Three-component condensation of substituted Meldrum's acids with methyl ketones and aminomethylating agent

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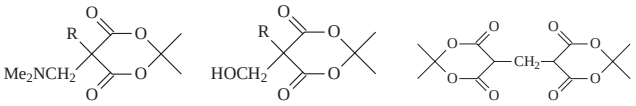
Three-component condensation of substituted Meldrum's acids with methyl ketones and aminomethylating agent in present of carboxylic anhydride, such as acetic anhydride, gives 5-(3-oxoalkyl)Meldrum's acids.

Keywords: Mannich bases, Meldrum's acid, methyl ketones, condensation

As described in our previous report, the Mannich bases of Meldrum's acid (isopropylidene malonate) **1**, which were prepared from isopropylidene malonates and an aminomethylating agent,[1] are versatile reagents with high reactivity.[2] Unlike a normal Mannich base, **1** is readily hydrolysed to the corresponding 5-hydroxymethyl derivatives of Meldrum's acid **2**.[3] Based on this fact, we considered it possible that Mannich bases **1** might condense with nucleophilic reagents, such as some ketones, to form carbon–carbon coupling compounds **3** [5-(3-oxoalkyl) derivatives of Meldrum's acid]. This idea is supported by the fact that the formation of the double condensation product **4** described by Chhabra *et al*.[4] is very easy. This can be considered as the reaction between Meldrum's acid (as a nucleophilic reagent) and its Mannich base formed in the course of reaction.

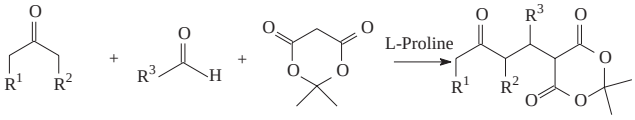


1 **2** **4**

In fact, as a target product, the 5-(3-oxoalkyl) derivative of Meldrum's acid was synthesized by List[5] using Meldrum's acid and aldehyde and ketone as raw materials (see Scheme 1). However, we observed that the yield of product is reduced along with a reduction in the size of group R^3. Hence it is hard to prepare compounds **3** (R^3=H), which was not listed in the article, from formaldehyde by List's method.

In the present investigation, we report a convenient procedure for carbon-carbon coupling to form 5-(3-oxoalkyl) derivatives of Meldrum's acid **5** (similar to **3**, R^2=R^3=H) using substituted Meldrum's acid and aminomethylating agent (to produce Mannich base **1**) and methyl ketones as reactants. When we treated isopropylidene 5-alkylmalonate **6** with aminomethylating agent [$(R^1{}_2N)_2CH_2$ + Ac_2O] in a methyl ketone instead of acetonitrile[1] at room temperature, we found that the precipitated crystal was not the corresponding Mannich base **1**, the expected product from our previous work,[1] but a carbon–carbon coupling compound **5** (see Scheme 2). The result is attributed to the high reactivity of Mannich base **1** to some compound containing active hydrogen.

According to Scheme 2, it is not hard to predict that when using acetone (R^2 = methyl) as methyl ketone, a mixture of mono-condensation and double-condensation product will be obtained. In the present investigation, however, the double-condensation one **7** is always produced even using a large excess of acetone. The double-condensation product was easily crystallised from the reaction mixture and separated simply by filtration with high purity after workup. The mother liquor which contains mono-condensation product (**5**, R=$PhCH_2$, R^2=methyl) and a small amount of double-condensation product can be recovered, and recycled as part of the methyl ketone (acetone) to react with Mannich base formed in the course of reaction to give the double-condensation product in improved yield. The existence of mono-condensation product in the mixture was confirmed by ^{1}H NMR single peak at 2.16 ppm for –COC<u>H</u>$_3$ group of **5** (R=$PhCH_2$, R^2=CH_3) in the mixture.



