Synthesis of Methylthio- and Aminoalkylidene Derivatives of Meldrum's Acid

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Reaction of Grignard reagents with isopropylidene bis(methyltio)methylenemalonate (**1**) resulted in conjugate addition to give an intermediate **2**, which could either be hydrolyzed to an isopropylidene (1-methylthioalkylidene)malonate **3** or reacted with ammonium chloride to give an isopropylidene (1-aminoalkylidene)malonate **4**.

It has been found that Grignard reagents readily add to isopropylidene alkylidenemalonates (alkylidene derivatives of Meldrum's acid) in a conjugate fashion, thus providing a convenient procedure for the synthesis of mono- or dialkyl (especially *tert*-alkyl) substituted Meldrum's acids.[1-3]

Recently, we reported[4] a facile method for the preparation of isopropylidene bis(methylthio)methylenemalonate (**1**), a yellow crystalline compound, which has an α,β-unsaturated structure similar to that of alkylidene derivatives of Meldrum's acid. We therefore investigated the behavior of **1** with Grignard reagents.

The experimental results (Table 1) show that **1** reacts readily with Grignard reagents to give addition intermediates **2**, which after hydrolysis with dilute hydrochloric acid, afford methylthioalkylidene derivatives **3** of Meldrum's acid. The overall result of the reaction is the substitution of an alkyl group for the methylthio group.

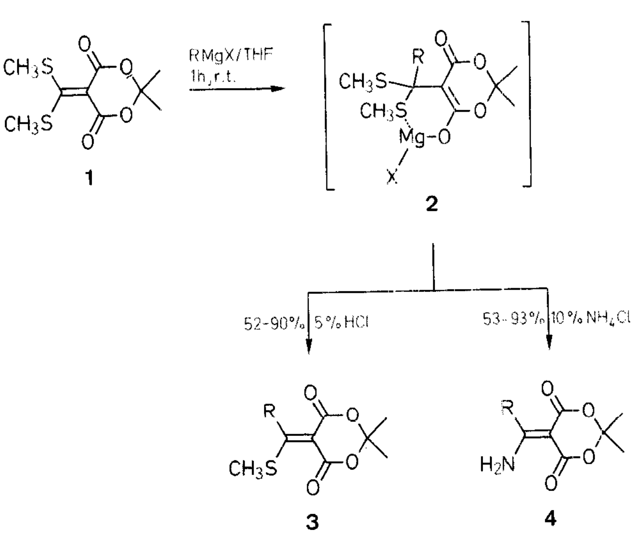


Table 1. Isopropylidene (1-Methylthioalkylidene)malonates **3** Prepared

Product No.	R	Yield (%)	m.p. (°C)	Molecular Formula[a]	IR (KBr)[b] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS$_{int}$)[c] δ(ppm)
3a	CH_3	90	118–119	$C_9H_{12}O_4S$ (216.2)	1705, 1495, 714	1.69 (s, 6H); 2.50 (s, 3H); 2.87 (s, 3H)
3b	CH_3CH_2	71	73–74	$C_{10}H_{14}O_4S$ (230.3)	1705, 1495, 712	1.33 (t, 3H, J = 7.2 Hz); 1.72 (s, 6H); 2.54 (s, 3H); 3.30 (q, 2H, J = 7.2 Hz)
3c	$CH_3CH_2CH_2$	60	92	$C_{11}H_{16}O_4S$ (244.3)	1705, 1495, 710	1.12 (t, 2H, J = 7.2 Hz); 1.70 (s, 6H); 1.71 (m, 2H); 2.54 (s, 3H); 3.24 (t, 3H, J = 7.2 Hz)
3d	$C_6H_5CH_2$	52	149–151	$C_{15}H_{16}O_4S$ (292.4)	1728, 1505, 1460, 703	1.70 (s, 6H); 2.38 (s, 3H); 4.77 (s, 2H); 7.27 (m, 5H)
3e	C_6H_5	87	164	$C_{14}H_{14}O_4S$ (278.3)	1708, 1515, 1483, 695	1.76 (s, 6H); 1.86 (s, 3H); 7.28 (m, 5H)

