# Meldrum's Acid

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1 Introduction

In 1908, A. N. Meldrum reported that the condensation of malonic acid with acetone, in acetic anhydride containing a small amount of sulphuric acid, gave a white crystalline solid, $C_6H_8O_4$, which *titrated* as a *monobasic* acid and lost carbon dioxide on heating.[1] He reasonably stated that 'there can hardly be a doubt' that the compound was the carboxylic acid (1). Sadly, this structure proved to be quite wrong, though forty years were to elapse before it was deduced that the condensation must involve only the carboxyl groups of the malonic acid. On this basis, Davidson and Bernhard[2] correctly assigned the structure of 'Meldrum's acid' as 2,2-dimethyl-1,3-dioxan-4,6-dione (2), whose properties therefore relate to those of other cyclic 1,3-diones such as dimedone (3) and barbituric acid (4).

(1)   (2)   (3)   (4)
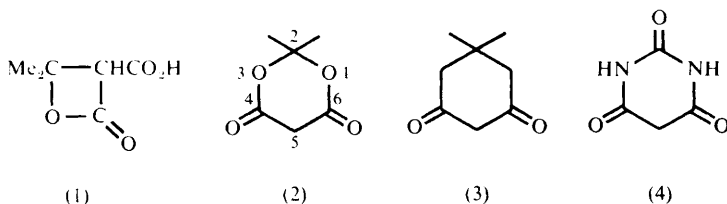
2 Preparation

The original method is invariably used for the preparation of 1,3-dioxan-4,6 diones[2] (Scheme 1). The procedure has some generality, and derivatives have

Scheme 1
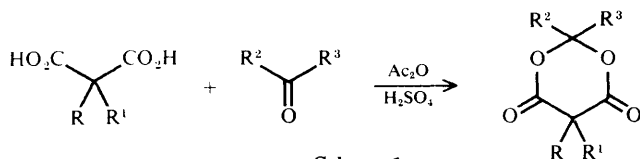
been made by condensing aliphatic[3] or aromatic[4] ketones, or aryl aldehydes,[5]

[1] A. N. Meldrum, *J. Chem. Soc.*, 1908, **93**, 598.
[2] D. Davidson and S. A. Bernhard, *J. Amer. Chem. Soc.*, 1948, **70**, 3426.
[3] B. Eistert and F. Geiss, *Chem. Ber.*, 1961, **94**, 929.
[4] J. Swoboda, J. Derkosch, and F. Wessely, *Monatsh.*, 1960, **91**, 188.
[5] A. Michael and N. Weiner, *J. Amer. Chem. Soc.*, 1936, **58**, 680.

with un-, mono-,[3,6] or di-substituted[2,7] malonic acids. The reaction is apparently ineffective for all alkyl aldehydes.

Despite the novelty of the reaction (Scheme 1), its mechanism remains un-investigated, though it has long been recognized that the first step involves acid catalysed formation of a mixed anhydride of malonic and acetic acids.[6,8]

An alternative—and unusual—source of Meldrum's acid is from the action of carbon suboxide on acetone in the presence of oxalic acid.[9] The function of the latter seems to be to supply the elements of water needed for the stoicheiometry.[10]

3 Physical and Chemical Properties

By the standards of organic chemistry 1,3-dioxan-4,6-dione derivatives are indeed strong acids. Meldrum's acid itself (pK 4.83)[11] is comparable in strength to acetic acid (pK 4.76) and is some ten pK units more acidic than acyclic malonate esters. The explanation of this facile proton loss—as with dimedone (pK 5.2)[2]—lies in the stability of the resultant anion (5), in which the π-orbitals are rigidly held in the ideal configuration for overlap. The meneidic[12] properties of this

(5)
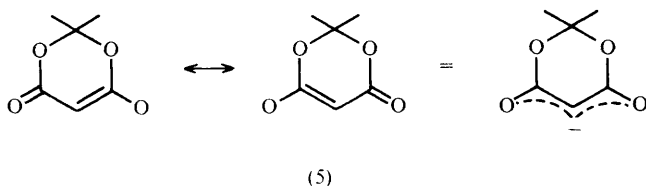
profoundly stable structure rationalize much of Meldrum's acid chemistry. Surprisingly, the tautomeric properties of dimedone and Meldrum's acid are quite different. The former exists predominantly in the mono-enol form, whereas Meldrum's acid is overwhelmingly ($>99.5\%$) the diketo tautomer.[13] It seems that no special explanation may be required for this anomaly, since esters are generally enolized to a much smaller extent than ketones.[14]

The problem of the conformation of the 1,3-dioxan-4,6-dione system has been approached by n.m.r.[15] and dipole-moment[16] methods. Although there is no

