

SYNLETT Spotlight 455

5-Alkyl and 5,5-Dialkyl Meldrum's Acids

Compiled by Inese Mierina



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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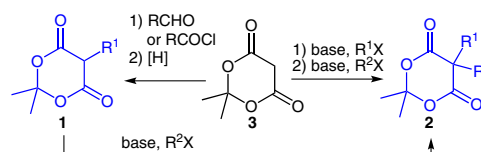
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Introduction

5-Alkyl and 5,5-dialkyl Meldrum's acids (**1** and **2**, respectively) are used in total synthesis.¹ Monoalkylated derivatives **1** are synthesized from Meldrum's acid **3** by condensation with aldehyde² (or by acylation³) followed by hydrogenation.

5,5-Dialkyl Meldrum's acids **2** can be obtained by alkylation of Meldrum's acid **3** or its monoalkylated derivatives **1** (Scheme 1).⁴ Herein, reactions of Meldrum's acids **1** and

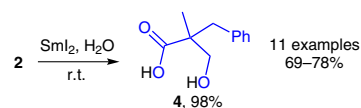
2 proceeding with destruction of 1,3-dioxane cycle are reviewed.



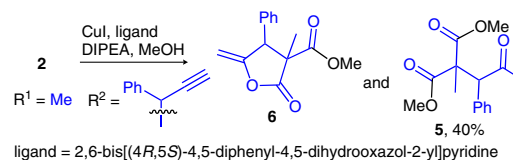
Scheme 1

Abstracts

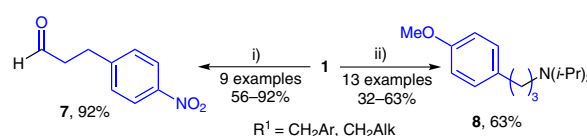
(A) Hydrolysis of Meldrum's acid **2** leads to malonic or acetic acid derivatives.⁵ Radical reduction of compound **2** with SmI₂ and H₂O forms 3-hydroxypropanoic acids **4** selectively. The first step is activation of Meldrum's acid via coordination of SmI₂ to the carbonyl group, followed by electron transfer.⁶



(B) Detz et al.⁷ have reported that dimethyl malonate **5** can be obtained from propargylic derivative **2**. The authors propose that the first step of the reaction cascade is copper-mediated addition of Meldrum's acid **2** to the triple bond and sequential methanolysis of the dioxane cycle forming lactone **6**, which is further cleaved with methoxide leading to compound **5**.

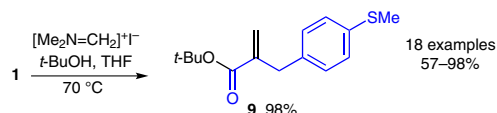


(C) β -Substituted aldehydes **7** can be synthesized by Lewis base promoted hydrosilylation of Meldrum's acids **1** with phenylsilane, followed by hydrolysis. In situ treatment of aldehyde **7** with an amine and sequential hydrogenation of the formed imine with H₂ in the presence of Pd/C or with NaBH(OAc)₃ gives γ -substituted amines **8**.⁸



i) 1) Et₃N (2 equiv), PhSiH₃ (3 equiv), THF, r.t.; 2) H₂O
ii) 1) Et₃N (2 equiv), PhSiH₃ (3 equiv), THF, r.t.; 2) R³R⁴NH (2 equiv), MeOH; 3) H₂, Pd/C

(D) 5-Alkyl Meldrum's acids **1** are used for the rapid synthesis of 2-alkyl acrylates **9** via Mannich-type reactions. The advantage of the method is the clean conversion into products due to the formation of volatile by-products – acetone, carbon dioxide, and dimethylamine.⁹



