# On the Synthesis of 5-Ethyl Meldrum's Acid

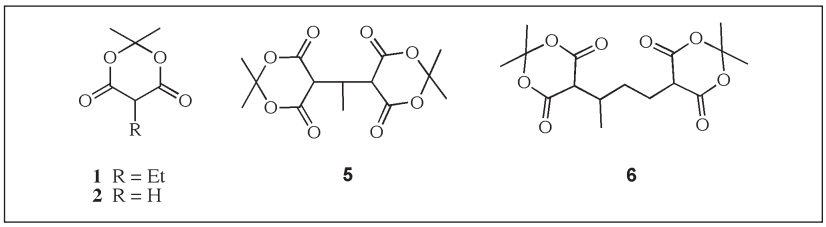


Rufine Akué-Gédu, Hayate El-Hafidi and Benoît Rigo*

Groupe de Recherche sur l'Inhibition de la Prolifération Cellulaire (EA 2692)
Ecole des Hautes Etudes d'Ingénieurs, 13 rue de Toul, 59046 Lille, France
e-mail: rigo@hei.fr

Daniel Couturier

Laboratoire d'Ingénierie Moléculaire, Université des Sciences et Technologies, 59655 Villeneuve d'Ascq, France
Received June 29, 2005




Reductive alkylation of Meldrum's acid with acetaldehyde can give, depending on the experimental conditions, either a new dimer (5-[3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione) or ethyl Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione). A best way to obtain this latter product is synthesis of 1-ethoxyethylidene Meldrum's acid from reaction of Meldrum's acid with triethyl orthoacetate, followed by a sodium borohydride reduction.

*J. Heterocyclic Chem.*, **43**, 365 (2006).

In conjunction with an ongoing program [1], we needed a convenient supply of 5-ethyl Meldrum's acid (**1**) [2]. Because the selective monoalkylation of Meldrum's acid **2** is difficult and that the dialkylated product **3** generally predominates [3], we choose to use a reductive alkylation between acetaldehyde and Meldrum's acid and to reduce the alkylidene derivative **4**, following the general method of Smith [4] (Figure 1).