[6] E. Ott, *Annalen*, 1913, **401**, 159.
[7] P. J. Scheuer and S. G. Cohen, *J. Amer. Chem. Soc.*, 1958, **80**, 4933.
[8] A. Michael and J. Ross, *J. Amer. Chem. Soc.*, 1933, **55**, 3684.
[9] O. Diels, R. Beckmann, and G. Tönnies, *Annalen*, 1924, **439**, 76.
[10] T. Kappe and E. Ziegler, *Angew. Chem.*, 1974, **86**, 529; *Angew Chem. Internat. Edn.*, 1974, **13**, 491.
[11] (a) K. Pihlaja and M. Seilo, *Acta. Chem. Scand.*, 1968, **22**, 3053; (b) K. Pihlaja and M. Seilo, *Acta. Chem. Scand.*, 1969, **23**, 3003.
[12] D. Lloyd and D. R. Marshall, *Angew. Chem.*, 1972, **84**, 447; *Angew. Chem. Internat. Edn.*, 1972, **11**, 404.
[13] M. Eigen, G. Ilgenfritz and W. Kruse, *Chem. Ber.*, 1965, **98**, 1623.
[14] A. Gero, *J. Org. Chem.*, 1954, **19**, 1960.
[15] P. Äyräs and A. Partanen, *Finn. Chem. Letters*, 1976, 110.
[16] (a) D. Körberl and P. Schuster, *Monatsh.*, 1972, **103**, 1483; (b) D. Körberl and O. E. Polansky, *Monatsh.*, 1973, **104**, 1421; (c) E. N. Klimovitskii, L. K. Yuldasheva, and B. A. Arbuzov, *Izvest. Akad. Nauk. S.S.S.R.*, Ser. khim., 1973, 1527.

overall agreement as yet, the consensus of opinion favours a boat structure for most derivatives, with a chair structure for 2,2,5,5-tetrasubstituted compounds. This last conclusion is confirmed by the *X*-ray structure of an esoteric derivative.[17] Other physical properties of the system which have been discussed include u.v.,[3] i.r.,[18] mass,[19] [1]H-,[20] and ^{13}C-n.m.r.[21] spectra.

The chemistry of Meldrum's acid is dominated by its susceptibility to nucleophilic attack at positions 4 and 6 and to electrophilic attack (*via* the anion) at position 5. Simple hydrolysis to the malonic acid is a common example of nucleophilic attack, and may be accomplished under acidic or basic conditions.[1] The reaction mechanism has been studied.[11] Use of alcoholic hydrogen chloride yields the malonate diester,[3,4] while 'solvolysis' by phenols gives monoaryl esters which can be easily converted to diaryl esters.[22] Ketones react with Meldrum's acid by displacement of acetone to give 2,2-disubstituted-1,3-dioxan-4,6-diones.[23] Nitrogen nucleophiles give a possible route to monoamides of malonic acid,[24] although the cleavage of the ring may be followed by decarboxylation, as is the case with aniline,[1] and Hector's base[25] (Scheme 2). Fragmentation of the ring may also be accomplished directly by pyrolysis.

$$+ \; RNHCOCH_2CO_2H$$
$$\longrightarrow CO_2 + RNHCOCH_3$$
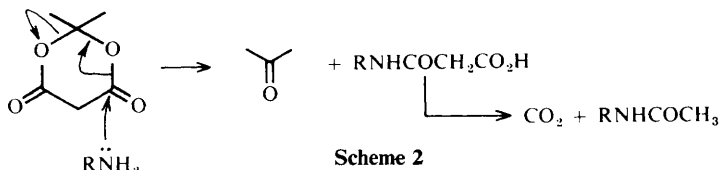
Scheme 2

In contrast to these examples, the reactions of Meldrum's acid with electrophiles generally leave the ring intact. Scheme 3 gives the flavour of the chemistry involved, which is considered in detail in later sections. Reaction of electrophiles at the carbonyl oxygen does not give stable cyclic products.[4,26,27]

4 5,5-Dialkyl Derivatives

These derivatives may be made by standard condensation methods, but an important alternative route is by the reaction of Meldrum's anion (5) with alkyl[6]

[17] P. G. Jones and O. Kennard, *Cryst. Struct. Comm.*, 1977, **6**, 97.
[18] (*a*) R. A. Abramovitch, *Canad. J. Chem.*, 1959, **37**, 361; (*b*) E. E. Ernstbrunner, *J. Mol. Structure*, 1973, **16**, 499.
[19] H. Egger, *Monatsh.*, 1967, **98**, 1245.
[20] I. Schuster and P. Schuster, *Tetrahedron*, 1969, **25**, 199.
[21] P. Äyräs, *Acta. Chem. Scand.*, 1976, **B30**, 957.
[22] (*a*) H. Junek, E. Ziegler, U. Herzog, and H. Kroboth, *Synthesis*, 1976, 332; (*b*) G. Uray, H. Junek and E. Ziegler, *Monatsh.*, 1977, **108**, 423.
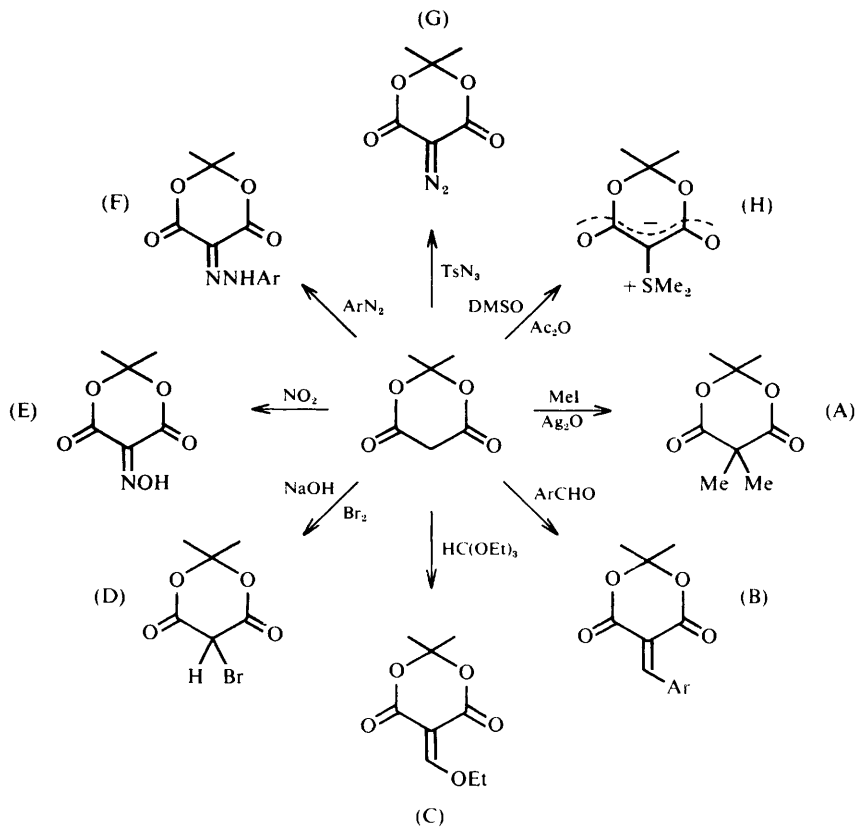[23] E. Ziegler, H. Junek, and H. Kroboth, *Monatsh.*, 1976, **107**, 317.
[24] (*a*) C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, 1954, **76**, 5563; (*b*) P. Crooy, R. De, Neys, J. Eliaers, R. Liveyns, G. Simonet, and J. Vandevelde, *Bull. Soc. chim. belges.*, 1977, **86**, 991.
[25] A. R. Butler, *J. Chem. Res.* (S), 1978, 50; (M), 0855.
[26] S. I. Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1961, 2042.
[27] G. A. Bihlmayer, P. Schuster, and O. E. Polansky, *Monatsh*, 1966, **96**, 145.

