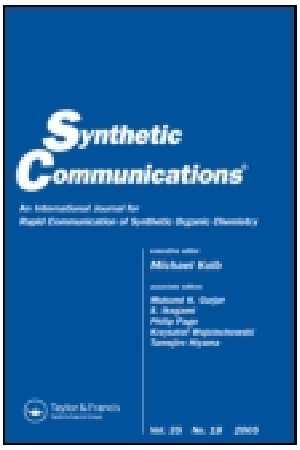

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 16 Aug 2006.

To cite this article: Uday V. Desai , D. M. Pore , R. B. Mane , S. B. Solabannavar & P. P. Wadgaonkar (2004): One Pot Synthesis of Monoalkylated and Mixed, Dialkylated Meldrum's Acid Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:1, 25-32

To link to this article: http://dx.doi.org/10.1081/SCC-120027234

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 1, pp. 25–32, 2004

One Pot Synthesis of Monoalkylated and Mixed, Dialkylated Meldrum's Acid Derivatives

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ABSTRACT

A simple one pot method, involving sequential Knoevenagel condensation of Meldrum's acid with aromatic aldehydes, conjugate reduction of ylidene Meldrum's acid using sodium borohydride followed by alkylation, to prepare mixed dialkylated derivatives of Meldrum's acid is described.

Key Words: Meldrum's acid; Knoevenagel condensation; Aldehyde.

Meldrum's acid (2,2-dimethyl-1, 3-dioxane-4, 6-dione) is an active methylene compound with rigid cyclic structure and high acidity ($pK_a = 4.9$)

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DOI: 10.1081/SCC-120027234 0039-7911 (Print); 1532-2432 (Online)

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and can undergo hydrolysis very easily.[1] It is well known that Meldrum's acid can undergo Knoevenagel condensation,[2a–e] Michael condensation,[3] acylation with acid chlorides[4,5] as well as acids.[6,7] The reports on alkylation studies of Meldrum's acid reveal that unlike dialkyl malonates it has a strong tendency to undergo bis alkylation even with one mole equivalent of alkyl halide[10] and only in exceptional cases monoalkylation results.[11–13] The interest in the synthesis of monoalkylated Meldrum's acid as well as mixed dialkylated Meldrum's acid continues to evolve due their use in the synthesis of dialkylated malonates as well as barbiturates.

The difficulties to prepare dialkylated Meldrum's acid wherein the two alkyl substituents are different, can be overcome by alkylation of monoalkylated Meldrum's acid, which in turn is prepared by the methods which include: 1) Knoevenagel condensation of Meldrum's acid with carbonyl compounds to ylidene Meldrum's acid followed by conjugate reduction with sodium borohydride[14a] or sodium tellurohydride[15] or by cuprous chloride catalyzed conjugate Grignard addition to ylidene Meldrum's acid;[16] 2) by condensation of Meldrum's acid with aromatic aldehydes in presence of formic acid and triethylamine;[17] 3) by reduction of acylated Meldrum's acid with sodium cyanoborohydride;[18] and 4) by reductive alkylation of Meldrum's acid with carbonyl compounds using borane-triethylamine.[19] All these methods require a multistep reaction sequence to be carried out separately. We herein report a simple, one pot method for the preparation of monoalkylated as well as mixed dialkylated Meldrum's acids.

The Knoevenagel condensation of Meldrum's acid with various aldehydes is a key step of the sequence of reactions and for that plethora of reagents are available.[2a–e,20a–b] Until recently, it was believed that 1,2-elimination of β-hydroxy intermediate, 3 (Sch. 1) in the reaction is inhibited by protic solvents as retro Knoevenagel reaction prevails. However, it has been demonstrated by Li[21] that, reaction can be effected in protic solvent like ethanol in the presence of potassium phosphate as a mild base or in water alone in the absence of any catalyst.[22–24] Recently potassium phosphate has also been used in the synthesis of hexasubstituted cyclotriphosphazenes,[25] as well as dithiocarbamates.[26]

In view of our continued interest in the chemistry of Meldrum's acid,[10,11] we ventured to undertake the one pot synthesis of monoalkylated as well as mixed dialkylated Meldrum's acid by sequential Knoevenagel condensation, sodium borohydride reduction and alkylation. The reaction sequence was carried out in ethanol medium but in the absence of catalyst, the yields of Knoevenagel condensation products, 4, being moderate (50–60%, TLC), it was catalyzed by the use of potassium phosphate as a base catalyst. This specific solvent-base combination not only effects Knoevenagel condensation of Meldrum's acid, 2, with aromatic aldehydes, 1 to give

