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Recent Applications of Meldrum's Acid in Organic Synthesis

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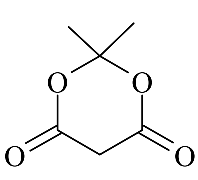
ABSTRACT

Reactions of Meldrum's acid and its derivatives in view of their application in synthesis of diaminofurans, ketenimines, amidoesters, triamides, and diionic compounds, observed during the last decade in our laboratory, are reviewed.

INTRODUCTION

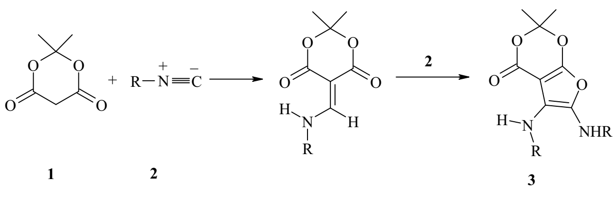
Meldrum's acid (**1**, isopropylidene malonate *or* 2,2-dimethyl-1,3-dioxane-4,6-dione), reported [1] by A. N. Meldrum in 1908, is a useful reagent of versatile reactivity. The chemistry of Meldrum's acid before 1990 has been extensively reviewed by McNab [2] and Chen [3]. In this review some of the new applications of **1** and its derivatives in organic synthesis, observed in our laboratory, are described.



1

SYNTHESIS OF DIAMINOFURANS

The possibility of α,α-addition of CH-acids to alkyl isocyanides has been studied [4]. Among several 1,3-dicarbonyl compounds studied, only Meldrum's acid (**1**) was found to react with alkyl isocyanides (**2**) producing 1:2 adducts (acid:isocyanide). These three-component condensation reactions produce fused furan ring systems **3**. These compounds may be formulated as having been derived from initial α,α-addition of the CH-acid to the isocyanide and subsequent rearrangement of the 1:1 adduct to a conjugated electron-deficient heterodiene, followed by [1+4] cycloaddition reaction with another molecule of the isocyanide to produce an iminolactone intermediate, which is converted into the furan ring system by proton transfer (Scheme 1).



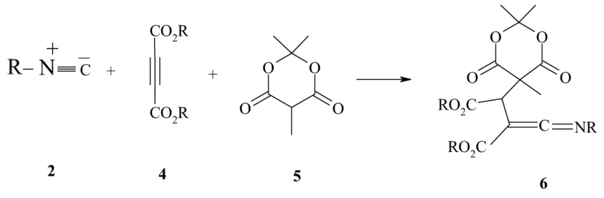
Scheme 1

Meldrum's acid has considerably higher acidity (pK_a 7.3) than acyclic analogues such as dimethyl malonate (pK_a 15.9) or even the diketone analogue 5,4-dimethylcyclohexane-1,3-dione (pK_a 11.2) [5]. Thus, alkyl isocyanides undergo α,α-addition with this dilactone. The origin of anomalously high acidity of

Meldrum's acid has been the subject of recent theoretical studies [6-8].

SYNTHESIS OF KETENIMINES

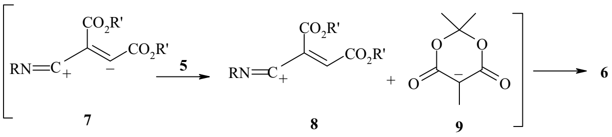
A simple one-pot preparation of stable ketenimines using alkyl isocyanides **2** and dialkyl acetylenedicarboxylates **4** in the presence of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (methyl Meldrum's acid, **5**), as a proton source / nucleophile, has been reported [9]. This three-component condensation reaction produces stable ketenimines **6** in fairy good yields (Scheme 2).



Scheme 2

The sp^2-hybridized carbon atom of the ketenimine residue in **6** appears at $\delta = 61.8\text{-}68.2$ ppm, as a result of strong electron delocalization. These compounds show strong absorption bands at about 2064-2090 cm^{-1} for the C=C=N moieties.

