Synthetic Applications of the Pyrolysis of Meldrum’s Acid Derivatives

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Received 11 July 2001

Abstract: The pyrolysis of Meldrum’s acid (2,2-dimethyl-1,3-dioxane-4,6-dione) 1 derivatives in solution and in the gas-phase takes place by loss of acetone and carbon dioxide to provide ketene intermediates. In particular, methylene Meldrum’s acid derivatives 7 often provide methyleneketenes 8, which act as substrates for internal hydrogen transfer leading to cyclisation reactions. The availability of versatile synthetic routes to 7 (in particular R = heteroatom) has led to 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. These reactions are discussed in the context of a rigorous understanding of the chemistry of the ketene intermediates involved. Most of the work was published in the period 1980–2000 but important references to earlier literature are also included.

Key words: heterocycles, hydrogen transfer, pericyclic reactions, Meldrum’s acid, pyrolysis

1 Introduction

The purpose of this review is to cover systematically recent work on the pyrolyses of derivatives of the cyclic acylal Meldrum’s acid (2,2-dimethyl-1,3-dioxane-4,6-dione) 1 1–3 with particular emphasis on the application of these processes in synthetic organic chemistry. The collapse of the Meldrum’s acid ring system is dominated by the generation of reactive ketene intermediates (Scheme 1) and bears some formal similarity to that of 1,3-dioxin-4-ones such as 2.4–6 In the case of the dione 1, ketene itself 3 is obtained with co-formation of acetone and carbon dioxide, whereas the dioxine 2 undergoes elimination of acetone to generate an α-oxoketene 4. This reaction is a hetero-retro-Diels–Alder reaction and for this reason, dioxine pyrolyses can often be carried out under mild conditions in solution (e.g. refluxing toluene) whereas Meldrum’s acid pyrolyses require temperatures greater than 200 °C in condensed phase. Most Meldrum’s acid pyrolyses are therefore carried out in the gas-phase under flash vacuum pyrolysis (FVP) conditions.7–9 The reactions shown in Scheme 1 are special cases of ketal pyrolysis, an area, which we have also reviewed recently.10

Scheme 1

In agreement with this interpretation, the O-methyl compound 5, obtained by treating Meldrum’s acid with diazomethane at −30 °C, has a half-life of only 5 min at room temperature due to cycloreversion to the ketene 6 (Scheme 2).11 Although this dioxinone is hence much less thermally stable than alkyl-substituted dioxinones such as 2, the system can be stabilised by formation of a related O-silyl derivative (decomposes at 50 °C in toluene) or by further C-substitution.11

Scheme 2

Since there are often other convenient routes to ketenes, most synthetically useful Meldrum’s acid pyrolyses are carried out with methylene derivatives 7, which are formally a source of methyleneketene intermediates 8 (Scheme 3).

The variety of products, which can be obtained from Meldrum’s acid pyrolyses is therefore dependent on the availability of efficient routes to derivatives 7, with a wide range of substituents R. These methods are briefly dis-
cussed in the following sections, but most depend on manipulation of the active methylene group of 1.

2 Meldrum’s Acid Derivatives

The gas-phase pyrolysis of Meldrum’s acid derivatives under FVP conditions was pioneered by the group of R. F. C. Brown and F. W. Eastwood in the early 1970’s. This work has been reviewed\(^7,8,12,13\) but the main features are summarised here since they provide the foundations for all the later applications. First, the nature of the key methyleneketene intermediates \(^8\) (and other related cumulenones) was recognised, and the ketenes were unambiguously characterised by matrix isolation or by microwave spectroscopy. On the synthetic side, the methyleneketenes were found to dimerise to cyclobutanediones \(^9\), or undergo addition reactions with nucleophiles or cycloadDITIONS with a limited range of trapping species. At higher temperatures decarbonylation of the methyleneketenes led to methylenecarbenes \(^10\) and hence to alkynes \(^11\), thereby providing a useful route from arylcarboxaldehydes to arylacetylenes. In addition a synthetic route to \(\beta\)-naphthols \(^12\) from 2-alkylarylcarboxaldehydes was invented (the McMullen reaction\(^14\)) via a 1,5-prototropic shift, electrocyclisation and tautomerism sequence (Scheme 4).

In recent years, extensions of this Meldrum’s acid pyrolytic methodology have been used to create unusual heterocyclic ring systems. These reactions generally require an intramolecular hydrogen shift from a remote site in the molecule, which has the effect of rearranging the methyleneketene intermediate to a more stable unsaturated ketene moiety, which can then collapse to the final product(s). The unique affinity of the methyleneketene system for such hydrogen transfers provides a rationalisation for the wide array of systems, which can be accessed by this methodology. In addition, matrix isolation techniques have been employed to characterise the wide range of structurally diverse ketene derivatives, which can be generated by such reactions.