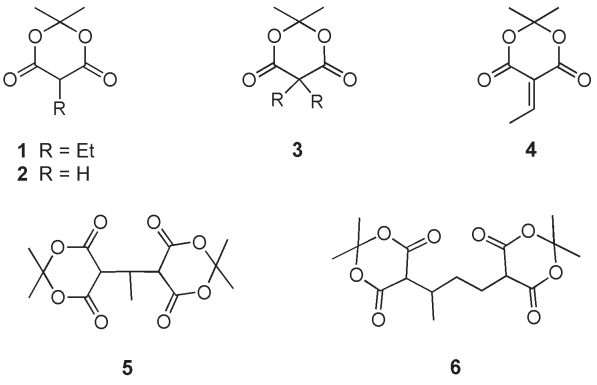


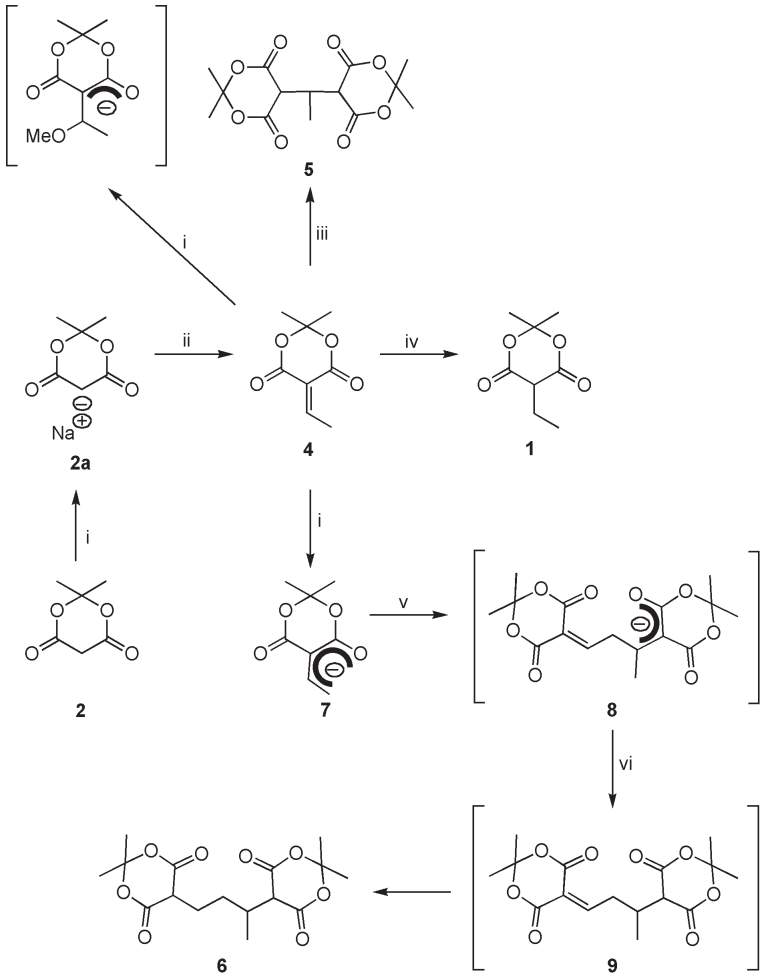

Figure 1

Concerning the synthesis of compounds **4**, in order to avoid a Michael reaction of Meldrum's acid with the ethylenic product **4**, giving dimer **5** [2c,5-9], Polanski and Margaretha recommend intercepting **4** with sodium methoxide. After acidification, **4** was described to be obtained in good yields (85%) [5]. Thus we carried out a Knoevenagel reaction between acetaldehyde hemiacetal and the sodium salt of Meldrum's acid formed *in-situ* in methanol. After acidification, the resulting product was reduced with sodium borohydride [4,10]. Surprisingly, a new dimer **6** was isolated in 40% yield (Scheme 1).

A possible mechanism for the formation of dimer **6** is described in Scheme 1: Compound **4**, which is vinylogue to Meldrum's acid, is strongly acidic [11], and reacts with sodium methoxide (or another sodium salt), to yield salt **7**. Michael addition of **7** to polarized ethylenic **4** gives salt **8**. Dimer **6** was then obtained after acidification and sodium borohydride reduction of the double bound of **8** (Scheme 1) [4].

In another experiment, following more closely literature procedures [5], the sodium salt of Meldrum's acid was formed in tetrahydrofuran, and then isolated. A solution of acetaldehyde hemiacetal in methanol was then slowly added to a *suspension* of this salt in the same solvent. Acidification of the residue obtained after evaporation leads, according to NMR, to a mixture of **4** (5-10%), **5** (85-90%) and **9** (0-5%). When this reaction was repeated in a methanol/dichloromethane solvent, the acidification step being performed in dichloromethane, alkylidene Meldrum's derivative **4** was obtained in more than 95% yield (NMR). This compound was not isolated, but the dichloromethane solution of compound **4** was directly treated with sodium borohydride, giving an 85% yield of the desired product **1**.

Scheme 1




Reaction conditions: (i) MeONa / MeOH or THF; (ii) MeCHO / MeOH or $CH_2Cl_2$; (iii) a) **2a** / MeOH, b) H+ ; (iv) $NaBH_4$ / $CH_2Cl_2$; (v) **4**, MeOH; (vi) $NaBH_4$ / MeOH.

It is necessary to point out the necessity to proceed very carefully when using old literature for the attribution of a structure to dimers obtained from the reaction of Meldrum's acid with aldehydes. Indeed compound **9a** related to dimer **9** has already been obtained in the reaction of Meldrum's acid with butyraldehyde [12]. No spectral data were provided for this compound, which was missassigned as dimer **5a** in another publication [5] (Figure 2). In the same way, structure **5** was attributed to the product obtained from the reaction of Meldrum's acid with acetaldehyde in dimethylformamide or from its reaction with crotonaldehyde (…obviously as the result of occurrence of a reverse aldol reaction [8]…). Because of identity of melting point (147-150 °C), we believe that the product thus isolated was in fact dimer **9**.