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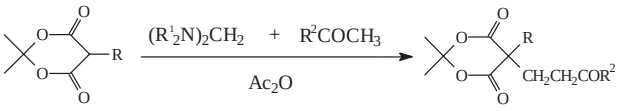
Scheme 1



6

	5	yield%
R = $PhCH_2$, R^2 = Et	**5a**	85
R = $PhCH_2$, R^2 = isobutyl	**5b**	83
R = $PhCH_2$, R^2 = cyclopropyl	**5c**	85
R = $PhCH_2$, R^2 = Ph	**5d**	92
R = $PhCH_2$, R^2 = furan-2-yl	**5e**	79
R = $PhCH_2$, R^2 = thiophen-2-yl	**5f**	74

Scheme 2

Experimental

General procedure for synthesis of **5**: To a stirred solution of **6** (3 mmol) and Ac_2O (3.1 mmol) and $(Me_2N)_2CH_2$ (3 mmol) in acetonitrile (2 ml) was slowly added R^2COCH_3 (3 mmol) at room temperature. The mixture was stirred at 60–65°C for 2 h to complete the reaction, then cooled to room temperature. The precipitated crystals were collected, washed with cold ethyl ether, dried and further purified by recrystalisation (using alcohol as solvent) to give pure product **5**. The filtrate was concentrated and the residue was isolated by a silica gel column chromatograph using ethyl ether as eluent to give another sample of **5**. The overall yield is given in Scheme 2.

General procedure for synthesis of **7**: (A) To a stirred solution of **6** (3 mmol) and Ac_2O (3.1 mmol) and $(Me_2N)_2CH_2$ (3 mmol) in acetonitrile (1 ml) was slowly added acetone (1 ml) at room temperature. The mixture was refluxed for 1 hour to complete the reaction, and cooled to room temperature. The precipitated crystals were collected by filtration, washed with cold ethyl ether, dried and further purified by recrystalization (using acetone as solvent) to give pure product **7** in moderate yields (the same yield 63% for **7g** and **7h**). The filtrate was treated as follows.

(B) The filtrate (from A) was concentrated under reduce pressure and the residue was added to stirred water. The precipitate was collected by filtration, dried and returned to a stirred solution of **6** (3 mmol) and Ac_2O (3.1 mmol) and $(Me_2N)_2CH_2$ (3 mmol) in acetonitrile (1 ml) and acetone (1 ml). The mixture was refluxed for 1 h to complete the reaction, and cooled to room temperature. The precipitated crystals were collected by filtration, washed with cold ethyl ether, dried and further purified by recrystalisation (using acetone as solvent) to give pure product **7** in good yields (the same yield 92% for **7g** and **7h**, based on 3 mmol of **6**, see Scheme 3).

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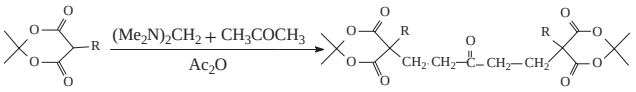

6
R = $PhCH_2$
R = p-$CH_3OC_6H_4CH_2$

7	yield%
7g	92
7h	92

Scheme 3

5a: M.p. 143–144°C; IR cm^{-1} (KBr): 1770, 1730, 1660, 1270, 1050, 720, 710; ^1H NMR δ 0.7(3H, s), 1.1(3H, t, *J*=7.2Hz), 1.6(3H, s), 2.5(6H, m), 3.4(2H, s), 7.3(5H, m); MS (*m/z*, %) 57(91.11), 77(15.69), 91(100.00), 131(15.81), 175(5.02), 232(14.53), 260(5.65); Anal. Calcd. for: C, 67.91; H, 6.97; Found: C, 67.99; H, 7.01.

