Tetrahedron Letters No. 28, pp 2595 - 2598, 1973. Pergamon Press. Printed in Great Britain.

THE CONJUGATE ADDITION OF A GLYOXALATE DERIVED CARBONYL ANION EQUIVALENT AND ITS APPLICATION TO THE SYNTHESIS OF 1,4-DICARBONYL COMPOUNDS

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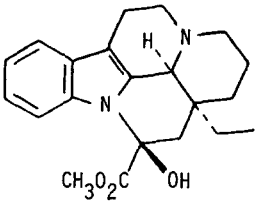
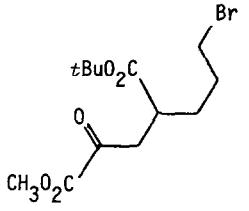
(Received in USA 4 May 1973; received in UK for publication 4 June 1973)

Recently, we initiated a program directed towards the simple and efficient synthesis of the *Hunteria* alkaloid vincamine (I).[1] From the outset of this work, we felt that the vincamine skeleton might be simplified in a strategically useful manner to the synthon II. This system contains carbon atoms essential to three of the five rings of vincamine and possesses the functionality requisite to convenient formation of these rings.[2]



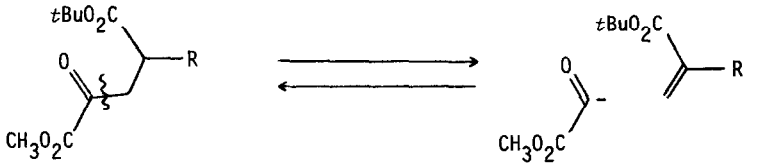
I



II

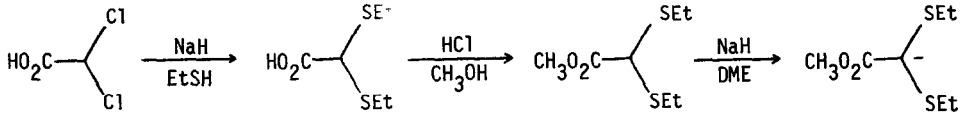
The synthon II represents an especially complex 1,4-dicarbonyl construction problem because one of these carbonyl groups is also part of an oxalate residue. Inspection of II shows

that it is fundamentally a five carbon unit, III, which can be disconnected *via* a *retro*-Michael reaction.[3] The synthetic equivalent of this disconnection thus becomes a Michael addition between the carbonyl anion derived from methyl glyoxalate and an acrylate ester.



