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A HIGHLY REACTIVE CARBONYL ANION EQUIVALENT DERIVED FROM ETHYL GLYOXALATE AND ITS CONJUGATE ADDITION TO MICHAEL RECEPTORS

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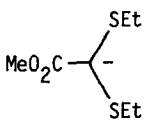
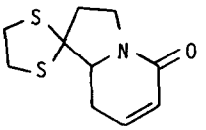
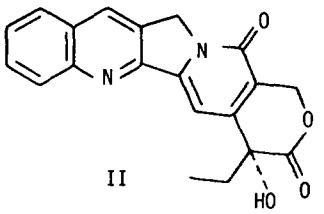
In a preceding communication, we described the novel conjugate addition behavior of the glyoxalate derived carbonyl anion equivalent I, and outlined its potential use in the total synthesis of vincamine.[1] It was also our desire to utilize this carbonyl anion equivalent within the context of a synthesis of the alkaloid camptothecin (II).[2] Our efforts to successfully realize this intention, however, were frustrated by the finding that the anion I could not be made to undergo high yield conjugate addition to the unsaturated lactam III[3] even under forcing conditions.



I



III

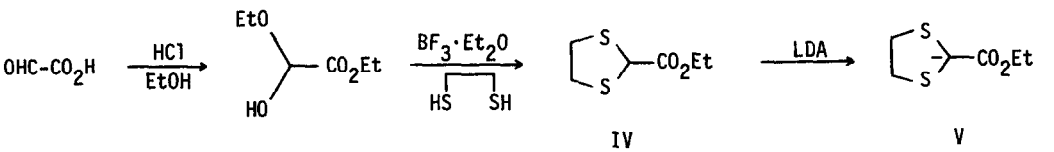


II

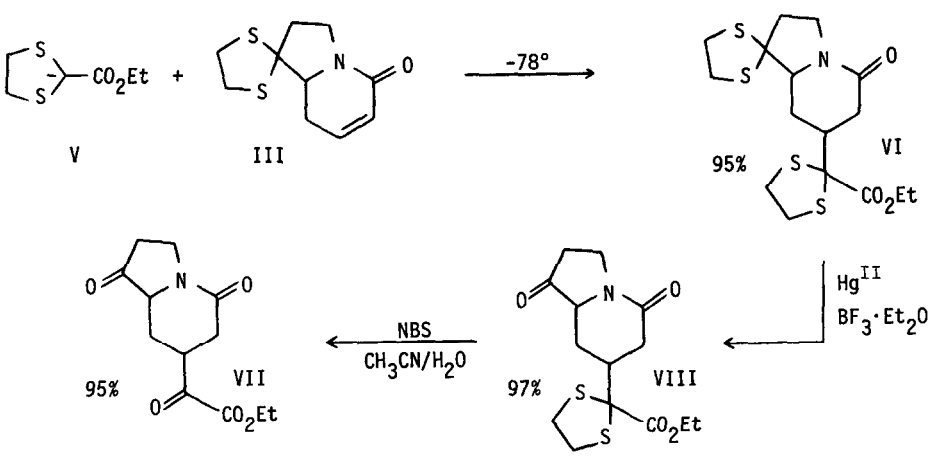
We felt that enhanced reactivity of the carbonyl anion equivalent towards Michael receptors might be achieved by sterically modifying the thioacetal moiety. To this end, we prepared the

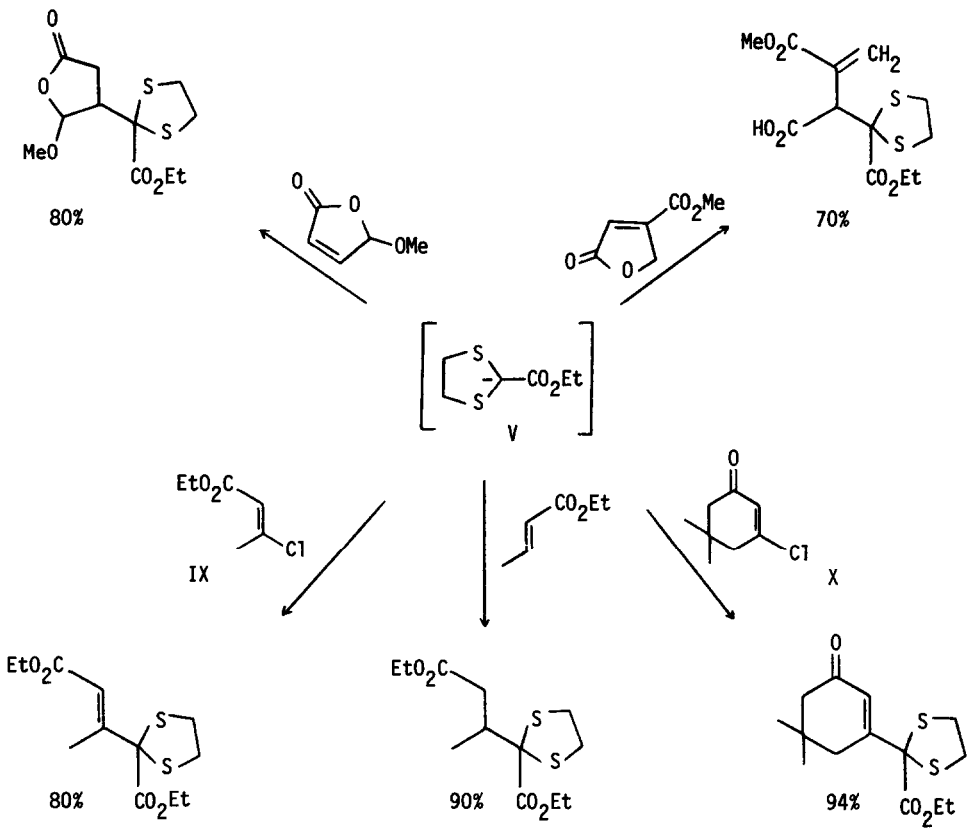
dithiolane derivative of ethyl glyoxalate, IV,[4] and herein wish to report that the conjugate base of IV, the carbonyl anion equivalent V, is indeed a more reactive species which undergoes high yield Michael addition to the lactam III as well as to other receptor systems.

