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SYNTHESIS OF ISOPROPYLIDENE 5-ALKYL-5-HYDROXY-METHYLMALONATES AND THEIR APPLICATION TO THE PREPARATION OF 2-ALKYLACRYLIC ACIDS

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SYNTHESIS OF ISOPROPYLIDENE 5-ALKYL-5-HYDROXY-METHYLMALONATES AND THEIR APPLICATION TO THE PREPARATION OF 2-ALKYLACRYLIC ACIDS

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ABSTRACT

Hydroxymethylated derivatives of isopropylidene 5-alkylmalonates **3** were synthesized, via which 2-alkylacrylic acids **4** were prepared using isopropylidene 5-alkylmalonates **1** as starting materials.

As is well-known, acyclic malonic ester is a versatile reagent. Its hydroxymethylated derivative, which is useful in some fields, is prepared from acyclic malonic ester and formaldehyde or paraformaldehyde (1–3). However, so far the preparation of hydroxymethylated cyclic malonic esters has been seldom reported. Only recently, Nemes and Laronze (4) reported that the trimolecular condensation

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of substituted indoles with paraformaldehyde and Meldrum's acid gave the adducts along with their hydroxymethylated derivatives as by-products. Here we report a convenient method for the preparation of the hydroxymethylated derivatives of isopropylidene 5-alkylmalonates.

Previously we synthesized Mannich bases of Meldrum's acid (the cyclic isopropylidene ester of malonic acid) and its 5-substituted derivatives (5). In the course of studies on their application in organic synthesis, we found that hydroxymethylated derivatives **3** are easily prepared from isopropylidene 5-alkylmalonates **1** via Mannich bases **2**.

After pouring the reaction mixture of isopropylidene 5-alkylmalonates 1, Ac_2O and $(Me_2N)_2CH_2$ in MeCN into water, we found that the final products were not Mannich bases 2 (5), but hydroxymethylated derivatives 3 (Sch. 1, Table 1).

The result shows that Mannich bases 2 (tertiary amines), unlike the normal tertiary amine which does not afford corresponding hydroxylated compound under general condition (6), can be hydrolyzed readily in the presence of faint acid to give hydroxymethylated derivatives 3, owing to their high reactivity. In view of the fact that the substituted isopropylidene malonates are easily hydrolyzed to give carboxylic acids (8,9), the hydrolysis of 3 with dehydration in the presence of strong acid can be anticipitated to give 2-alkylacrylic acids. Thus, treatment of 3 with hydrobromic acid afforded the expected 2-alkylacrylic acids 4 (Sch. 2, Table 1).

In conclusion, the new compounds **3** were easily prepared from isopropylidene 5-alkylmalonates **1** by aminomethylation and then hydrolysis at room temperature. The hydrolysis of compounds **3** provided a simple and effective way of synthesis of 2-alkylacrylic acids **4**. Further studies on reactivity of new compounds **3** will be reported in due course.

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Table 1. Physical Property and Date or IR, ¹H NMR, and Microanalysis of 3 and 4

Product	Formula	1 H NMR ^{<i>a</i>} δ (ppm)	$IR (cm^{-1})$	Microanalysis Found/Calc.	m.p. Uncorrected (°C)
3 a	C ₁₄ H ₁₆ O ₅	0.93 (3H, s) 1.66 (3H, s) 3.08 (1H, s) 3.18 (2H, s) 4.26 (2H, s) 7.27 (5H, m)	3440, 1760, 1735, 1720, 1605, 1500, 1395, 1385, 1060, 750, 710	C 63.71/63.61 H 6.09/6.10	138–139
3b	C ₁₆ H ₁₈ O ₅	1.60 (3H, s) 1.78 (3H, s) 2.40 (1H, s) 2.77 (2H, d) 4.17 (2H, s) 5.74–6.71 (2H, m) 7.33 (5H, m)	3450, 1770, 1725, 1600, 1500, 1400, 1385, 1060, 970, 750, 700	C 66.18/66.20 H 6.29/6.25	130
3c	$C_{15}H_{18}O_6$	1.00 (3H, s) 1.65 (3H, s) 2.37 (1H, s) 3.13 (2H, s) 3.75 (3H, s) 4.21 (2H, s) 6.73–7.18 (4H, q)	3450, 1770, 1720, 1615, 1395, 1385, 1515, 1040, 850	C 61.14/61.22 H 6.15/6.16	122–123
4a	$C_{10}H_{10}O_2$	3.62 (2H, s) 5.57 (1H, d) 6.38 (1H, d) 7.25 (5H, m) 9.61 (1H, w)	2500–3300, 1685, 1620, 1495, 1230, 965, 925, 835, 740, 700	C 74.00/74.06 H 6.24/6.21	70 68–69, lit. (7)
4b	$C_{12}H_{12}O_2$	2.54, 3.20 (2H, dd) 5.40 (1H, d) 6.38 (1H, d) 6.02–6.60 (2H, m) 7.21–7.38 (5H, m) 10.70 (1H, w)	2500–3300, 1690, 1625, 1225, 965, 945, 835, 750, 690	C 76.35/76.57 H 6.58/6.43	66–68
4c	C ₁₁ H ₁₂ O ₃	3.57 (2H, s) 3.77 (3H, s) 5.55 (1H, d) 6.36 (1H, d) 6.78–7.07 (4H, q) 10.40 (1H, w)	2500–3300, 1680, 1625, 1610, 1580, 1510, 1250, 960, 940, 910, 850, 820	C 68.78/68.74 H 6.19/6.08	86–67

^{*a*1}H-NMR spectra were determined in CDCl₃ solution, using TMS as the internal standard.



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EXPERIMENTAL

Preparation of 3: General Procedure. To a stirred solution of **1** (R = alkyl; 2.5 mmol) and Ac₂O (2.6 mmol) in acetonitrile (2 mL) was slowly added (Me₂N)₂CH₂ (2.5 mmol) with cooling. The mixture was stirred at room temperature for 30 min to complete the reaction, then poured into water (20 mL). The whole mixture was stirred at room temperature for 20 min. The precipitated crystal was collected by filtration and washed with water to give **3**.

Preparation of 4: General Procedure. A mixture of **3** (2.5 mmol), acetic acid (5 mL), 40% hydrobromic acid (2 mL), and water (2.5 mL) was refluxed for 2 h, then poured into water (30 mL) after cooling. After the resulting mixture had stood overnight in a refrigerator, it was filtered, and the crystalline precipitate was washed three times with water and further purified by recrystallization with ether–petroleum ether to give pure product **4**.

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