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BOROHYDRIDE REDUCTION OF SUBSTITUTED ISOPROPYLIDENE METHYLENEMALONATES

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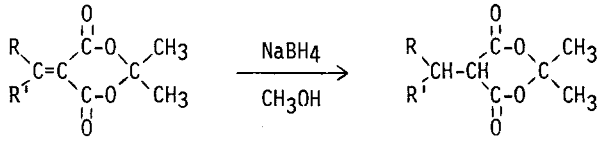
Knoevenagel-type products derived from Meldrum's Acid are readily reduced by sodium borohydride to give monosubstituted isopropylidene malonates in high yield.

Isopropylidene malonate (Meldrum's Acid) will condense with aromatic aldehydes[1] under mild conditions to give Knoevenagel-type products, often in high yield. The facility by which these reactions take place under mildly basic or non-basic conditions can be attributed to the high acidity (pK_a~5)[2] of this cyclic ester. Under certain conditions such condensation products can also be obtained from aliphatic aldehydes[3] and ketones[1c,4].

Reduction of the carbon-carbon double bond of some of these products has been accomplished by catalytic hydrogenation[5] and by treatment with lithium aluminum hydride[6]. The resultant monosubstituted isopropylidene malonates have potential utility as organic reagents[7], or could be hydrolyzed and decarboxylated to give the corresponding carboxylic acids[5]. The recent report[8] that some monosubstituted derivatives of Meldrum's Acid undergo smooth ethanolysis with concomitant decarboxylation when heated with ethanol-pyridine in the presence of copper powder should further increase their utility as organic intermediates.

We wish to report a simple method for the reduction of substituted isopropylidene methylenemalonates. We have found that sodium borohydride[9] will give high yields of the reduced product within a few minutes at room temperature in methanol solution. A general procedure is as follows: The substituted isopropylidene methylenemalonate (1), 50 mmoles, was stirred in 75 mls. of methanol and sodium borohydride, 25 to 50 mmoles[10], was added slowly over a period of ten minutes with external cooling as necessary to keep the temperature between 15 to 25 degrees. After stirring for an additional five minutes, 200 mls. of 1N hydrochloric acid was added and the resultant suspension chilled. The crystalline product (2) was removed by filtration and washed with cold water. The specific results are presented in the Table.



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a: R = R' = CH_3
b: R = Ph, R' = H
c: R = Ph-CH=CH, R' = H
d: R = 2-Furyl, R' = H
e: R = 3-Indolyl, R' = H

Table. Borohydride Reductions of Isopropylidene Methylenemalonates.
Product, yield, m.p.(recrystallization solvent), and comments.

2a	85%	104-5(hexane-toluene)	NMR(CDCl$_3$)δ: 1.2(d)6H, 1.8(s)6H, 2.7(m)1H, 3.4(d)1H.
2b	97%	80-1(hexane)	lit. m.p. 80-1[5].
2c	96%	108-9(hexane-toluene)	Reduction occurred at the double bond conjugated to the carbonyl system. NMR(CDCl$_3$)δ: 1.8(s)6H, 3.0(m)2H, 3.7(t)1H, 6.4(m)2H, 7.3 (m)5H. Converted to ethyl 5-phenyl-4-pentenoate[11] in 72% yield by refluxing with ethanol-pyridine (10:2) and copper powder[8].
2d	98%	92-3(hexane-toluene)	Converted to ethyl 2-furylpropionate[12] in 71% yield by the method indicated for **2c**.
2e	89%	122-3(methanol-water)	The reaction mixture had to be further diluted with 1,2-dimethoxyethane (2 mls. per mmole) in order to enhance the solubility of **1e**. Converted to ethyl 3-indolylpropionate[13] in 67% yield by the method indicated for **2c**.

References and Notes

1. For some examples see: (a) P. Schuster, O. E. Polansky, and F. Wessely, *Monatsh. Chem.*, **95**, 53, (1964); (b) G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Aust. J. Chem.*, **27**, 2605 (1974); (c) J. A. Hedge, C. W. Kruse, and H. R. Snyder, *J. Org. Chem.*, **26**, 3166 (1961).

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3. P. Margaretha and O. E. Polansky, *Tetrahedron Letters*, 4983 (1969).

4. G. A. Bihlmayer, F. J. Kunz, and O. E. Polansky, *Monatsch. Chem.*, **97**, 1293 (1966). G. J. Baxter and R. F. C. Brown, *Aust. J. Chem.*, **28**, 1551 (1975).

5. G. Swoboda, J. Swoboda, and F. Wessely, *Monatsh. Chem.*, **95**, 1283 (1964).

6. A. Stephen and F. Wessely, *Monatsh. Chem.*, **98**, 184 (1967).

7. F. X. Smith and G. G. Evans, *Tetrahedron Letters*, 1237 (1972), *J. Heterocyclic Chem.*, **13**, 1025 (1976). A. Scoville and F. X. Smith, *J. Heterocyclic Chem.*, **14**, 1081 (1977). L. G. Siperko and F. X. Smith, *Synthetic Communications*, in press. For some recent applications of the unsubstituted ester see: R. B. Mane and G. S. K. Rao, *Chem. and Ind.*, 786 (1976), Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978), and reference 8.

8. Y. Oikawa, H. Hirasawa, and O. Yonemitsu, *Tetrahedron Letters*, 1759 (1978).

9. For some comparable reductions of acyclic unsaturated esters with sodium borohydride see: J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965), and S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966). Reduction of the cyclic isopropylidene esters seem especially facile. This may be due to the special stability of the flat cyclic carbanionic intermediates formed in the reaction. For some reactions that can be explained on a similar basis see ref. 5 and P. Schuster, *Oesterr. Chem. Ztg.*, **68**, 252 (1967). Also see: S. Danishefsky and R. K. Singh, *J. Org. Chem.*, **40**, 3807 (1975), for a special effect termed "spiroactivation".

10. Esters **1a** and **1d** were cleanly reduced with a one half mole equivalent of borohydride. A full mole equivalent of borohydride was used in the reduction of **1b**, **1c**, and **1e** in order to ensure obtaining a product free of starting material.

11. Identified by hydrolysis to 5-phenyl-4-pentenoic acid, m.p. 89-90 (ethanol-water); lit. m.p. 90: E. H. Farmer and C. G. B. Hose, *J. Chem. Soc.*, 962 (1933).

12. IR corresponds to that reported: A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, 657 (1959).

13. Identified by hydrolysis to 3-indolylpropionic acid, m.p. 131-3 (ether-hexane); lit. m.p. 134 "Dictionary of Organic Compounds", Fourth Edition, Oxford University Press, New York, New York (1965).

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