β-ARYLTHIOALKYLATION OF 2-METHOXY-1,3-BUTADIENE

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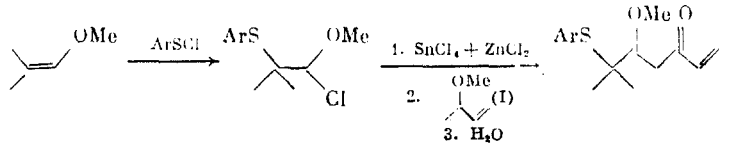
The β-arylthioalkylation of 2-methoxy-1,3-butadiene is regiospecific at the alkoxy-substituted C=C bond, giving 6-arylthioalk-1-en-3-ones.

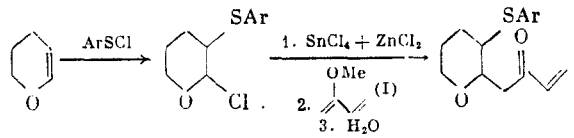
It has been reported that in the presence of Lewis acids the adducts of arylsulfenyl chlorides and vinyl ethers react smoothly with vinyl ethers to give β-arylthioalkylation products [1]. The β-arylthioalkylation of methoxyallene has also been reported [2].

The aim of the present investigation was to examine the possible use of 2-methoxybuta-1,3-diene (I) in this reaction. 2-Methyl-1-methoxy-2-*p*-tolylthiopropyl chloride (II) (the adduct of 2-methyl-1-methoxyprop-1-ene (III) and ArSCl) in the presence of a mixture of $SnCl_4$ and $ZnCl_2$* has been found to readily alkylate the alkoxydiene (I) to give a single product, 6-methyl-6-*p*-tolylthio-5-methoxyhept-1-en-2-one (IV) in 60% yield.



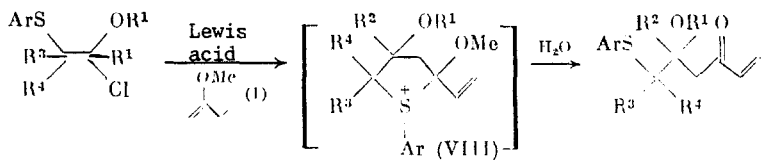
(III) (II) (IV), 60%

β-arylthioalkylation of the 2-methoxybuta-1,3-diene adduct (VI), obtained from the dihydropyran (V) and ArSCl, is also regiospecific, giving 2-(but-3′-en-2′-onyl)-3-*p*-tolylthiooxane (VII) in 58% yield.



(V) (VI) (VII), 58%

In both instances, the structures of the products isolated (IV) and (VII) correspond to attack of the C-electrophile (II), (VI) on C^1, and of the O-nucleophile (H_2O) on the C^2 of the alkoxydiene (I). This regiospecificity, and the absence of oligomeric products, lead to the conclusion that the β-arylthioalkylation of 2-methoxybuta-1,3-diene takes place in the same way as the reaction of vinyl ethers and methoxyallene, via the cyclic intermediate (VIII).



*For the use of "mixed" Lewis acids see, for example, [3].

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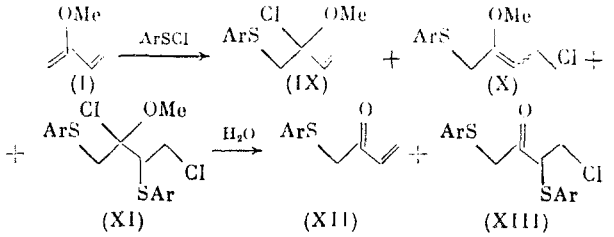
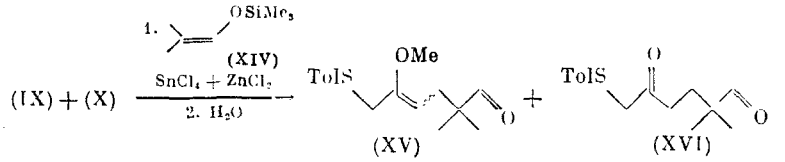
The structure and stoichiometric composition of the alkylation products (IV) and (VII) were confirmed by IR, ^1H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. According to its ^1H and ^{13}C NMR spectra, the compound (VII) was isolated as the pure diastereoisomer, in which the substituents are tentatively assigned the threo configuration.

