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TWO CONVENIENT METHODS FOR THE GENERATION OF "METHYLENE MELDRUM'S ACID" FOR DIELS-ALDER REACTIONS.

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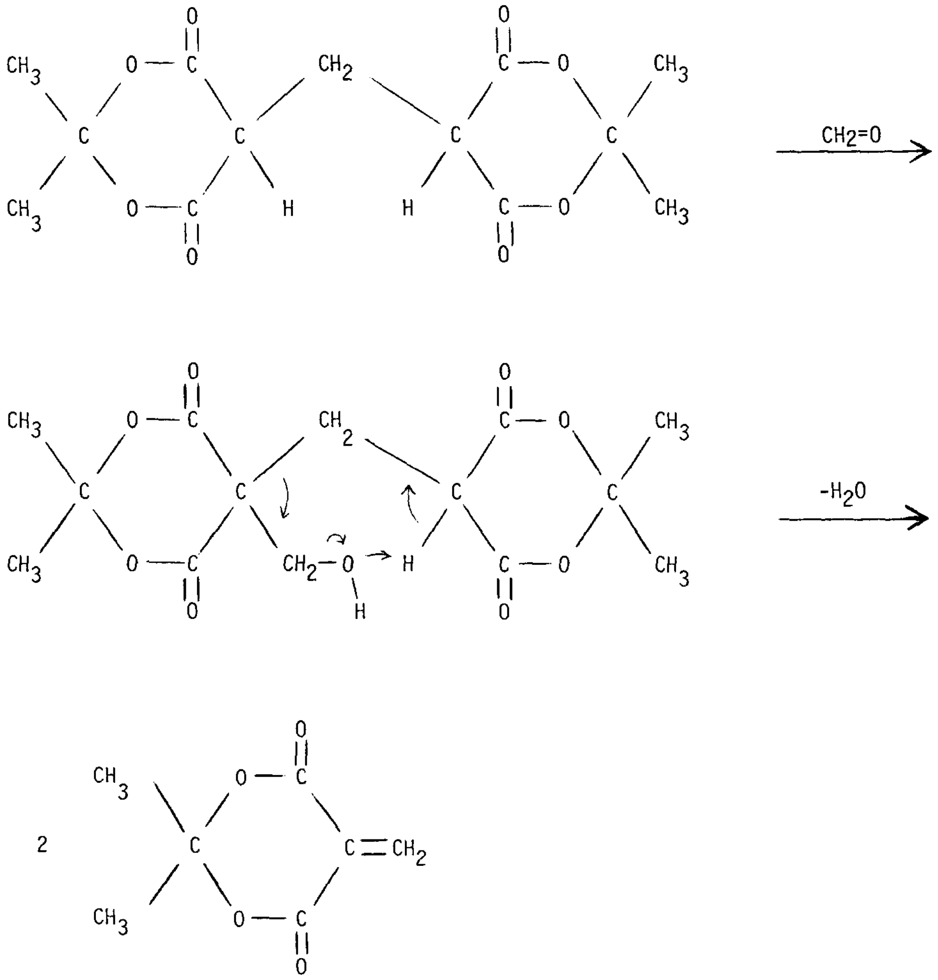
Summary: The transient isopropylidene methylenemalonate can be easily generated by treating either Meldrum's acid or diisopropylidenemethylenedimalonate with formaldehyde, and trapped by reactive dienes.

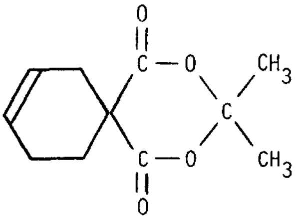
Isopropylidene methylenemalonate (5-methylene-2,2-dimethyl-1,3-dioxane-4,6-dione; "methylene Meldrum's acid") is a transient species with high reactivity as a dienophile.[1,2] The previously reported method for the generation of this species for Diels-Alder-type reactions involves the oxidation of the 5-methyl-5-phenylseleno derivative of Meldrum's acid in the presence of dienes.[2] We wish to report that methylene Meldrum's acid can be generated by treating either Meldrum's acid or diisopropylidene methylenedimalonate with formaldehyde and trapped by reactive dienes.

Two recent articles[3] in which Meldrum's acid, various aldehydes, and indole were shown to condense to give isopropylidene 3-indolylmethylmalonates and the likely intermediacy of the methylene malonates in these reactions, led us to explore similar reaction conditions for the one pot preparation of Diels-Alder adducts. We found that reactive dienes will give good yields of the cycloaddition products when Meldrum's acid, formaldehyde and the diene are allowed to react in acetonitrile with proline as a catalyst; these are the same reaction conditions previously advanced for the preparation of the above mentioned indole derivatives.