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Scheme 3

(or activated heterocyclic[28]) halides [Scheme 3, equation (A)]. This almost invariably[29] gives the dialkyl derivative, and the procedure has been logically extended to the preparation of *spiro* compounds from dibromoalkanes.[30]

Since the formation of anions such as (5) cannot compete, hydrolysis of 5,5-disubstituted-1,3-dioxan-4,6-diones becomes almost instantaneous[31] under basic conditions. Malonate mono- and di-esters are also available, by standard methods.

[28] (a) F. X. Smith and G. G. Evans, *Tetrahedron Letters*, 1972, 1237; (b) F. X. Smith and G. G. Evans, *J. Heterocyclic Chem.*, 1976, **13**, 1025; (c) F. X. Smith and A. Scoville, *J. Heterocyclic Chem.*, 1977, **14**, 1081.
[29] R. B. Mane and G. S. K. Rao, *Chem. and Ind.*, 1976, 786.
[30] J. A. Hedge, C. W. Kruse, and H. R. Snyder, *J. Org. Chem.*, 1961, **26**, 992.
[31] K. Pihlaja and J. Ketola, *Finn. Chem. Letters*, 1976, 123.

Of particular interest are the spiro cyclopropyl derivatives[32] *e.g.* (14) whose Michael-type reactions with nucleophiles are reminiscent of those of the 5-methylene compounds (Section 5). Intramolecular decomposition of the ring-opened product may lead to lactones[32,33] (Scheme 4) or lactams.[32]

Scheme 4
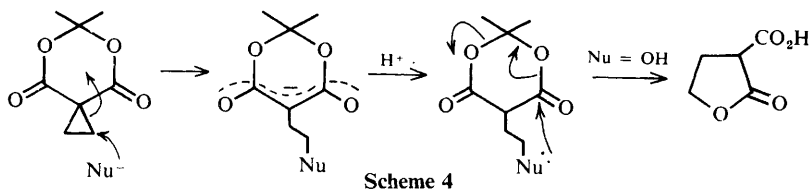
5 5-Methylene Derivatives[34]

In some instances, reaction of a carbonyl compound (or its equivalent) with malonic acid proceeds directly by a double condensation to give 5-methylene derivatives of 1,3-dioxan-4,6-diones[5,35] and a corresponding procedure using carbon suboxide is known.[36] However, the preparative method of choice involves Knoevenagel condensation of Meldrum's acid with a carbonyl component [Scheme 3, equation (B)]. This reaction proceeds easily for aromatic[37,38] or hindered aliphatic aldehydes[38] or aliphatic ketones,[39,40] though aromatic ketones require activation either by the use of a catalyst,[41] or by their prior conversion to a ketimine.[42] Simple aliphatic aldehydes often give the 2:1 condensation product, by Michael addition of Meldrum's acid to the intermediate 5-methylene compound[3,39]—a process which is of paramount importance also in dimedone chemistry. In these examples, the 5-methylene compound is available by the cunning use of methoxide as a competitive nucleophile in the Michael addition. The adduct (6; Nu = OMe) so obtained may be decomposed with acid to the required product.[43]

The activation of a carbonyl compound by *O*-methylation is particularly important when the resulting salt is resonance stabilized. Base catalysed condensation of such cations with Meldrum's acid has afforded 5-methylene

[32] (*a*) S. Danishevsky and R. K. Singh, *J. Amer. Chem. Soc.*, 1975, **97**, 3239; (*b*) S. Danishevsky and R. K. Singh, *J. Org. Chem.*, 1975, **40**, 3807; (*c*) R. K. Singh and S. Danishevsky, *J. Org. Chem.*, 1976, **41**, 1668.

[33] F. P. Schmook and O. E. Polansky, *Monatsh.*, 1969, **100**, 1631.

[34] For a review, see F. J. Kunz, P. Mzrgaretha, and O. E. Polansky, *Chimia (Switz.)*, 1970, **24**, 165.

