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TWO-CARBON MICHAEL ACCEPTORS. ACETYL CATION EQUIVALENTS

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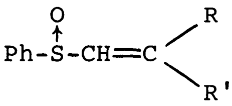
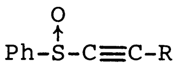
Base-induced Michael condensation of chloromethoxyvinyl phenyl sulfoxides or sulfones with active methylene compounds were examined. The newly introduced functionalized substituents were converted into acetyl group by the subsequent treatment.

In an effort to introduce acyl group into angular positions of fused ring systems,[1)] we reported previously[2)] that variously functionalized substituents which were presumed to be convertible into acyl group were successfully introduced into active methylene compounds using the β-halovinyl phenyl sulfoxides 1a, b or the ethynyl phenyl sulfoxide 2a, b as two-carbon Michael acceptors.

However, in the process of converting these substituents into acyl group, we were encountered with the problem of introducing oxygen functions into the desired position.[3)] For example, treatment of 3 prepared from 1b with methoxide anion did not give the vinyl ether 4, but many unidentified products were only obtained. Therefore, we concluded that Michael acceptors themselves should possess oxygen functions on the required position. We report here the syntheses and the reactions of the new reagents developed along this line.

The failure of converting 3 into 4 would be attributable to a severe steric hindrance around the β-carbon atom of the vinyl sulfoxide moiety of 3. Therefore, replacement of at least one of the chlorines of dichlorovinyl sulfoxide 1b with methoxyl group was expected to proceed without difficulty. In fact, when 1b was treated with sodium methoxide (1.3 equiv.) in methanol for 3 h at room tempera-





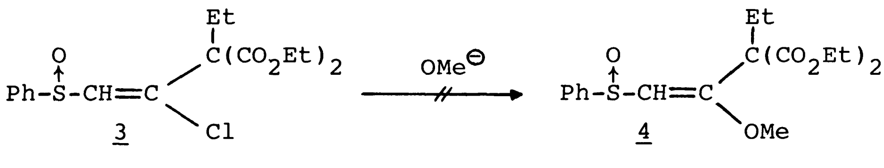
$\mathrm{Ph\text{-}\overset{O}{\overset{\uparrow}{S}}\text{-}C{\equiv}C\text{-}R}$

1a : R = H, R'= Br (E,Z isomers)

1b : R = R' = Cl

2a : R = H

2b : R = Br



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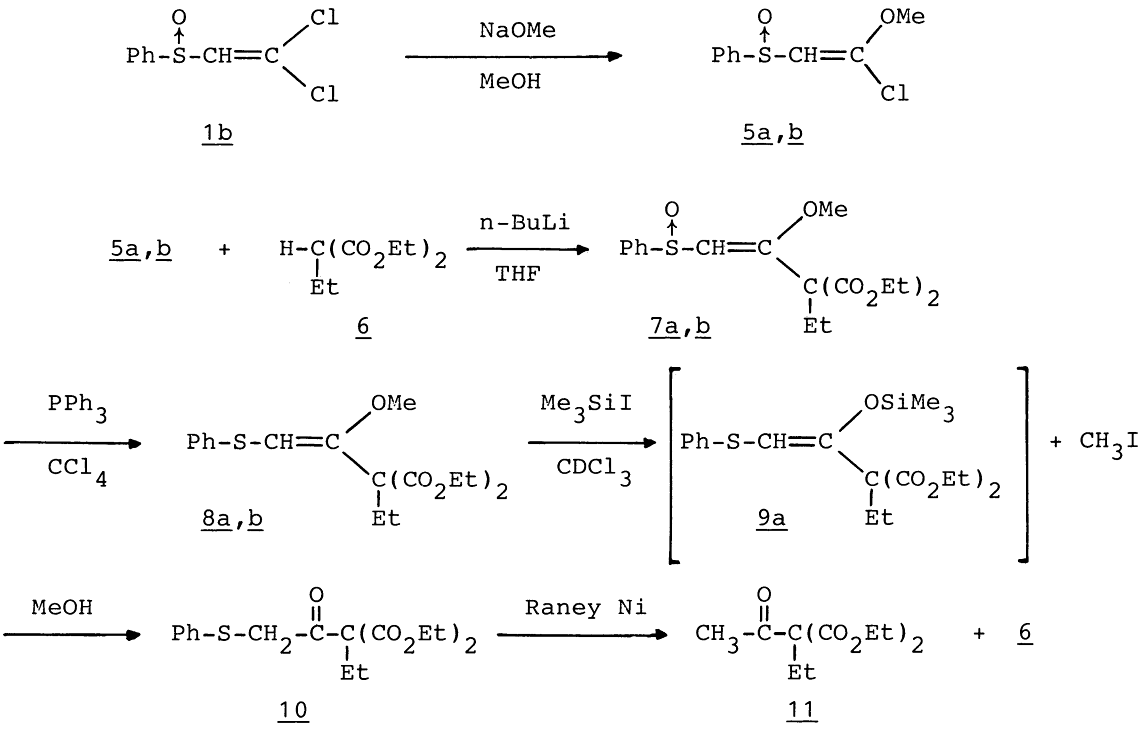
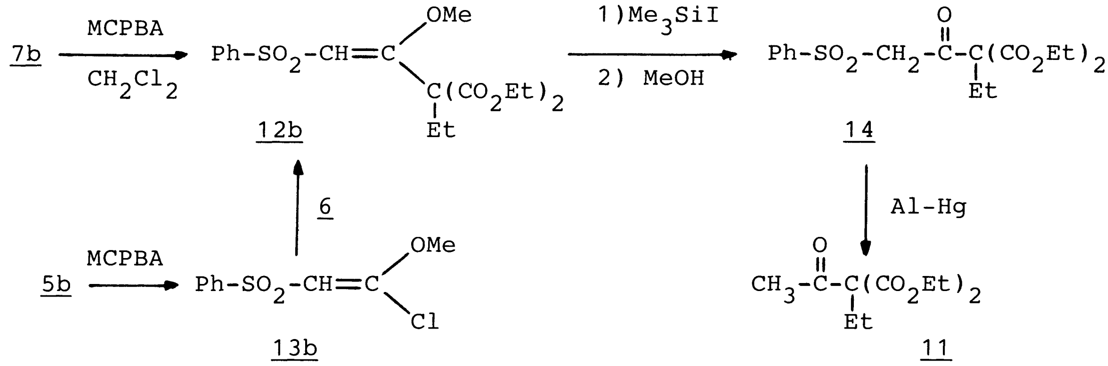
ture, an isomeric mixture of the chloromethoxyvinyl derivatives 5a, 5b4) were obtained in yields of 30 and 25%, respectively, along with the starting material 1b (28%) after chromatography. [5a: oil, IR(neat) 1610,1040 cm^{-1}; NMR(CCl$_4$) δ 3.89 (3H, s), 5.63(1H, s). 5b: oil, IR(neat) 1595,1040 cm^{-1}; NMR (CCl$_4$) δ 3.72(3H, s), 5.78(1H, s)].

