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Spotlight 455

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

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

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Introduction

5-Alkyl and 5,5-dialkyl Meldrum’s acids (1 and 2, respectively) are used in total synthesis. Monoalkylated derivatives 1 are synthesized from Meldrum’s acid 3 by condensation with aldehyde 2 (or by acylation 3) 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). Herein, reactions of Meldrum’s acids 1 and 2 proceeding with destruction of 1,3-dioxane cycle are reviewed.

Abstracts

(A) Hydrolysis of Meldrum’s acid 2 leads to malonic or acetic acid derivatives. 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.

(B) Detz et al. 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 NaBH₄ gives γ-substituted amines 8.

(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.

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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 SmI₂ in H₂O.exo-trig/exo-trig radical cyclization cascade occurs, when substituent R₂ 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 hydrolysis of Meldrum’s acids 2 (R² = 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 S₆,2 mechanism is proposed.11 Treatment of Meldrum’s acid derivatives 2 (R¹ = H, 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 O₂ in the presence of Cu(NO₃)₂.13 These reaction conditions are compatible with unsaturated bonds in substituent R¹. 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 2H-pyran-2-one 20. Hydrolysis of acetal moiety results in 4-formyl pyran-2-one 21.14

I Copper- and iron-11 or silver-catalyzed16 tandem cyclization–hydrolysis–decarboxylation of 5-propargyl Meldrum’s acid 2 is an efficient approach for the synthesis of Z-3-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.

References