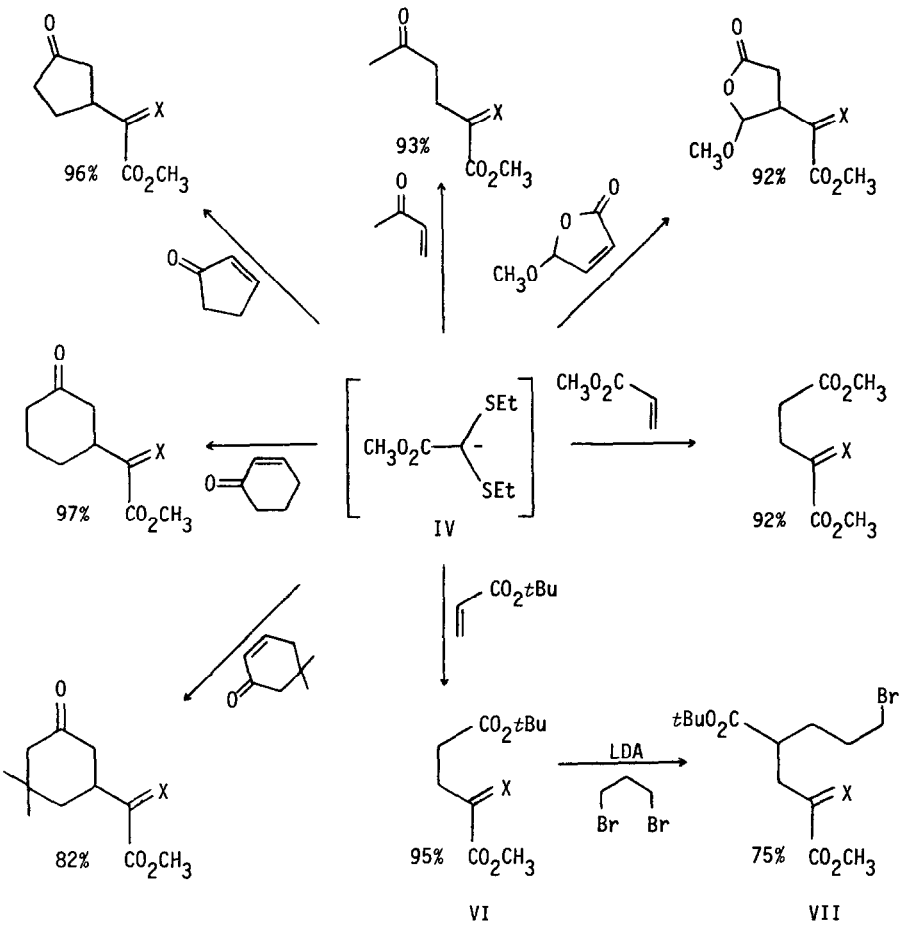
III

We now wish to report that the carbonyl anion equivalent IV, generated from the glyoxalate derivative V, undergoes smooth conjugate addition to a variety of Michael receptors thereby providing a highly useful method of preparing 1,4-dicarbonyl systems which bear an oxalate residue. Although the glyoxalate V was known, the existing synthesis of this material was not amenable to its preparation in significant amounts.[4] We have prepared V in 75% overall yield by reaction of dichloroacetic acid, ethyl mercaptan, and sodium hydride in THF solution followed by esterification of the resulting diethylmercaptoacetic acid with methanol and gaseous hydrogen chloride.[5] Compound V on reaction with sodium hydride is readily converted into the carbonyl anion equivalent IV at room temperature of below.



V IV

The conjugate addition reactions of IV are best carried out by adding at 4° the glyoxalate derivative V (1 equivalent) to a 0.3 molar dimethoxyethane solution containing sodium hydride (0.3 equivalents), allowing this mixture to stir 40 minutes, and then adding the Michael receptor (1 equivalent).[6] A summary of some of the Michael adducts prepared in this manner is given below.



All of the indicated Michael adducts [X = $(SEt)_2$] hydrolyze very rapidly into their corresponding keto analogues (X = O) using N-bromosuccinimide in aqueous acetonitrile.[7] On the other hand, hydrolysis with mercuric oxide in absolute methanol gives the corresponding ketals [X = $(OCH_3)_2$].[8] The adduct VI [X = $(SEt)_2$] smoothly alkylates, at -78°, with 1,3-dibromopropane using lithium diisopropylamide as the base.[9] The conversion of this product, VII [X = $(SEt)_2$] into vincamine is in progress.[10]

In summary, it is clear that the indicated reactions of anion IV allow the simple and convenient synthesis of 1,4-dicarbonyl compounds which in most cases would be difficult to obtain

by other means. The practical application of IV to the synthesis of more complex molecules is also obvious since it undergoes the conjugate addition reaction under mild conditions with ideal stoichiometry.

Acknowledgment. We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, and the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

REFERENCES

1. E. Schlittler and A. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953).
2. The ester groups in II are differentiated in the indicated manner for selective lactam formation at a later stage of the synthesis. Therefore, it is not tactically pertinent to view II as a simple 2-keto glutaric acid derivative. Indeed, it is easily possible to prepare the dimethyl ester diethylthioketal of II by the usual means, however, it is not possible to differentiate these ester groups in a viable manner.
3. An entirely different approach to the synthesis of systems like II is presented in an accompanying communication.
4. Compound V was first prepared by I. Minamida, Y. Ikeda, K. Uneyama, W. Tagaki, and S. Oae, *Tetrahedron*, **24**, 5293 (1968).
5. The yields reported are for isolated products. All compounds exhibited satisfactory spectral and physical properties.
6. Dimethylformamide may also be used as the solvent in these reactions.
7. The method described by E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971), was used in these reactions. Hydrolysis yields are always in excess of 90%.
8. The general hydrolysis method described by E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971) was used in these instances.
9. A convenient method of carrying out this type of ester alkylation has been described by R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Letts.*, in press.
10. Work being carried out in these laboratories by Dr. R. J. Cregge.