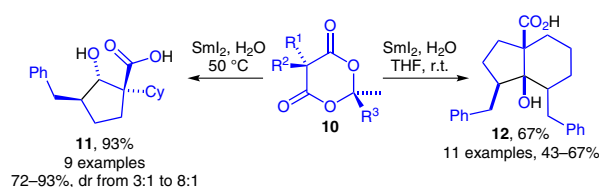
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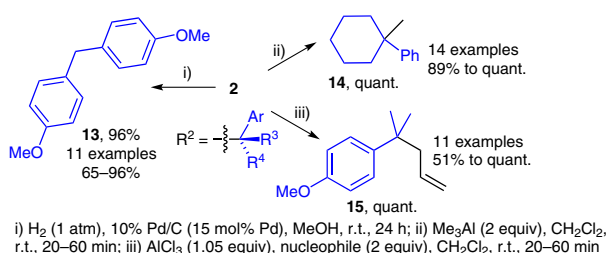
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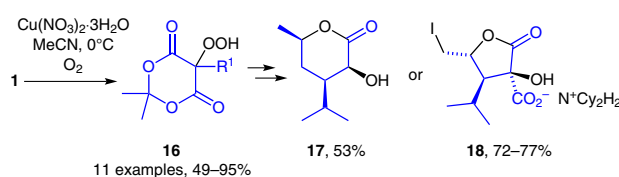
(E) Derivatives of 5-(but-3-enyl) Meldrum's acid **10** are suitable for the synthesis of cyclopentanols **11** via radical cyclization upon treatment with SmI_2 in H_2O .⁶ *Exo-trig/exo-trig* radical cyclization cascade occurs, when substituent R^2 is an alkene or alkyne; such a transformation gives fused bicyclic system **12**.¹⁰



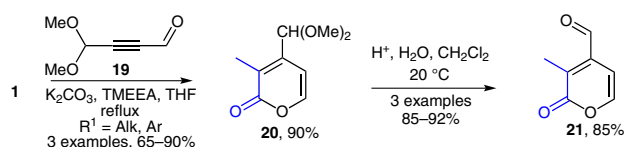
(F) Meldrum's acid can act as a carbon-based leaving group. Catalytic hydrogenolysis of Meldrum's acids **2** ($\text{R}^1 = \text{H}$) is an excellent route for the synthesis of compounds **13** both with secondary and tertiary benzylic stereocenters in 65–96% yield under mild reaction conditions. As the reaction proceeds with inversion at the stereocenter, an $\text{S}_{\text{N}}2$ mechanism is proposed.¹¹ Treatment of Meldrum's acid derivatives **2** ($\text{R}^1 = \text{H}, \text{Me}$) with nucleophiles in the presence of Lewis acids furnishes compounds **14** and **15**. The yields vary from 51% to quantitative.¹²



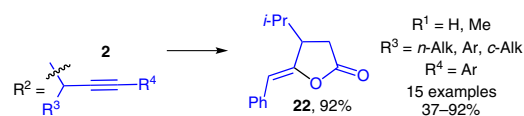
(G) Johnson and co-workers reported the hydroperoxidation of 5-alkyl Meldrum's acids **1** with O_2 in the presence of $\text{Cu}(\text{NO}_3)_2$.¹³ These reaction conditions are compatible with unsaturated bonds in substituent R^1 . The peroxides **16** are suitable for intramolecular oxidation of unsaturated bonds via electrophilic activation; such an approach was used for the synthesis of lactones **17** and **18**.



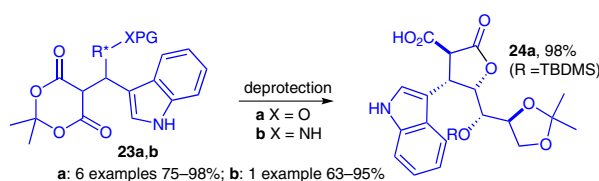
(H) Addition of 5-substituted Meldrum's acid **1** to prop-2-ynal **19** forms 3-(1,3-dioxan-5-yl)-4,4-dimethoxy-but-2-enal. The thermolysis of 2,3-unsaturated aldehyde intermediate provides a synthetic procedure to 2*H*-pyran-2-one **20**. Hydrolysis of acetal moiety results in 4-formyl pyran-2-one **21**.¹⁴



(I) Copper- and iron-¹⁵ or silver-catalyzed¹⁶ tandem cyclization–hydrolysis–decarboxylation of 5-propargyl Meldrum's acid **2** is an efficient approach for the synthesis of *Z*- γ -alkylidene lactones **22**. The compatibility of copper(I) and iron(III) is not established yet. The authors¹⁵ suggest that copper(I) activates the alkyne moiety, but iron(III) interacts with the oxygen atom.



(J) Intermolecular cleavage of Meldrum's acid derivatives with nucleophiles is well known. Sapi et al.¹⁷ reported the tandem deprotection–intramolecular cyclization of Meldrum's acids **23** applied for the synthesis of lactones **24a** and lactame **24b**.



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