Biographical Sketches

**Abd El-Aal Gaber** (left) studied at the University of Assiut (Egypt) from 1978–1982 and he received his Ph.D. in organic chemistry from the same University in 1989. In 1994 and 1996 he carried out post-doctoral work on photochemistry of conjugated enones at MPI für Strahlenchemie (Germany) with Professor K. Schaffner and Dr. J. Leitich. In 1999, he worked at the University of Gakushuin (Japan) as a visiting researcher with Professor K. Mochida on the photochemistry of germanium compounds. Since 2000, he has been a Professor at Assiut University. Currently he is spending study leave at The University of Edinburgh (Scotland) working with Dr. H. McNab in the area of flash vacuum pyrolysis. His research interests are devoted to the study of pyrolysis and photochemistry of or-

**Hamish McNab** (right) graduated from the University of St. Andrews (Scotland) in 1971 and obtained a Ph.D. (1974) in the field of nitrogen heterocyclic chemistry under the supervision of Dr. D. Lloyd. He carried out post-doctoral work on flash vacuum pyrolysis at the Australian National University with Professor W.D. Crow from 1975–76. He has been at The University of Edinburgh since 1977, where he is now a Reader in Chemistry. His research interests are broadly concerned with the discovery of new pyrolytic processes and their application in synthesis, and with the chemistry of unusual heterocyclic systems. He has published over 200 papers.
2.1 Cyclisations and Other Processes Preceded by a 1,3-Prototropic Shift

Suprafacial thermal 1,3-hydrogen shifts are formally disallowed for most π-systems. However, ketenes possess a low-energy LUMO in the plane of the molecule and so such shifts may occur with low activation energy.

Most synthetically useful reactions of this type involve aminomethylene Meldrum’s acid derivatives. Thus, upon pyrolysis, aminomethylene Meldrum’s acids, which contain a free NH undergo formal 1,3-prototropic shift at the methyleneketene stage to generate iminoketenes, which lead to products (Schemes 5 and 6). These precursors are easily made by reaction of a primary amine with methoxymethylene Meldrum’s acid (Figure 1). In the special case of aminomethylene Meldrum’s acid itself the iminoketene and the aminomethyleneketene are in equilibrium in the gas-phase via a 1,3-prototropic shift; at higher temperatures the major product is the unstable aminoaacetylene formed by decarbonylation of 16. Iminoketenes formed from the gas-phase pyrolysis of N-alkylaminomethylene Meldrum’s acid derivatives generally undergo a sequence of subsequent H-shifts to give enaminoenaminones, which can be isolated in preparative yields of up to 90% (e.g. Scheme 6). Deuterium labelling experiments have confirmed the sequence shown in Schemes 6, though further scrambling can occur if the intermediates experience a longer contact time in the hot zone. Some related reactions are discussed in more detail in Section 2.7.

The formation of quinolin-4-ones by pyrolysis of N-arylaminomethylene Meldrum’s acid derivatives has been known in solution since 1969 and in the gas-phase since 1983. The precursors can be obtained by reaction of a primary aromatic amine with 13, hence the methodology provides an efficient two-step route from anilines to quinolin-4-ones. Matrix isolation studies have confirmed that both the methyleneketene and the iminoketene (characterised by IR spectroscopy) are initially formed in the pyrolysis, but at higher temperatures electrocyclisation and rearomatisation by hydrogen shift gives rise to the quinolin-4-one (Scheme 7). This sequence, either under FVP conditions (typically 600 °C, 0.01 Torr) or, more usually, in solution [typically boiling diphenyl ether (259 °C) or dowtherm], is of considerable value in the synthesis of quinolin-4-ones and related heterocyclic systems.
Thus, the use of substituted arylamines in place of aniline gives quinolinones substituted in the benzene ring, including multiply substituted examples. In addition, methods have been developed - often using the thioacetal as the basic starting material - to synthesise the Meldrum’s acid precursors to provide quinolinones substituted in the 2-position with (for example) aryl, methylthio, amino or cyano substituents.

This route has been employed by a number of groups in the synthesis of polycyclic marine alkaloids, which are of interest because of their cytotoxic properties. For example, two such cyclisations have been used to create pyridine rings in a synthesis of meridine by Delfourne and co-workers (Scheme 8). Similarly, Kubo and co-workers used Meldrum’s acid quinolinone cyclisations in two complementary routes to 11-hydroxyascididemin (Figure 3) and related alkaloids.

Pyrolysis of an open-chain analogue of gave a more complex set of products, due to the possibility of acyl shifts and deacylation processes at the high temperatures involved. Cyclisation onto C=C double bonds in heterocyclic rings has also been observed (e.g. Scheme 10). There are many other examples, in the patent literature.