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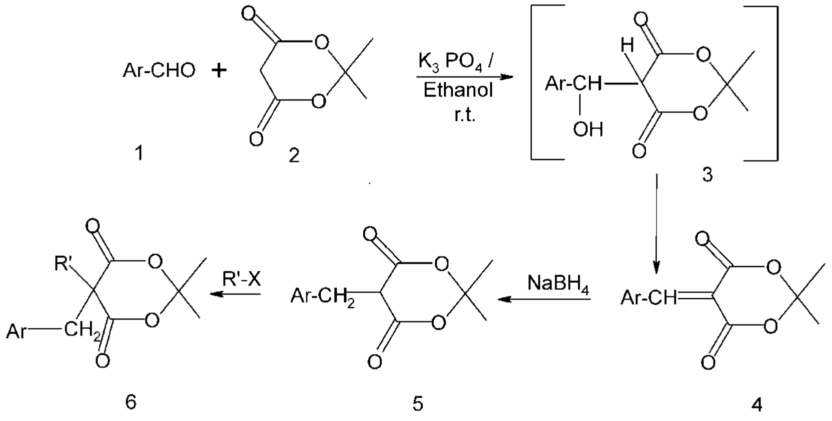

Scheme 1.

arylidene Meldrum's acids, 4 in high yields (85 to 90%) but also permits the reduction of 4 with sodium borohydride in the same pot to furnish monoalkylated Meldrum's acids, 5, which can be either isolated or can be alkylated with various alkyl halides to yield mixed dialkylated Meldrum's acids, 6, in the same pot (Sch. 1).

The overall sequence of reactions was carried out at room temperature and can be monitored easily by TLC. Further, the reaction can be arrested at any desired stage viz. at arylidene Meldrum's acid stage 4, at monoalkylation product stage 5, or can be taken directly to get mixed dialkylated Meldrum's acid, 6. The results obtained during the condensation of various aldehydes with Meldrum's acid, followed by reduction and alkylation are summarized in Tables 1 and 2.

In summary, the potassium phosphate catalyzed procedure described herein is a convenient and easy method to prepare either exclusively monoalkylated or mixed dialkylated Meldrum's acids in high overall yields. The resultant monoalkylated Meldrum's acids, 5 on refluxing with alcohol, are known to give α-monosubstituted malonic acid half esters, which are otherwise difficult to prepare and are highly useful for the preparation of α-substituted acrylic esters.[27–29]

EXPERIMENTAL

Meldrum's acid was prepared according to the reported procedure.[1] Various aldehydes (E. Merck, Lancaster and Sd Fine chemicals) and

Table 1. Preparation of dialkylated Meldrum's acid 6.

					Melting point	
Entry	R	R′	Time (h)	Yield (%)[a]	Obs. °C	Lit. °C
a	Ph	CH_3	4	90	120	119-120[11]
b	Ph	C_2H_5	4.5	84	131	—
c	Ph	Ph-CH_2	5	84	228	230[11]
d	4-MeOPh	CH_3	4.5	91	84	—
e	4-MeOPh	C_2H_5	5	76	112	—
f	4-MeOPh	Ph-CH_2	4.5	76	164	—
g	4-Cl Ph	CH_3	5.5	91	80	—
h	4-Cl Ph	C_2H_5	6	72	114	—
i	4-Cl Ph	Ph-CH_2	6	70	145	—

[a]Yields refer to pure isolated products.

potassium phosphate (Across) were used as received. IR spectra were recorded on Perkin–Elmer-298 instrument while PMR spectra were recorded on Bruker (200 MHz) in $CDCl_3$ as a solvent and δ values are expressed in ppm. The mass spectra were recorded on Finnigan mat 1020 spectrometer.

Typical Procedure

Preparation of 5-benzyl-5-methyl-2,2-dimethyl-1,3-dioxan-4,6-dione, 6a: To a stirred solution of Meldrum's acid (0.72 g, 5 mmol) in ethanol (20 mL)

Table 2. Preparation of monoalkylated Meldrum's acid 5.