Unlike anion I, the carbonyl anion equivalent V is not generated from its conjugate acid IV using sodium hydride. Instead, the much stronger base lithium diisopropylamide (LDA) is necessary to quantitatively form the anion V.[5] This result required that the Michael addition reaction of V be carried out starting with a full equivalent of the anion.[6] Typically, one molar solutions of V are prepared at -78° by adding IV (1 equivalent) to a THF solution of LDA (1 equivalent).[7] After 15 minutes, the Michael receptor (1 equivalent, neat or dissolved in THF) is then added to the solution of V. Uniformly excellent yields of conjugate addition products are formed under these conditions.[8] Furthermore, unwanted side products such as double Michael addition adducts are not observed when these reactions are carried out at -78°.[9]



The adducts derived from V smoothly and rapidly hydrolyze into their corresponding keto analogues using N-bromosuccinimide in aqueous acetonitrile.[10] A summary of some products obtained with V are given below.





Adduct VI may be converted into VII in two stages since dithiolane ketal residues adjacent to a carboxylate functionality are inert to hydrolysis with mercury salts.[10] Thus, treatment of VI with mercuric oxide and boron trifluoride etherate in aqueous THF gives the ketone VIII in nearly quantitative yield.[11] Subsequent hydrolysis of VIII with NBS in aqueous acetonitrile affords VII also in very high yield.[12]

The reaction of V with the β-chloro substituted Michael receptors IX and X provides, after hydrolysis, a novel preparation of α, β-unsaturated 1, 4-dicarbonyl systems. In addition, anion V reacts cleanly with ethyl crotonate whereas reaction with anion I leads in part to crotonate self-condensation.

In conclusion, the chemistry described for the carbonyl anion equivalent V together with that previously reported for I will clearly permit the ready synthesis of a variety of 1, 4-di-

carbonyl systems under widely different and stoichiometrically ideal experimental conditions.

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REFERENCES

1. R. J. Cregge, J. L. Herrmann, R. F. Romanet, and R. H. Schlessinger, *Tetrahedron Letts.*, in press.

2. M. E. Wall, C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim., *J. Amer. Chem. Soc.*, **88**, 388 (1966).

3. Lactam III has been synthesized in 50% overall yield starting from ethyl N-ethoxycarbonyl-3-pyrrolidinone-2-acetate. The 3-pyrrolidinone was prepared as described by J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1960).

4. The dithiolane IV was prepared by treating glyoxylic acid (Eastman Practical Grade) with absolute ethanol in the presence of 3A molecular sieves to give a mixture of ethyl glyoxalate diethyl acetal and ethyl hemiacetal. This mixture was then reacted with 1,2-ethane dithiol and boron trifluoride etherate in ether solution to give IV in essentially quantitative overall yield.

5. Anion formation was demonstrated by deuteration using deuterium oxide.

6. Michael addition reactions are usually carried out using a catalytic amount of base. For a recent review of the Michael reaction, see "Modern Synthetic Reactions," 2 ed., H. O. House, W. A. Benjamin, Inc., Menlo Park, California, 1972, Chapter 9.

7. Lithium diisopropylamide (LDA) was prepared by treatment of diisopropylamine with *n*-butyllithium at 4° for 15 minutes. This reagent when properly prepared is colorless to faintly yellow.

8. The yields reported are for isolated products. All compounds exhibited satisfactory spectral and physical properties.

9. Side products will sometimes occur when the reactions of V are carried out at 0 to 5°.

10. The method described by E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971), was used. Hydrolysis yields are always excellent.

11. The hydrolysis method described by E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971), was employed in this instance.

12. The direct conversion of VI into VII can be carried out with N-bromosuccinimide in aqueous acetonitrile.