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KETENE THIOACETAL MONOXIDES: SOME CONJUGATE ADDITION-ALKYLATION REACTIONS LEADING TO UNSYMMETRICAL 1,4-DICARBONYL SYSTEMS

J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, and R. H. Schlessinger

Department of Chemistry, University of Rochester

Rochester, New York 14627

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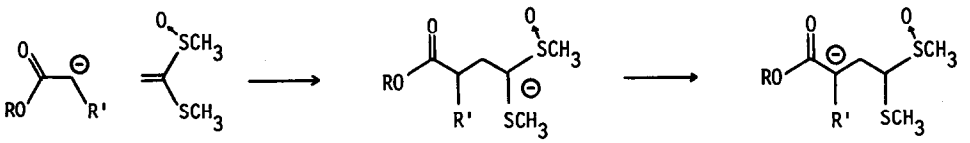
In the foregoing communications, we have outlined both the preparation[1] and conjugate addition behavior[2] of an interesting class of two-carbon Michael receptors, ketene thioacetal monoxides. Receptors like I were found to undergo the Michael reaction with ester enolates of disparate reactivity, *e.g.*, dimethyl sodio malonate (II) and *t*-butyl α-lithio acetate (III). The conjugate addition reaction of either of these ester enolates with I would initially lead to for mation of the sulfur stabilized anion systems IVa and IVb. Anion IVa could undergo an exchange reaction giving rise to the enolate anion V while anion IVb should be regio stable.[3]



II; R = CH_3, R'= CO_2CH_3

III; R = *t*-Bu, R'= H

I

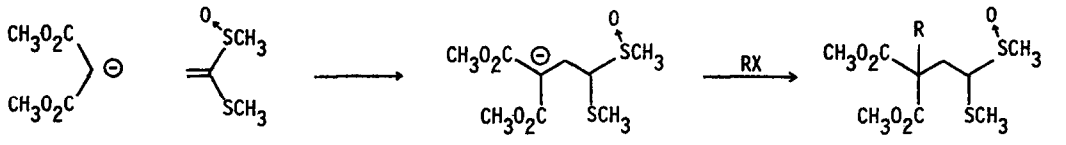
IVa; R = CH_3, R'= CO_2CH_3

IVb; R = *t*-Bu, R'= H

V; R = CH_3, R'= CO_2CH_3

We felt that if such anions could be trapped with alkylating agents the result would be an interesting opportunity to substitute at either the alpha carbon of the ester residue (anion V) or at the alpha carbon of the Michael receptor (anion IVb). Pursuant to this supposition, ester enolates derived from dimethyl malonate, ethyl crotonate, and *t*-butyl acetate were reacted with receptor I and the reactions quenched with a variety of alkylating agents.

Dimethyl sodio malonate (II), prepared by reaction of dimethyl malonate (1 equivalent) with sodium hydride (1.02 equivalents) in THF solution (0.5 molar) was treated at 0° with I (1 equivalent, neat). After 1 hour the alkylating agent (1.1 equivalents, neat) was added to the reaction and the resulting mixture stirred at 23° for 8 hours. In all cases, alkylation occurred exclusively *via* the enolate anion V. A summary of some typical results are given below.[4]



II I V

RX = CH_3I, R = CH_3, yield 97%

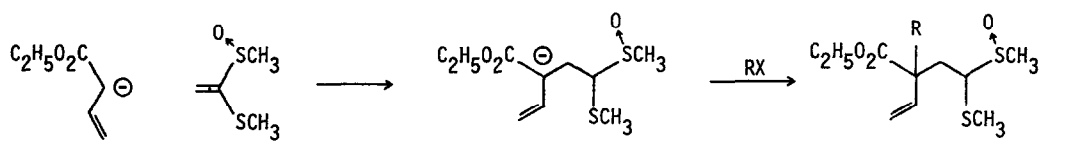
RX = C_2H_5I, R = C_2H_5, yield 87%

RX = C_3H_7I, R = C_3H_7, yield 75%

RX = CH_2=$CHCH_2Br$, R = CH_2=$CHCH_2$, yield 98%

RX = HC≡CCH_2Br, R = HC≡CCH_2, yield 91%[5]

Ethyl α-lithio crotonate (VI) exhibits the same conjugate addition-alkylation behavior with receptor I as observed for dimethyl sodio malonate. Thus, *in situ* alkylation of the Michael adduct derived from VI and I affords products arising from the enolate VII. Anion VI is generated



