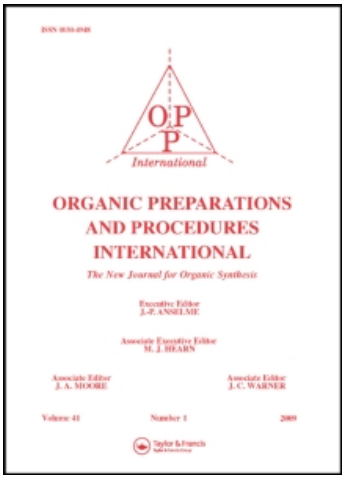

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A CONVENIENT PREPARATION OF 5,5-DIALKYL MELDRUM'S ACIDS

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A CONVENIENT PREPARATION OF 5,5-DIALKYL MELDRUM'S ACIDS

Submitted by (08/21/91) Bang-Chi Chen[†] and Ping Lue*[††]

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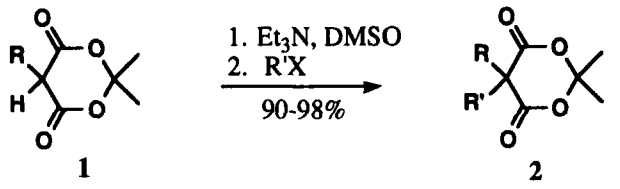
Meldrum's acid (**1**, 2,2-dimethyl-1,3-dioxane-4,6-dione, isopropylidene malonate), discovered by Meldrum,[1] is an attractive alternative to acyclic malonate esters in organic synthesis.[2] 5,5-Dialkyl Meldrum's acids are versatile synthetic intermediates and their applications in organic transformations have been amply demonstrated and well documented.[2,3] As a consequence, many efforts have been aimed at developing efficient methods for the preparation of these synthetically useful compounds.[2,4] On the other hand, however, each of the existing methods suffers one or another disadvantages such as low yield, apparently resulting from the hydrolytic ring-opening by the base employed; or tedious, often chromatographic separation of products. We now report a convenient method for preparation of 5,5-dialkyl Meldrum's acids (**2**) based on our recent observation that triethylamine in dimethyl sulfoxide acts as a homogeneous, but strong enough base in the reaction of Meldrum's acid with carbon disulfide.[5]

When treated with triethylamine in dimethyl sulfoxide, Meldrum's acid (**1**) reacts readily with alkyl halides[6] at room temperature to afford 5,5-dialkyl Meldrum's acids (**2**). The reaction is convenient, involving stirring of the reaction mixture at room temperature. Since the reaction gives high yield (>90%) of product, work-up becomes very simple. Addition of water to the reaction

mixture washes away dimethyl sulfoxide and triethylamine hydrobromide or hydroiodide formed in the reaction, affording essentially pure products **2**. Unsymmetrical dialkyl Meldrum's acids are also obtained in very high yields when monosubstituted Meldrum's acids are used as starting materials. To extend the scope of the reaction, two bishalides, α,α'-dibromo-*o*-xylene (**3**) and 2,2'-bis(bromomethyl)-1,1'-biphenyl (**5**), were reacted similarly and in both cases gave excellent yields of

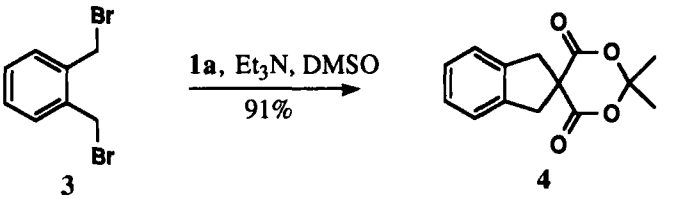


1

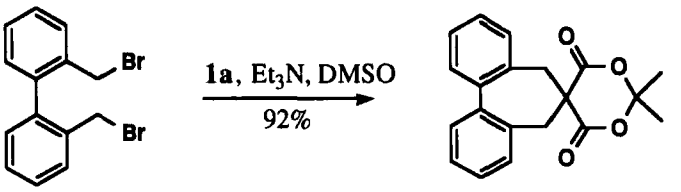
a) R = H, b) R = CH_3
c) R = Ph, d) R = $PhCH_2$

2

a) R = R' = $PhCH_2$, b) R = CH_3, R' = $PhCH_2$
c) R = Ph, R'=CH_3, d) R = Ph, R' = $PhCH_2$
e) R = $PhCH_2$, R' = CH_3, f) R = $PhCH_2$, R' = $PhCH_2$



3 **4**



5 **6**

novel, spiro derivatives of Meldrum' acid (**4**) and (**6**).