[35] D. T. Mowry, *J. Amer. Chem. Soc.*, 1947, **69**, 2362.

[36] H. Hopff and G. Hegar, *Helv. Chim. Acta*, 1961, **44**, 2016.

[37] E. J. Corey, *J. Amer. Chem. Soc.*, 1952, **74**, 5897.

[38] P. Schuster, O. E. Polansky, and F. Wessely, *Monatsh.*, 1964, **95**, 53.

[39] J. A. Hedge, C. W. Kruse, and H. R. Snyder, *J. Org. Chem.*, 1961, **26**, 3166.

[40] G. Swoboda, J. Swoboda, and F. Wessely, *Monatsh.*, 1964, **95**, 1283.

[41] G. J. Baxter and R. F. C. Brown, *Austral. J. Chem.*, 1975, **28**, 1551.

[42] G. A. Bihlmayer, F. J. Kunz, and O. E. Polansky, *Monatsh.*, 1966, **97**, 1293.

[43] P. Margaretha and O. E. Polansky, *Tetrahedron Letters*, 1969, 4983.

compounds derived from cyclopropenium,[44] pyrylium,[45] and other hetero-cyclic[46] salts. Eistert has made similar products from chloropyrylium salts,[47] and even, in a peculiar redox reaction, from the unsubstituted pyrylium salt itself.[48]
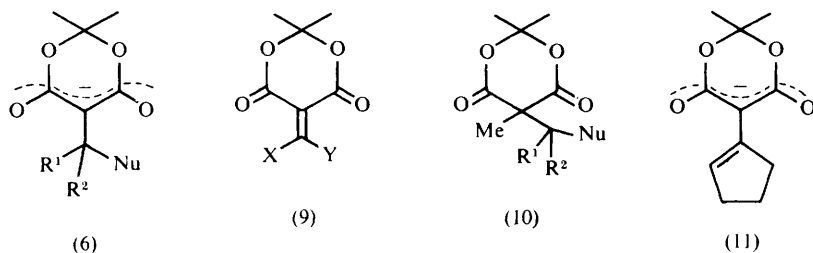
The parent 5-methylene compound (7) is apparently highly reactive, and cannot be prepared by standard methods. The sequence which was ultimately successful (Scheme 5) employs a unique oxidative process in the key step.[49]
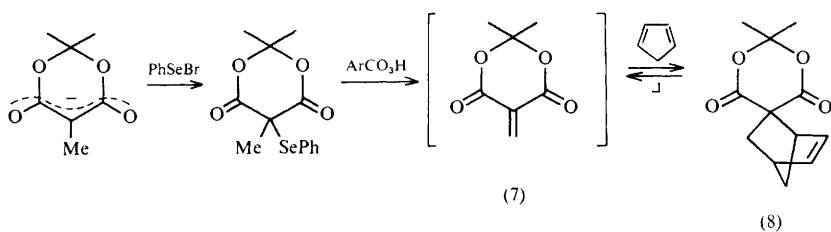
Scheme 5

A number of functional derivatives of 5-methylene compounds are known. Thus (9; X = H, Y = OEt) is readily available from Meldrum's acid and triethylorthoformate[50] [Scheme 3, equation (C)], while addition of an amine to this reaction mixture gives the amino compounds (9; X = H, Y = NHR) in a one-pot synthesis of wide generality.[50,51] The diamino compound (9; X = Y = NHC$_6$-H$_{11}$), which is an extended urea, can be made from dicyclohexylcarbodi-imide,[52] and the 'amides' (9; X = OH, Y = NHR) from isocyanates.[53]

A remarkable property of 5-methylene derivatives in general is that like the parent 1,3-dioxan-4,6-dione, they are unexpectedly strong acids.[34,54] In this

[44] T. Eicher, T. Pfister, and N. Kreuger, *Org. Prep. Proc. Internat.*, 1974, **6**, 63 (*Chem. Abs.*, 1974, **81**, 3403).
[45] (a) J. A. Van Allan and G. A. Reynolds, *J. Heterocyclic Chem.*, 1971, **8**, 803; (b) J. A. Van Allan and G. A. Reynolds, *J. Heterocyclic Chem.*, 1972, **9**, 669; (c) J. R. Wilt, G. A. Reynolds, and J. A. Van Allan, *Tetrahedron*, 1973, **29**, 795.
[46] R. Neidlein and M. H. Salzl, *Annalen*, 1977, 1938.
[47] B. Eistert and T. J. Arackal, *Chem. Ber.*, 1975, **108**, 2397.
[48] B. Eistert, A. Schmitt, and T. J. Arackal, *Chem. Ber.*, 1976, **109**, 1549.
[49] R. F. C. Brown, F. W. Eastwood, and G. L. McMullen, *Austral. J. Chem.*, 1977, **30**, 179.
[50] G. A. Bihlmayer, G. Derflinger, J. Derkosch, and O. E. Polansky, *Monatsh.*, 1967, **98**, 564.
[51] Sterling Drug Inc., Brit. 1,147,759 (*Chem. Abs.*, 1969, **71**, 70 125).
[52] A. Stephen, *Monatsh.*, 1966, **97**, 695.
[53] U. Herzog and H. Reinshagen, *Eur. J. Med. Chem.-Chim. Ther.*, 1975, **10**, 323.
[54] P. Schuster, A. Stephen, O. E. Polansky, and F. Wessely, *Monatsh.*, 1968, **99**, 1246.