Because of the ease by which Meldrum's acid and formaldehyde react to give an aldol-Michael bis adduct[4] and the ease by which such adducts dissociate[1a,4], one might question the intermediacy of of this compound in the above reactions. Indeed, diisopropylidene methylenedimalonate has recently been used as a source of "methylene Meldrum's acid" for the introduction of functionalized 3-carbon chains onto monohydroxyanthraquinones.[5] In this regard, we tested the reactivity of the aldol-Michael bis adduct, which we employed in place of Meldrum's acid and formaldehyde, under the otherwise same reaction conditions (room temperature) and found it to be unreactive. However, if a mole equivalent of formaldehyde was added to the aldol-Michael bis adduct under these reaction conditions, a rapid reaction ensued and a good yield of the Diels-Alder adduct was obtained after a short while. One could hypothesize that the formaldehyde reacts with the bis adduct to form a methylol derivative as shown in the Scheme. This methylol derivative could then rapidly undergo a retro-Michael-type reaction with the formation of two mole equivalents of methylene Meldrum's acid. The attachment of the methylol group to the bis adduct would possibly make the molecule more reactive towards a retro-Michael-type reaction.

SCHEME. A possible mechanism for the generation of methylene Meldrum's acid from diisopropylidene methylenedimalonate and formaldehyde (entirely speculative).





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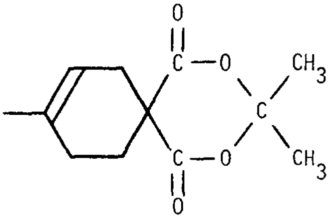

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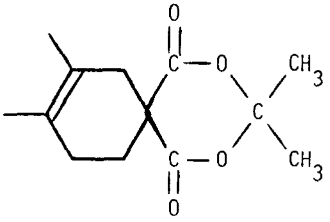

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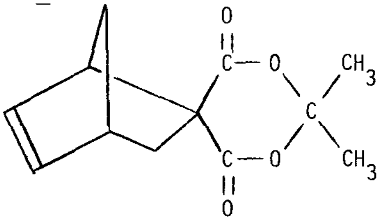

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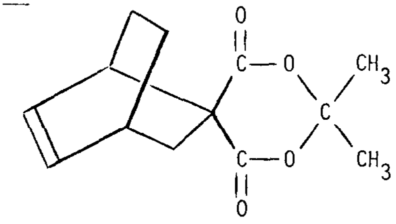

V

TABLE. Diels-Alder Adducts

Adduct	Diene Used	Yield		m.p.	lit. m.p.
I	1,3-butadiene	50(a)	61(b)	82-3	(c)
II	isoprene	80(a)	82(b)	79-80	(c, d)
III	2,3-dimethyl-1,3-butadiene	72(a)	85(b)	87-8	(c)
IV	cyclopentadiene	50(a)	81(b)	86-7	86.5-88 (2)
V	1,3-cyclohexadiene	78(a)	82(b)	80-1	78.5-79 (2)

(a) from Meldrum's acid and formaldehyde

(b) from the aldol-Michael bis adduct and formaldehyde

(c) gave satisfactory analysis for carbon and hydrogen (± 0.3%)

(d) degraded to 4-methyl-3-cyclohexenecarboxylic acid, m.p. 95-6, lit. m.p. 99 (6)

EXPERIMENTAL

Preparation of Diels-Alder Adducts using Meldrum's Acid and Formaldehyde: Meldrum's acid, 1.44 g (10 mmoles), the diene (10 mmoles), and proline, 0.1 g, were stirred in 10 ml acetonitrile. Formaldehyde, 1 ml of a 37% aqueous solution (10 mmoles) was added (exothermic). After stirring for one hour at room temperature the mixture was poured onto ice, whereupon the Diels-Alder adduct crystallized. The product was removed by filtration and washed with water. The specific results are given in the Table.

Preparation of Diels-Alder Adducts using Diisopropylidene Methylenedimalonate and Formaldehyde: Diisopropylidene methylenedimalonate[7], 3.00 g (10 mmoles), the diene (20 mmoles), and proline, 0.1 g, were stirred in 10 ml acetonitrile. Formaldehyde, 1 ml of a 37% aqueous solution (10 mmoles), was added. The bis adduct, which was initially insoluble, dissolved over a 5-10 minute period. After stirring for a total of one hour at room temperature the mixture was poured onto ice, whereupon the Diels-Alder adduct crystallized. The product was removed by filtration and washed with water. The specific results are given in the Table.

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7. We used large pure crystals of the bis adduct filtered directly from the reaction solution described in reference 4 and washed with DMF. If an excess of formaldehyde is used, a lower melting material is obtained as also described in reference 4. This lower melting substance of uncertain composition will react directly with the dienes without adding additional formaldehyde.

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