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 previously²⁾ 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 <u>3</u> prepared from <u>1b</u> with methoxide anion did not give the vinyl ether <u>4</u>, 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 $\underline{3}$ into $\underline{4}$ would be attributable to a severe steric hindrance around the β -carbon atom of the vinyl sulfoxide moiety of $\underline{3}$. Therefore, replacement of at least one of the chlorines of dichlorovinyl sulfoxide $\underline{1b}$ with methoxyl group was expected to proceed without difficulty. In fact, when $\underline{1b}$ was treated with sodium methoxide (1.3 equiv.) in methanol for 3 h at room tempera-



[†]Research fellow from Tokyo College of Pharmacy (1978-1980). Present address: Hokkaido University. ture, an isomeric mixture of the chloromethoxyvinyl derivatives $\underline{5a}$, $\underline{5b}^{4}$ were obtained in yields of 30 and 25%, respectively, along with the starting material $\underline{1b}$ (28%) after chromatography. [$\underline{5a}$: oil, IR(neat) 1610,1040 cm⁻¹; NMR(CCl₄) & 3.89 (3H, s), 5.63(1H, s). $\underline{5b}$: oil, IR(neat) 1595,1040 cm⁻¹; NMR (CCl₄) & 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(CDCl₃) δ 4.20(3H, s), 6.04(1H, s)] in 60% yield. Then, cleavage of the O-CH₃ bond of the vinyl ether in $\frac{7a}{2}$ was attempted. Direct treatment of $\frac{7a}{2}$ with Me₃SiI⁵ (1.37 equiv.), however, proceeded only incompletely to afford a mixture of the vinyl sulfide <u>8a</u> (53%) [IR(neat) 1735,1610 cm⁻¹; NMR(CDCl₃) & 3.85(3H, s), 6.07 (1H, s)] and the starting material <u>7a</u> (45%), the methoxyl group being unaffected. This process was achieved by a modified procedure. Treatment of the sulfoxide $\frac{7a}{4}$ with PPh₃ in refluxing CCl₄⁶ for 3 h produced the sulfide $\frac{8a}{4}$ in quantitative yield. The sulfide 8a was allowed to react with an excess of Me3SiI (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 <u>10</u> [IR(neat) 1760-1720 cm⁻¹; NMR(CCl₄) δ 4.01 (2H, s); MS(m/e) 338(M⁺)] in 75% yield. Desulfurization of <u>10</u> 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 $\frac{7b}{2b}^{8}$ was obtained in 48% yield by the condensation of <u>5b</u> with <u>6</u>. However, the sulfide <u>8b</u> obtained from <u>7b</u> in a similar manner described for <u>8a</u> did not produce the keto sulfide <u>10</u> on Me₃SiI treatment. On the other hand, the corresponding sulfone <u>12b</u> prepared by MCPBA



oxidation of <u>7b</u> in quantitative yield produced the keto sulfone <u>14</u> [56% yield, IR(neat) 1760-1720, 1320, 1160 cm⁻¹; NMR(CCl₄) δ 4.50(2H, s); MS(m/e) 370(M⁺)] by Me₃SiI treatment (2.5 equiv., 7 d). Reductive desulfonylation of <u>14</u> proceeds now quite readily by using Al-Hg⁹ (aqueous THF, 80 °C, 2 h) to afford <u>11</u> in 63% yield. The intermediary sulfone <u>12b</u> can also be prepared by the condensation of <u>6</u> with the sulfone <u>13b</u> prepared from <u>5b</u> (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 (<u>15a</u>) (MeLi, 2.2 equiv.) in THF with chloromethoxyvinyl sulfoxide <u>5</u> resulted in complicated mixtures. Therefore, condensation of chloromethoxyvinyl sulfone <u>13b</u> which was presumed to be more reactive Michael acceptor than <u>5</u> with <u>15a</u> was attempted. The enol acetate was allowed to react with the sulfone <u>13b</u> in THF-HMPA (4:1) at -78 °C for 30 min, then gradually warmed to 0 °C to afford keto sulfone <u>16a</u> in 79% yield after purification by column chromatography, while the condensation with <u>13a</u> produced <u>16a</u> in 64% yield. It should be noted that the expected Michael adduct <u>18</u> was not obtained under these experimental conditions.¹⁰ Subsequent desulfonylation of <u>16a</u> carried out in a similar manner as above afforded 2-acetyl-2-methylcyclohexanone (<u>17a</u>) in 56% yield. A similar treatment of decalone enol acetate (<u>15c</u>) gave a desired ketone <u>17c</u> 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.



cyclic ketone enol acetates and desulfurization							
	Michael reaction				Desulfurization		
	Substrate	Acceptor	Yield/% ^{a)}	Product ^{b)}	Yield/% ^{a)}	Product ^{b)}	
	<u>15a</u>	<u>13a</u>	64	<u>16a</u>	65	<u>17a</u>	
		<u>b</u>	79				
	<u>15b</u>	<u>b</u>	88	<u>16b</u> c)	56	<u>17b</u> c)	
	<u>15c</u>	<u>a</u>	22	<u>16c</u>	54	<u>17c</u>	
		b	40				

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

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

- 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., <u>1974</u>, 3365; J. Org. Chem., <u>44</u>, 4781 (1979); E, J. Corey and R. H. Wollenberg, J. Am. Chem. Soc., <u>96</u>, 5581 (1974); See also, R. T. Hansen, D. B. Carr, and J. Schwarts, ibid., <u>100</u>, 2244 (1978).
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- 3) We have recently succeeded in the conversion of the chlorovinyl sulfoxide moiety in $\underline{3}$ into the ethynyl group in one step, which will be reported elsewhere.
- The less polar isomer on TLC was tentatively assigned as <u>5a</u> and the more polar one, as <u>5b</u>.
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- 6) J. P. A. Castrillon and H. H. Szmant, J. Org. Chem., <u>30</u>, 1338 (1965).
- 7) The progress of the reaction was monitored by an increase of signals at δ 2.1 due to CH₃I and 5.82 due to the vinyl proton of <u>9a</u> produced.
- 8) The physical constants for the products in b isomer series are as follows. <u>7b</u> mp 70-71 °C; IR(KBr) 1755,1730,1595,1030 cm⁻¹; NMR(CDCl₃) & 3.59(3H, s),5.57 (1H, s), <u>8b</u> IR(neat) 1740,1600 cm⁻¹; NMR(CDCl₃) & 3.70(3H, s),5.42(1H, s), <u>13b</u> mp 82-83 °C; IR(nujol) 1590, 1310, 1140 cm⁻¹; NMR(CDCl₃) & 3.79(3H, s), 5.97 (1H, s).
- 9) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., <u>87</u>, 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. (Received June 11, 1984)