Reaction of methoxymethylene Meldrum’s acid with amides (or acylation of aminomethylene Meldrum’s acid) provides the amido derivatives whose FVP at 500–550 °C (0.01 Torr) gave the 2-substituted 1,3-oxazin-6-ones in preparative yields of 62–80% (Scheme 11). In this case the hydrogen transfer step to give the iminoketene is followed by an electrocyclisation in which the C=O unit of the amide is incorporated into the oxazinone ring (Scheme 11).
In addition, 2,4-disubstituted 1,3-oxazin-6-ones \(32\) (Figure 4) could be obtained by condensed-phase pyrolysis of appropriate Meldrum’s acid derivatives at 175–185 °C in the absence of solvent.\(^{32}\)

Figure 4

Iminoketene intermediates can also be trapped by C=X groups in heterocyclic rings. For example, thiazolopyrimidinones (e.g. \(33\), 66%), pyridopyrimidinones (e.g. \(34\), 86%) and pyrazolopyrimidinones (e.g. \(35\), 48%) (Figure 5) have been obtained by pyrolysis of aminomethylene Meldrum’s acids derived from 2-aminothiazole, 2-aminopyridine and 3-aminopyrazole respectively, either in solution or in the gas-phase.\(^{20,33}\) (See also ref. \(^{21}\) for other examples.)

Figure 5

Mesomeric betaines can also be made, by trapping the iminoketene with an atom, which has a lone pair of electrons. Thus, FVP of the \(\text{N}N\)-disubstituted aminomethylene Meldrum’s acid derivatives \(39\) (obtained by reaction of a secondary amine with the methylene Meldrum’s acid derivatives \(13\) or \(24\) or related compounds) is perhaps the simplest and most direct synthetic route to 1-substituted 3-hydroxypyrroles and their tautomers, \(1H\)-pyrrol-3-(2\(H\))-ones \(43\) (Scheme 13).\(^{35}\) A detailed study of the mechanism by matrix isolation has shown that an intermediate anhydride \(40\) is formed as the precursor of the methyleneketene \(41\).\(^{36}\) A particularly stable methyleneketene \(44\) (Figure 6), whose spectra in solution persist even up to room temperature, has been isolated from such precursors.\(^{36}\) The subsequent formation of \(1H\)-pyrrol-3(2\(H\))-ones \(43\) from the methyleneketene \(41\) (Scheme 13) requires a 1,4-hydrogen transfer from a site adjacent to the nitrogen atom (confirmed by deuterium labelling\(^{37}\)) to generate an essentially planar 1,5-dipolar intermediate \(42\), which then undergoes an electrocyclic ring closure.\(^{38}\) In agreement with this mechanism, the configuration of a chiral centre at the site of hydrogen transfer (e.g. Scheme 13, \(R^2 = \text{Me}, R^3 = \text{Ph}\)) is partially lost in the final pyrrolone.\(^{38}\)

Scheme 12

Scheme 13

2.2 Cyclisations Preceded by a 1,4-Prototropic Shift

Whereas a 1,3-hydrogen shift in a methyleneketene intermediate can generate isomeric ketene derivatives, a 1,4-shift is more unusual since a dipolar species must result. These reactions are only observed when a heteroatom (N or S) is present in the appropriate position to accommodate the formal positive charge of the dipole. Nevertheless, six π-electrons are involved in the process, which therefore becomes isoelectronic with the suprafacially allowed 1,5-shift reactions discussed in section 2.3.

The gas-phase pyrolysis of \(\text{N}N\)-disubstituted aminomethylene Meldrum’s acid derivatives \(39\) (obtained by reaction of a secondary amine with the methylene Meldrum’s acid derivatives \(13\) or \(24\) or related compounds) is perhaps the simplest and most direct synthetic route to 1-substituted 3-hydroxypyrroles and their tautomers, \(1H\)-pyrrol-3(2\(H\))-ones \(43\) (Scheme 13).\(^{35}\) A detailed study of the mechanism by matrix isolation has shown that an intermediate anhydride \(40\) is formed as the precursor of the methyleneketene \(41\).\(^{36}\) A particularly stable methyleneketene \(44\) (Figure 6), whose spectra in solution persist even up to room temperature, has been isolated from such precursors.\(^{36}\) The subsequent formation of \(1H\)-pyrrol-3(2\(H\))-ones \(43\) from the methyleneketene \(41\) (Scheme 13) requires a 1,4-hydrogen transfer from a site adjacent to the nitrogen atom (confirmed by deuterium labelling\(^{37}\)) to generate an essentially planar 1,5-dipolar intermediate \(42\), which then undergoes an electrocyclic ring closure.\(^{38}\) In agreement with this mechanism, the configuration of a chiral centre at the site of hydrogen transfer (e.g. Scheme 13, \(R^2 = \text{Me}, R^3 = \text{Ph}\)) is partially lost in the final pyrrolone.\(^{38}\)
This route is a synthetically valuable method of making 1-substituted 3-hydroxypyrroles. The 1-substituent (R1) can be alkyl or aryl (but not H, because the 1,3-shift described in Section 2.1 intervenes). The method can be applied to N-alkyl- or N-aryl-C-unsubstituted, 2-substituted, 5-substituted, 2,2-disubstituted or 2,5-disubstituted derivatives. Isolated yields from the pyrolysis step are generally in the range 60–80%. Since the FVP reaction is carried out under reduced pressure, it is especially useful for making 1,2-disubstituted compounds, which are highly sensitive to atmospheric oxygen. When the group R1 also contains a hydrogen atom in a position a to the nitrogen atom, little selectivity is observed in the hydrogen transfer step unless one of the groups is benzyl. In this case highly regioselective hydrogen transfer occurs to give N-substituted 2-phenyl-3-hydroxypyrroles exclusively.

