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A NEW SOURCE OF METHYLENE MELDRUM'S ACID. REACTIONS WITH ENAMINES

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A NEW SOURCE OF METHYLENE MELDRUM'S ACID. REACTIONS WITH ENAMINES

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ABSTRACT

The unsymmetrical Knoevenagel–Michael product derived from Meldrum's acid, phenyl Meldrum's acid and formaldehyde was prepared as a pure, stable and crystalline product. This compound readily dissociates under the reaction conditions to produce methylene Meldrum's acid. This Knoevenagel–Michael product was used to explore a new application of methylene Meldrum's acid: the reaction with enamines.

Methylene Meldrum's acid (isopropylidene methylenemalonate or 2,2-dimethyl-5-methylene-1,3-dioxane-4,6-dione) (I) is a reactive dienophile and Michael acceptor with a fleeting existence.^[1] Early methods for the generation of this intermediate involve oxidation reactions of 5-seleno derivatives.^[2] Several years ago we described a method of

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generation that used either a mixture of formaldehyde and Meldrum's acid or a mixture of the Knoevenagel–Michael adduct (II) of Meldrum's acid and formaldehyde with additional formaldehyde.^[3] More recently a novel betaine (III) prepared from pyridine, formaldehyde, and Meldrum's acid was reported by Zia-Ebrahimi and Huffman and shown to form methylene Meldrum's acid under certain conditions.^[4] These workers demonstrated that this compound could be used to form products in high yield with dienes, indole and active methylene compounds (Scheme 1).



We wish to report a new convenient source of methylene Meldrum's acid (I). This source is the stable crystalline Knoevenagel–Michael *bis* adduct (IV) derived from Meldrum's acid, phenyl Meldrum's acid and formaldehyde. This compound appears to readily generate methylene Meldrum's acid (I) in the presence of enamines and reacts with the enamines forming phenyl Meldrum's acid (V) as a byproduct (Scheme 2).



Scheme 2.

METHYLENE MELDRUM'S ACID

This present work is the result of an attempt to find a source of methylene Meldrum's acid that could be used to test its reactivity with enamines. The idea that enamines would be reactive with methylene Meldrum's acid is suggested by the previously reported reaction^[4,5] with indole which can be considered a cyclic aromatic enamine. The enamines attack the electron deficient double bond of the Meldrum's acid derivative and this results in 3-oxoalkylmalonate derivatives after aqueous workup. The following five 3-oxoalkylmalonate derivatives have been formed in good yield (Scheme 3).



Scheme 3.

For such reactions with ordinary enamines it would be presumably necessary to generate methylene Meldrum's acid (I) under anhydrous conditions and in non-hydroxylic solvents. Examination of the reactivity of the unsymmetrical *bis*-adduct (IV) showed it to be markedly more reactive than the symmetrical adduct (II). We also found product (III) of Zia-Ebrahimi and Huffman to be quite reactive toward these enamines under similar conditions. Compounds VI through VIII were formed with comparable yields by this method. Also it might be noted, that as far as we know, there are no prior reports of other unsymmetrical Knoevenagel–Michael *bis*-adducts derived from Meldrum's acid and a mono substituted Meldrum's acid.

EXPERIMENTAL

Meldrum's Acid, phenyl Meldrum's acid, 37% formaldehyde and piperidine were obtained from commercial sources and used without purification in the preparation of diisopropylidene 1-phenyl-1,1,3,3propanetetracarboxylate. Enamines 1-piperidino-1-cyclopentene, 1-morpholino-1-cyclohexene and 1-morpholino-1-cycloheptene were also obtained from commercial sources and used without purification in the reactions with Meldrum's acid while the aza cyclic enamine was synthesized in benzene and reacted in situ with Meldrum's acid. Melting points were determined in a capillary tube on a Thomas Hoover MP apparatus. IR spectra were recorded on a Mattson Instruments Polaris Spectrometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Varian EM360L CW 60 MHz spectrometer upgraded with an Anasazi Instruments, Inc. EFT FT NMR upgrade with Carbon-13 accessory. Carbon type assignments were made from ¹³CNMR DEPT data. Quantitative Technologies Inc. Whitehouse, NJ and Atlanta Microlab, Inc. Norcross, GA performed analyses.

Diisopropylidene 1-Phenyl-1,1,3,3-Propanetetracarboxylate (IV): Meldrum's Acid, 14.4 g (100 mmol) and phenyl Meldrum's acid, 22.0 g (100 mmol) were stirred in 200 mL of absolute ethanol and 9.0 mL of 37% formaldehyde (100 mmol) was added followed by twenty drops of piperidine. After stirring for two days, the crystalline product was removed by filtration and washed with additional ethanol. The white crystalline product melted at 165°C with vigorous gas evolution. 70% Yield. ¹H NMR (60 MHz, CDCl₃) δ 8.01 (br s, 5H), 4.84 (t, 1H), 3.59 (d, 2H), 2.38 (br s, 9H), 1.80 (s, 3H). ¹³C NMR (60 MHz, CDCl₃) δ 164.99 (4 C=O), 134.69 (C), 129.39 (2 CH), 129.83 (CH), 125.67 (2CH), 106.38 (C), 105.61 (C), 56.85 (C), 41.34 (CH), 36.38 (CH₂), 29.70 (CH₃), 29.26 (CH₃), 27.84 (CH₃), 27.60 (CH₃). IR (Nujol) 1725, 1760 cm⁻¹ (C=O). Anal. Calcd for C₁₉H₂₀O₈: C, 60.63; H, 5.32. Found: C, 60.56; H, 5.33.