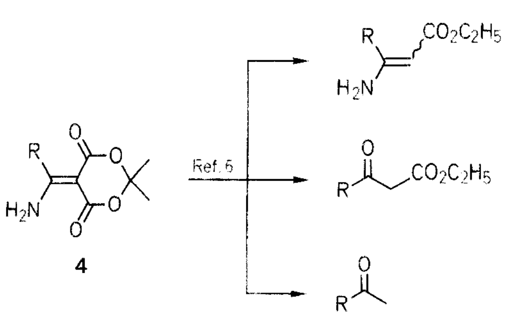
[a] Satisfactory microanalysis obtained: C ±0.26, H ±0.12.
[b] Recorded on a Perkin Elmer 683 spectrophotometer.
[c] Recorded on a JOEL FX 90Q spectrometer.

Table 2. Isopropylidene(1-Aminoalkylidene)malonates **4** Prepared

Product No.	R	Yield (%)	m.p. (°C) found	m.p. (°C) reported[6]	^{1}H-NMR (CDCl$_3$/TMS$_{int}$) δ(ppm)
4a	CH_3	93	163	163	1.65 (s, 6H); 2.58 (s, 3H); 6.44 (s, 2H)
4b	CH_3CH_2	76	95–96	96	1.30 (t, 3H, J = 7.2 Hz); 1.73 (s, 6H); 3.09 (q, 2H, J = 7.2 Hz); 6.90 (s, 2H)
4c	$CH_3CH_2CH_2$	59	104–105	106	1.05 (t, 3H, J = 7.2 Hz); 1.70 (m, 2H); 1.72 (s, 6H); 3.00 (t, 2H, J = 7.2 Hz); 7.17 (s, 2H)
4d	$C_6H_5CH_2$	53	164–165	166	1.68 (s, 6H); 4.42 (s, 2H); 6.10 (s, 2H); 7.24 (m, 5H)
4e	C_6H_5	68	163–164	164	1.74 (s, 6H); 6.10 (s, 2H); 7.36 (m, 5H)

The distinct advantage of the present method is that further substitution, even with three equivalent excess of Grignard reagents, does not occur. This was not the case in a report, by Ittah,[5] in which mono-substituted products could not be separated when Grignard reagents reacted with diethyl bis(methylthio)methylenemalonate. It should be indicted that in our method reverse addition of Grignard reagents is necessary.

Aminoalkylidene derivatives **4** of Meldrum's acid are useful synthetic intermediates. For example, **4** can be inverted into β-enamino esters, β-keto esters or methyl ketones, under different conditions.[6]



Meldrum's Acid Derivatives 3 and 4; General Procedure:

To a well stirred solution of isopropylidene bis(methylthio)methylene malonate (0.62 g, 2.5 mmol) in tetrahydrofuran (5 ml) was added Grignard reagent (7.5 mmol) dropwise in a period of ten minutes. The resultant mixture was allowed to stir for further one hour

Isopropylidene (1-Methylthioalkylidene)malonates **3**: To the reaction mixture obtained above is added 5% hydrochloric acid (10 ml), in order to hydrolyze the addition product. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (3 × 10 ml). The combined organic solution is washed with water (3 × 30 ml) and dried with magnesium sulfate. Evaporation of solvent gives the crude product, which is recrystallized from petroleum tetrahydrofuran ether to afford pure **3**.

Isopropylidene (1-Aminoalkylidene)malonates **4**: To the reaction mixture obtained above is added, rather the hydrochloric acid, 10% ammonium chloride (10 ml), and the solution is stirred for an additional twenty minutes. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (3 × 10 ml). The combined organic solution is washed with water (3 × 30 ml) and dried with magnesium sulfate. Evaporation of solvent gives the crude product, which is recrystallized from tetrahydrofuran petroleum ether to afford pure **4**

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