ONE-POT CONVERSION OF A REPRESENTATIVE SERIES OF CARBOXYLIC ACIDS TO THE CORRESPONDING METHYL KETONES

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Abstract

The use of imidazolide activation method for direct acylation of Meldrum's acid with carboxylic acids, and the subsequent acidic hydrolysis of the acylated products to methyl ketones, provide a simple and efficient method for a one-pot conversion of carboxylic acids to the corresponding methyl ketones.

Several methods that have been reported for the direct conversion of carboxylic acids to the corresponding methyl ketones. The use of methyllithium by House[1] and Tegner[2] we find appropriate for preparative scale. The method suffers from the usual restrictions or disadvantages associated with high chemical reactivity of metallated species. Other investigators,[3,4] have reported on the acylation of Meldrum's acid using acyl chlorides in the presence of a base. The acylated Meldrum's acids were subsequently hydrolysed under strongly acidic conditions, yielding the corresponding methyl ketones in moderate to low yields .

The method for acylation of Meldrum's acid with acyl chlorides is based on work reported by Yonemitsu et.al.[5] He reported a general and versatile synthesis of β-keto esters through the acyl Meldrum's acids, which readily underwent alcoholysis to β-keto esters.

Here we present a particularly simple and convenient one-pot conversion of carboxylic acids to the corresponding methyl ketones, (Table-1) under mild conditions.

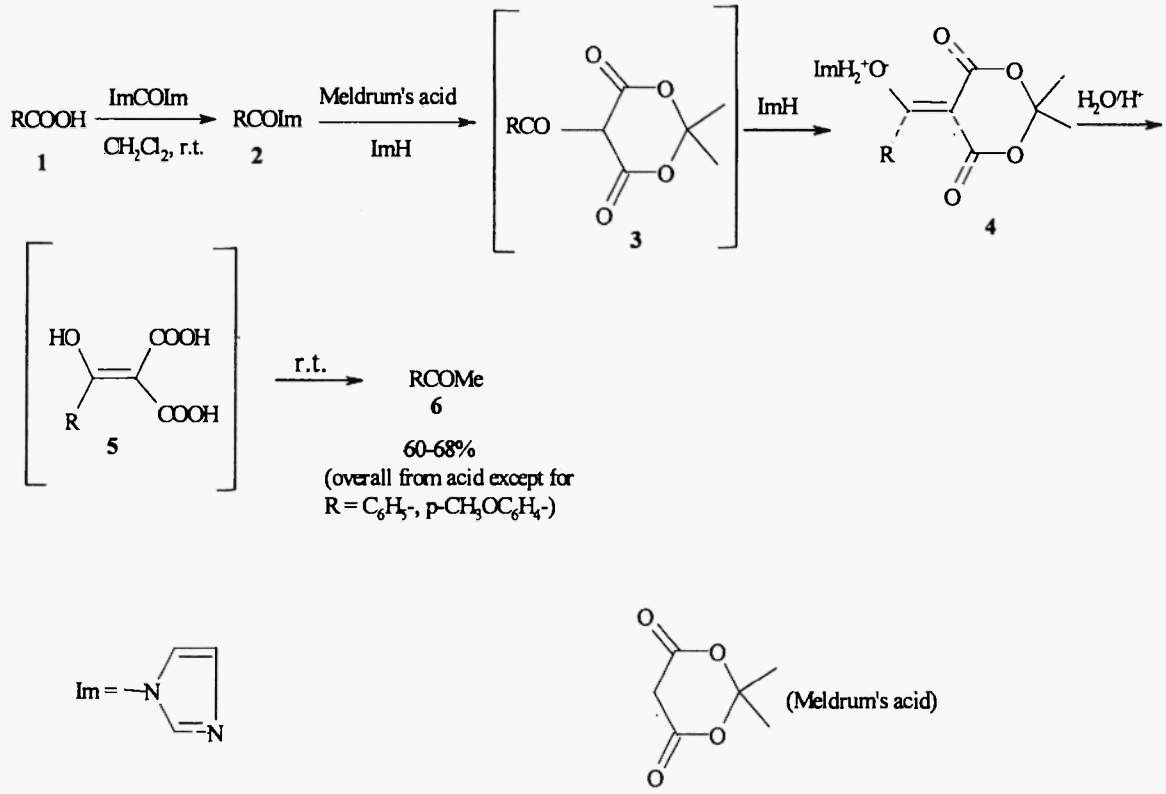
This work is based on previous communications,[6,7] in which we have reported *C*-acylation of active methylene compounds (among these the Meldrum's acid) with α-amino acids, using as activating reagent the 1,1'-carbonyldiimidazole (CDI).