5b: M.p. 123–124°C; IR cm^{-1} (KBr): 1770, 1730, 1700, 1400, 1280, 1240, 1210, 950, 710; ^1H NMR δ 0.7(3H, s), 0.9(6H, *J*=6.4, d), 1.6(3H, s), 2.2(1H, m, *J*=6.4 and 6.8Hz), 2.3(2H, d, *J*=6.8Hz), 2.5(4H, m), 3.3(2H, s), 7.3(5H, s); MS (*m/z*, %) 77(11.83), 85(100.00), 91(84.90), 103(8.20), 113(4.01), 260(13.96), 288(3.10); Anal. Calcd. for: C, 69.34; H, 7.56; Found: C, 69.52; H, 7.61.

5c: M.p. 191–192°C; IR cm^{-1} (KBr): 1770, 1730, 1700, 1380, 1300, 1270, 710; ^1H NMR δ 0.7(3H, s), 0.9(2H, m), 1.1(2H, m), 1.6(3H, s), 1.9(1H, m), 2.5(2H, t), 2.7(2H, t), 3.4(2H, s), 7.3(5H, m); MS (*m/z*, %) 69(100.00), 77(9.73), 91(50.53), 131(3.5), 175(1.66), 244(7.53); Anal. Calcd. for: C, 69.07; H, 6.71; Found: C, 68.82; H, 6.80.

5d: M.p. 187–188°C; IR cm^{-1} (KBr): 1780, 1735, 1680, 1600, 1580, 1495, 1395, 1380, 1275, 750, 710, 690; ^1H NMR δ: 0.72(3H, s), 1.65(3H, s), 2.5–3.2(4H, m), 3.40(2H, s), 7.2–7.9(10H, m); Anal. Calcd. for: C, 72.12; H, 6.05; Found: C, 71.89; H, 5.99.

5e: M.p. 158–160°C; IR cm^{-1} (KBr): 1770, 1730, 1720, 1380, 1290, 710; ^1H NMR δ 0.7(3H,s), 1.6(3H, s), 2.6(2H, t, *J*=8Hz), 3.0(2H, t, *J*=8Hz), 3.4(2H, s), 7.3(8H, m); MS (*m/z*, %) 77(7.25), 91(100.00), 95(2.15), 131(5.16), 175(2.53), 298(1.11); Anal. Calcd. for: C, 67.41; H, 5.66; Found: C, 67.76; H, 5.75.

5f: M.p. 186–188°C; IR cm^{-1} (KBr): 1770, 1740, 1730, 1340, 1270, 1200, 700; ^1H NMR δ 0.7(3H, s), 1.6(3H, s), 2.5(4H, m), 3.3(2H, s), 7.3(8H, m); MS (*m/z*,%) 77(9.21), 91(52.79), 111(100.00), 131(3.78), 175(2.43), 286(6.71), 314(2.91)**;** Anal. Calcd. for: C, 64.50; H, 5.41; Found: C, 64.88; H, 5.3.

7g: M.p. 175–176°C; IR cm^{-1} (KBr): 1770, 1735, 1605, 1495, 1380, 1270, 730, 700; ^1H NMR δ 0.73(6H, s), 1.61(6H, s), 2.47(8H, s), 3.31(4H, s), 7.24(10H, m); MS (*m/z*, %) 58(10.3), 91(100), 117(46.0), 145(41.8), 406 (72.1), 434(5.6), 492(4.0), 550(0.03, M^+); Anal. Calcd. for: C, 67.62; H, 6.22; Found: C, 67.63; H, 64.15.

7h: M.p. 224–225°C; IR cm^{-1} (KBr): 1775, 1735, 1610, 1510, 1395, 1385, 1250, 1040, 860; ^1H NMR δ 0.80(6H, s), 1.62(6H, s), 2.44(8H, s), 3.26(4H, s), 3.75(6H, s), 6.73–7.15(10H, m); MS (*m/z*,%) 58(62.29), 121(100), 147(10.83), 175(26.03), 406(1.71), 450(4.41), 466(7.06), 494(1.23), 508(0.44), 524(2.29), 552(1.16), 610(0.23, M^+); Anal. Calcd. for: C, 64.91; H, 6.27; Found: C, 64.78; H, 6.26.

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