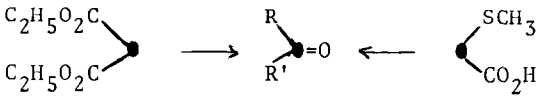
Tetrahedron Letters No. 44, pp 3797 - 3800, 1975. Pergamon Press. Printed in Great Britain.

# 2-METHYLTHIOACETIC ACID AND DIETHYL MALONATE AS ACYL ANION EQUIVALENTS. SYNTHESIS OF JUVABIONE

Barry M. Trost and Yoshinao Tamaru
Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706

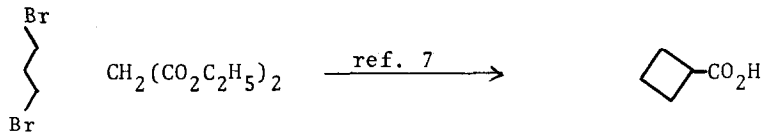
(Received in USA 29 August 1975; received in UK for publication 23 September 1975)

Acyl anions have rapidly become useful synthons. Thioacetals,[1] thioacetal monosulfoxides,[2] protected cyanohydrins,[3] and enol ethers[4] have served in this role. The facile oxidative decarboxylation of carboxylic acids[5] makes them prime candidates as inexpensive and easily manipulated acyl anion equivalents. In this Communication, we wish to report the realization of this scheme using very readily available methylthioacetic acid and diethyl malonate in this role.

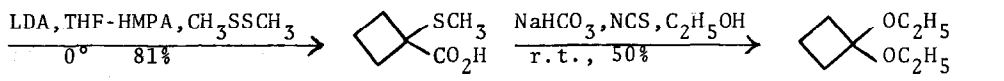



1

The well-known ability to monoalkylate or dialkylate diethyl malonate followed by hydrolysis has not led us to explore this aspect extensively. A simple application illustrated in equation 1 provides one of the most facile routes to cyclobutanone,[6] isolated as its ketal. The cleanliness of the oxidative decarboxylative reaction as determined by spectroscopic examination of the crude reaction suggests to us the lower yields arise due to the high volatility of the product on the scale on which we operate.



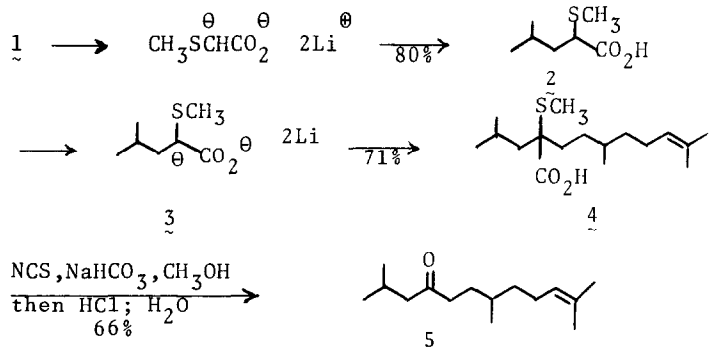

Eq. 1




bp 125° @ 10-15 mm

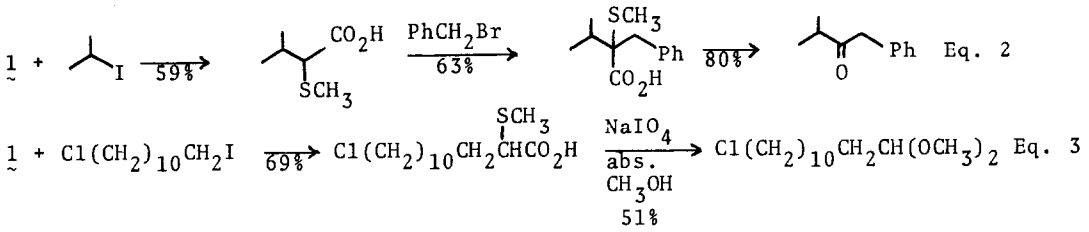
bp 62-3° @ 62 mm

A more direct acyl anion equivalent is the dianion of methylthioacetic acid 1 easily accessible by reaction of methylmercaptan with chloroacetic acid.[8,9] Treatment of 1 with 2.4 eq of lithium diisopropylamide in a 1:1 (v:v) ratio of THF:HMPA at 0° for 2 hr generates its dianion. Addition of isobutyl bromide at -20° and allowing the reaction to stir at RT gives 80% of 2 after distillation, bp 110-4° @ 22 mm.[10] Formation of the dianion 3