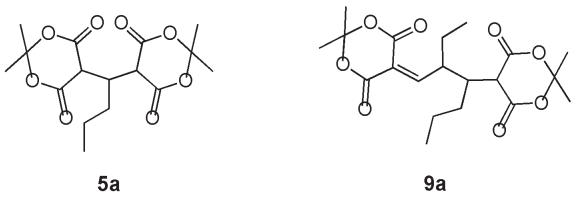


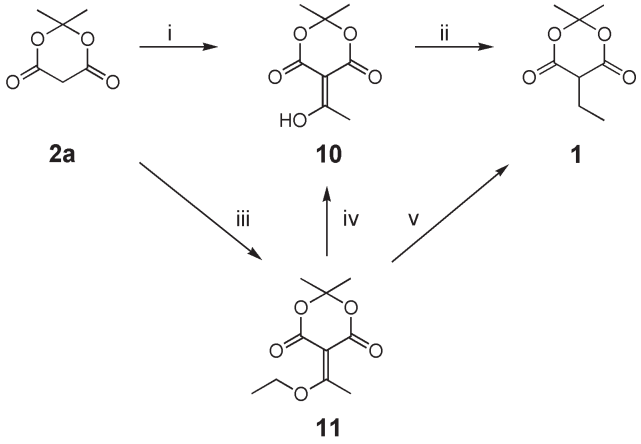

Figure 2

Interestingly, although many mentions on the easy Michael reaction of Meldrum's acid with ethylenic compounds such as **4** (to give dimers like **5**) can be found in literature [2c,5-10], we were not able to find any authentic description of dimer **5**. In the same way, to the best of our knowledge, dimer **6** observations or characterization were not reported.

The results described above are strongly dependent upon the exact temperature and duration of the reaction (as well as the physical states of sodium borohydride (powder *vs.* pellets) and more convenient synthesis were needed. A

possibility to obtain compound **1** is a one-pot reduction [13] of enol **10** [14a,b], obtained by using a slightly modified literature procedure for acylation of Meldrum's acid [14a] (42% total yield) (Scheme 2). However, a best synthesis of ethyl compound **1** is the sodium borohydride reduction in acetic acid (72%), of 1-ethoxyethylidene Meldrum's acid **11**. This product was very easily obtained from the reaction of Meldrum's acid with triethyl orthoacetate in dichloromethane solution (reflux 120 h, 93%) [14c]. It is to be noted that the reaction must be conducted under inert atmosphere to avoid hydrolysis to compound **10**. The hydrolysis occurs also quantitatively and very rapidly, when **11** is stirred in hydrated tetrahydrofuran. This synthesis of enol **10** is easier to perform and gives a purer product than the previous acetylation of Meldrum' acid [14a,b] (Scheme 2).

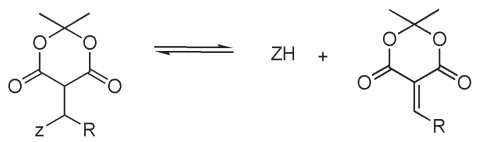
Scheme 2




Reaction conditions: (i) $Ac_2O$ / $Et_3N$ / DMAP / $CH_2Cl_2$, -25°C; (ii) $NaBH_4$ / AcOH, 20°C; (iii) $CH_3C(OEt)_3$ / $CH_2Cl_2$, reflux; (iv) THF / $H_2O$, 20°C; (v) $NaBH_4$ / AcOH, 20°C.

These results indicate that when compounds such as **1** or **4** are desired, a proper choice of experimental conditions can lead to good yields, without the need of the more sophisticated methods sometimes recommended in literature [7,12,15]. Furthermore this shows how the acidity (and reactivity) of alkylidene Meldrum's acid derivatives can be tuned by a slight change in solvent polarity (from methanol to dichloromethane). A strong influence of the solvent in equilibrium as indicated in Scheme 3 was already observed, often by NMR methods [6,8,12,16].

Scheme 3




ZH = Meldrum's acid [8,15], PhSH[14], $R_2NH$[16]

## EXPERIMENTAL

Melting points were determined using an Electrothermal apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were carried out in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatography was performed on precoated Kieselgel $60F_{254}$ plates. Microanalyses were performed by the "Service Central de Microanalyses" of CNRS in Vernaison, France.

5–Ethyl–2,2–dimethyl–1,3–dioxane–4,6–dione (**1**) from 5-Ethylidene-2,2-dimethy–1,3–dioxane–4,6–dione (**4**).

