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ALLENIC CARBANIONS IN SYNTHESIS I. THE ACYLACETATE UNIT

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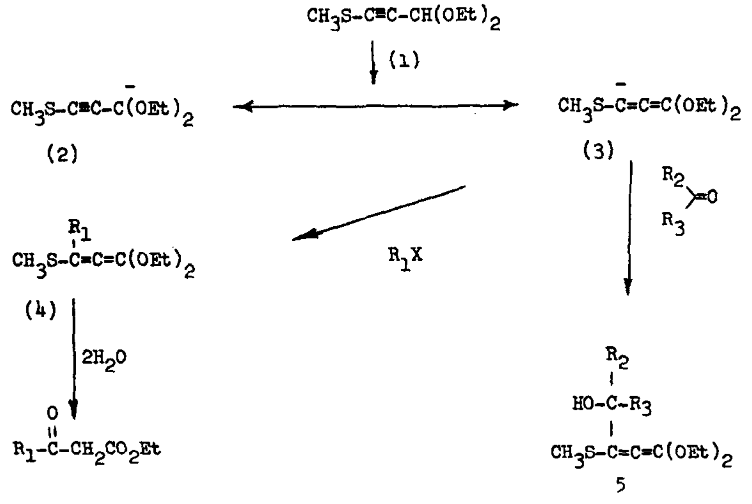
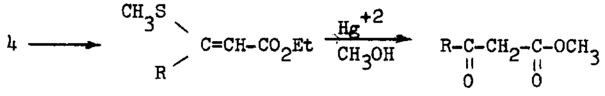
"Nucleophilic" carbonyl groups in the guise of systems more capable of stabilizing a carbanion have proven to be a source of valuable new synthetic methods.[1] We now wish to report the utilization of the allenic carbanion derived from 1-thiomethyl-3,3-diethoxypropyne(1) for the introduction of an acylacetate unit.[2]

Conceptually, removal of a hydrogen from 1 would generate a stabilized allenic carbanion that in either resonance form would provide a masked β-ketoester upon subsequent alkylation or addition reactions.



Investigation has shown that the carbanion (2 ↔ 3) can readily be formed at low temperatures (-78°C) using lithium diethylamide in tetrahydrofuran. The carbanion was observed to react entirely in the allenic form.

Alkylation with primary alkyl halides occurred in high yields to provide ketene acetals (4) that were subsequently converted to a mixture of E and Z ethyl β-thiomethylacrylates (6, Chart 1). Hydrolysis in the presence of mercuric chloride gave the corresponding acetoacetic esters in quantitative yields.



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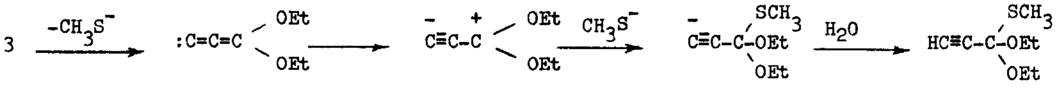
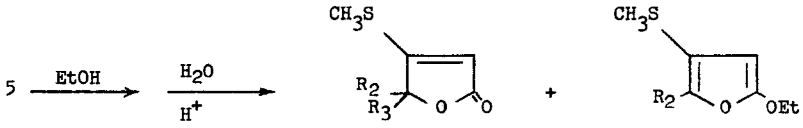
The addition of halides other than 1° resulted in either the formation of elimination products or the recovery of the halides and the isolation of a propiolic acid orthoester, presumably formed via an α-elimination to a resonance stabilized carbene and recombination to the acetylide.



The reaction with aldehydes and ketones gave addition products that could be efficently purified only as the stable β-thiomethylbutenolides (Chart II). In the case of aldehyde addition products (ie. R_3 = H) small amounts of furans (<5%) were also observed.