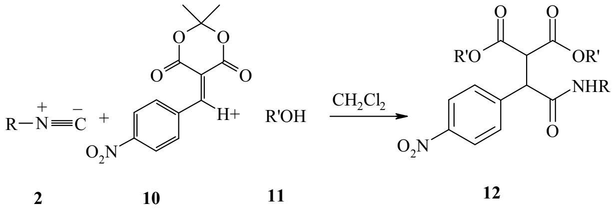
Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate **7** between the alkyl isocyanide and dialkyl acetylenedicarboxylate [10]. Protonation of **7** by methyl Meldrum's acid and subsequent attack of the resulting nucleophile generated to the positively charged ion **8** afforded ketenimine **6** (Scheme 3).



Scheme 3

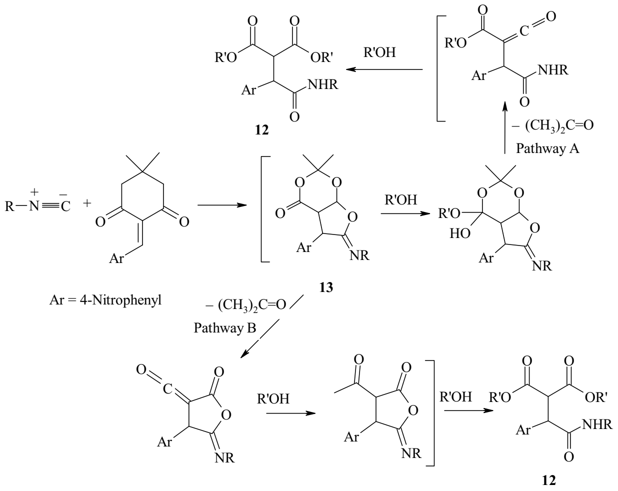
SYNTHESIS OF DIALKYL 2-ALKYLAMINO-2-OXO-ETHYLMALONATES

The condensation product of Meldrum's acid and 4-nitrobenzaldehyde reacts smoothly with alkyl isocyanides in the presence of alcohols to produce dialkyl 2-[1-p-nitrophenyl-2-alkylamino-2-oxo-ethyl] malonates (**12**) in 92-96% yield [10]. This reaction provides a useful synthetic route to highly functionalized amidoesters (Scheme 4).



Scheme 4

Two reasonable possibilities have been proposed for the formation of **12**. The first of these mechanisms (Scheme 5) involves the [1+4] cycloaddition reaction of the electron-deficient heterodiene moiety of isopropyledene *p*-nitrobenzalmalonate with the isocyanide to form an iminolactone intermediate. As it is known that acylated Meldrum's acids are readily transformed into β-ketoesters by alcoholysis [11], the subsequent reaction of the iminolactone **13** with alcohol leads to formation of product **12** (see pathway A in Scheme 5).



Scheme 5

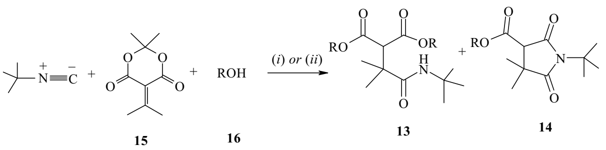
Since the reaction works well with *tert*-butyl alcohol as the alcohol component, the proposed addition to the vinylogous carbonate **13** in pathway A is expected to be slow. The loss of acetone from **13** first and then subsequent addition of R'OH to the so-formed ketene has been suggested as the preferred mechanism (see pathway B in Scheme 5).

SYNTHESIS OF AMIDOESTERS AND PYRROLIDIN-2,5-DIONES

Alkylidene Meldrum's acids are readily accessible from Meldrum's acid and carbonyl compounds (ketones and aldehydes) in a relatively large scale [12]. These compounds have been reported to be reasonably good Michael acceptors [13, 14], as well as highly reactive dienophiles in Diels-Alder reactions [15]. However, synthetic applications of these Meldrum's acid derivatives have received little attention.