Condensation of 5a (1 equiv.) with diethyl ethylmalonate (6)(1.3 equiv.) in THF using n-BuLi (1.1 equiv.) at 65 °C for 2 h under argon atmosphere yielded 7a [mp 83-85 °C; NMR(CDCl$_3$) δ 4.20(3H, s), 6.04(1H, s)] in 60% yield. Then, cleavage of the O-CH$_3$ bond of the vinyl ether in 7a was attempted. Direct treatment of 7a with Me$_3$SiI5)(1.37 equiv.), however, proceeded only incompletely to afford a mixture of the vinyl sulfide 8a (53%) [IR(neat) 1735,1610 cm^{-1}; NMR(CDCl$_3$) δ 3.85(3H, s), 6.07 (1H, s)] and the starting material 7a (45%), the methoxyl group being unaffected. This process was achieved by a modified procedure. Treatment of the sulfoxide 7a with PPh$_3$ in refluxing CCl$_4$6) for 3 h produced the sulfide 8a in quantitative yield. The sulfide 8a was allowed to react with an excess of Me$_3$SiI (3 equiv.) in CDCl$_3$ for 6 d,7) then the reaction was stopped by the addition of methanol to yield the β-keto sulfide 10 [IR(neat) 1760-1720 cm^{-1}; NMR(CCl$_4$) δ 4.01 (2H, s); MS(m/e) 338(M$^+$)] in 75% yield. Desulfurization of 10 with Raney Ni deactivated with acetone produced the desired diethyl (acetyl)ethylmalonate (11) in 20% yield along with 6 (24% yield). The compound 6 should be formed from 11 by deacetylation catalyzed by basic Raney Ni.

In the same way, the isomeric methoxyvinyl sulfoxide 7b8) was obtained in 48% yield by the condensation of 5b with 6. However, the sulfide 8b obtained from 7b in a similar manner described for 8a did not produce the keto sulfide 10 on Me$_3$SiI treatment. On the other hand, the corresponding sulfone 12b prepared by MCPBA

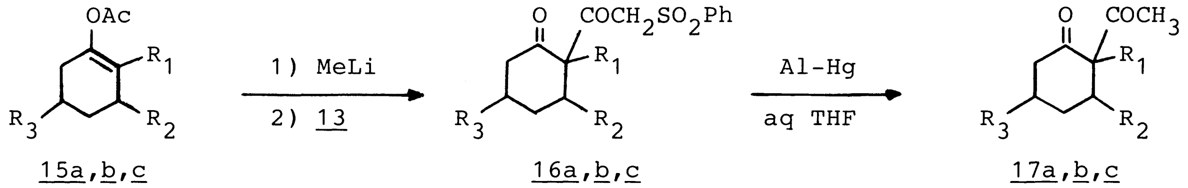


oxidation of 7b in quantitative yield produced the keto sulfone 14 [56% yield, IR(neat) 1760-1720, 1320, 1160 cm^{-1}; NMR(CCl_4) δ 4.50(2H, s); MS(m/e) 370(M^+)] by Me_3SiI treatment (2.5 equiv., 7 d). Reductive desulfonylation of 14 proceeds now quite readily by using Al-Hg[9] (aqueous THF, 80 °C, 2 h) to afford 11 in 63% yield. The intermediary sulfone 12b can also be prepared by the condensation of 6 with the sulfone 13b prepared from 5b (MCPBA oxidation, quantitative yield).