case, it is a manifestation of Lewis acidity,[55] due to the formation of pseudobase adducts or anbadons (6) for which the driving force is clearly the meneidic tendency of the stable anion. The whole range of hard and soft nucleophiles, from alkoxides[55] to phosphines[56] show this behaviour. The pseudobase may be quenched with iodomethane to give the alkylated products (10).[40,56] In some cases where the 5-methylene compound has a β-hydrogen available, proton loss (*i.e.* Brønsted acid behaviour) can compete with pseudobase formation [*e.g.* (11)].[57]

Clearly the pseudobases (6; Nu = OH) are simply intermediates in the hydrolysis of 5-methylene derivatives to Meldrum's acid and the carbonyl component, and the kinetics and mechanism of this process have been studied.[58] Under certain conditions, the heterocyclic ring may be preferentially hydrolysed, providing a route to 2-methylenemalonates.[37,58] Reduction of 5-methylene-1,3-dioxan-4,6-diones to the corresponding 5-alkyl compound is possible catalytically,[30] or using lithium aluminium hydride.[59] Reaction with $Fe_2(CO)_9$ gives a π-complex,[60] while the labile formyl derivative (9; X = H, Y = OH), produced by hydrolysis of the ethoxy compound, gives a chelate with copper acetate.[50]

The 5-methylene derivatives of Meldrum's acid are excellent dienophiles, and give a potential route to cyclohexenes with unusual substituents.[49,61] This reaction has recently been exploited by two groups in natural product synthesis[62,63] and further developments in this area are awaited with interest. The 1,3-dipolar cycloaddition of diazoalkanes[64] has been studied in great detail. In all cases, cyclopropane derivatives are obtained, although the reaction may proceed twice[65] (Scheme 6; $R^1 = Ph$, $R^2 = H$) and traces of further alkylation can sometimes be detected.[33] That the initial reaction is indeed a standard 1,3-dipolar cycloaddition, was proved by an elegant kinetic study,[66] whose results were vindicated by the isolation of an intermediate pyrazoline[67] (Scheme 6; $R^1 = Pr^i$, $R = CO_2Et$).

6 5-Halogeno Derivatives

Although the 5-chloro compound has been prepared,[68] the known chemistry of 5-halogeno derivatives of Meldrum's acid is almost wholly associated with brominated materials. Both the 5-bromo and the 5,5-dibromo compounds are formed by direct halogenation of Meldrum's acid in the presence of one[6] or

[55] P. Schuster, O. E. Polansky, and F. Wessely, *Tetrahedron Suppl. 8 Part 2*, 1966, 463.
[56] P. Margaretha and O. E. Polansky, *Monatsh.*, 1969, **100**, 576.
[57] J. Leitich, P. Schuster, and A. Eitel, *Tetrahedron*, 1967, **23**, 2221.
[58] P. Margaretha, P. Schuster, and O. E. Polansky, *Tetrahedron*, 1971, **27**, 71.
[59] A. Stephen and F. Wessely, *Monatsh.*, 1967, **98**, 184.
[60] E. Korner von Gustorf, O. Jaenicke, and O. E. Polansky, *Z. Naturforsch. B.*, 1972, **27**, 575.
[61] F. J. Kunz and O. E. Polansky, *Monatsh.*, 1969, **100**, 920.
[62] W. G. Dauben, A. P. Kozikowski, and W. T. Zimmermann, *Tetrahedron Letters*, 1975, 515.
[63] G. A. Mock, A. B. Holmes, and R. A. Raphael, *Tetrahedron Letters*, 1977, 4539.
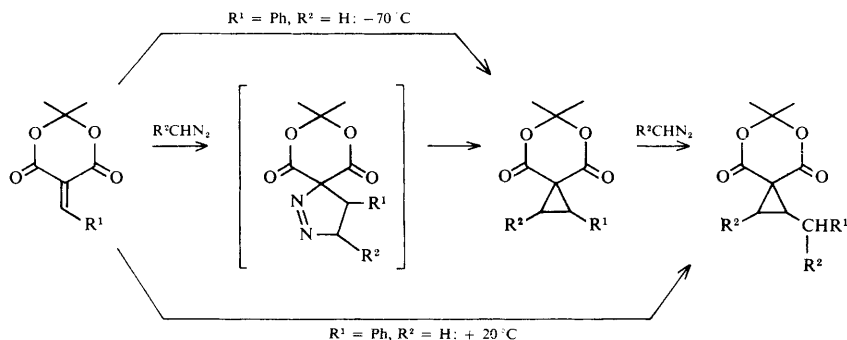[64] F. Wessely and A. Eitel, *Monatsh.*, 1964, **95**, 1577.
[65] G. Swoboda, A. Eitel, J. Swoboda, and F. Wessely, *Monatsh.*, 1964, **95**, 1355.
[66] F. Nierlich, P. Schuster, and O. E. Polansky, *Monatsh.*, 1971, **102**, 438.
[67] H. Kisch, F. Mark, and O. E. Polansky, *Monatsh.*, 1971, **102**, 448.
[68] O. Y. Neiland and B. Y. Karele, *Zhur. org. Khim.*, 1971, 1674.

$R^1 = Ph, R^2 = H: -70\,°C$

$R^1 = Ph, R^2 = H: +20\,°C$

Scheme 6

two[69] moles of base respectively [Scheme 3, equation (D)]. A unique situation pertains to iodine-containing derivatives, since a phenyliodonium ylid is well characterized[68] yet no classical iodo compound has ever been reported.