Scheme 1 shows a one-pot, three step sequence (**1**→**2**, **2**→**4**, **4**→**6**) for ketone formation. The carboxylic acid **1** is converted by CDI to the imidazolide **2**. In the second step, the liberated imidazole (ImH) is suffiently basic (pK_a=14.5) for proton abstraction from the Meldrum's acid (pK_a = 5.1) The acyl Meldrum's acid **3** is converted by the imidazole to the stable enol-imidazolinium salt **4**.

In the third step by the addition of a 10% hydrochloric acid solution to the dichloromethane solution of the reaction, the methyl ketone **6** is formed from the unstable enol **5** as acyl malonic acid, which can be separated after

concentration of the organic phase in good yields and in high purity, as revealed by TLC, IR and ^{1}H NMR spectra. Identity was secured by comparison with authentic materials.[9]

The critical acylation step of Meldrum's acid (**2→4**) was monitored[8] by ^{1}H NMR spectroscopy. The resultant methyl ketones were identified and characterized by direct comparison with authentic materials,[9] using TLC, IR and ^{1}H NMR spectra (see Experimental).



R = n-C_3H_7-, n-C_4H_9-, n-C_5H_{11}-, n-C_6H_{13}-, C_6H_5-, p-$CH_3OC_6H_4$-, p-$O_2NC_6H_4$-, $C_6H_5CH_2$-, $C_6H_5CH_2CH_2$-, p-$CH_3OC_6H_4CH_2$-

Scheme- 1

In conclusion, a one-pot overall conversion of carboxylic acids to the corresponding methyl ketones has been achieved by acylation of Meldrum's acid with a simple experimental procedure involving imidazolide activation. The acylated Meldrum's acid is transformed to desired products, under mild acidic conditions. The method gave good yields of aliphatic methyl ketones and was less successful for the preparation of aryl methyl ketones unless the arene function was substituted by a strongly electron–withdrawing group . The application of the method to chiral and polyfunctional carboxylic acids, is in our immediate plan.

Table-1: Reactions and products.

RCOOH		Steps and Reactions time in hours			RCOMe		
entry	R	1→2	2→4	4→6	mp or bp (mmHg), °C	lit. mp or bp (mmHg), °C	Yield%[a]
1	n-C_3H_7	0.5	48	2	100-101 (760)	102.4 (760)[11]	65
2	n-C_4H_9	0.5	48	2	126-127 (760)	127.2 (760)[11]	63
3	n-C_5H_{11}	0.5	48	2	150-151 (760)	151.5 (760)[11]	66
4	n-C_6H_{13}	0.5	48	2	171-172 (760)	172.9 (760)[11]	68
5	C_6H_5-	0.5	48	2	200-201 (760)	202 (760)[11]	17
6	p-$CH_3OC_6H_4$-	0.5	48	2	37-39	38-39[11]	10
7	p-$O_2NC_6H_4$-	2	72	5	79-80	81[12]	81
8	$C_6H_5CH_2$-	0.5	24	2	209-211 (760)	210-212 (760)[11]	60
9	$C_6H_5CH_2CH_2$-	0.5	48	2	116-118 (15)	232-234 (760)[13]	68
10	p-$CH_3OC_6H_4CH_2$-	0.5	48	2	132-133 (3)	150 (20)[14]	61

(a) Yields refered on distilled or recrystallized products

Experimental

Melting points were determined with a Gallenkamp melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded with a Nicolet Magna 560 spectrometer, as neat or nujol mulls, and were calibrated against the polystyrene 1601 cm^{-1} band. Analytical thin layer chromatography, (TLC) was performed on E. Merck precoated silica 60 F_{254} plates. The ^1H NMR spectra, were recorded on Varian Gemini 2000 300MHz spectrometer. The Meldrum's acid was prepared from malonic acid and acetone, according to the method of Davidson and Bernhard.[10] Dichloromethane was distilled from calcium hydride, and stored over 4-Å molecular sieves.