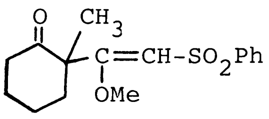


Furthermore, this new method was applied to cyclic ketones having α-alkyl substituent. The reaction of the lithium enolate generated from 2-methylcyclohexanone enol acetate (15a) (MeLi, 2.2 equiv.) in THF with chloromethoxyvinyl sulfoxide 5 resulted in complicated mixtures. Therefore, condensation of chloromethoxyvinyl sulfone 13b which was presumed to be more reactive Michael acceptor than 5 with 15a was attempted. The enol acetate was allowed to react with the sulfone 13b in THF-HMPA (4:1) at -78 °C for 30 min, then gradually warmed to 0 °C to afford keto sulfone 16a in 79% yield after purification by column chromatography, while the condensation with 13a produced 16a in 64% yield. It should be noted that the expected Michael adduct 18 was not obtained under these experimental conditions.[10] Subsequent desulfonylation of 16a carried out in a similar manner as above afforded 2-acetyl-2-methylcyclohexanone (17a) in 56% yield. A similar treatment of decalone enol acetate (15c) gave a desired ketone 17c having an acetyl group on the angular position of a fused ring system in a moderate yield. These results are summarized in Table 1 including additional experiments.

Synthetic studies on β, β-disubstituted indoline alkaloids possessing acetyl group on the angular position are now in progress based on the new method developed here.



	R_1	R_2	R_3
a	Me	H	H
b	iso-Pr	H	Me
c	$-(CH_2)_4-$		H



18

Table 1. Condensation of chloromethoxyvinyl sulfones 13 with cyclic ketone enol acetates and desulfurization

	Michael reaction			Desulfurization	
Substrate	Acceptor	Yield/%a)	Productb)	Yield/%a)	Productb)
15a	13a	64	16a	65	17a
	b	79			
15b	b	88	16bc)	56	17bc)
15c	a	22	16c	54	17c
	b	40			

a) Isolated yield by column chromatography. b) All the compounds were characterized by IR, NMR, and MS spectra. c) Approximately 1:1 mixture of diastereisomers determined by NMR and/or GLC analysis.

References

1) Other methods done on this line are based on the Michael attack of acyl anion equivalents to cyclic enone systems: R. K. Boeckman, Jr., and K. J. Bruza, Tetrahedron Lett., 1974, 3365; J. Org. Chem., 44, 4781 (1979); E, J. Corey and R. H. Wollenberg, J. Am. Chem. Soc., 96, 5581 (1974); See also, R. T. Hansen, D. B. Carr, and J. Schwarts, ibid., 100, 2244 (1978).
2) I. Hori and T. Oishi, Tetrahedron Lett., 1979, 4087. Addition of Michael acceptors to angular carbanions has also been reported: Y. Ban, T. Ohnuma,and T. Oishi, ibid., 1975, 727; T. Ohnuma, N. Hata, H. Fujiwara, and Y. Ban, J. Org. Chem., 47, 4713 (1982).
3) We have recently succeeded in the conversion of the chlorovinyl sulfoxide moiety in 3 into the ethynyl group in one step, which will be reported elsewhere.
4) The less polar isomer on TLC was tentatively assigned as 5a and the more polar one, as 5b.
5) M. E. Jung and M. A. Lyster, J. Org. Chem., 42, 3761 (1977); G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, ibid., 44, 1247 (1979), and references cited therein. Conversion of sulfoxides into sulfides is also reported: G. A. Olah, B. G. B. Gupta, and S. C. Narang, Synthesis, 1977, 583.
6) J. P. A. Castrillon and H. H. Szmant, J. Org. Chem., 30, 1338 (1965).
7) The progress of the reaction was monitored by an increase of signals at δ 2.1 due to CH_3I and 5.82 due to the vinyl proton of 9a produced.
8) The physical constants for the products in b isomer series are as follows. 7b mp 70-71 °C; IR(KBr) 1755,1730,1595,1030 cm^{-1}; NMR($CDCl_3$) δ 3.59(3H, s),5.57 (1H, s), 8b IR(neat) 1740,1600 cm^{-1}; NMR($CDCl_3$) δ 3.70(3H, s),5.42(1H, s), 13b mp 82-83 °C; IR(nujol) 1590, 1310, 1140 cm^{-1}; NMR($CDCl_3$) δ 3.79(3H, s), 5.97 (1H, s).
9) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 87, 1345 (1965).
10) The process of facile formation of the ketosulfones compared with the relatively stable enol ether such as 7,12 to acid catalysts, is not clear, however, LiCl produced during the reaction may be involved in the transformations.

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