Treatment of the 5-bromo-derivative (12; R = H) with nucleophiles can give rise to three possible modes of reaction (Scheme 7). The trivial case, in which
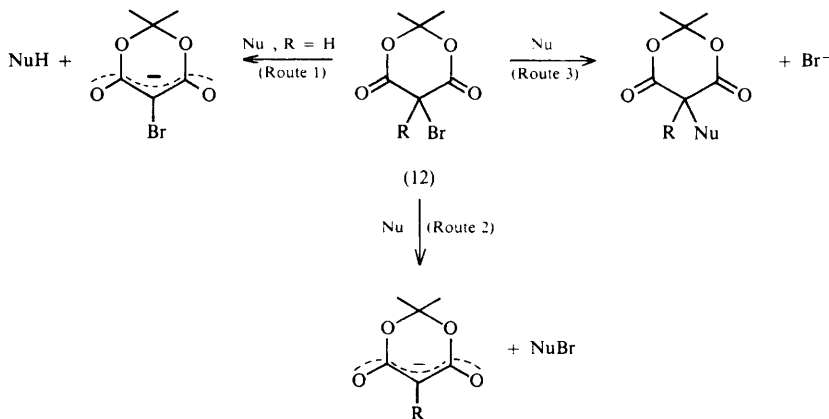

Scheme 7

the nucleophile acts as a base, is the dominant route even for such mild bases as aniline.[69] The ubiquitous anion may also be formed by nucleophilic attack at the halogen atom (Scheme 7, route 2). This route is particularly important

[69] H. R. Snyder and C. W. Kruse, *J. Amer. Chem. Soc.*, 1958, **80**, 1942.

for (12; R = Me), the use of which as a brominating agent for carbanions has been recommended.[70] Trost's process of 'transfer alkylation' is a subtle application of this principle, in which the anion leaving group re-attacks the brominated substrate at a remote site, to complete a chain extension sequence.[71] Although there is no unambiguous example of a simple S_N reaction from (12; R = H), this mechanism can apparently give rise to products with hard nucleophiles and (12; R = Me).[72]

The 5,5-dibromo compound (12; R = Br) is also a useful brominating agent,[73] but little else is known of its chemistry save for two astonishing reactions.[69] Basic hydrolysis gives carbon tetrabromide in a process which, for its total destruction of a stable system to C_1 fragments is reminiscent of the bromopicrin reaction.[74] Secondly, simple dissolution in dimethylformamide yields the coupled derivative (13) in 30% yield. The mechanisms of these reactions are overdue for investigation.
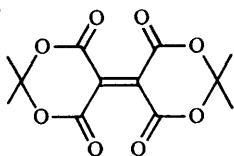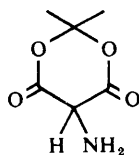
(13)   (14)

7 5-Nitrogen-containing Derivatives

Although Davidson and Bernhard reported a colour reaction of Meldrum's acid with sodium nitrite,[2] it was not until 1961 that two groups independently isolated the oxime as an unstable yellow solid[3,26] [Scheme 3, equation (E)]. Its reduction over platinum dioxide provides the only known route to the 5-amino compound[3] (14), but otherwise the properties of this compound are unknown. Similarly little studied are the hydrazones, prepared by coupling with appropriate diazo compounds[75] or diazonium salts[3] [Scheme 3, equation (F)]. The parent 4,5,6-trione of which these compounds are formal derivatives, remains unprepared, despite a number of attempts.[76,77]

The most important nitrogen-containing derivative of Meldrum's acid is the diazo-compound (15), formed by diazotization of the amine,[3] or, more conveniently, by direct reaction with *p*-toluenesulphonyl azide[75] [Scheme 3, equation (G)]. Photolysis or thermolysis of (15) generates 'Meldrum's carbene'[78] which

[70] (a) J. P. Marino, *J.C.S. Chem. Comm.*, 1973, 861; (b) E. Vedejs, W. R. Wilber, and R. Twieg, *J. Org. Chem.*, 1977, **42**, 401.
[71] B. M. Trost and L. S. Melvin jun., *J. Amer. Chem. Soc.*, 1976, **98**, 1204.
[72] R. F. C. Brown, F. W. Eastwood, S. T. Lim, and G. L. McMullen, *Austral. J. Chem.*, 1976, **29**, 1705.
[73] R. Bloch, *Synthesis*, 1978, 140.
[74] A. R. Butler and H. F. Wallace, *J. Chem. Soc. (B)*, 1970, 1758.
[75] (a) M. Regitz and D. Stadler, *Annalen*, 1965, **687**, 214; (b) M. Regitz, A. Liedhegener, and D. Stadler, *Annalen*, 1968, **713**, 101.
[76] M. Regitz and H-G. Adolph, *Annalen*, 1969, **723**, 47.
[77] A. Hochrainer and F. Wessely, *Monatsh.*, 1966, **97**, 1.
[78] M. Jones Jr., W. Ando, M. E. Hendrick, A. Kulczycki jun., P. M. Howley, K. F. Hummel, and D. S. Malament, *J. Amer. Chem. Soc.*, 1972, **94**, 7469.

may be trapped with soft nucleophiles to give ylides,[79,80] or with olefins in the presence of triplet sensitizer to give the predicted *trans* cyclopropane derivatives.[78] In the absence of trapping agent, the normal ketocarbene Wolff ring-contraction takes place (Scheme 8), though under extreme conditions, the system may be totally destroyed, with acetone and carbon monoxide as dominant products.[81]

Scheme 8

8 Ylides

Meldrum's acid ylides (16) of the sulphonium,[77,79] selenonium,[82] arsonium,[80] and iodonium[68] series have been prepared. Their syntheses require either condensation of Meldrum's acid itself with a highly oxidized hetero-component (possibly generated *in situ*),[83] or the decomposition of the diazo-compound (15) in the presence of the hetero-component itself (Scheme 9). In addition, the

a; M = S, R = dialkyl, n = 2 (X = OAc)
b; M = Se, R = Me, n = 2, X = Br
c; M = As, R = Ph, n = 3 (X = OAc)
d; M = I, R = Ph, n = 1, X = OAc

Scheme 9

dimethylsulphonium ylid (16a) is available from the bromo compound[77] (12; R = H) and from the iodonium ylid[68] (16d).