VI I VII

RX = CH_3I, R = CH_3, yield 96%

RX = C_3H_7I, R = C_3H_7, yield 96%

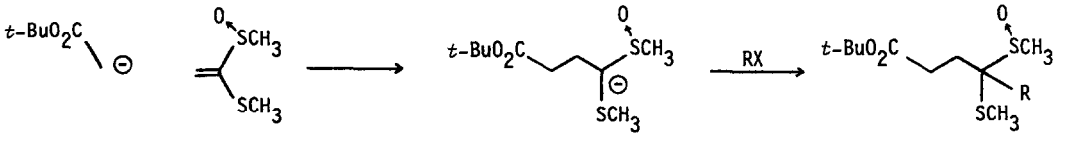
RX = $(CH_3)_2CHI$, R = $(CH_3)_2CH$, yield 74%

RX = CH_2=$CHCH_2Br$, R = CH_2=$CHCH_2$, yield 90%

RX = HC≡CCH_2Br, R = HC≡CCH_2, yield 85%[5]

at -78° by adding neat ethyl crotonate (1 equivalent) to a 1 molar THF solution containing lithium diisopropylamide (1 equivalent) and hexamethylphosphoramide (1 equivalent).[6] The receptor I (1 equivalent, 1 molar in THF) is then slowly added (-78°) followed after 1 hour by the alkylating agent (1.15 equivalents, neat).

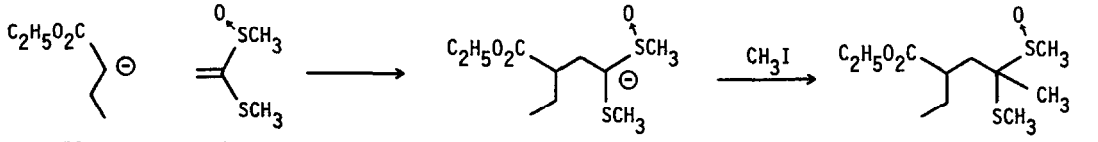
Reaction of *t*-butyl α-lithio acetate (III) with receptor I leads to the regio stable anion IVb. However, anion IVb is not thermally stable and decomposes into a variety of products at temperatures above -78°. As a result, alkylation of this anion must be carried out at -78°.[7] Enolate III is generated at -78° by adding neat *t*-butyl acetate (1 equivalent) to a 0.5 molar THF solution of lithium diisopropylamide (1 equivalent). Receptor I (1 equivalent, 0.5 molar in THF) is slowly added at -78° followed after 10 minutes by the alkylating agent (1.1 equivalents) dissolved in hexamethylphosphoramide (1.0 equivalents). Enolates such as ethyl α-lithio butyrate (VIII) may also be employed for these reactions with the same constraints on the alkylation step.



III I IVb

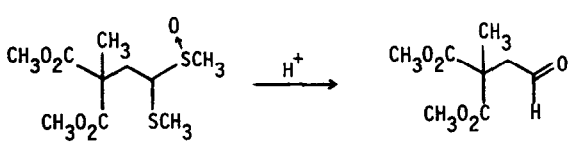
RX= CH_3I, R = CH_3, yield 91%

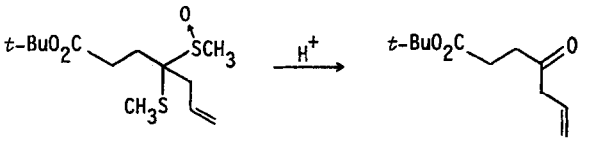
RX = CH_2=$CHCH_2Br$, R = CH_2=$CHCH_2$, yield 88%



VIII I

Hydrolysis of the above addition products in aqueous acetonitrile containing perchloric acid yields the corresponding aldehydes or ketones in essentially quantitative yield.[8]





These results show that efficient constructions of highly unsymmetrical 1,4-dicarbonyl compounds can be realized *via* the conjugate addition-alkylation reaction sequence outlined herein. This synthetic method is of preparative significance since these reactions can be carried out on both a small and large scale under conditions of nearly ideal stoichiometry.

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REFERENCES

1. J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Letts.*, in press.
2. J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *ibid.*, in press.
3. This predilection was based on an assumed ordering of pK_b values for the anions involved.
4. It is interesting to note that substituted malonate derivatives do not add to receptor I.
5. The yields given are for isolated products. All compounds exhibited satisfactory spectral and physical properties.
6. For a more complete description of the preparation of ethyl α-lithio crotonate, see J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Letts.*, in press.
7. Anions of this type alkylate readily with a wide variety of reagents at room temperature. At low temperatures however, they combine only with reactive alkylating agents. For a description of these anion systems, generated by other means, see J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *ibid.*, in press.
8. For more detailed hydrolysis data, see reference 7.