Alkoxydienes such as methoxyallene [4] and 1-methoxybuta-1,3-diene [5] have also been used as precursors of sulfur electrophiles in the arylthioalkylation of π-donors of various types. The possible use of 2-methoxybuta-1,3-diene (I) in this way required a study of the directionality of the reaction of (I) with ArSCl. According to the literature [6], this reaction is a regiospecific 1,2-addition (—40°C, Et_2O), as shown by the composition of the hydrolysis products, or reduction of the reaction mixture. We tried to obtain direct information on the composition of the products of the reaction of (I) with ArSCl (Ar = *p*-Tol, *p*-ClC_6H_4) from the PMR spectra of mixtures obtained under a variety of conditions (CCl_4—C_6D_6, 1:3; $CDCl_3$, D^8—THF, temperature range —70°C-20°C, differing orders of addition of the reactants). In all instances, mixtures of a few adducts were obtained, in which were identified signals assigned to the adducts from 1,2-addition of (IX), 1,4-addition of (X), and the bis-adduct (XI).* Treatment of the reaction mixture obtained by reacting *p*-TolSCl with (I) (pentane, —78°C) with water afforded 4-*p*-tolylthiobut-1-en-3-one (XII, 61% yield) and 2,4-di-*p*-tolylthiobutan-3-onyl chloride (XIII, 7% yield). Clearly, under these conditions the allyl chlorides (IX) and (X) give the same hydrolysis product (XII), corresponding to 1,2-addition of the electrophile ArS^+ and the nucleophile OH^- to (I).



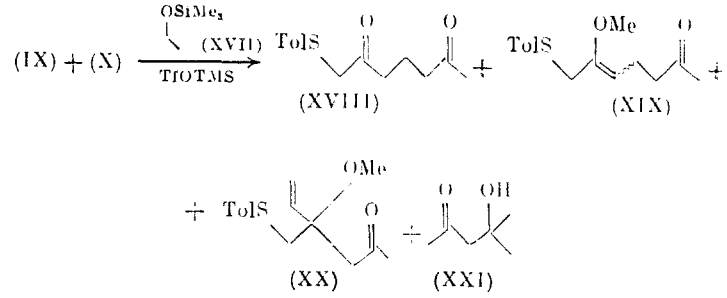
The reaction of the mixed adducts (IX)-(XI) with the trimethylsilyl ether of the enol (TMSEE)† of isobutyraldehyde (XIV) in the presence of Lewis acids ($SnCl_4$ + $ZnCl_2$, $SnCl_4$, $TiCl_4$, TMSOTf) is regiospecific, but involves 1,4-addition to (I) of the electrophile ArS^+ and the C-nucleophile, to give 2,2-dimethyl-6-*p*-tolylthiohexane-1,5-dione (XVI) as the main product (57% yield when a 1:1 mixture of $SnCl_4$ and $ZnCl_2$ was used), in admixture with 2,2-dimethyl-5-methoxy-6-*p*-tolylthiohex-4-en-1-one (XV, 7%).



However, attempts to use the TMSEE of other carbonyl compounds in this reaction were unsuccessful. For example, in the reaction of the mixture of (IX) and (X) with acetone TMSEE (XVII) in the presence of $ZnCl_2$ + $SnCl_4$ (1:1) the yield of the 1,4-adduct 1-*p*-tolylthioheptane-2,6-dione (XVIII) was only 5%. When the mixture of $SnCl_4$ and $ZnCl_2$ was replaced by a catalytic quantity of TfOTMS (0.1 equiv.), in addition to the 1,4-addition products (XVIII) (8%) and 2-methoxy-1-*p*-tolylthiohept-2-en-6-one (XIX) (11%), there was obtained 4-vinyl-4-methoxy-5-*p*-tolylthiopentan-2-one (XX) (4%), the structure of which corresponds to the addition of the electrophile ArS^+ to C^1 and of the C-nucleophile to C^2 of the starting 2-methoxybuta-1,3-diene. The reaction of the adducts (IX) and (X) with methyl cyclopropyl ketone also gave a mixture of products.

*Adducts (IX) and (X) are formed in similar amounts. It was not possible to obtain quantitative data on the composition of the mixtures as a result of the presence of unidentified impurities and overlapping of the signals.

†For the use of TMSEE in reactions with sulfur electrophiles, see for example [7, 8].



The structure and empirical formulae of (XII), (XIII), (XV), (XVI), and (XVII)-(XX) were confirmed by NMR and IR spectroscopy, mass spectrometry, and elemental analysis.

These findings show that (I) can be used as a π-donor nucleophile in β-arylthioalkylation reactions. However, the use of (I) as a precursor for the preparation of a sulfur-bearing electrophile in this reaction does not appear promising in view of the low selectivity of the reaction of (I) with ArSCl, and the subsequent reaction of the resulting mixture of adducts with the π-donors.

