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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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 SmI_2 and H_2O 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 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 H_2 in the presence of Pd/C or with $\text{NaBH}(\text{OAc})_3$ gives γ -substituted amines **8**.⁸

i: 1) Et_3N (2 equiv), PhSiH_3 (3 equiv), THF, r.t.; 2) H_2O
ii: 1) Et_3N (2 equiv), PhSiH_3 (3 equiv), THF, r.t.; 2) $\text{R}^3\text{R}^4\text{NH}$ (2 equiv), MeOH; 3) H_2 , 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

(E) Derivatives of 5-(but-3-enyl) Meldrum's acid **10** are suitable for the synthesis of cyclopentanol **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**.

References

- (1) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, 37, 789.
- (2) Tóth, G.; Kövér, K. E. *Synth. Commun.* **1995**, 3067.
- (3) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, F. X. *J. Org. Chem.* **1980**, 45, 4606.
- (4) Chan, C.-C.; Huang, X. *Synthesis* **1982**, 452.
- (5) (a) Scheuer, P. J.; Cohen, S. G. *J. Am. Chem. Soc.* **1958**, 80, 4933. (b) Jacobs, R. T.; Wright, A. D.; Smith, F. X. *J. Org. Chem.* **1982**, 47, 3769.
- (6) Collins, K. D.; Oliveira, J. M.; Guazzelli, G.; Sautier, B.; De Grazia, S.; Matsubara, H.; Helliwell, M.; Procter, D. J. *Chem.–Eur. J.* **2010**, 16, 10240.
- (7) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. *Chem.–Eur. J.* **2011**, 17, 5921.
- (8) Frost, C. G.; Hartley, B. C. *J. Org. Chem.* **2009**, 74, 3599.
- (9) Frost, C. G.; Penrose, S. D.; Gleave, R. *Synthesis* **2009**, 627.
- (10) Sautier, B.; Lyons, S. E.; Webb, M. R.; Procter, D. J. *Org. Lett.* **2012**, 14, 146.
- (11) Wilsily, A.; Nguyen, Y.; Fillion, E. *J. Am. Chem. Soc.* **2009**, 131, 15606.
- (12) Mahoney, S. J.; Lou, T.; Bondarenko, G.; Fillion, E. *Org. Lett.* **2012**, 14, 3474.
- (13) Krabbe, S. W.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2012**, 14, 5932.
- (14) Akué-Gédu, R.; Hénichart, J.-P.; Couturier, D.; Rigo, B. *Tetrahedron Lett.* **2004**, 45, 9197.
- (15) Li, S.; Jia, W.; Jiao, N. *Adv. Synth. Catal.* **2009**, 351, 569.
- (16) Jia, W.; Li, S.; Yu, M.; Chen, W.; Jiao, N. *Tetrahedron Lett.* **2009**, 50, 5406.
- (17) (a) Dardennes, E.; Kovács-Kulyassa, Á.; Renzetti, A.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2003**, 44, 221. (b) Dardennes, E.; Kovács-Kulyassa, Á.; Boisbrun, M.; Petermann, C.; Laronze, J.-Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, 16, 1329. (c) Dardennes, E.; Gérard, S.; Petermann, C.; Sapi, J. *Tetrahedron: Asymmetry* **2010**, 21, 208.