Alcohols

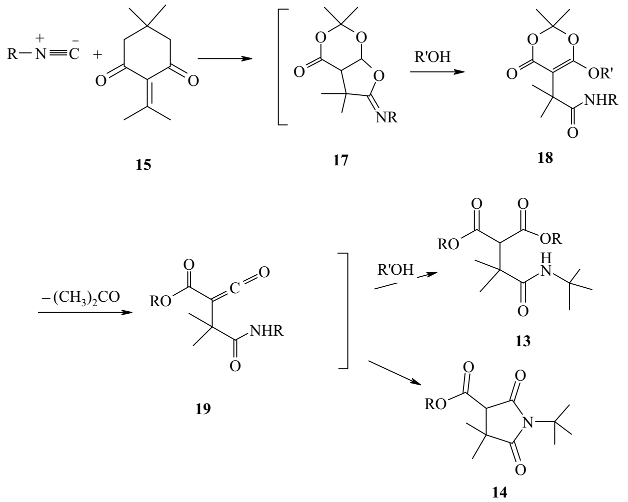
A simple one flask synthesis of highly-functionalized amidoester **13** and substituted pyrrolidine **14** has been reported [16]. The reaction of equimolar amounts of *tert*-butyl isocyanide with isopropylidene Meldrum's acid (**15**) in the presence of various alcohols in dichloromethane at room temperature afforded dialkyl 2-(1-*tert*-butylcarbamoyl-1-methyl-ethyl)-malonates **13** and alkyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate **14** in an overall yield of 65-95 % (Scheme 4). In the presence of excess (3 equivalents) alcohol, the amidodiester **13** was the major product (Scheme 6).



Scheme 6 : (*i*) CH_2Cl_2, r.t., isocyanide:1:2 (1:1:1); (*ii*) CH_2Cl_2, r.t., isocyanide:1:2 (1:1:3)

The ^{15}N NMR spectrum of **14** exhibits a single resonance at about $\delta = 185$ ppm. This shift is in excellent agreement with the previously reported values for *N*-alkylsuccinimides [17]. The ^{15}N resonance of the imino nitrogen atom is expected to appear above 300 ppm [18].

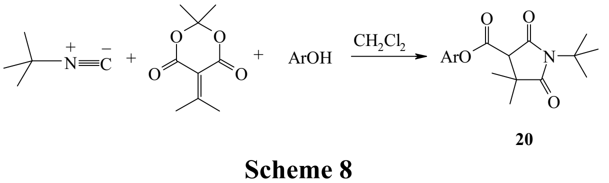
The first step of this transformation involves the [1+4] cycloaddition reaction of the electron-deficient heterodiene moiety of isopropylidene Meldrum's acid with the isocyanide [19, 20], producing an iminolactone intermediate **17**. Conjugate addition by the alcohol on the enone moiety of **17,** followed by cleavage of the 5-membered ring gives **18** and hence the ketene **19** by well precedented [21] electrocyclic ring opening of *O*-alkylated Meldrum's acids. The ketene **19** can then be trapped by the alcohol to give the malonates **13**. Compound **14** may be considered as a product of intramolecular reaction between the amide and ketene moieties of **19** (Scheme 7).



Scheme 7

Phenols

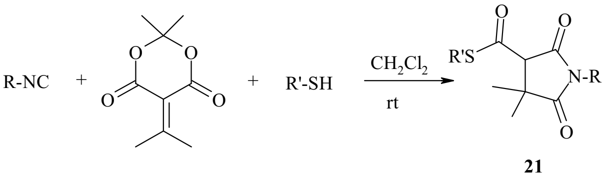
Reaction of *tert*-butyl isocyanide with isopropylidene Meldrum's acid in the presence of phenols in dichloromethane leads to aryl 1-(*tert*-butyl)-4,4-dimethyl-2,5-dioxo-3-pyrrolidinecarboxylates (**20**) in good yields [22]. The ^{15}N NMR spectrum of these compounds exhibited a signal at about 186 ppm for the imide nitrogen atom (Scheme 8).



