Introduction

Meldrum’s acid (1, isopropylidene malonate or 2,2-dimethyl-4,6-dioxo-1,3-dioxane), was first synthesized by Meldrum in 1908 and the structure was incorrectly assigned as the β-lactone of β-hydroxyisopropylmalonic acid (β,β-dimethyl-β-propiolactone-α-carboxylic acid). It was only 40 years later that Davidson and Bernhard assigned the correct structure. Meldrum’s acid has attracted considerable attention due to its high acidity (pKa = 4.97) and rigid cyclic structure. Acylated derivatives (synthetic equivalents of mixed ketenes) readily undergo alcoholysis to give β-keto esters. Alkylidene derivatives are strong electrophiles and can undergo Diels-Alder reactions with high diastereoselectivity. This versatile tool is a key intermediate for a large number of important building blocks and there remains much to discover.

Abstracts

(A) Substituted γ-pyrones 6 can be used in the synthesis of polycarbonate- and spiroketal-containing natural products and as cycloaddition substrates for the construction of polycyclic systems. Acylated Meldrum’s acid 3 reacts with a vinyl ether 4 with loss of acetone and ring closure to the pyrone ring followed by decarboxylation. The γ-pyrone can then be obtained refluxing with a PTSA–H₂O mixture (40–85% yield). A variety of acid chlorides and vinyl ethers can be used to prepare mono-, di- and trisubstituted pyrones.

(B) Optically active β-lactams 9 are obtained in excellent yields (up to 93%) and with complete stereoselectivity from Meldrum’s acid derivatives 7 and S-thiazolines 8.
(C) 2-Alkyl and 2-aryl 4-quinolones 14 can be prepared starting from Meldrum’s acid 1 via their derivatives bisalkylthiolydine 10 (32–77% yield) and alkyl- and arylthioalkylidene 11 (52–90% yield). Further reaction with arylamines 12 gives the aminothioalkylidene derivatives 13 (54–87% yield) which provide the quinolone products upon heating (60–96% yield).8

(D) The reaction of Meldrum’s acid and its 5-substituted derivatives 15 with conjugated azoalkenes 16, in the presence of triethylamine, produces the corresponding hydrazones 17 (71–98% yield) via 1,4-conjugate addition. The hydrazone products then undergo decarboxylative alcoholysis and simultaneous cyclization to give 3-unsubstituted and 3-monosubstituted 1-amino-1H-pyrrol-2-(3H)-ones 18 (55–96% yield).9

(E) C-Dialkylation of Meldrum’s acid and 5-benzyl Meldrum’s acid can be achieved through Mitsunobu dehydration using allylic and arylmethyl alcohols as alkylating agents. With primary alcohols, the alkylations always take place at the carbon bearing the hydroxyl group. For secondary alcohols, a catalytic amount of Pd(0) must be added to enhance the regioselectivity of C-alkylation over O-alkylation. Using (Ph3P4)Pd(0) as a catalyst, the reaction occurs specifically at the less hindered carbon, and the configuration of the resulting double bond is always trans.10

(F) 5-Substituted 3-isoxazolols 27 can be synthesized in a three-step procedure starting from Meldrum’s acid. After conversion into the acylated derivative 24 (74–100% yield), aminolysis with N,O-bis(tert-butoxycarbonyl)hydroxylamine (25) leads to the N,O-diBoc β-keto hydroxamic acid 26 (53–91% yield). Treatment with hydrochloric acid promotes cyclization to the desired product (76–99% yield).11

(G) The pyrolysis of Meldrum’s acid derivatives in solution and in gas phase takes place by loss of acetone and carbon dioxide to provide ketene intermediates. In particular, methylene derivatives often provide methyleneketenes, which act as substrates for internal hydrogen transfer, leading to cyclization reactions. These cyclization reactions are used for the efficient preparation of a diverse range of cyclic compounds such as quinolinones, 3-hydroxythiophenes, naphthols, azepin-3(2H)-ones or pyrrolizin-3-ones, initiated respectively by 1,3-, 1,4-, 1,5-, 1,6 or 1,7-prototropic shifts.12

References

(1) Meldrum, A. N. J. Chem. Soc. 1908, 93, 598.