General Procedure for the Reaction of Methylene Meldrum's acid (I) with Enamines: The *bis*-adduct (IV), 10 nmol, was stirred in 5.0 mL of THF resulting in a white slurry. Ten millimoles of the enamine were then added with continued stirring. A clear yellow solution formed rapidly and after fifteen minutes the mixture solidified to a nearly white paste. The paste was dissolved in 40 mL of 0.25 M aqueous HCl solution. The phenyl Meldrum's acid byproduct (V), which separated as a white precipitate, was removed by filtration. The aqueous filtrate was extracted with four 15 mL portions of methylene chloride. The extracts were combined, dried over magnesium sulfate and filtered. The methylene chloride was removed by rotary evaporation yielding the white solid products. Alternatively, similar yields were

obtained by chilling the initial aqueous filtrate for twelve hours followed by collection of the product crystals by filtration.

Isopropylidene 2-Oxocyclopentylmethylmalonate (VI) from 1-Piperidino-1-cyclopentene: Colorless crystals. 78% yield m.p. 138°C dec. (heptane). ¹H NMR (60 MHz, CDCl₃) δ 4.53 (dd, 1H), 2.18 (om, 9H), 2.02 (s, 3H), 1.90 (s, 3H). ¹³C NMR (60 MHz, CDCl₃) δ 220.36 (1 C=O), 164.75 (1 C=O), 164.47 (1 C=O), 104.62 (C), 44.24 (CH), 43.40 (CH), 38.53 (CH₂), 30.64 (CH₂), 28.56 (CH₃), 26.31 (CH₂), 26.26 (CH₃), 20.56 (CH₂). IR (Nujol) 1770, 1745 cm⁻¹ (C=O). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.96; H, 6.71.

Isopropylidene 2-Oxocyclohexylmethylmalonate (VII) from 1-Morpholino-1-cyclohexene: Colorless crystals. 82% yield m.p. 120°C dec. (heptane). ¹H NMR (60 MHz, CDCl₃) δ 3.79 (dd, 1H), 2.21 (om, 11H), 1.57 (s, 3H), 1.51 (s, 3H). ¹³C NMR (60 MHz, CDCl₃) δ 212.54 (1 C=O), 165.29 (1 C=O), 164.54 (1 C=O), 104.77 (C), 47.24 (CH), 44.53 (CH), 42.56 (CH₂), 35.37 (CH₂), 29.14 (CH₃), 28.33 (CH₂), 27.69 (CH₂), 26.73 (CH₃), 25.56 (CH₂). IR (Nujol) 1780, 1750, 1700 cm⁻¹ (C=O). Anal. Calcd for C₁₃H₁₈O₅: C, 61.41; H, 7.13. Found: C, 61.47; H, 7.10.

Isopropylidene 2-Oxocycloheptylmethylmalonate (VIII) from 1-morpholino-1-cycloheptene: Colorless crystals. 76% yield m.p. (heptane). 94°C dec. (heptane). ¹H NMR (60 MHz, CDCl₃) δ 3.84 (dd, 1H), 2.10 (om, 13H), 1.52 (s, 3H), 1.47 (s, 3H). ¹³C NMR (60 MHz, CDCl₃) δ 215.05 (1 C=O), 164.68 (1 C=O), 164.23 (1 C=O), 104.40 (C), 48.52 (CH), 43.98 (CH), 42.78 (CH₂), 31.94 (CH₂), 29.67 (CH₂), 28.95 (CH₂), 28.62 (CH₃), 28.34 (CH₂), 26.45 (CH₃), 24.45 (CH₂). IR (Nujol) 1790, 1750, 1700 cm⁻¹ (C=O). Anal. Calcd for C₁₄H₂₀O₅: C, 62.67; H, 7.51. Found: C, 62.82; H, 7.55.

General Procedure for the Reaction of Methylene Meldrum's Acid with Aza Cyclic Enamines to form 3-Oxoalkylmalonates (IX) and (X): The N-carboxy-4-(N-morpholino)-1,2,5,6-tetrahydropyridine enamines were formed by combining 10 mmol of the N-Carboxy-4-piperidones with 10 mmol of morpholine and a catalytic amount of tosic acid in 80 mL of benzene. The solutions were refluxed with a Dean-Stark trap for twelve hours. Upon cooling to room temperature, 10 mmol of diisopropylidene 1phenyl-1,1,3,3-propanetetracarboxylate (IV) was added. After 60 min, 40 mL of 0.25 M HCl was added and the mixtures were vacuum filtered using a Buchner funnel. The benzene layer was isolated from the aqueous layer using a separatory funnel. The benzene solution was dried over magnesium sulfate and the benzene removed by rotary evaporation to yield the white solid product.

