COMMUNICATIONS

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A Convenient Direct Method for the Preparation of β-Keto-Acids

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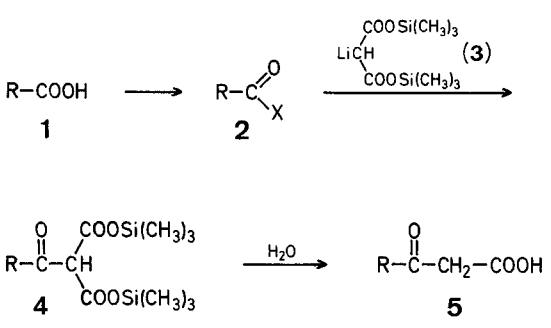
Synthetic β-keto-acids (3-oxoalkanoic acids) have been used extensively for biochemical investigations, especially for studies of the mechanism of (enzyme-induced) decarboxylations[1], for the preparation of ketones[2], and as valuable intermediates in the synthesis of some natural products[3,4,5].

β-Keto-acids have in general been prepared by two methods, i.e., by acidic or basic hydrolysis of the corresponding esters (mostly obtained by acylation of α-anions of appropriate esters)[6], and, more recently and more directly, by acylation of di-anions of suitable carboxylic acids[2,7]. These methods yield satisfactory results for relatively simple β-keto-acids. However, serious difficulties may be encountered in the synthesis of β-keto-acids from carboxylic acid derivatives having base- or acid-sensitive groups.

In an early stage of our total synthesis of the antibiotic malonomicin[5], we were interested in the formation of a β-keto-acid derived from aminomalonic acid. Conventional methods for the preparation of this acid from suitable precursors were troublesome. To overcome the problems connected with the base-sensitivity of the protective groups in the starting material, we developed a direct synthesis (which is related to investigations of Schmidt and Schwochau[8]) which affords the desired product[5] in high yield and high purity. This result shows that the new method in principle is compatible with the presence of functional groups which are susceptible to attack by reagents usually employed in the synthesis of β-keto-acids.

In order to investigate the scope of our method, we applied it to the synthesis of a series of both purely aliphatic and aryl-substituted 3-oxoalkanoic acids (see Table). The carboxylic acids **1** were converted into acid chlorides **2** (or other suitable activated derivatives) and submitted to the reaction with the mono-anion of bis[trimethylsilyl] malonate **(3)**[8] at 0°. Subsequent short treatment with water at room temperature led to hydrolysis and decarboxylation of the intermediate triacyl compound **4** to yield the β-keto-acid **5**, obtained as a pure solid compound by suction filtration or extraction and recrystallization.



By using a 100% excess of **3** (the excess is consumed by the acidic **4**), the yields of **5** could be improved to >90% in several cases. The less satisfactory results obtained in some cases are probably due to steric hindrance **(5b,i)** or to good water solubility **(5c)** of the product.

In the case of **5a** it was found that comparable results may also be obtained with other activated carboxylic acid derivatives **2** such as mixed anhydrides (acyl carbonates) and *O*-1-benzotriazolyl derivatives (1-acyloxybenzotriazoles).

As has been observed[8], this type of reaction can also be applied to the preparation of β-keto-esters by using the anion of ethyl trimethylsilyl malonate. Again in this case it is recommendable to use two equivalents of the malonate anion in order to obtain high yields. Thus, the reaction with 3-ethoxypropanoyl chloride gives ethyl 5-ethoxy-3-oxopentanoate (a useful component in Robinson anellations[9]) in 90% yield.

β-Keto-acids (5); General Procedure:

A 1.56 normal solution (6.5 ml) of butyllithium in hexane is added over 10 min to a stirred solution of bis[trimethylsilyl] malonate[8] (2.48 g, 10 mmol) in dry ether (20 ml) under a nitrogen atmosphere at −60°. The mixture is then allowed to warm to 0° and a solution of the carboxylic acid derivative **2** (5 mmol) in dry ether or tetrahydrofuran (10 ml) is added in one portion. The mixture is stirred for another 10 min at 0° and then shaken thoroughly with cold 5% aqueous sodium hydrogen carbonate (50 ml) during 5–10 min. The aqueous layer is acidified to pH 1–2 with cold 4 normal sulfuric acid or concentrated citric acid solution, and extracted several times with ether or ethyl acetate. The extract is dried with magnesium sulfate and evaporated in vacuo at room temperature to give the crude β-keto-acid. To remove minor amounts of malonic acid (present especially after extraction with ethyl acetate), the products are redissolved in benzene and the solutions filtered **(5a–e)**, or they are washed with a small quantity of water **(5f, g, h)**. Evaporation of the solvent or the adhering water in vacuo at room temperature leaves the acid **5** as a colourless solid which is almost pure according to ^{1}H-N.M.R. analysis. The product is recrystallized from benzene/petroleum ether **(5b–f)** or from methanol/water **(5a, g, h)**.

Ethyl 5-Ethoxy-3-oxopentanoate; Typical Procedure:

To a stirred solution of ethyl trimethylsilyl malonate (22.5 g, 0.11 mol) in dry ether (100 ml) in a nitrogen atmosphere at −60°, a 1.45 normal solution (76 ml) of butyllithium in hexane is added over a period of 10 min. The mixture is then allowed to warm to 0° in an ice bath, and a solution of 3-ethoxypropanoyl chloride[14] (7.51 g, 0.055 mol) in dry ether (50 ml) is added rapidly. The mixture is stirred for another 10 min at 0°, then a saturated sodium hydrogen carbonate solution (250 ml) is added, and the mixture is stirred vigorously for 5–10 min. The water layer is then extracted with ether (2×), the combined organic layers are washed with saturated sodium chloride solution, dried with magnesium sulfate, and concentrated in vacuo to give a slightly yellow oil (10.3 g) which is distilled to afford pure ethyl 5-ethoxy-3-oxopentanoate; yield: 9.31 g (90%); b.p. 65–67°/0.05 torr.

The product thus obtained was identical with an authentic sample[9].

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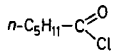
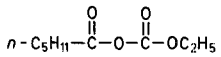
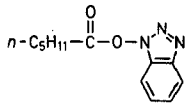
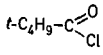
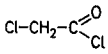
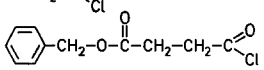
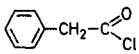
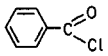
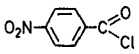
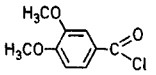
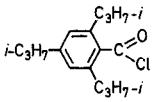
Table. Preparation of β-Keto-acids (**5**) from Carboxylic Acid Derivatives (**2**)

2	Reaction time	Product	Yield[a] [%]	m.p.[b] (Lit. m.p.)	^{1}H-N.M.R. ($CDCl_3$)[c] δ [ppm]		Ketone/Enol ratio[d]
					CO—CH_2COOH	—C(OH)=CH—COOH	
	10 min	**5a**	91	73° (75–76°)[10]	3.51	5.04	6:1
	10 min	**5a**	88				
	10 min	**5a**	74				
	10 min	**5b**	21	45° (47–49°)[11]	3.62	5.11	3:1
	4 h	**5b**	63				
	16 h	**5b**	57				
	10 min	**5c**	72	65° (67–69°)[12]	4.22	5.41	2:1
	10 min	**5d**[e]	92	50°	3.57	5.27	>10:1
	10 min	**5e**	93	70° (72°)[7]	3.58	4.99	3:1
	10 min	**5f**	92	110° (101–102°)[13]	4.09	5.73	3:1
	10 min	**5g**	92	133° (132–133°)[13]	4.21	6.03	1:1
	10 min	**5h**[f]	82	98°	4.04	5.18	9:1
	4 h	**5h**	82				
	16 h	**5i**	0				

[a] Yield of pure isolated product.
[b] Final melting temperature of recrystallized compound.
[c] Except for **5g** which was measured in acetone-d_6.
[d] Estimated from ^{1}H-N.M.R. spectrum.
[e] $C_{13}H_{14}O_5$ (250.24) calc. C 62.39 H 5.64; found 62.23 5.79
The ^{1}H-N.M.R. and ^{13}C-N.M.R. spectra were compatible with the assigned structure.
[f] Known compound; m.p. not given in Ref. [4].

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