Scheme 8

Mercaptanes and Thiophenols

Similar reaction conditions, described above, were employed for mercaptanes and thiophenols. Reaction of alkyl isocyanides with isopropylidene Meldrum's acid in the presence of mercaptanes and thiophenols at room temperature in CH_2Cl_2 leads to aryl 1-(*tert*-butyl)-4,4-dimethyl-2,5-dioxo-3-pyrrolidinecarboxylates (**21**) in good yields [23] (see Scheme 9).



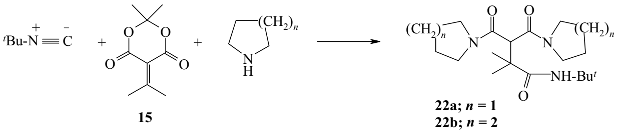
Scheme 9

SYNTHESIS OF TRIAMIDES

tert-Butyl isocyanide undergoes a smooth addition reaction with 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of primary or secondary amines, yielding *N-tert*-butyl-2,2-dimethyl-butyramide derivatives and/or 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxamides [24].

Pyrrolidine and Piperidine

The reaction of *tert*-butyl isocyanide with 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of pyrrolidine or piperidine has been carried out in dichloromethane at room temperature. The colorless crystals separated from these reaction mixtures were identified as *N-tert*-butyl-2,2-dimethyl-4-oxo-3-(pyrrolidine-1-carbonyl)-4-pyrrolidine-1-yl-butyramide **(22a)** or *N-tert*-butyl-2,2-dimethyl-4-oxo-3-(piperidine-1-carbonyl)-4-piperidine-1-yl-butyramide **(22b)** (see Scheme 10).



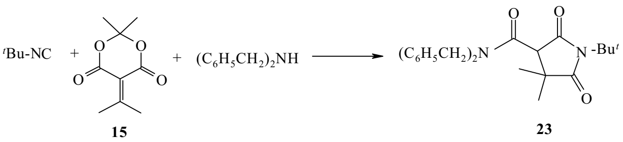
Scheme 10

The ^{15}N NMR spectrum of **22b** exhibits two signals at about 122 ppm (N-C=O) and 129 ppm (NH-C=O) in the amide region of the spectrum.

The triamides **22** result from an initial [1+4] cycloaddition reaction of the electron-deficient heterodiene moiety of **15** with *tert*-butyl isocyanide, producing an iminolactone intermediate. Conjugate addition by the amine on the enone moiety of this iminolactone, similar to that shown in Scheme 7.

Dibenzylamine

Under the reaction conditions given for pyrrolidine and piperidine, only one product was isolated from the reaction mixture of dibenzylamine, *tert*-butyl isocyanide and **15** (see Scheme 11). Structure **23** was assigned to the isolated product on the basis of its elemental analyses and IR, ^{1}H, ^{13}C, and ^{15}N NMR spectra.

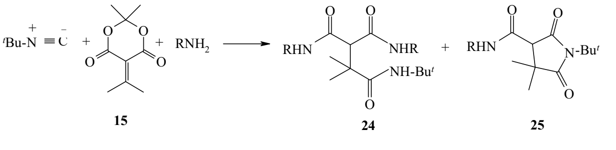


Scheme 11

The observed ^{15}N shift for the imide moiety of **23** is in excellent agreement with the previously reported values for *N*-alkylsuccinimides [17].

Aniline, p-Toluidine, 1-Naphthylamine, Allylamine, and Benzylamine

The reaction of *tert*-butyl isocyanide with isopropylidene *Meldrum*'s acid in the presence of aniline, *p*-toluidine, 1-naphthylamine, allylamine, or benzylamine was carried out in dichloromethane at ambient temperature. Structures 24 and 25 (Scheme 12) were assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, ^{13}C, and ^{15}N NMR spectra.