The method has been used as the key cyclisation step in constructing the central alkoxy pyrrole ring in the synthesis of analogues of the alkoxy pyrrole natural product prodigiosin (e.g. Figure 6).

FVP of the oxazolidine derivatives (e.g. 46) under the standard conditions (600 °C, 0.01 Torr) forms a special case (Scheme 14). It appears from deuterium labelling experiments that cyclisation of the methyleneketene 47 takes place in the usual way, but the fused pyrrolone is unstable under the reaction conditions. Cleavage of formaldehyde takes place to give the key 1,3-dipole 48, which rearranges to the products 49 and 50 (70% combined yield) by hydrogen shift and skeletal rearrangement respectively. These results are in line with previous work on oxazolidine pyrolysis.

In a second unusual example, the bis-pyrrole 52 was obtained in 42% yield by pyrolysis of the propargyl derivative 51 (Scheme 15). No mechanism is suggested for this transformation.

The substrates 53 (obtained by condensation of Melrum’s acid with activated lactams) cyclise smoothly under FVP conditions to the bicyclic pyrrolones 54, generally in purified yields in excess of 70% (Scheme 16). When the nitrogen substituent in 53 is an allyl group, cyclisation to the fused seven-membered rings 56 compete with formation of 55; the larger ring size is favoured at lower pyrolysis temperatures (Scheme 16). In contrast, substrates 57 bearing a terminal chloride atom on the N-substituent cyclise with transfer of the halogen atom giving access to a range of pyrrolizidine, indolizidine and quinolizidine derivatives 58 which are good precursors of alkaloids such as isoretironecanol and lupinine (Scheme 17).
As an extension of this work involving the formation of nitrogen heterocycles, it was found that FVP of alkylsulfanyl methylene Meldrum’s acid derivatives 59 at 600–625 °C gave analogous 3-hydroxythiophenes [thiophene-3(2H)-ones] 62 (Scheme 18).49 These precursors can be made by reaction of a thiol with methoxymethylene Meldrum’s acid 13.49 By analogy with pyrrolone formation, it is assumed that the cyclisation involves a methylenekeketene intermediate 60, but cyclisation to the five-membered ring is too rapid for these species to be detected by in situ photoelectron spectroscopy.51 The later stages of the mechanism are thought to involve a symmetry-allowed 1,4-hydrogen shift from the ketene 60 to generate a planar dipolar species 61, followed by a 6π electrocyclisation (Scheme 18).49 In agreement with this, the configuration of a chiral centre at the cyclisation site is lost in the cyclisation process.49

Scheme 18

The synthetic route to thiophenones proved to be just as versatile as the corresponding pyrrolone synthesis. As well as the parent compound (62, R2 = R3 = H, 80%), a range of 2-alkyl, 2-aryl, 2-carbomethoxy and 2,2-disubstituted derivatives were made in 44–92% yield by pyrolysis of the appropriate Meldrum’s acid precursors (Scheme 18).49 In addition, 5-methylsulfanyl-, 5-aryl-, 5-alkyl- or 5-heteroaryl-3-hydroxythiophenes were obtained from precursors 59 further substituted at the methylene position; these Meldrum’s acid derivatives were made from the thioacetal 24.49 Bis-thiophenones, linked at the 2-position, have also been reported.53 In contrast, alkoxymethylene Meldrum’s acid derivatives do not serve as precursors to furan-3(2H)-ones; reactions of these substrates are described in Sections 2.7.

2.3 Cyclisations Preceded by a 1,5-Prototropic Shift

1,5-Prototropic shifts are thermally allowed for a suprafacial transition state. Such reactions may be commonly observed in the pyrolysis of methylene Meldrum’s acid derivatives provided the 1,5-shift results in the rearrangement of a methylenekeketene to a vinylketene.

The McMullen reaction to give β-naphthols14 is one of the earliest examples of the synthetic utility of gas-phase Meldrum’s acid pyrolyses under FVP conditions (Scheme 4). Recently, this process has been used to provide a short and efficient synthesis of the naphthol 63, which is a precursor of an intercalating moiety of enediyne antibiotics (Scheme 19).52

Scheme 19

McMullen cyclisations have also been observed in the indole series. Knoevenagel condensation of the appropriate indolecarboxaldehyde with Meldrum’s acid gave the precursors 64, 65 and 67, which upon FVP at 600 °C (0.01 Torr) gave the hydroxycarbazoles 68–70 in 40, 89 and 82% yield respectively (Scheme 20).53 In the corresponding pyrolysis of 66, an alternative cyclisation ensues, involving a 1,7-prototropic shift from the N-H (see Section 2.5).