A solution of sodium methoxide in methanol (28%, 90.3 g, 1.67 mol) was added to a stirred suspension of Meldrum's acid (241 g, 1.67 mol) in tetrahydrofuran (500 mL). After one hour, the sodium salt of Meldrum's acid was filtered, washed with acetone then dried under vacuum. Acetaldehyde (470 mL, 8.37 mol) was slowly added to ice cooled methanol (1370 mL), giving a solution of acetaldehyde hemiacetal. The solution of acetaldehyde hemiacetal was rapidly added to a suspension of the sodium salt of Meldrum's acid in dichloromethane (1000 mL). The reaction is very fast (5 min). The resulting solution was quickly (2 min) acidified with 1 *M* hydrochloric acid. The organic phase was decanted then dried ($MgSO_4$). The solution of product **4** was not evaporated but used directly in the next step. If isolated, compound **4** presents the same physical properties as described in literature [5,7], mp 52-53 °C (51-53 °C) [2c], IR ν $cm^{-1}$: 1765, 1740, 1630; $^1H$ NMR (deuteriochloroform) δ ppm: 1.75 (s, 6H), 2.50 (d, *J* = 7.5 Hz, 3H), 8.03 (q, *J* = 7.5 Hz, 1H).

The dichloromethane solution of **4** obtained in the preceding step was cooled at 0 °C (ice/salt bath) then sodium borohydride powder (12 g, 0.319 mol) was slowly (15 min) added. The ice bath was removed and the solution was allowed to rise to room temperature. Excess of reducing agent was quenched by addition of methanol (50 mL) and then acidification with 1 *N* hydrochloric acid. The organic phase was decanted then dried ($MgSO_4$). The oil obtained upon evaporation was purified by preparative chromatography (Si60, 200-400 mesh, 1 Kg, ethyl acetate/heptane 1/1), giving **1** as a white powder (244 g, 85%): mp (ethyl acetate) 108-109°C (107-109°C) [15]; TLC ($SiO_2$, ethyl acetate/ heptane 1/1) 0.45; 'H NMR (deuteriochloroform) δ ppm: 1.06 (t, *J* = 7.4 Hz, 3H), 1.77 (s, 3H), 1.79 (s, 3H), 2.17 (dq, *J* = 4.9, 7.4 Hz, 2H), 3.50 (t, *J* = 4.9 Hz, 1 H); $^{13}C$ NMR (deuteriochloroform) δ ppm: 10.6, 20.0, 26.8, 28.3, 47.0, 104.7, 165..4.

Synthesis of **1** from **10**.

A solution of Meldrum's acid (30.0 g, 0.208 mol), triethylamine (34.8 ml, 0.250 mol) and dimethylaminopyridine (1.0 g, 0.008 mol) in dichloromethane (200 mL) was magnetically stirred in a cooled bath (inner temperature: -25 °C). A solution of acetyl chloride (18.0 g, 0.230 mol) in dichloromethane (50 mL) was added during 1 hour while keeping the temperature between -20 and -25 °C, then the cooling bath was removed. The mixture was stirred at room temperature for 12 hours to give enol **10**, identical to the compound described in literature [14].

Dichloromethane (100 mL) and acetic acid (160 mL) were added, and then sodium borohydride powder (10.1 g, 0.267 mol) was added over 75 min. After stirring for 12 hours, the solution was acidified with 36% HCl, and then washed 2 times with water. The aqueous phase was extracted with dichloromethane and this organic phase was washed with water. The combined organic phases were washed once with water, dried ($Na_2SO_4$) and evaporated. The residue was purified by preparative chromatography (Si60, 200-400 mesh, 500 g, ethyl acetate/heptane 1/1), giving **1** as a white powder (15 g, 42%), identical to the compound obtained from **4**.

Synthesis of **1** from **11**.

Crude compound **11** obtained from 25 g of Meldrum's acid (0.173 mol) was dissolved in a mixture of dichloromethane (100 mL) and acetic acid (155 mL). The solution was kept at 20 °C by using a large water bath while sodium borohydride powder (9 g, 0.238 mol) was added over 45 min. The mixture was stirred at room temperature for 12 hours to give quantitatively Meldrum's derivative **1**. Acetic acid was evaporated, and then the residue was partitioned between water and dichloromethane. After drying and evaporation of the solvents, crystallized compound **1** was washed with heptane to give 18.8 g (63%) of product identical to the compound obtained from **4**. It is not necessary to purify this product by preparative chromatography before using it in other reactions [1].

5-[1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**).

