmium reagent and no side products were formed. The EI-MS spectrum of the compound showed peak at  $m/z$  57 and was attributed to the loss of keto group from the parent molecule.

The <sup>1</sup>H NMR spectrum of **3a** displayed two new peaks at  $\delta$  1.08 (t,  $J$  = 7.3 Hz, 3H, Me) and at  $\delta$  2.49 (q,  $J$  = 7.3 Hz, 2H, CH<sub>2</sub>CO). Its <sup>13</sup>C NMR spectrum exhibited two extra peaks as compared to **2a** that were identified as CH<sub>3</sub> and CH<sub>2</sub> by DEPT-135 <sup>13</sup>C NMR. The 2D NMR also confirmed the formation of  $\gamma$ -ketoester (**3a**). The physical, spectroscopic and the literature data revealed that isobutyl hydrogen succinate (**1b**) and isopentyl hydrogen succinate (**1c**) have been identified in wine<sup>30</sup>. Benzyl hydrogen succinate (**1d**), m.p. 117-119 °C<sup>25</sup> has been synthesized in 52 % yield by exposure of benzyl  $\beta$ -formyl propionate to air for 30 days. In the series **3a-d** only benzyl  $\gamma$ -ketoester (**3d**) is known<sup>26</sup>. This compound was prepared<sup>26</sup> in low yield (24 %) by reaction of benzyl acrylate with excess propanoyl chloride in the presence of Mg and in DMF as solvent. Our methodology gave **3d** in 71 % overall yield. The spectroscopic data of **3d** are identical with that reported in the literature<sup>26</sup>.

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