Scheme 20

The formation of the benz[c,d]indol-5-one system 74, albeit in only 8% yield - from the related precursor 71 forms a special case. This unusual cyclisation probably requires an initial 1,5-sigmatropic shift of the proton at the 1-position of the indole ring of the methylenekeketene 72 to give the ketene 73. The reaction pathway is completed by an electrocyclic ring closure onto the 4-position of the indole system and a prototropic shift to give the tricyclic ketone 74 (Scheme 21).53
A 1,5-prototropic shift is involved in the thermal cyclisation reactions of the hydrazone derivatives 75 under FVP conditions at 550 °C (0.01 Torr) to give pyridazin-3-ones 76 (Scheme 22). This work provides a general route to 2-aryl or 2-t-butyl derivatives with optional substituents on the 4- or 5-positions in yields of 38–83%. At higher pyrolysis temperatures (750 °C, 0.01 Torr), the t-butyl substituents are lost by a retro-ene process to provide a route to the 2-unsubstituted compounds 77 in good yield. The precursors are easily made by Knoevenagel condensation of the appropriate α-dicarbonyl hydrazone with Meldrum’s acid. Pyrolysis of derivatives which have undergone deuterium exchange at the nitrogen atom, provide access to 4-deuteriated pyridazinones.

Reactions of methoxymethylene Meldrum’s acid 13 with 3-hydroxypyrroles gives ‘Meldrumsated’ products (e.g. 78–80) which, upon FVP at 600 °C (0.01 Torr) cyclise to the fused pyrones 81–83 respectively (Scheme 23). A 1,5-hydrogen shift is formally involved in these reactions, though the mechanism may not always be concerted. It is of interest that the pyranopyrrole 83 is formed exclusively rather than the pyrrolizin-3-one 84 (c.f. Section 2.5).

In a final example of a 1,5-prototropic shift, the bicycle 88 is obtained by FVP of the oxazolidine derivative 85. This compound has no hydrogen atoms in the correct position for a 1,4-prototropic shift (c.f. Scheme 14) and instead the methyleneketene 86 is thought to participate in a retro-ene process to provide the iminoketene 87 which undergoes an intramolecular cycloaddition to give the product (Scheme 24).

Other 1,5-shifts reactions are implicated in non-cyclisation processes, see Section 2.7.
plane LUMO orbital, as appears to be the case with 1,3-protonotropic shifts.

Thus, FVP of 5-[(3-N,N-disubstituted-amino)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-diones \[89\] at 500–550 °C (0.01 Torr) leads to the 1H-azepin-3-(2H)-ones \[92\] in high yield (64–75%) contaminated by a small amount of cyclopentadienone dimer \[95\]. Again, the precursors are obtained by Knoevenagel condensation methodology using enaminals as the carbonyl component.\[56\] The formation of \[92\] and \[95\] can be rationalised by the mechanism of Scheme 25. Hydrogen transfer in the methyleneketene \[90\] leads to a 1,7-dipolar intermediate \[91\], which bears a vinyllogous relationship to the 1,5-dipole \[42\] (Scheme 13) involved in pyrrolone formation. The 1,7-dipole can either collapse to the azepinone \[92\] by electrocyclisation or to the bicyclic intermediate \[93\] by cycloaddition across the carbonyl component of the ketene. Further collapse of \[93\] gives cyclopentadienone (forming \[95\] by dimerization), and the imine \[94\] (Scheme 25).\[56\]

Scheme 25

The route has been applied to a range of 1-alkyl or aryl compounds and to 1,2-disubstituted and 1,2,2-trisubstituted derivatives.\[56\] Unlike the corresponding pyrrolones, these azepinones show no tendency to rearrange in solution to the hydroxyazepine tautomer. This pyrolytic method is the only general synthesis of 1H-azepin-3-(2H)-ones; the preparative work was followed by investigations of their structures,\[56b,57\] spectroscopic properties\[56,58\] and reactions with electrophiles,\[57,59\] bases\[59,60\] and dienophiles.\[59,61,62\] An azepinone, substituted at the 7-position by a dimethylamino group, has been made by a similar route.\[62\]

Reaction of N,N-disubstituted enamines with methoxymethylene Meldrum’s acid \[13\] gives access to related precursors such as \[96\] (Scheme 26), whose FVP at 600 °C (0.01 Torr) provides a general route to azepinones with a carbonyl substituent at position 6 (e.g. \[97\]) (Scheme 26).\[29\]

Scheme 26

Flash vacuum pyrolysis of the vinylogous aminomethylene Meldrum’s acid \[98\] does not lead to the nine-membered azoninones. Instead, the exclusive formation of \[N,N\]-dimethylbenzamide \[99\] (73%) can be explained by an initial electrocyclisation followed by migration of the dimethylamino group and collapse of the dioxanedione ring (Scheme 27).\[56a\]

