REACTION OF α-ALKOXYACROLEINS WITH THIOLS

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The addition of thiols to acrylic systems plays an important role in the mechanism of the anti-tumor action of these compounds [1].

In contrast to most α,β-unsaturated carbonyl compounds which characteristically undergo addition across the conjugated system [2], the addition of a series of nucleophiles in the case of α-alkoxyacroleins proceeds only at the 1,2-positions [3]. the sodium enolates of cyclohexanone, methylcyclohexanone and dimedone do not undergo 1,4 addition to α,β-unsaturated α-alkoxyketones and α-alkoxyesters but the carbanion of sodium dimethyl malonate is a rather effective nucleophile [4].

We have studied the nucleophilic, electrophilic and radical reaction of α-ethoxyacrolein (Ib) with thiols with butanethiol and thiophenol in order to elucidate the regioselectivity of (Ib) with thiols and the possibility of synthesizing the corresponding thio derivatives.

The reaction of methanethiol with acrolein proceeds exothermally even in the absence of catalyst to give 3-methylthiopropanal in 94% yield [5]. In contrast, (Ib) does not react with butanethiol and other alkanethiols at 20°C in the absence of catalyst. The presence of a catalytic amount of K_2CO_3 initiates the 1,4-addition leading to 2-ethoxy-3-butylthiopropanal in 15% yield using $Cu(OAc)_2$ as a polymerization inhibitor.

$$\underset{\text{(Ia, b)}}{C_4H_9SH + CH_2{=}C(OR)CHO} \rightarrow \underset{\text{(II a, b)}}{C_4H_9SCH_2CH(OR)CHO} \quad (1)$$

$R = CH_3$ (a), C_2H_5 (b).

Carrying out the reaction in a superbasic medium such as C_4H_9SNa or NaOH in DMSO increases the yield of (IIb) to 30 and 40%, respectively; this reaction is accompanied by considerable tar formation.

The reaction of (Ib) with butanethiol in the presence of azoisobutyronitrile (AIBN) at 90°C gives the same product in 70% yield. Under analogous conditions, the addition of butanethiol to (Ia) gives an 86% product yield.

On the other hand, heating (Ib) with butanethiol in the absence of initiator at 90°C for 11 h leads to 2-ethoxy-2-butylthiopropanal (IIIa) in about 30% yield.

$$CH_2{=}C(OC_2H_5){-}CHO \xrightarrow{RSH,\ H^+} \underset{\text{(IIIa, b)}}{CH_3C(OC_2H_5)SR{-}CHO} \quad (2)$$

$R = C_4H_9$ (a), C_6H_5 (b).

Reaction (2) predominates upon the use of acid catalysts. Thus, thiophenol in the presence of HCl adds to (Ib) to form 2-ethoxy-2-phenylthiopropionaldehyde (IIIb) in 46% yield after 2 h reaction. The same reaction initiated by p-$MeC_6H_4SO_3H$ gives the isomer 1-ethoxy-1-phenylthiopropanone (IVb) in 37% yield in addition to adduct (IIIb)

$$\underset{\text{(IV a, b)}}{CH_3C(OC_2H_5)SRCHO \rightarrow CH_3COCH(OC_2H_5)SR}$$

$R = C_4H_9$ (a), C_6H_5 (b).

The reaction of (Ib) with butanethiol both in the presence of HCl and $CH_3C_6H_4SO_3H$ gives 1-ethoxy-1-butylthiopropanone (IVa) as the only product in 50 and 60%, respectively.

The PMR spectral data for these compounds are given in Table 1.

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TABLE 1. PMR Spectral Parameters for (IIa), (IIb), (IIIa), (IIIb), (IVa) and (IVb) (3-10% solutions in $CHCl_3$ d)

Compound	Chemical shifts δ, ppm (J, Hz)								
	CHO CH–O | S	CH_3 (butyl)	CH_3 (ethyl)	CH_2 (butyl)	SCH_2 (butyl)	SCH_2	OCH_2 (ethyl) OCH_3	C_6H_5	$CH_3C(O)S$ CH_3CO
(IIa)	9,48 d (2,0)	0,80 t (7,0)	–	1,47 m	2,56 t (7,0)	2,69 d (4,0) 2,72 d (6,0)	3,60	–	–
(IIb)	9,50 d (2,0)	0,82 t (7,0)	1,19 t (7,0)	1,47 m	2,56 t (7,0)	2,69 d (4,0) 2,70 d (6,0)	3,54	–	–
(IIIa)	9,06 s	0,89 t (7,0)	1,24 t (7,0)	1,40 m	2,52 m (7,0)	–	3,63 m	–	1,50 s
(IIIb)	9,11 s	–	1,28 t (7,0)	–	–	–	3,53 m	7,27 m	1,44 s
(IVa)	4,70 s	0,92 t (7,0)	1,21 t (7,0)	1,45 m	2,43 t	–	3,28–3,99 m		2,15 s
(IVb)	5,02 s	–	1,24 t (7,0)	–	–	–	3,59–4,02 m	7,27 m	2,01 s