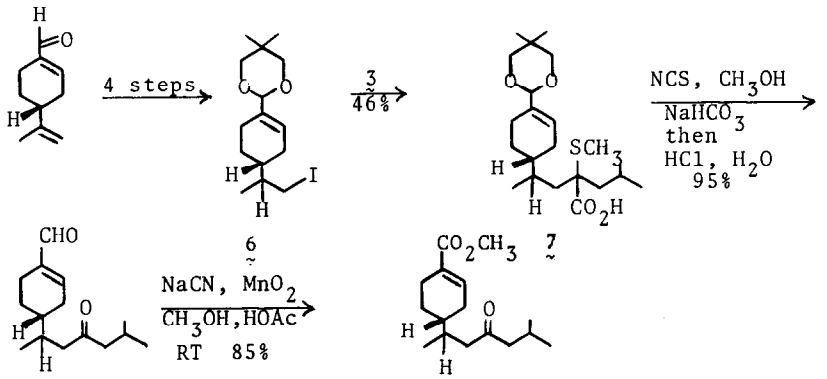

in an identical fashion followed by addition of citronellyl iodide (-25° for 1.5 hr and RT for 2.5 hr) gave the bisalkylated product 4, which after oxidative decarboxylation gave the ketone 5 (ir 1720 $cm^{-1}$; nmr δ 5.12, 1H, t, J = 7 Hz; 1.68 and 1.62, 3H each, s; 0.91, 6H, d, J = 6 Hz; 0.89, 3H, d, J = 6 Hz).

Secondary halides may be employed as illustrated by the synthesis of 3-methyl-1-phenyl-2-butanone (eq. 2). Oxidative decarboxylation may be performed after monoalkylation to constitute an aldehyde synthesis (eq. 3). In this case, the oxidizing agent for the oxidative decarboxylation must be anhydrous sodium metaperiodate in anhydrous methanol. Because of the low




solubility of sodium metaperiodate under these conditions, it must be ground into a fine powder to increase its surface area and reaction times on the order of 20 hr are common.[11]

A short synthesis of juvabione illustrates an application of the method.[12] The iodide 6 was available by standard methods from (+)-perillaldehyde. Alkylation of the dianion 3 with 6 gave the desired acid which, when subjected to oxidative decarboxylation in anhydrous methanol followed by




hydrolysis with aqueous hydrochloric acid, gave the keto aldehyde in nearly quantitative yield (ir 1740, 1695, 1650 $cm^{-1}$; nmr δ 9.42, 1H, s; 6.72, 1H, m; 0.93 , 6H, d, J = 7 Hz; 0.89, 3H, d, J = 8 Hz). Direct formation of the methyl ester from the aldehyde by the procedure of Corey et al[12] completes the synthesis. Comparison of the spectral data for our synthetic material with the literature confirms the structure.

Acknowledgment. We wish to thank the National Science Foundation, the National Institutes of Health, and the Wisconsin Alumni Research Foundation

for their generous support of our programs. We want to express our special thanks to Dr. Alan Thomas for a generous gift of (+)-perillaldehyde.

References

1. a) D. Seebach and M. Kolb, Chem. Ind. (London), 17, 687 (1974); D. Seebach, Synthesis, 17 (1969); b) T. Mukaiyama, K. Narasaka, and M. Furusato, J. Amer. Chem. Soc., 94, 8641 (1972); G. Schill and C. Merkel, Synthesis, 397 (1975).

2. K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 3151 (1971); J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, ibid., 3267 (1973).

3. G. Stork and L. Maldonado, J. Amer. Chem. Soc., 93, 5286 (1971); S. Hunig and G. Wehner, Synthesis, 180, 391 (1975).

4. J. E. Baldwin, G. A. Höfte, and O. W. Lever, J. Amer. Chem. Soc., 96, 7125 (1974).

5. B. M. Trost and Y. Tamaru, J. Amer. Chem. Soc., 97, 3528 (1975).

6. J. R. Salaun and J. M. Conia, Chem. Commun., 1579 (1971); J. M. Conia, P. Leriverend, and J. L. Ripoll, Bull. soc. chim. France, 1803 (1961).

7. G. B. Heisig and F. H. Stodola, Org. Syn. Coll. Vol. III, 213 (1955).

8. For the dianion of phenylthioacetic acid see K. Iwai, M. Kawai, H. Kosugi, and H. Uda, Chem. Letters (Japan), 385 (1974).

9. Note that α-phenylthiocarboxylic acids do not undergo oxidative decarboxylation satisfactorily.

10. No yields have been optimized. Structures have been confirmed by spectral data and new compounds have satisfactory elemental compositions.

11. The use of sodium metaperiodate appears to be general for the formation of aldehydes. It also may be used for the oxidative decarboxylation to generate ketones in comparable yields to NCS.

12. a) K. Mori and M. Matsui, Tetrahedron, 24, 3127 (1968); b) K. S. Ayyar and G.S.K. Rao, Can. J. Chem., 46, 1467 (1968); c) B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, J. Amer. Chem. Soc., 92, 336 (1970); d) A. J. Birch, P. L. Macdonald, and V. H. Powell, J. Chem. Soc. (C), 1469 (1970); e) A. A. Drabkina and Y. S. Tsizin, J. Gen. Chem. USSR Engl. Transl., 43, 422, 691 (1973); f) R. J. Crawford, U. S. Patent 3,676,506; Chem. Abstr., 77, 113889e (1972); g) J. Ficini, J. d'Angelo, and J. Noire, J. Amer. Chem. Soc., 96, 1213 (1974).

13. E. J. Corey, N. W. Gilman, and B. E. Ganem, J. Amer. Chem. Soc., 90, 5616 (1968).