				Melting point	
Entry	R	Time (h)	Yield (%)[a]	Obs. °C	Lit. °C
a	Ph	2.5	77	79	80–81[13]
b	4-MeOPh	2.0	91	84	85[13]
c	4-ClPh	2.5	84	127	—
d	3-ClPh	4.0	82	104	—
e	4MePh	2.0	79	110	111–112[30]
f	4HOPh	2.5	91	130	120
g	2 O_2NPh	3.0	63	122	—
h	2ClPh	2.5	82	124	126[30]

[a]Yields refer to pure isolated products.

was added potassium phosphate (0.2 g, 0.94 mmol) followed by solution of benzaldehyde (0.53 g, 5 mmol) in ethanol (5 mL). Stirring was continued until completion of reaction (TLC) and to it sodium borohydride (0.4 g, 10.5 mmol) was added. On completion of reduction (TLC), methyl iodide (1 g, 7 mmol) was added and the reaction mixture was further stirred until alkylation is over (TLC). Water (20 mL) was added and mixture was extracted with ether. The ether extract was washed with water repeatedly, dried over anhydrous sodium sulphate and solvent was removed to get 6a (1.12 g, 90%), mp 120°C (Lit[13] mp 119–120°C).

The monoalkylated Meldrum's acid derivative, 5a can be obtained by carrying out the workup of the reaction mixture after reduction with sodium borohydride is over.

Spectral data of new 5,5-dialkylated Meldrum's acid, 6:

6b. 0.63 (3H, s), 0.96 (3H, t), 1.55 (3H, s), 2.20 (2H, q), 3.31 (3H, s), 4.14 (2H, q), 7.2–7.3 (5H, m).

6d. 0.38 (3H, s), 1.61 (3H, s), 1.73 (3H, s), 3.28 (2H, s), 3.76 (3H, s), 6.28 (2H, d), 7.10 (2H, d). MS m/z (%): 278 (M^+, 23), 148 (15), 121 (100), 77 (30).

6e. 0.74 (3H, s), 0.97 (3H, t), 1.58 (3H, s), 2.21 (2H, q), 3.27 (3H, s), 3.76 (3H, s), 6.80 (2H, d), 7.10 (2H, d). MS m/z (%): 292 (M^+, 5), 206 (16), 121(100), 77 (6).

6f. 0.64 (3H, s), 0.72 (3H, s), 3.41 (4H, m), 3.76 (3H, s), 6.78 (2H, d), 7.2 (7H, m). MS m/z (%): 354 (M^+, 4), 91 (37), 121 (100) 77 (7).

6g. 0.98 (3H, s), 1.55 (3H, s), 1.68 (3H, s), 3.23 (2H, s), 7.04 (2H, d), 7.18 (2H, d). MS m/z (%): 282 (M^+, 5), 196 (84), 180 (17), 145 (27), 125 (100), 89 (28) 115 (36).

6h. 0.78 (3H, s), 0.98 (3H, t), 1.60 (3H, s), 2.2 (2H, q), 3.29 (2H, s), 7.16 (2H, d), 7.24 (2H, d).

6i. 0.62 (3H, s), 0.75 (3H, s), 3.42 (2H, s), 3.44 (2H, s), 7.16 to 7.28 (9H, m) MS m/z (%): 358 (M^+, 15), 272 (100), 289 (32), 256 (17), 226 (17), 125 (22), 91 (32).

Spectral data of new monoalkylated Meldrum's acids: 5:

5c. 1.57 (3H,S), 1.73 (3H, s), 3.45 (2H, d), 3.73 (1H, t), 7.25 (4H, s); MS m/z (%): 268 (M^+, 4), 182 (100), 139 (31), 103 (37), 77 (15).

5d. 1.61 (3H, s), 1.77 (3H, s), 3.45 (2H, d), 3.76 (1H, t), 7.23–7.34 (4H, m); MS m/z (%): 268 (M^+, 3), 182 (46), 138 (55), 131 (100), 77 (41.3).

5f. 1.48 (3H, s), 1.73 (3H, s), 2.19 (1H, s), 3.44 (2H, d), 3.73 (1H, t), 6.75 (2H, d), 7.18 (2H, d); MS m/z (%): 250 (M^+, 11), 164 (100), 147 (30), 120 (42), 107 (68), 91 (33), 77 (16), 65 (20).

5g. 1.78 (3H, s), 1.82 (3H, s), 3.65 (2H, d), 4.21 (1H, t), 7.45 to 8.03 (4H, m).

ACKNOWLEDGMENT

One of the authors (UVD) thanks UGC, New Delhi, for financial assistance.

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Received in the USA July 15, 2003

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