EXPERIMENTAL SECTION

All melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating spectrometer or on a Perkin-Elmer Model 1800 Fourier Transform spectrometer. ^1H NMR spectra were recorded on a JEOL FX90Q (90 MHz) or on a Bruker WP-250 FT (250 MHz) spectrometer using TMS as an internal standard.

General Procedure: To a stirred solution of **1** (10 mmol) in 15 ml of DMSO was added triethylamine (2.86 ml, 20.5 mmol, half amount for monosubstituted **1b-d**). The solution was stirred at room temperature for 0.5 hr. The alkyl halide (see Table, 20 mmol for **1a**, 10 mmol for **1b-d** and 5 mmol

for **3** or **5**) was added and the reaction was stirred overnight. Addition of 100 ml of water precipitated a white solid which was collected and purified by recrystallization from tetrahydrofuran/*n*-hexane. The physical and spectral data of products **2** were identical with the reported values. The results are summarized in Table.

TABLE. Preparation of 5,5-Dialkyl Meldrum's Acids **2**.

Substrate	R'X	Product	Yield (%)	mp. (°C)	lit. (°C)	^{1}H NMR (δ)
1a	$PhCH_2Br$	**2a**	98	230-231	232-233[a]	0.58 (s, 6H), 3.40 (s, 4H), 7.06 (s, 10H)
1b	$PhCH_2Br$	**2b**	95	119-120	119-120[a]	0.84 (s, 3H), 1.56 (s, 3H), 1.70 (s, 3H), 3.26 (s, 2H), 7.17 (m, 5H)
1c	CH_3I	**2c**	90	145-147	146-148[b]	1.30 (s, 3H), 1.69 (s, 3H), 2.51 (s, 3H), 7.30 (m, 5H)
1c	$PhCH_2Br$	**2d**	92	84-85	84-86[c]	1.24 (s, 3H), 1.42 (s, 3H), 3.72 (s, 2H), 7.45 (m, 5H)
1d	CH_3I	**2e**	93	119-120	119-120[a]	0.84 (s, 3H), 1.56 (s, 3H), 1.70 (s, 3H), 3.26 (s, 2H), 7.17 (m, 5H)
1d	$PhCH_2Br$	**2f**	98	231-233	232-233[a]	0.58 (s, 6H), 3.40 (s, 4H), 7.06 (s, 10H)

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Compounds **4** and **6** had the following physical and spectral data:

4, mp. 156-157 °. MS, m/e (rel intensity): 246 (M^+), 160 (44), 116 (100), 115 (83), 89 (13); IR (KBr) 3027, 1736, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ, 1.84 (s, 6H), 3.75 (s, 4H), 7.25-7.45 (m, 4H).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28, H, 5.73; Found: C, 68.20, H, 5.73

6, mp. 177-178 °. MS, m/e (rel intensity): 322 (M^+), 236 (35), 192 (81), 191 (100), 189 (33), 165 (39), 96 (16), 95 (25), 82 (46), 63 (30), 58 (38); IR (KBr) 3026, 1743, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ, 1.81 (s, 6H), 3.10 (AB quartet, J_{AB} = 14 Hz, 4H), 7.18-7.50 (m, 8H).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52, H, 5.63; Found: C, 74.40, H, 5.61

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6. Less reactive halides, such as *n*-butyl iodide, gave lower yields (60%).

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SYNTHESIS OF N-SUBSTITUTED 2-ALKYL-4-ARYLOXAZOLE-5-CARBOXAMIDES

Submitted by (11/06/91)

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In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides,[1-4] we recently reported the synthesis of *N*-substituted 2,4-diaryloxazole-5-carboxamides.[5] The first step of this synthesis consisted in the preparation of *N*-substituted 2-acyloxy-3-oxoarylpropionamides which were cyclized to *N*-substituted 2,4-diaryloxazole-5-carboxamides upon treatment with ammonium formate in acetic acid. Similar oxazole syntheses have been little investigated[6,7] because the starting α-acyloxy-β-ketoesters are not readily available. In contrast, a wide variety of *N*-substituted α-acyloxy-β-ketocarboxamides can be prepared by reacting acyl glyoxals, isocyanides and carboxylic acids. In order to evaluate the potential of this synthetic method for the preparation of oxazole derivatives, we attempted the synthesis of *N*-substituted 2-alkyl-4-aryloxazole-5-carboxamides (**5**).

The first step of this synthesis consisted in the Passerini reaction between arylglyoxal (**1**), aliphatic carboxylic acids (**2**) and isocyanides (**3**) which afforded *N*-substituted 2-acyloxy-3-oxoarylpropionamides (**4**). Since treatment of compounds **4** with ammonium formate in boiling acetic acid