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ALLENIC CARBANIONS IN SYNTHESIS II. β-KETOALDEHYDE AND β-DIKETONE EQUIVALENTS.

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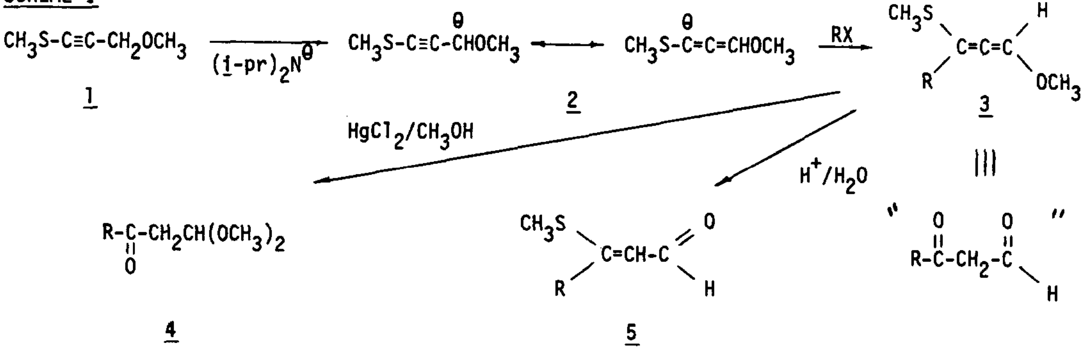
The previous paper in this series[1] has described the use of a suitably substituted allenic carbanion as a nucleophilic acyl equivalent[2] for the acyl acetate unit. We would now like to report that this method of introducing 1,3-oxygenation patterns has been extended to the preparation of functionality corresponding to a β-ketoaldehyde or a β-diketone.

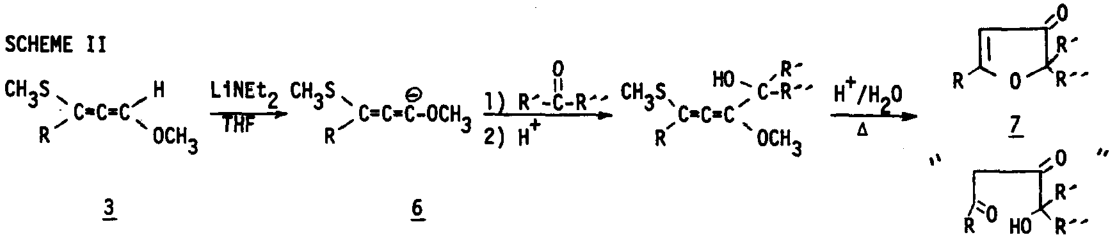
The concept that was again invoked is based on the observation that anions generated from a propargyl system often show reaction products derived from the corresponding allenic carbanion.[3] Accordingly, 1-thiomethyl-3-methoxy propyne[4] (1) was treated with lithium diethyl amide in tetrahydrofuran at low temperatures (-78^0) and the resulting carbanion (2) found to react entirely in the allenic form to provide, upon alkylation, the corresponding substituted allene (3, Scheme I, Table I). The dual functionality of this masked β-keto aldehyde permits the selective hydrolysis[5] of either the thioenol ether (Hg^{+2}/CH_3OH)[5] or the enol ether (H^+/H_2O)[6] as shown in Scheme I (Table II).[7]

SCHEME I



The monoalkylated allene (3) which possesses the requisite hydrogen adjacent to an allenic ether was subjected to the conditions of proton abstraction (i.e. lithium diethylamide/THF) and again produced another reactive allenic carbanion (6). The synthetic utility of this two-step process is illustrated by the synthesis of 3-furanones by sequential alkylation-addition (Scheme II, Table III).