EXPERIMENTAL

NMR spectra were obtained on Bruker WM-250 instruments (250 MHz for ^1H and 62.5 MHz for ^{13}C), solvent $CDCl_3$, internal standard TMS. The chemical shifts δ are given in ppm, and the coupling constants in Hz. Mass spectrometry was carried out with a Varian MATCH-6 instrument.

p-TolSCl and *p*-ClC_6H_4SCl were obtained by chlorinating the thiophenols with SO_2Cl_2 in CCl_4 at —10°C. 2-Methyl-1-methoxyprop-1-ene was obtained by pyrolysis of isobutyric acid methyl acetal in the presence of $NH_4H_2PO_4$. The isobutyraldehyde, acetone, and methyl cyclopropyl ketone TMSEE were obtained as described in [9].

6-Methyl-6-*p*-tolylthio-5-methoxyhept-1-en-2-one (IV). To a solution of 159 mg (1 mmole) of *p*-TolSCl in 10 ml of CH_2Cl_2 was added dropwise at —78°C under argon a solution of 86 mg (1 mmole) of 2-methyl-1-methoxyprop-1-ene in 2 ml of CH_2Cl_2, followed by a solution, previously cooled to —78°C, of 0.12 ml (1 mmole) of $SnCl_4$ in 1 ml of CH_2Cl_2 and 136 mg (1 mmole) of $ZnCl_2$. After 5 min, a solution of 126 mg (1.5 mmoles) of 2-methoxybuta-1,3-diene in 2 ml of CH_2Cl_2 was added. The mixture was stirred for 1 h at —78°C, then poured into a sat. solution of $NaHCO_3$. The mixture was then extracted with ether, dried over $CaCl_2$, and the residue after removal of the solvent purified by TLC on silica to give 165 mg (60%) of (IV), R_f 0.65 (ether—hexane, 1:1; Silufol), n_D^{22} 1.5410, M^+ 278. PMR spectrum: 1.21 and 1.24, two s (6H, $C(CH_3)_2$), 2.36 s (3H, CH_3), 3.12 (AB region of an ABX spectrum, 2H, J_{AB} = 17, J_{AX} = 9, J_{BX} = 2.5, CH_2), 3.31 s (3H, OCH_3), 3.77 (X region of the ABX spectrum, 1H, C<u>H</u>OCH_3), 5.90 and 6.38 m (3H, $CH{=}CH_2$), 7.27 m (4H, H_{arom}). Found: C 69.15; H 8.30; S 11.43%. $C_{16}H_{22}O_2S$. Calculated: C 69.03; H 7.96; S 11.49%.

2-(But-3′-en-2′-onyl)-3-*p*-tolylthiooxane (VII) was obtained in 58% yield by the method described for (IV), R_f 0.49 (ether—hexane, 1:1; Silufol), n_D^{22} 1.5645, M^+ 276. PMR spectrum: 1.60 and 2.15 m (4H, CH_2CH_2), 2.34 s (3H, CH_3), 2.81 (A region of an ABX spectrum, 1H, J_{AB} = 16, J_{AX} = 9, CHC=O) 2.84 m (1H, $CH_2C\underline{H}_2O$), 3.31 (B region of the ABX spectrum, 1H, J_{BX} = 2.5, CHC=O), 3.33 (Y region of an A′B′XY spectrum, 1H, $J_{A'Y} = J_{XY}$ = 12.5, $J_{B'Y}$ = 3.25, SCH), 3.82 (X region of an ABX spectrum, 1H, OCH), 3.83 m (1H, $CH_2C\underline{H}_2O$),5.83 and 6.30, two m (3H, $CH{=}CH_2$), 7.22 m (4H, H_{arom}). ^{13}C NMR spectrum: 21.076 (CH_3), 27.059 and 31.623 (CH_2CH_2), 44.030 ($\underline{C}H_2C{=}O$), 49.111 (CHS), 67.930 (OCH_2), 78.101 (OCH), 126.270 ($=CH_2$), 129.207, 129.764, 133.774 and 136.910 (C_{arom}), 137.885 (=CH), 198.735 (C=O). Found: C 69.36; H 7.56; S 11.69%. $C_{16}H_{20}O_2S$. Calculated: C 69.53; H 7.29; S 11.60%.