EXPERIMENTAL

Nucleophilic Addition of butanethiol to α-Ethoxyacrolein. a) A sample of 0.2 g (1.4 mmole) K_2CO_3 and 0.01 g $Cu(OAc)_2$ were added to a mixture of 2.92 g (0.029 mole) (Ib) and 2.61 (0.03 mole) butanethiol. Spontaneous warming of the reaction mixture was noted. The mixture was maintained at 20°C for 2 h. Vacuum distillation gave 0.81 g (14.5%) 2-ethoxy-3-butylthiopropanal (IIb), which was identified by gas–liquid chromatography and PMR spectroscopy.

b) A sample of 0.02 g (0.5 mmole) NaOH and 0.1 g hydroquinone were added to a solution of 5.28 g (0.05 mole) (Ib) and 4.51 g (0.05 mole) butanethiol in 7 ml DMSO, stirred for 1 h and then washed with water. The organic layer was dried over $MgSO_4$. Vacuum distillation gave 2.55 g (27.5%) (IIb), which was identified by gas–liquid chromatography and PMR spectroscopy.

c) A sample of 0.52 g (4.7 mmoles) n-BuSNa in 1 ml DMSO was added to a mixture of 5.1 g (0.05 mole) (Ib), 4.387 g (0.05 mole) butanethiol, 4 ml DMSO and 0.01 g hydroquinone. The reaction mixture was treated by analogy to the above procedure. Vacuum distillation gave 2.55 (27.5%) (IIb), which was identified by gas–liquid chromatography and PMR spectroscopy.

Radical Addition of Butanethiol to α-Alkoxyacroleins. a) A mixture of 2.0 g (0.2 mole) (Ib), 0.1 g AIBN and 10.32 g (0.1 mole) butanethiol was heated in an ampule at 90°C for 3 h. Vacuum distillation gave 12.2 g (64%) (IIb), bp 87°C (4 mm), n_D^{20} 1.4650, d_4^{20} 0.9847. Found, %: C 57.27; H 9.39; S 16.92. $C_9H_{18}O_2S$. Calculated, %: C 56.84; H 9.46; S 16.86. IR spectrum (near, ν, cm^{-1}): 1735 (C=O).

b) Analogously, 17.2 g (0.2 mole) (Ia), 0.1 g AIBN and 9.0 g (0.1 mole) butanethiol gave 15.2 g (86%) (IIa), bp 72.5-73.5°C (2.5 mm), n_D^{20} 1.4731, d_4^{20} 1.0202. Found, %: C 54.76; H 8.96; S 18.74. $C_8H_{16}O_2S$. Calculated, %: C 54.54; H 9.08; S 18.21. IR spectrum (neat, ν, cm^{-1}): 1730 (C=O).

Electrophilic Addition of Thiols to α-Ethoxyacrolein. a) A sample of 0.1 ml conc. hydrochloric acid was added to a mixture of 15 g (0.15 mole) (Ib) and 16.63 g (0.15 mole) thiophenol and stirred for 2 h at 60°C. Vacuum distillation gave 14.5 g (46%) (IIIb) with bp 130°C (4 mm), n_D^{20} 1.5430, d_4^{20} 1.0999. Found, %: C 62.96; H 6.68; S 14.98. $C_{11}H_{14}O_2S$. Calculated, %: C 62.85; H 6.66; S 15.25. IR spectrum (neat, ν, cm^{-1}): 1732 (C=O).

b) A sample of 0.01 g TsOH was added to a mixture of 6 g (0.06 mole) (Ib) and 6.6 g (0.06 mole) thiophenol and maintained for 48 h at about 20°C. Vacuum distillation gave 4.8 g (37%) 1-ethoxy-1-phenylthio-2-propanone (IVb), bp 125°C (5 mm), n_D^{20} 1.5450, d_4^{20} 1.0925. Found, %: C 62.82; H 6.76; S 15.42. $C_{11}H_{14}O_2S$. Calculated, %: C 62.85; H 6.66; S 15.25. IR spectrum (neat, ν, cm^{-1}): 1730 (C=O).

c) A sample of 0.01 g TsOH was added to a mixture of 6 g (0.06 mole) (Ib) and 5.4 g (0.06 mole) butanethiol and the reaction mixture spontaneously warmed to 90°C. The mixture was maintained for 72 h at about 20°C. Vacuum distillation gave 6.5 g (57%) 1-ethoxy-1-butylthiopropanone (IVa), bp 80°C (4 mm), n_D^{20} 1.4620, d_4^{20} 0.9736. Found, %: C 56.82; H 9.89; S 16.75. $C_9H_{18}O_2S$. Calculated, %: C 56.84; H 9.46; S 16.86. IR spectrum (neat, ν, cm^{-1}): 1725 (C=O).