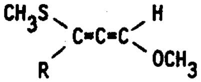
SCHEME II



General Procedure (alkylation, addition, hydrolysis to furanone - Scheme II)

To a 50 ml RB flask containing 15.0 ml dry THF under N_2 at -25°C is added 3.0 ml 2.04 M n-butyl lithium. .15 ml Diisopropylamine is subsequently added and allowed to react for 15 minutes at about -20°C. .70 g 1-Methylthio-3-methoxy propyne dissolved in 2 ml dry THF is added slowly and allowed to react 60 minutes at temperatures below -60°C. 1 Equivalent of the alkylating agent dissolved in 2 ml dry THF is introduced slowly at <-60° and then allowed to come to room temperature over a period of 60 minutes. The temperature is again dropped to -65° and 3.0 ml 2.04 M n-butyl lithium is added dropwise and reacted two hours at temperatures below -60°C. A slight excess of the aldehyde or ketone dissolved in 2 ml dry THF is added and allowed to react for 15 minutes at the reduced temperature and then raised to room temperature over 60 minutes. 10 ml distilled H_2O is added and allowed to stir 10 minutes. The aqueous phase is extracted with 3x10 ml U.S.P. ether and the combined organic layers are washed with 10 ml sat'd. NaCl solution, dried over $MgSO_4$ for 30 minutes, filtered, and solvent removed *in vacuo*. .20 g Allene is dissolved in 10 ml of acetonitrile and 5 ml distilled H_2O. To this solution is added .01 g p-TSA and the mixture raised slowly to reflux temperature. After refluxing for approximately 24 hrs., 5.0 ml of saturated $NaHCO_3$ solution is added and the aqueous phase is extracted with 3x10 ml U.S.P. ether. The combined organic layers were washed with 10 ml saturated NaCl solution, dried over $MgSO_4$ for 30 min, filtered, and solvent removed *in vacuo*.

Table I Monosubstituted Allenes

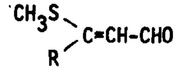


3

R	X	Alkylation Time (hr)	Yield %	NMR Spectral Data (Allenic H)
CH_3-	I	0.5	73	q, 6.91, 1H, J=2
CH_3CH_2-	Br	0.5	93	t, 6.92, 1H, J=2
THP-O-CH_2CH_2-	Cl	13.5	54	t, 6.91, 1H, J=2
	Br	15.5	82	
$CH_3(CH_2)_4$-	I	5.5	94	t, 6.90, 1H, J=1.5
$(CH_3)_2CH$-	Br	14.5	54	d, 6.93, 1H, J=1.5
	Br	13 (1 eq. HMPA)	86	

Table II Hydrolysis of Monosubstituted Allenes

Conditions: H^+/H_2O ⟶

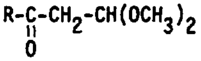


$(CH_3S)(R)C{=}CH{-}CHO$

5

R	Reaction Time (hr)	E:Z	Yield %	NMR Spectral Data (C=CH)
C_2H_5-	3	1:8	80	d, 5.98, 1H, J=6.5 (E)
				d, 5.66, 1H, J=7 (Z)
i-Pr-	1	1:3	85	d, 5.99, 1H, J=7 (E)
				d, 5.60, 1H, J=7 (Z)

Conditions: $2Hg^{++}/H_2O$ ⟶

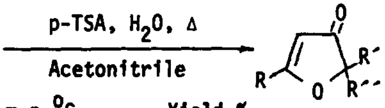


$R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}CH(OCH_3)_2$

4

R[8]	Reaction time (hr)	Yield %	NMR Spectral Data
CH_3-	2	42	s, 2.17, 3H; d, 2.73, 2H; s, 4.79, 6H; t, 5.5, 1H.
Et-	2	55	t, 1.03, 3H; q, 2.49, 2H; d, 2.71, 2H; s, 3.35, 6H; t, 4.80, 1H.