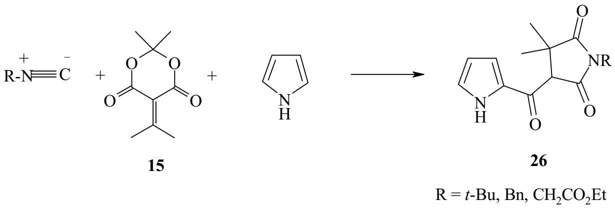


Scheme 12

The ^{15}N NMR spectrum of 25 exhibited two signals at about δ = 122 and 185 ppm, downfield from external liquid ammonia, which is assigned to the amido and imido nitrogen atom, respectively [17, 18].

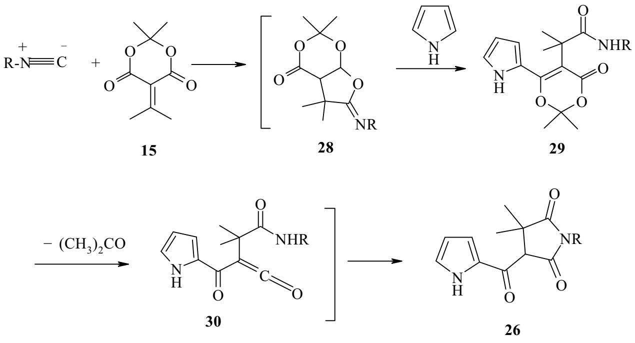
ACYLATION OF PYRROLE AND INDOLE

The reaction of alkyl isocyanides with isopropylidene Meldrum's acid **15** in the presence of pyrrole or indole in CH_2Cl_2 at room temperature leads to 1-alkyl-3,3-dimethyl-4-(1*H*-pyrrole-2-carbonyl)-pyrrolidine-2,5-diones (**26**) or 1-alkyl-4-(1*H*-indole-3-carbonyl)-3,3-dimethyl-pyrrolidine-2,5-diones (**27**) [25]. The reaction of alkyl isocyanides with **15** in the presence of pyrrole proceeded at room temperature in CH_2Cl_2 and was complete within 24 hours. The ^{1}H NMR and ^{13}C NMR spectra of the crude products clearly showed the formation of **26** (Scheme 13).



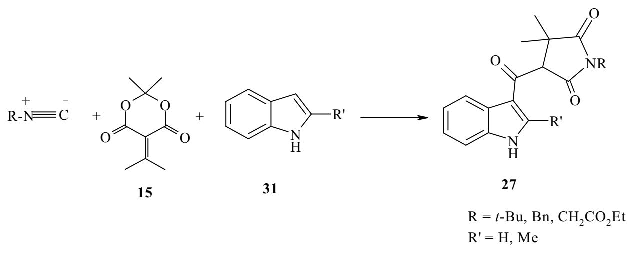
Scheme 13

The plausible way of formation of the product is proposed in Scheme 14. The reaction starts from [4+1] cycloaddition of the isocyanide to the electron-deficient heterodiene moiety of isopropylidene Meldrum's acid to form intermediate iminolactone **28.** Then conjugate addition of pyrrole to the enone moiety of **28**, results in opening of the five-membered ring to form amide **29,** that eliminates acetone to form ketene **30** by electrocyclic ring opening of *O*-alkylated Meldrum's acids. Ring closure of the ketene leads to the product **27**.



Scheme 14

Similar reaction conditions, described above, were employed for indole (**31a**) and 2-methylindole (**31b**). Thus the reaction of alkyl isocyanides with isopropylidene Meldrum's acid in the presence of **31a** or **31b** at room temperature in CH_2Cl_2 leads to **27** (see Scheme 15) [25].

