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Acyl Meldrum's acid derivatives: application in organic synthesis

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This review is focused on an important class of Meldrum's acid derivatives commonly known as acyl Meldrum's acids. The preparation methods of these compounds are considered including the recently proposed and rather rarely used ones. The chemical properties of acyl Meldrum's acids are described in detail, including thermal stability and reactions with various nucleophiles. The possible mechanisms of these transformations are analyzed.
The bibliography includes 134 references.

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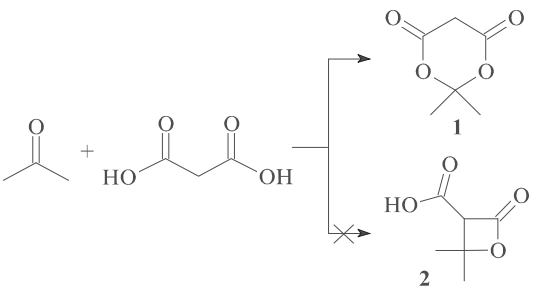
I. Introduction

2,2-Dimethyl-4,6-dioxo-1,3-dioxane **1** is a very useful reagent in the synthesis of heterocyclic compounds. This molecule is commonly known as Meldrum's acid with the name from its discoverer, Scottish scientist Andrew Norman Meldrum. It was synthesized in 1908 by the reaction between acetone and malonic acid in the presence of acetic anhydride and sulfuric acid (Scheme 1).[1] Taking into account the results of elemental analysis and the acidity (pK_a = 4.83 in water)[2,3] of the final compound, Meldrum misidentified its structure as the β-lactone of β-hydroxyisopropylmalonic acid (β,β-dimethyl-α-carboxy-β-propiolactone **2**). Only 40 years later, Davidson and Bernhard determined the correct structure of Meldrum's acid **1**.[4] This structure was finally confirmed in 1985 when the first crystal structure analysis of Meldrum's acid was carried out.[5] In addition, this investigation established the boat conformation of the six-membered ring of Meldrum's acid, which had been previously postulated based on the measured dipole moment.[6,7]

Scheme 1



Despite the fact that more than 100 years has passed from the discovery of Meldrum's acid, this reagent is still very important and popular in organic synthesis. It can react with various electrophiles at C(5) and nucleophiles at C(4) and C(6) atoms. It has been used as a reactant in the synthesis and design of a vast range of organic compounds having utility in the context of drugs and pharmaceuticals. The chemistry of Meldrum's acid and its derivatives has been described in comprehensive reviews[8–10] and in one very short review.[11] There are also some specialized subject reviews, like for example: Meldrum's acid in the synthesis of natural products,[12] Meldrum's acid in domino and multicomponent reactions,[13–15] Meldrum's acid in catalytic carbon–carbon bond forming processes[16] and Meldrum's acids in flash vacuum pyrolysis techniques.[17–19] The current review is focused solely on the chemistry of an important class of Meldrum's acid derivatives, acylated Meldrum's acids.

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