4-*p*-Tolylthiobut-1-en-3-one (XII). To 84 mg (1 mmole) of 2-methoxybuta-1,3-diene in 3 ml of pentane at —78°C was added dropwise 150 mg (0.95 mmole) of *p*-TolSCl. After 5 min, the mixture was poured into a solution of $NaHCO_3$, extracted with Et_2O, and dried over Na_2SO_4. The residue after removal of the solvent was chromatographed on a silica plate to give 120 mg (61%) of 4-tolylthiobut-1-en-3-one (XII) and 10 mg (7%) of 2,4-di-*p*-tolylthiobutan-3-onyl chloride (XIII). (XII): R_f 0.45 (ether—hexane, 1:2; Silufol), n_D^{20} 1.5814, M^+ 192. PMR spectrum: 2.30 s (3H, CH_3), 3.75 s (2H, SCH_2), 5.75-6.80 m (3H, $CH{=}CH_2$), J_1 = 17, J_2 = 10, J_3 = 2), 7.20 m (4H, H_{arom}). Found: C 68.67; H 6.48%. $C_{11}H_{12}OS$. Calculated: C 68.71; H 6.29%. (XIII): R_f 0.63 (ether—hexane, 1:2; Silufol), M^+ 366, 368. PMR spectrum: 2.32 and 2.35 two s (6H, two CH_3 groups), 3.5-4.2 m (5H, CH_2Cl, CHS, CH_2S), 7.05-7.25 m (8H, H_{arom}).

Alkylation of the Mixed Adducts of ArSCl to 2-Methoxybuta-1,3-diene with Isobutyraldehyde TMSEE. To 84 mg (1 mmole) of 2-methoxybuta-1,3-diene in 3 ml of pentane at —78°C was added dropwise 159 mg (1 mmole) of *p*-TolSCl. The mixture was then diluted with 10 ml of CH_2Cl_2 (the mixture of Lewis acids was previously stirred for 10 min at 20°C), and after 2-3 min 173 mg (1.2 mmoles) of isobutyraldehyde TMSEE was added. The mixture was stirred for 30 min at —78°C, then poured into $NaHCO_3$ solution, extracted with ether, dried over Na_2SO_4, and the solvent removed. The residue was purified by TLC on silica to give 20 mg (7%) of 2,2-dimethyl-5-methoxy-6-p-tolylthiohex-4-en-1-one (XV), 150 mg (57%) of 2,2-dimethyl-6-p-tolylthiohexane-1-5-dione (XVI), and 25 mg (7%) of 2,4-di-p-tolylthiobutan-3-onyl chloride (XIII). (XV): R_f 0.72 (ether—hexane, 1:1), M^+ 278. PMR spectrum: 1.0 s (6H, $C(CH_3)_2$), 2.03 d (2H, J = 5.5, CH_2), 2.31 s (3H, CH_3), 3.49 s (3H, OCH_3), 3.54 s (2H, SCH_2), 4.33 t (1H, J = 5.5, =CH), 7.20 m (4H, H_{arom}), 9.38 s (1H, CHO). (XVI): n_D^{22} 1.5404, R_f 0.46 (ether—hexane, 1:1), M^+ 264. PMR spectrum: 1.03 s (6H, $C(CH_3)_2$), 1.74 d.d (2H, $J_1 = J_2$ = 8, CH_2), 2.31 s (3H, CH_3), 2.50 d.d (2H, $J_1 = J_2$ = 8, CH_2), 3.59 s (2H, SCH_2), 7.18 m (4H, H_{arom}), 9.39 s (1H, CHO). Found: C 68.14; H 7.62%. $C_{15}H_{20}O_2S$. Calculated: C 68.03; H 7.83%.

Alkylation of the Mixed Adducts of ArSCl to 2-Methoxybuta-1,3-diene with Acetone TMSEE was carried out as described for the reaction with isobutyraldehyde TMSEE, except that the Lewis acid used was 22 mg (0.2 mmole) of TfOTMS. There was obtained 8% of 1-*p*-tolylthioheptan-2,6-dione (XVIII), 11% of 2-methoxy-1-*p*-tolylthiohept-2-en-6-one (XIX), and 4% of 4-vinyl-4-methoxy-5-*p*-tolylthiopentan-2-one (XX). (XVIII): R_f 0.20 (ether—hexane, 1:1. Silufol), M^+ 264. PMR spectrum: 1.82 q (2H, CH_2, J = 9), 2.10 s (3H, CH_3), 2.32 s (3H, CH_3), 2.41 and 2.63, two t (4H, two CH_2 groups), 3.61 s (2H, SCH_2). (XIX): R_f 0.39 (ether—hexane, 1:1; Silufol), M^+ 278. PMR spectrum: 2.07 s (3H, CH_3), 2.25 m (4H, CH_2CH_2), 3.50 s (3H, OCH_3), 3.57 s (2H, SCH_2), 4.44 t (1H, J = 7, =CH), 7.19 m (4H, H_{arom}). (XX): R_f 0.44 (ether—hexane, 1:1; Silufol), M^+ 278. PMR spectrum: 2.12 s (3H, CH_3), 2.32 s (3H, CH_3), 2.95 d.d (2H, CH_2, J = 15), 3.20 s (3H, OCH_3), 3.40 d.d (2H, SCH_2, J = 12), 5.28 m (2H, $=CH_2$), 5.87 m (1H, =CH), 7.20 m (4H, H_{arom}).

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