Thermal Addition of butanethiol to α-Ethoxyacrolein. A mixture of 12.4 g (0.124 mole) (Ib) and 11.17 g (0.124 mole) butanethiol was heated on a steam bath for 11 h. Vacuum distillation gave 7 g (30%) (IIIa), bp 73°C (4 mm), n_D^{20} 1.4780, d_4^{20} 0.9906. Found, %: C 56.63; H 9.30; S 16.56. $C_9H_{18}O_2S$. Calculated, %: C 56.84; H 9.46; S 16.86. IR spectrum (neat, ν, cm^{-1}): 1725 (C=O).

CONCLUSIONS

The nucleophilic or radical addition of thiols to α-alkoxyacroleins leads to 2-alkoxy-3-organylthiopropanals. Depending on the reaction conditions, the product of the electrophilic reaction of the same reagents is a 2-alkoxy-2-organylthiopropanal or 1-alkoxy-1-organylthiopropanone.

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SILYLATION OF CARBONYL COMPOUNDS IN A CHROMATO-MASS SPECTROMETER COLUMN

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Poole and Zlatkis [1] have observed the formation of the silyl ethers of enols upon the silylation of ketoalcohols underliquid-phase conditions. Recently, in a study of the mechanism of the catalytic hydrogenation of cyclic ketones by reaction chromato-mass spectrometry entailing the silylation of the reaction mixture in a chromatographic column we observed that enol silyl ethers may also be obtained under gas-phase conditions [2]. In the present work, this tecunique was used to prepare silyl ethers of the enol forms of various aldehydes and ketones during a mass spectrometric study and previously unexamined features of their dissociative ionization are discussed.

The carbonyl compounds taken included aldehydes (octanal and 2-ethylhexanal), symmetrical (4-heptaonone) and unsymmetrical ketones (2-heptanone, 2-octanone, 4-octanone, and 2-nonanone) and cyclic ketones (cyclopentanone and cyclohexanone). The aldehydes were obtained in the course of a single experiment by the gas-phase dehydrogenation of 1-octanol and 2-ethyl-1-hexanol in a microreactor filled with copper filings at 320°C situated before the chromatographic column [3]. Commercial N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane was used for the silylation [4]. In the case of the ketones, the silylating agent was introduced into the chromatograph injector 4-5 sec after the introduction of the sample. In order to obtain enol ethers from the aldehydes, the silylating agent was introduced at the same time to the space between the dehydrogenation reactor and the chromatographic column. The analysis with temperature programming (from 100°C at 5 deg/min) provided sufficient contact time of the silylating agent with the substrate and most complete separation of the unreacted BSTFA, the products of its hydrolysis, the enol silyl ether, and the carbonyl compound. This permitted us to record "high purity" mass spectra for the trimethylsilyl (TMS) ethers of the enols.

Various ratios of the sample and silylating agent from 1:1 to 1:5 were tested. Chromatographic zones and mass spectra corresponding to the enol TMS ethers were recorded for all these ratios and all the carbonyl compounds studied. The amount of these ether products was found to increase with increaisng fraction of the silylating agent. This finding indicates rapid enolization of the carbonyl compounds due to the presence of trimethylchlorosilane in the agent, which forms HCl upon hydrolysis.

The electron impact mass spectra of enol TMS esters (I)-(IX) given in the experimental were thus obtained. We should note that isomeric enol ethers (IVa)-(VIIa) and (IVb)-(VIIb) do ot separate under these chromatographic conditions. Thus, the recorded mass spectra are overall spectra for both isomers in an unknown ratio.

The mass spectra of all the ethers studied contain significant $M^{+\cdot}$ peaks, whose intensity is especially high in the case of the ethers of cyclic enols (VIII) and (IX). As in the case of other TMS derivatives, the spectra of (I)-(IX) display strong peaks for the Me_3Si^+ (m/z 73) and $Me_2{}^+SiOH$ (m/z 75) ions; the Me_3Si^+ ion gives the largest peak in virtually all cases (the m/z 75 peak is the largest signal only in the spectrum of (IX)).

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