General procedure **1→6**

To a solution or suspension of the carboxylic acid **1** (5 mmol), in 5 ml dry dichloromethane, 1,1'-carbonyldiimidazole (5.1 mmole) was added. The reaction flask was protected with a calcium chloride drying tube, and the mixture was stirred, at room temperature, for the proper time (see Table 1). Meldrum's acid (5 mmol) was then added to the solution, and the mixture was stirred at room temperature for 24-72 h (see Table). To the solution, 6 ml of 10% hydrochloric acid was then added, and the two phase system was stirred vigorously, at room temperature, for 2-5 h (see Table). The organic layer was separated, washed with a 5% sodium bicarbonate and water, dried and concentrated to a liquid residue (Table entries 1-5 and 8-10) or a solid residue (Table entries 6 and 7), which proved to be almost-more than 95% (^1H NMR)-pure methyl ketones.

2-Pentanone. Bp 100-101 °C, lit.[11] 102.4 °C; IR (neat): ν_{CO} 1706; ^1H NMR ($CDCl_3$), δ 0.92 (t, 3H, J=7Hz), 1.30-1.95 (m, 2H), 2.18 (s, 3H), 2.42 (t, 2H, J=7Hz).

2-Hexanone. Bp 126-127 °C, lit.[11] 127.2 °C; IR (neat): ν_{CO} 1712; ^1H NMR ($CDCl_3$), δ 0.70-2.00 (m, 7H), 2.14 (s, 3H), 2.41 (t, 2H, J=7Hz).

2-Heptanone. Bp 150-151 °C, lit.[11] 151.5 °C; IR (neat): ν_{CO} 1706; ^1H NMR ($CDCl_3$), δ 0.89 (t, 3H, J=7Hz), 1.08-2.00 (m, 6H), 2.14 (s, 3H), 2.42 (t, 2H, J=7Hz).

2-Octanone. Bp 171-172 °C, lit.[11] 172.9 °C; IR (neat): ν_{CO} 1706; ^{1}H NMR ($CDCl_3$), δ 0.88 (t, 3H, J=7Hz), 1.05-2.00 (m, 8H), 2.12 (s, 3H), 2.41 (t, 2H, J=7Hz).

Acetophenone. Bp 200-201 °C, lit.[11] 202 °C; IR (neat): ν_{CO} 1678; ^{1}H NMR ($CDCl_3$), δ 2.62 (s, 3H), 7.21-7.65 (m, 3H), 7.88-8.12 (m, 2H).

4-Methoxyacetophenone. Mp 37-39 °C (from ether), lit.[11] 38-39 °C; IR (Nujol mull): ν_{CO} 1669; ^{1}H NMR ($CDCl_3$), δ 2.54 (s, 3H), 3.85 (s, 3H), 6.87 and 7.94 (two d, 4H, J=9.5Hz).

4-Nitroacetophenone. Mp 79-80 °C (from ethanol), lit.[12] 81 °C; IR (Nujol mull): ν_{CO} 1683; ^{1}H NMR ($CDCl_3$), δ 2.69 (s, 3H), 7.85-8.40 (m, 4H).

Phenylacetone. Bp 209-211 °C, lit.[11] 210-212 °C; IR (neat): ν_{CO} 1706; ^{1}H NMR ($CDCl_3$), δ 2.14 (s, 3H), 3.67 (s, 2H), 7.21 (s, 5H).

4-Phenyl-2-butanone. Bp 116-118 °C (15 mmHg), lit.[13] 232-234 °C; IR (neat): ν_{CO} 1706; ^{1}H NMR ($CDCl_3$), δ 2.04 (s, 3H), 2.45-310 (m, 4H), 7.20 (s, 5H).

4-Methoxyphenylacetone. Bp 132-133 °C (3 mmHg), lit.[14] 150 °C (20 mm Hg); IR (neat): ν_{CO} 1718; ^{1}H NMR ($CDCl_3$), δ 2.13 (s, 3H), 3.69 (s, 2H), 3.83 (s, 3H), 6.72 and 7.00 (two d, 4H, J=8.8Hz).

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8. Samples (usually 1 ml) were withdrawn periodically from the reaction flask mixture and concentrated in vacuum (at room temperature). Their solids or retinous mass residues examined by ^{1}H NMR spectroscopy. Especially the two singlet signals ($-CH_2-$ and $>CMe_2$) of the Meldrum's acid stepwise disappeared with the simultaneous predominance of only one new singlet for $>CMe_2$ of **4**.
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