Isopropylidene 3-(*N*-Ethoxycarbonyl-3-oxo-piperidinyl)methylmalonate (IX) Derived from *N*-Carbethoxy-4-(*N*-morpholino)-1,2,5,6-Tetrahydropyridine: Colorless crystals. 80% yield m.p. 119°C dec. ¹H NMR (60 MHz,

CDCl₃) δ 3.81 (om, 3H), 2.50 (om, 9H), 1.49 (s, 3H), 1.46 (s, 3H) 0.80 (t, 3H). ¹³C NMR (60 MHz, CDCl₃) δ 208.68 (1 C=O), 164.92 (1 C=O), 164.41 (1 C=O), 154.51 (C=O), 104.95 (C), 62.12 (CH₂), 48.55 (CH₂), 46.61 (CH), 44.18 (CH), 43.70 (CH₂), 41.02 (CH₂), 28.99 (CH₃), 26.65 (CH₃), 24.61 (CH₂), 15.22 (CH₃). IR (Nujol) 1800, 1750, 1680 cm⁻¹ (C=O). Anal. Calcd for C₁₅H₂₁NO₇: C, 55.04; H, 6.47; N 4.28. Found: C, 54.96; H, 6.48; N, 4.22.

Isopropylidene 3-(*N*-*t*-butoxycarbonyl-3-Oxo-piperidinyl)methylmalonate (IX) Derived from *N*-*t*-Butoxycarbonyl-4-(*N*-morpholino)-1,2,5,6-tetrahydropyridine: Colorless crystals. 75% yield m.p. 132°C dec. ¹H NMR (60 MHz, CDCl₃) δ 4.39 (om, 2H), 3.96 (om, 2H), 3.27 (om, 2H), 2.89 (om, 4H), 2.09 (s, 3H), 2.00 (s, 3H), 1.73 (s, 9H). ¹³C NMR (60 MHz, CDCl₃) δ 209.86 (1 C=O), 165.40 (1 C=O), 164.92 (1 C=O), 154.07 (C=O), 104.86 (C), 80.13 (C), 46.11 (CH), 43.57 (CH), 43.11 (CH₂), 40.77 (CH₂), 40.41 (CH₂), 28.80 (CH₃), 28.00 (3CH₃), 25.89 (CH₃), 23.89 (CH₂). IR (Nujol) 1787, 1750, 1710, 1682 cm⁻¹ (C=O). Anal. Calcd for C₁₇H₂₅NO₇: C, 57.45; H, 7.09; N 3.95. Found: C, 57.49; H, 7.04; N, 3.90.

Reaction of Pyridiniummethyl Meldrum's acid (III) with Enamines: The Pyridiniummethyl Meldrum's acid (10 mmoles) was stirred in 5 mL of THF. Ten millimoles of the enamine were added followed by 2 drops of methyl-sulfonic acid. The mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water, made slightly acidic with hydrochloric acid, and the crystalline product removed by filtration. Products VI through VIII were formed with comparable yields to enamine reactions with Diisopropylidene 1-phenyl-1,1,3,3-propanetetracarboxylate (IV).

REFERENCES

- 1. McNab, H. Meldrum's Acid. Chem. Soc. Rev. 1978, 7, 345.
- Brown, R.F.C.; Eastwood, F.W.; McMullen, G.L. Methyleneketenes and Methylenecarbenes. Evidence for the Pyrolytic Generation of Methyleneketene (Propadienone). Aust. J. Chem. 1977, 30, 179.
- Buzinkai, J.F.; Hrubowchak, D.M.; Smith, F.X. Two Convenient Methods for the Generation of Methylene Meldrum's Acid for Diels– Alder Reactions. Tetrahedron Letters. 1985, 26, 3195.
- Zia-Ebrahimi, M.; Huffman, G.W. Synthesis and Utility of a Novel Methylene Meldrum's Acid Precursor. Synthesis 1996, 215; Zia-Ebrahimi, M.; Reutzel, Susan, M.; Dorman, Douglas, E.; Spangle, Larry S.; Deeter, Jack, B. X-ray Crystallography and Solid-State NMR as Complementary Tools: Characterization of Novel Methylene

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Meldrum's Acid Precursors. Chem. Mater. **1994**, *6*, 822–826; Zia-Ebrahimi M. Preparation of Methylene Meldrum's Acid Precursors. US Patent 5 243 053, September 7, 1993.

 Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. Meldrum's Acid in Organic Synthesis. A Convenient One-pot Synthesis of Ethyl Indolepropionates. Tetrahedron Letters. 1978, 20, 1759; Farlow, D.S.; Flaugh, M.E.; Horvath S.D.; Lavagnino, E.R.; Pranc P. Two Efficient Synthesis of Indole-3-Propionic Esters and Acids. Further Applications of Meldrum's Acid. Org. Prep. Proc. Int. 1981, 13(1), 39.

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