A solution of acetaldehyde hemiacetal in methanol (acetaldehyde: 100 mL, 1.70 mol; methanol 675 mL) was added (30 min) to a *solution* of the sodium salt, formed *in-situ* by adding MeONa (16 g, 28% in methanol, 0.29 mol) to Meldrum's acid (41.8 g, 0.29 mol) in methanol (500 mL). The mixture was stirred for 15 min, and then methanol was evaporated. Dichloromethane (500 mL) was added then the mixture was acidified with 1 *N* hydrochloric acid. The aqueous phase was extracted three time with methylene dichloride, then the organic phase was dried ($Na_2SO_4$) and evaporated giving a mixture of **4**, **5** and **9**. Upon addition of ether dimer **5** (82 g, 90%) deposed as a viscous, slightly yellow oil which was purified by preparative chromatography (Si60, 200-400 mesh, 500 g, ethyl acetate/heptane 1/1); IR ν $cm^{-1}$ 1775, 1740, 1640, 1200; $^1H$ NMR (deuteriochloroform) δ ppm: 1.51 (d, *J* = 6.7 Hz, 3H), 1.79 (s, 6H), 1.83 (s, 6 H), 3.30–3.50 (m, 1H), 4.28 (d, *J* = 6 Hz, 2 H).

*Anal*. Calcd. for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77; O, 40.73. Found: C, 53.11; H, 5.98; O, 40.97.

5-[3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**).

A solution of acetaldehyde hemiacetal in methanol (acetaldehyde: 20.5 mL, 0.350 mol; methanol 140 mL) was added (10 min) to a *suspention* of the sodium salt of Meldrum's acid (10 g, 0.060 mol) (*cf.* preparation of **1** from **4**) in methanol (100 mL). The mixture was stirred for 30 min, and then neutralized with 1 *N* hydrochloric acid. Sodium borohydride pellets, (1.1 g, 0.030 mol) were added to the solution. The mixture was stirred for 30 min then acidified with 1 *N* hydrochloric acid. The solvent was evaporated in part, dichloromethane was added and the solution was washed with water. The organic phase was decanted then dried ($Na_2SO_4$) to give a mixture of **1** and **6**. The oil obtained upon evaporation was purified by preparative chromatography (Si60, 200-400 mesh, 500 g, ethyl acetate/heptane 1/1) giving **1** (4.1 g, 40%) and **6** as a white powder mp 115-117 °C (4 g, 40%). IR ν $cm^{-1}$ 1780, 1740, 1205; $^1H$ NMR (deuteriochloroform) δ ppm: 1.16 (d, *J* = 7.1 Hz, 3H), 1.75, (s, 3H), 1.77 (s, 3H), 1.79 (s, 3H), 1.81 (s, 3H), 1.64-2.01 (m, 2H), 2.01-2.15 (m, 1H), 2.15-2.34 (m, 1H) , 2.46–2.65 (m, 1H), 3.59 (d, *J* = 2.8 Hz, 1H) , 3.60 (t, *J* = 4.90 Hz, 1H); $^{13}C$ NMR δ ppm: 16.4, 24.2, 26.5, 27.0, 28.1, 28.3, 30.9, 32.9, 45.8, 50.4, 104.6, 104.8, 164.2, 164.8, 165.0, 165.1.

*Anal.* Calcd. for $C_{16}H_{22}O_8$: C, 56.13; H, 6.48; O, 37.39. Found: C, 55.83; H, 6.75; O, 37.72.

5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**10**) from **11**.

The crude compound **11** obtained from 12.5 g of Meldrum's acid (87 mmol) was dissolved in a mixture of tetrahydrofuran (10 mL) and water (2.3 g, 130 mmol). The solution was stirred for 4 hours giving quantitatively a solution of enol **10**. After drying ($Na_2SO_4$) the solvents were evaporated. The residue crystallized in a diethyl ether/heptane mixture, to give 9.7 g (60%) of crystallized **10**, identical to the compound obtained following the literature [14a]. $^1H$ NMR (deuteriochloroform) δ ppm: 1.74 (s, 6H), 2.68 (s, 3H).

5-(1-Ethoxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**11**).

A solution of Meldrum's acid (25 g, 0.173 mol) and triethyl orthoacetate (95 mL, 85 g, 0.520 mol) in dichloromethane (125 mL) was stirred for 120 hours in a water bath heated at 50 °C (nitrogen). Solvents were evaporated (rotary evaporator then 0.05 mmHg, bath temperature: 20 °C) to give a slightly yellow residue containing 93% (NMR) of enol ether **11**, identical to the compound obtained following the literature [14c], and 5-6 % of diethyl malonate. The crude mixture was used directly in the next syntheses. $^1H$ NMR (deuteriochloroform) δ ppm: 1.51 (t, *J* = 7.1 Hz, 3H), 1.70, (s, 6H), 2.73 (s, 3H), 4.43 (t, *J* = 7.1 Hz, 2H).

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