Scheme 27

Seven-membered rings are also obtained by gas-phase pyrolysis of β-functionalised alkylaminomethylene Meldrum’s acid derivatives \[100–104\] in a vertical flow system at 500-520 °C (16 Torr) (Scheme 28).\[63\] The reaction is very general, with oxazepinones \[106\],\[63,64\] thiazepinones \[107\],\[65\] dithiepinones \[108\],\[65\] oxathiepinones \[49b,65\] and diazepinones \[66\] all obtained in yields of 47–79% from the appropriate precursors. In addition, α-functionalised alkylaminomethylene Meldrum’s acid derivatives undergo an analogous cyclisation to give larger rings (Section 2.6). The precursors all contain the appropriate structural features for 1,4-hydrogen shift and cyclisation to give 5-membered pyrrolole or thiophenone rings \[111\] (X = NR or S) (c.f. Schemes 13 and 18) but this mode of reaction was never observed. The exact mechanism of the cyclisation is apparently rather unusual. Although a 1,6-migra-
tion of hydrogen is formally involved to give the seven-membered rings, this cannot be a sigmatropic process due to the saturated components of the chains. Instead, the formation of the heterocycles 106–110 has been rationalised by addition of the hydroxy group to the aminomethyleneketene intermediates 105. Such nucleophile-electrophile processes are exceedingly rare in the gas-phase; it is possible that the reactions may occur by a concerted process involving a 4-membered transition state, or be catalysed in some way by an intermolecular component at the relatively high pressures involved. The absence of pyrroliones or thiophenones 111 (X = NR or S) as co-products suggests that it is unlikely that the cyclisations take place in the condensed phase on warming the trap. Further work aimed at clarifying these points would be of interest.

Scheme 28

In contrast, pyrolysis of the o-mercaptoaniline derivative 112 at 550 °C led exclusively to benzothiazole 115 (77%) rather than a benzothiazepinone. It is thought that attack of the amino group on the C3 carbon of the methyleketene 113 leads to an unstable intermediate 114, which can aromatise to 115 by elimination of ketene 116 formed from the unstable ethynol (Scheme 29). In agreement with the mechanism, ketene 116 was detected in the pyrolysate by low-temperature IR spectroscopy.

Scheme 29

2.5 Cyclisations Preceded by a 1,7-Prototropic Shift

1,7-Prototropic shifts in Meldrum’s acid pyrolysis chemistry are confined to a single important class of substrate, viz. those derived from the condensation products of Meldrum’s acid and nitrogen-containing 5-membered ring heterocyclic aldehydes. Although this process formally proceeds by an antarafacial transition state, the low-lying ketene LUMO may be involved.

FVP of the pyrrole-2-carboxaldehyde derivative 117 at 600 °C (0.01 Torr) results in the formation of pyrrolizin-3-one 120 in high yield (Scheme 30). This process is one of the most general synthetic routes to this formally antiaromatic heterocyclic π-system. As well as the parent compound 120, the method has been applied to the synthesis of 1-substituted, 5-substituted, 6-substituted and 7-substituted pyrrolizinones from the appropriate substituted pyrrole-2-carboxaldehyde precursor. Typically, yields are in the range 70–90% and many of these reactions can be carried out on a multi-gram scale. In addition, the acetoxymethyl derivative 122 (Figure 7), prepared by this route, was used as the precursor for a short synthesis of the pyrrolizidine alkaloid 3,8-didehydroheliotridin-5-one 123.

Scheme 30

The mechanism of the cyclisation probably involves generation of the methyleneketene 118 in the usual way, followed by a 1,7-sigmatropic shift to provide the ketene 119 and finally an electrocyclisation to give the product 120 (Scheme 30). The nature of the hydrogen shift was established by deuterium labelling. Although this key step precludes the formation of 2-substituted derivatives from Meldrum’s acid precursors, the direct formation of ketenes 119 by FVP of acrylate derivatives (e.g. 121) has given an alternative approach which has considerably broadened the scope of the pyrolytic route to pyrrolizinones and related compounds.
The methodology has also been extended to the related ‘azapyrrolizinone’ ring systems 124–126 (Figure 8) by using the appropriate imidazole or pyrazole derivatives as the precursors.74,75 In these cases, the volatility of the Mel- drum’s acid precursor may lead to low yields of the heterocycles, and acrylate-derived pyrolytic routes to the imidazole-derived iminoketene intermediates have been developed.75

FVP of the corresponding 5-((indol-2-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-diones 127 leads in a similar way to the pyrrolo[1,2-α]indol-3-ones (128; R = H, Me or Ph) (Scheme 31).53,76 In the case of the phenyl derivative, pyrolysis at a higher temperature leads to benzo[c]carbazole 130; this is formed via the carbene 129, which then undergoes intramolecular C–H insertion. (Scheme 31).76

The thermal behaviour must involve an intramolecular addition of the terminal group (YH) to the central double bond of the appropriate methyleneketene as discussed in Section 2.4.