Table III Aqueous Hydrolysis of Substitution-Addition Products[9]



R	R′	R′′	m.p.°C	Yield %	NMR Spectral Data
C_2H_5-	CH_3-	CH_3-	-	67	t, 1.22, 3H; s, 1.28, 6H; q, 2.47, 2H; s, 5.26, 1H
CH_3-	C_6H_5-	C_6H_5-	107-108	93	s, 2.28, 3H; s, 5.35, 1H; 6m, 7.35, 10H
C_2H_5-	C_6H_5-	C_6H_5-	70-71.5	75	t, 1.17, 3H; q, 2.58, 2H; s, 5.35, 1H; bm, 7.35, 10H

ACKNOWLEDGMENTS: Support for this research was provided by the National Institute of Allergy and Infectious Disease: (2R01-AE-10597-04) and by the Research Corporation.

1. R. M. Carlson and J. L. Isidor, Tetrahedron Lett., 4819 (1973).
2. D. Seebach and M. Kolb, Chem. and Ind., 17, 687 (1974); R. M. Carlson and A. R. Oyler, Tetrahedron Lett., 2615 (1974), J. E. Baldwin, G. A. Höfle, O. W. Lever, J. Amer. Chem. Soc., 96, 7125 (1974) and references cited therein.
3. L. Brandsma, H. J. T. Bos, and J. F. Arens in H. G. Viehe, Chemistry of Acetylenes, Marcel Dekker, New York (1969), pp. 815-917, see also Y. Leroux and C. Roman, Tetrahedron Lett., 2585 (1973).
4. 1-Methylthio-3-methoxypropyne was prepared by the addition of 1 equivalent of dimethyldisulfide to 1-lithio-3-methoxypropyne at -30°C and allowing the reaction mixture to remain at room temperature for 3 days. The preparation of 3-methoxypropyne is described in L. Brandsma, Preparative Acetylene Chemistry, Elsevier Publishing Co., 1971, p. 172.
5. Hg^{+2}/CH$_3$OH produces compound types (i.e. acetals of β-ketoaldehydes) that have been prepared previously by: Ionic addition to acetylenes, E. Winterfeldt in H. G. Viehe, Chemistry of Acetylenes, Marcel Dekker, New York (1969) chapter 4. Addition of alcohols to β-alkoxymethylene ketones (R-CO-CH=CH-OR') that are available by O-alkylation of α-formyl ketones; L. R. Fedor, N. C. De, and S. K. Gurwara, J. Amer. Chem. Soc., 95, 2905 (1973) and D. Nasipuri, et al., Indian J. Chem., 10, 897 (1972). Miscellaneous other processes: A. N. Nesmeyanov and M. I. Rybinskaya, Izv. Akad. Nauk. SSSR Ser Khim. 1764 (1966). Chem. Abstr., 66, 94945 (1967); Z. I. Shramova and A. P. Skoldinov, Zk. Org. Khim., 1, 1737, 1743 (1965) Chem. Abstr., 64, 3397 (1966).
6. The acid-catalyzed hydrolysis generates alkylthioacrolein derivatives that have been previously prepared by: Nucleophilic addition of mercaptans to acetylenic aldehydes; E. Winterfeldt ref 5, and N. Engelhard and A.Kolb, Ann, 673, 136 (1964); Alkylation and hydrolysis of suitable substituted thiocarbonyl derivatives, F. Clesse and H. Quinou, C. R. Acad. Sci. Ser. C1971, 272, 326.
7. Synthetic applications of these selective hydrolyses will be described in a forthcoming paper from these laboratories.
8. W. Franke, R. Kraft, and K. Kosswig, in "Neure Methoden der präparativen organischen Chemie," Band II, W. Foerst Ed., Verlag Chemie, Weinheim, Bergstr, 1960 p. 1.
9. When benzophenone was used as the carbonyl compound, one equivalent of HMPA was added to the reaction 30 minutes before addition of the ketone, the bath was then packed with dry ice and allowed to come to room temperature overnight. In the work-up, the combined organic layers are treated with 4 x 10 ml distilled H$_2$O before they are washed with saturated NaCl.