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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.\(^1\) 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).\(^4\) 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.\(^5\) Radical reduction of compound 2 with SmI\(_2\) and H\(_2\)O forms 3-hydroxypropanoic acids 4 selectively. The first step is activation of Meldrum’s acid via coordination of SmI\(_2\) 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 hydroisilylation 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 H\(_2\) in the presence of Pd/C or with NaBH\(_3\)CO\(_3\) gives γ-substituted amines 8.\(^8\)

(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.\(^9\)

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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$_2$O.$^9$ 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 hydrolysis of Meldrum’s acids 2 (R$^2$ = 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 S$_2$2 mechanism is proposed.$^{11}$ Treatment of Meldrum’s acid derivatives 2 (R$^1$ = 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 O$_2$ in the presence of Cu(NO$_3$)$_2$. 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 thermalization 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-catalyzed$^{15}$ tandem cyclization–hydrolysis–decarboxylation of 5-propargyl Meldrum’s acid 2 is an efficient approach for the synthesis of Z-$^2$-alkylidene lactones 22. The compatibility of copper(I) and iron(III) is not established yet. The authors$^{15}$ suggest that copper(I) activates the alkynie 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.$^{15}$ reported the tandem deprotection–intramolecular cyclization of Meldrum’s acids 23 applied for the synthesis of lactones 24a and lactame 24b.

References