2.6 Cyclisations Involving Remote Prototropic Shifts

As an extension of the process shown in Scheme 28, various 8-membered and large-ring (up to 17-membered) heterocycles 135–138 were prepared in reasonable yields as the only products by pyrolysis of the Meldrum’s acid derivatives 131–134 at a temperature of 420–500 °C (16 Torr) (Scheme 32).64–66 The enone units of the 8-membered rings 135a–138a are exclusively formed in the Z-configuration; those of the macrocycles tend to adopt the Z-configuration in the enamino lactam series 133a (except for the case of n = 5, where an E/Z mixture is obtained) whereas the enaminolactones adopt the E-configuration 135b.64–66 The thermal behaviour must involve an intramolecular addition of the terminal group (YH) to the central double bond of the appropriate methyleneketene as discussed in Section 2.4.

2.7 Eliminations and Other Non-Cyclisation Processes

Decarbonylation of a methyleneketene to a methylenecar- bencene and subsequent rearrangement to an alkyne is a classic reaction sequence of these intermediates (Scheme 4).7,8,12,13 Low-yielding formation of 2- and 3-ethynylindoles 139 and 140 (Figure 9) (<20%) has been observed by the FVP of condensation products of Mel- drum’s acid and indolecarboxaldehydes, in cases where alternative cyclisations cannot take place (c.f. Schemes 20, 21 and 31).53

In a more synthetically useful process, the methylene ketene derived from the thiophenyl compound 141 (readily obtained by reaction of thiophenol with methoxymethylene Meldrum’s acid 13) undergoes decarbonylation and rearrangement under FVP conditions at 600 °C (0.01 Torr) to provide a useful synthetic route to phenylthioacetylene 142 in 68% yield (Scheme 33).77

In similar fashion, the hydrazones and oximes 143–147 lose acetone, carbon dioxide and carbon monoxide to generate the isocyanides 148 as the primary products, which in certain cases, can rearrange at higher temperatures to the corresponding cyano compounds 149 (Scheme 34).17

Figure 7

Figure 8

Figure 9
The precursors are generally easily made by azo-coupling or nitrosation reactions on Meldrum’s acid itself.

The oxime 147 forms a special case, since nitrosoketene 150 can be obtained (Scheme 34). The chemistry of this intermediate has been studied extensively by Katagiri and co-workers. When the pyrolysis is carried out in solution (refluxing toluene), the nitrosoketene 150 can be trapped by [3+2] cycloaddition with ketones to give the nitrones 151 (rather than the isomeric [4+2] products, c.f. Scheme 36). These pyrolysis conditions are much milder than for most Meldrum’s acid derivatives, which suggests that tautomerism to the dioxinone 147a (Figure 10) may be involved in the mechanism. In addition, if a carbonyl group of 147 is O-methylated by diazomethane, very mild conditions are needed for ring cleavage. If a chiral ketone is used as the trapping agent, the product may be formed as a single diastereomer. The nitrones 151 themselves have been employed in further 1,3-dipolar cycloaddition reactions, ultimately as a source of unusual amino acids both in racemic and enantiopure form.

Reactions of 147 with carboimidides give intermediate adducts 153 which collapse at room temperature to the cyano-compounds 154 (Scheme 35). Heating hydroxymethylene Meldrum’s acid 155 at 80 °C in the presence of an alcohol provides a simple and direct synthetic route to formylacetic esters 158 (Scheme 36). Since these conditions are particularly mild for solution decomposition of Meldrum’s acid derivatives, the reaction is probably initiated by 1,5-prototropic shift to the dioxinone 155a, which then undergoes cycloreversion to the ketenes 156 (or 157) which are trapped by the nucleophile (Scheme 36). Similarly, the ketene 157 can be trapped by [4+2] cycloaddition with ketones (c.f. Scheme 34) to provide a general route to 6-unsubstituted dioxinones 159 (c.f. Scheme 1) in 49–75% yield.

5-Alkylidene Meldrum’s acid derivatives (e.g. 160) (prepared by Knoevenagel condensation, or from the thioacetal 24 or by reaction of Meldrum’s acid with trimethyl orthoacetate) also undergo a 1,5-hydrogen shift to provide the enol form of the Meldrum’s acid system (e.g. 161), prior to thermal breakdown of the ring. This leads to the generation of carboxy(vinyl)ketenes 162 as the initial intermediates which decarboxylate to methyleneketenes 163; a further sequence of hydrogen shifts leads to vinylketenes 165 (probably via hydroxyacetylenes 164).
Similar mechanisms also ensue when the 5-alkylidene derivative contains a methylthio- or alkoxy substituent at the methylene position.\textsuperscript{25} Contrary to an earlier report,\textsuperscript{51b} alkoxy(methyl)methyleneketene \textsuperscript{163} (R = Me, X = O) does not isomerize to (1-alkoxyvinyl)ketenes \textsuperscript{166}.\textsuperscript{91} All of these intermediates have been fully characterised by matrix isolation, IR spectroscopy and the structures have been supported by theoretical calculations. This detailed mechanistic work provides strong support for the more synthetically orientated studies, such as the formation of the thiophenone \textsuperscript{167} (c.f. Section 2.2)