The most noteworthy property of these ylides is their remarkable stability, inevitably associated with the dipolar canonical form (16).

All are crystalline solids which may be handled without special precautions. The dimethylsulphonium and phenyliodonium ylides (16a) and (16d) show

[79] W. Illger, A. Liedhegener, and M. Regitz, *Annalen.*, 1972, **760**, 1.
[80] I. Gosney and D. Lloyd, *Tetrahedron*, 1973, **29**, 1697.
[81] S. L. Kammula, H. L. Tracer, P. B. Shevlin, and M. Jones jun., *J. Org. Chem.*, 1977, **42**, 2931.
[82] E. Ernstbrunner and D. Lloyd, *Annalen*, 1971, **753**, 196.
[83] J. I. G. Cadogan and I. Gosney, *JCS Perkin I*, 1974, 466.

pronounced thermal stability by comparison with related systems, while the stability of the selenonium and arsonium ylides (16b) and (16c) is reflected in their lack of reactivity with aldehydes in attempted Wittig reactions.

The iodonium ylid (16d) gives 5-chloro-1,3-dioxan-4,6-dione on treatment with hydrogen chloride.[68]

9 Pyrolysis

The pyrolysis of Meldrum's acid derivatives has long been known to give ketenes.[6] The mechanism presumably involves homolysis of a C—O bond, followed by cleavage of acetone and carbon dioxide, both of which are found in the pyrolysate along with the ketene.[84] (Scheme 10). Using flash vacuum
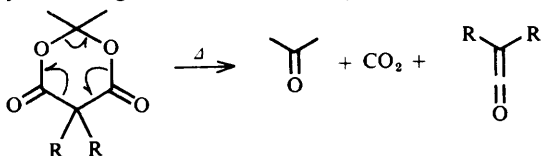
Scheme 10

pyrolysis, this route may be used to prepare ketenes which are difficult to obtain by conventional methods—notably cyclopropylketene[85]—but the technique has been applied most particularly to the generation of methyleneketenes from 5-methylene derivatives. Thus phenylmethyleneketene (17) has been identified by its i.r. spectrum at $-196\,°C$, by its dimerization to the cyclobutandione derivative (18), and by various trapping experiments[84] (Scheme 11). Methyleneketenes
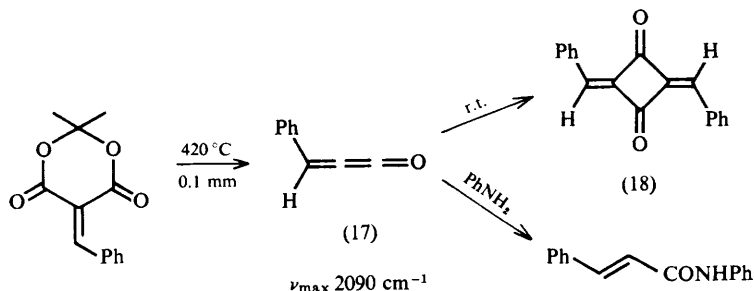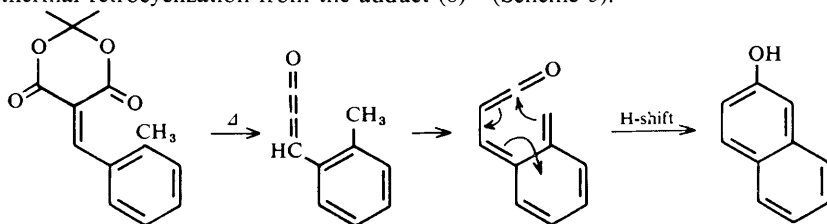

Scheme 11

are available thus, in two steps, from aryl aldehydes[84] and ketones[86] or alkyl ketones:[84] those derived from aliphatic aldehydes tautomerize if possible to vinyl ketenes.[84] Other more interesting intramolecular reactions which may take place in the presence of a suitable trapping group, include an elegant phenol

[84] R. F. C. Brown, F. W. Eastwood, and K. J. Harrington, *Austral. J. Chem.*, 1974, **27**, 2373.
[85] G. J. Baxter, R. F. C. Brown, F. W. Eastwood, and K. J. Harrington, *Tetrahedron Letters*, 1975, 4283.
[86] R. F. C. Brown, F. W. Eastwood, K. J. Harrington, and G. L. McMullen, *Austral. J. Chem.*, 1974, **27**, 2393.

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synthesis[87] (Scheme 12). Recently, the parent methyleneketene has been identified from the pyrolysis of the very reactive compound (7), itself generated *in situ* by thermal retrocyclization from the adduct (8)[49] (Scheme 5).