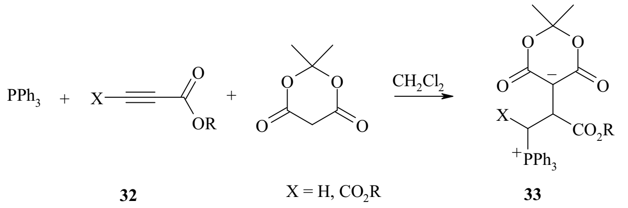


Scheme 15

SYNTHESIS OF DIIONIC COMPOUNDS

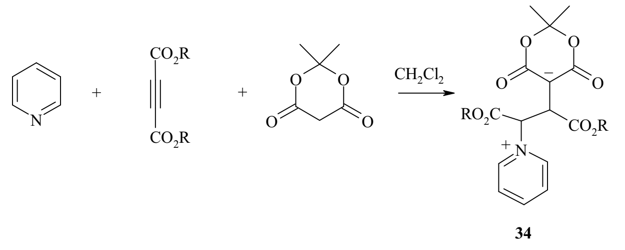
1,4-Diionic Compounds

Meldrum's acid has been employed as CH-acid in preparation of novel 1,4-diionic phosphorus compounds derived from alkyl propiolates [26] or dialkyl acetylenedicarboxylates [27, 28]. The reactive 1:1 intermediate produced in the reaction between Ph_3P and alkyl propiolates or dialkyl acetylenedicarboxylates was trapped by Meldrum's acid to produce **33** (X = H) or **33** (X = CO_2R) (Scheme 16).



Scheme 16

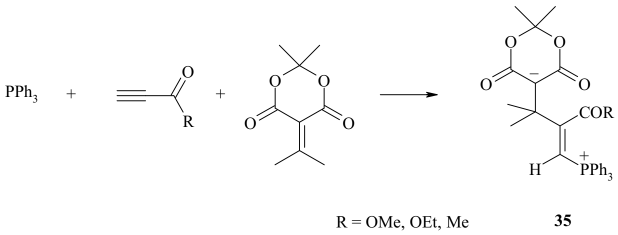
Similarly, stable 1,4-diionic pyridinium betaines **34** have been reported [29] through the reaction of Meldrum's acid with dialkyl acetylenedicarboxylates in the presence of pyridine (Scheme 17).



Scheme 17

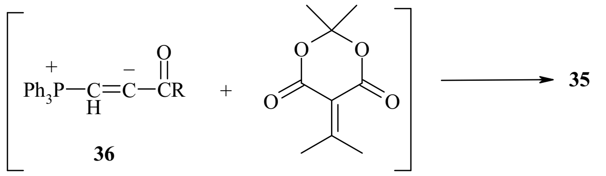
1,5-Diionic Compounds

The reactive 1:1 intermediate produced in the reaction between triphenylphosphine and alkyl propiolates or ethynyl phenyl ketone was trapped by isopropylidene Meldrum's acid to produce alkyl 3-(isopropylidenemalonate -5- yl -5- ylid) -3- methyl -2- triphenylphosphoniomethylidene-butanoates (**35**, R = *O*-Alkyl) or 3-(isopropylidenemalonate-5-yl-5-ylid)-3-methyl -2- triphenylphosphoniomethylidene - butanone (**35**, R = Me) in 75-86% yield [30]. These 1,5-diionic phosphorus betaines exist as (*Z*) geometrical isomer in $CDCl_3$ solution (Scheme 18).



Scheme 18

Compound **35** apparently results from the initial addition of triphenylphosphine to the acetylenic system and subsequent attack of the reactive zwitterionic intermediate **36** to isopropylidene Meldrum's acid leading to 1,5-diionic compound **35** (Scheme 19).



Scheme 19

SUMMARY

During the last decade, Meldrum's acid has been widely used in organic synthesis. Application of Meldrum's acid derivatives, such as isopropylidene Meldrum's acid in preparation of amidoesters, triamides, and diionic organic compounds, have not been documented in the chemistry of acyclic malonates. It is hoped that this brief review will stimulate more interest in the development of existing and new applications of Meldrum' acid and its derivatives in organic synthesis.

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