A dichotomy is observed in the pyrolyses of aminomethylene Meldrum’s acid derivatives \textsuperscript{168} in which the key imidoylketenes \textsuperscript{177} are generally the initial observable intermediates, though they may be formed via the usual methyleneketenes \textsuperscript{176},\textsuperscript{93} or, more likely, via a 1,3-\textsuperscript{97} or 1,5-hydrogen shift\textsuperscript{96} in the Meldrum’s acid derivatives themselves (to give \textsuperscript{174} or \textsuperscript{175} respectively). At higher temperatures, elimination of HX from the initial Meldrum’s acid derivatives \textsuperscript{173} takes place to generate transient intermediates \textsuperscript{181} (observable by on-line mass spectrometry in favourable cases\textsuperscript{94,98}), which leads to the important iminopropadienones \textsuperscript{182} - formally the imines of carbon suboxide.\textsuperscript{94,95,97} The relative importance of the imidoylketene and iminopropadienone pathways is strongly dependent on the nature of X. Methoxy and thiomethoxy substituents (X = MeO or MeS) are relatively poor leaving groups and so the imidoylketene route dominates except at high temperatures; iminopropadienones are formed even at low temperatures when X is an amino substituent (Scheme 39).\textsuperscript{97}

Further reactions of the imidoylketenes \textsuperscript{177} are controlled by the nature of the groups X and R. When R = aryl, standard electrocyclisation to a quinolinone \textsuperscript{179} (c.f. Section 2.1) ensues,\textsuperscript{93,96,97} and the Meldrum’s acid derivatives can be used as precursors in preparative routes to 2-substituted quinolinones. In addition, reversible 1,3-migration of the substituent X - particularly important when X = OMe or SMe - generates oxoketenimines \textsuperscript{178}, which in some cases can be isolated and purified by distillation even when R = aryl.\textsuperscript{96,97} The oxoketenimines can also be trapped with nucleophiles to provide malonic acid derivatives \textsuperscript{180}.\textsuperscript{93,97}

The iminopropadienones \textsuperscript{182} (R = alkyl or aryl) are surprisingly stable, being unchanged at 1000 °C under FVP conditions and are still observable by IR spectroscopy at
They react with 2 equivalents of nucleophiles to afford malonic acid imide derivatives 184 and with 1 equivalent to give ketenamines 183.

When the Meldrum’s acid derivative 173 contains an N-substituent, which can be lost as an alkene by a retro-ene process (e.g. t-butyl or i-Pr), cyano compounds are generated in addition to the intermediates described in the previous paragraphs (c.f. Scheme 38). Some possible modes of formation of cyanoketene 186, for example, are shown in Scheme 40. The major route has been found to be via the iminopropadienones 185, which undergo a facile retro-ene type alkene elimination to give cyanoketene 186 at temperatures above 300 °C (Scheme 40). Alternatively, elimination of acetone and CO₂ from 173 leads to the imidoylketene 187, which undergoes a facile 1,3-shift of the X group to give oxoketenimines 188 (c.f. Scheme 39). At a higher temperatures, retro-ene alkene elimination from the oxoketenimine 188 gives the cyanoacetic acid derivatives 189, which can eliminate HX to produce cyanoketene 186. Cyanoketene 186 is a highly reactive compound which is unstable even at 80 K.

The dithia-compound 190 has no hydrogen atoms in a geometrically feasible position for transfer, and consequently the methyleneketene 191 is, unusually stable in solution to −50 °C and can take part in cycloaddition reactions. Pyrolysis at higher temperatures caused decarbonylation to the carbene 192, rearrangement to 193 and loss of ethylene to give ethenedithione 194 which is stable in the gas-phase at high temperatures but very unstable in the condensed state (Scheme 41).

When Meldrum’s acid chemistry was first reviewed by one of us in 1978 a total of 90 references were cited and the section on pyrolysis occupied little more than one page. The versatility of Meldrum’s acid as a reagent is highlighted by the fact that, now, there are more than 100 papers per year on the topic, and just the synthetic aspects of its pyrolysis reactions can justify this dedicated review.

We have shown in the previous sections that Meldrum’s acid chemistry can give access to a range of unusual heterocyclic systems [e.g. 3-hydroxypyrroles, 3-hydroxythiophenes, 1H-azepin-3(2H)-ones etc.] as well as being the method of choice for making some more prosaic systems (e.g. quinolinones). Of equal importance, the field has been enriched by matrix isolation studies, which have provided fundamental information on ketene reactive in-
termed and on the reaction sequences. Many of these reactions of Meldrum's acid derivatives also provide a case study for the application of gas-phase methods (FVP) as an invaluable tool for the synthetic organic chemist. Finally, the completion of this review in 2001 marks the 125th anniversary of the birth of Andrew Norman Meldrum on 19th March 1876, in Alloa, Scotland.

Acknowledgement

We are grateful to the Royal Society (UK) for a Developing World Fellowship (to A.M.G.).

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