Scheme 12

Pyrolysis of Meldrum's acid derivatives at high temperatures causes decarbonylation of the intermediate ketene to give a carbene, which then rearranges to valence-satisfied products. Reactions of this type include the generation of acyloxycarbenes and their rearrangement to α-diketones in excellent yield (Scheme 13).[72] Similarly, methylenecarbenes generated from methylneeketenes
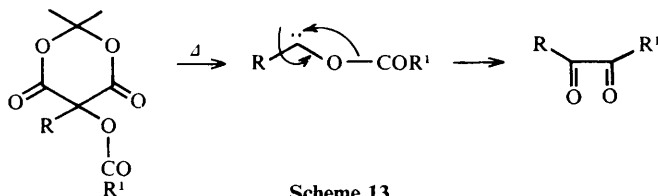
Scheme 13

show hydrogen migration to give acetylenes, although intramolecular cyclization products may also be detected in favourable instances.[86]

10 Some Synthetic Uses

As with simple malonic ester syntheses, the presence in Meldrum's acid of a highly active methylene group adjacent to an ester function, allows the molecule to be manipulated to give a wide range of possible products. At the simplest level, Meldrum's acid can act as a methylene synthon by hydrolysis and exhaustive decarboxylation of its derivatives. For certain heterocyclic systems, the conditions needed for this sequence are surprisingly mild[28,45] (Scheme 14). Intermolecular cleavage by other nucleophiles can also give useful products; a particularly beautiful example is Dauben's two step synthesis of δ-damascone[62] (19) Scheme 15). This is the only known example of a potentially general ketone synthesis from Meldrum's acid.

We have already met examples of intramolecular nucleophilic attack (Scheme 4). Under extreme conditions, cleavage of acetone may be followed by decarboxylation to give lactams[88] (Scheme 16); in these cases, Meldrum's acid acts as the synthetic equivalent of ketene.

[87] (a) R. F. C. Brown and G. L. McMullen, *Austral. J. Chem.*, 1974, **27**, 2385; (b) G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Austral. J. Chem.*, 1974, **27**, 2605.
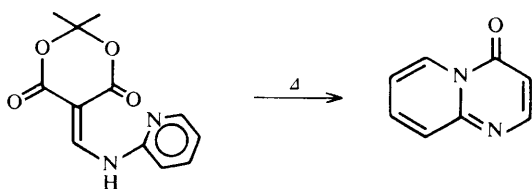[88] G. Y. Lesher, U.S. 3,907,798 (*Chem. Abs.*, 1976, **84**, 44130).
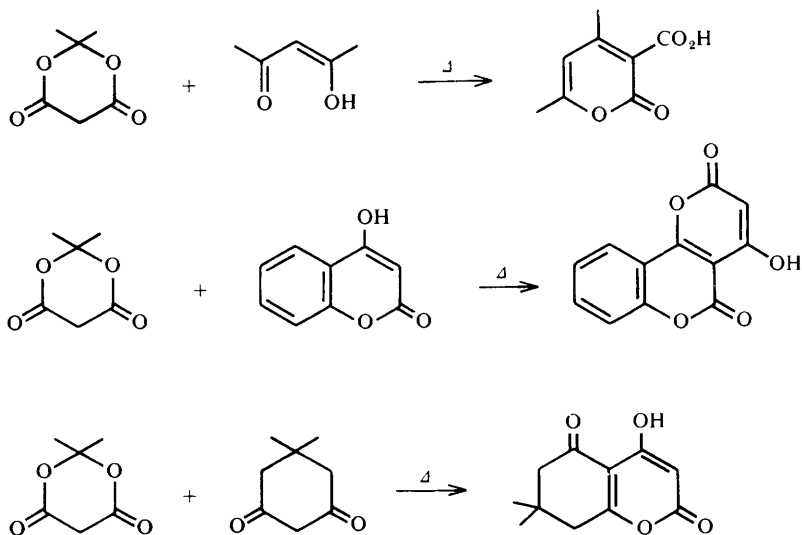
356
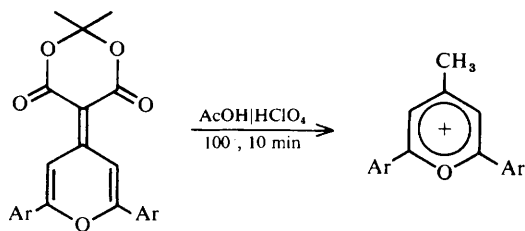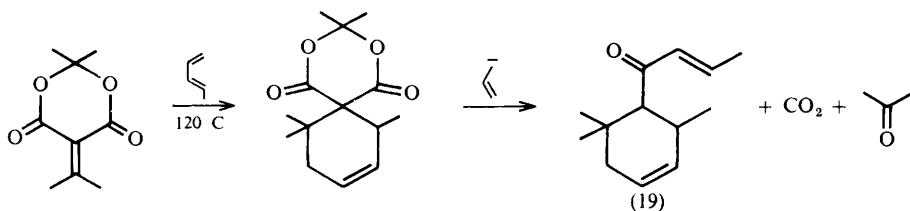
Scheme 14

Scheme 15

Scheme 16

Scheme 17

Finally, a widespread use of Meldrum's acid in heterocyclic chemistry is in the preparation of α-pyrones and 2-pyridones. A variety of such reactions is known, and some are of formidable complexity, but a common feature is that the Meldrum's acid behaves as a C_3O_2 synthon[45,89,90] (Scheme 17).

[89] (a) E. Ziegler, H. Junek, and U. Herzog, *Monatsh*, 1971, **102**, 1096; (b) E. Ziegler, H. Junek and U. Herzog, *Monatsh*, 1971, **102**, 1626.
[90] O. S. Wolfbeis, *Monatsh*, 1977, **108**, 499.