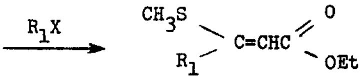
Typical Experimental Procedure:

To 15 ml of dry THF (N_2) at -30° was added 0.2 ml of diethyl amine followed by 5.0 ml of n-butyl lithium in hexane (11 mmol). The solution was cooled to -78° and 1.74 g (10.0 mmol of 3,3-diethoxy-1-methylthiopropyne[3] was added over a period of 3 min. Stirring was then continued at -78° (Dry-Ice/acetone) for an additional 2.5 hrs.[4]

To 10.0 mmol of anion formed at -78° as previously described was added 1.09 g (10.0 mmol) of bromoethane. Stirring was continued at -78° for one hour. Workup consisted of hexane dilution, filtration, and evaporation of the filtrate to give 1.8 g (89%) of 1,1-diethoxy-3-methylthio-1,2-pentadiene. Subsequent treatment of the product with aqueous THF containing a trace of p-TSA quantitatively generated E,Z ethyl 3-methylthio-2-pentanoate in a 1:1 isomer ratio.

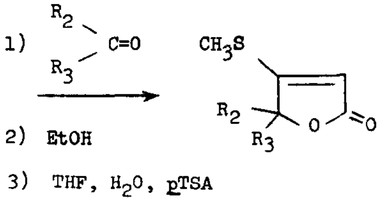
To a solution consisting of 0.11 g (0.55 mmol) of ethyl 3-methylthio-2-pentanoate dissolved in 2 ml of methanol was added 0.30 g (1.10 mmol) of mercuric chloride in 3 ml of methanol.[5] An immediate precipitate formed and the solution was stirred for one hour at 25°. The solvent was removed in *vacuo* and the residue was triturated with hexane. The hexane solution was filtered and evaporated to give a quantitative yield of methyl 3-ketopentanoate.

Chart I (Alkylation*)



R =	CH_3-	C_2H_5-	$(CH_3)_2CH$-CH_2-
% yield =	90	89	80

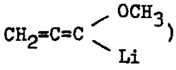
Chart II (Addition)



R_2	$-CH_3$	$-C_6H_5$	$-C_2H_5$	$-CH_3$	n-C_7H_{15}
R_3	$-CH_3$	H	H	H	H
% yield	92	85	63	81	70
mp.	97-98°	89-90°	-	-	-

*All new compounds have been isolated and found to possess the expected spectroscopic properties and/or elemental analysis.

References

1. For a good review including a conceptual discussion see D. Seebach, *Angew. Chem. Int. Ed.* **8**, 639 (1969), for later methods see for example D. Seebach, *Synthesis*, 17 (1969); K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, 1383, 2681 (1972); H. M. Walborsky, W. H. Morrison, G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); F. A. Carey and A. S. Court. *J. Org. Chem.*, **37**, 939 (1972); G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971); E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971); K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 2964 (1973) and reference 5 cited below.
2. The development of these methods was stimulated by recent observations by Arens and Brandsma on the ability of simple metallated allenic ethers and thioethers (eg.  $CH_2{=}C{=}C\begin{smallmatrix} OCH_3 \\ Li \end{smallmatrix}$) to undergo alkylation and hydroxyalkylation: L. Brandsma, H. J. T. Bcs, and J. F. Arens in H. G. Viehe, *Chemistry of Acetylenes*, Marcel Dekker, New York (1969), pp. 815-817; S. Hoff, L. Brandsma, and J. F. Arens, *Rec. Trav. Chim. Pays-Bas* **87**, 916, 1179 (1968). For recent synthetic applications see: Y. Leroux and C. Roman, *Tetrahedron Lett.* 2585 (1973) and references therein.
3. 3,3-Diethoxy-1-methylthiopropyne is formed by the addition of 1 equivalent of dimethyldisulfide to 1-lithio-3,3-diethoxypropyne in ether at room temperature (45%, bp 53°/0.3 mm), see: L. Brandsma, H. E. Wijers, and C. Jonker, *Rec. Trav. Chim. Pays-Bas*, **82**, 208 (1963). The preparation of 3,3-diethoxypropyne is described in L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier Publishing Co. (1971) p. 118.
4. Using this procedure and quenching with ethanol giver 70% ethyl E-3-methythioorthoacrylate, 20% ethyl Z-3-methylthioorthoacrylate and 10% 1,1-diethoxy-3-methylthioallene (nmr analysis)
5. E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35**, 777 (1970).

Acknowledgment:

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