Ring-opening Reactions of Heterocyclic Metal-organics. IV. The Synthesis of Acetylenic Mixed Ketenethioacetals and Thio-seleno-acetals

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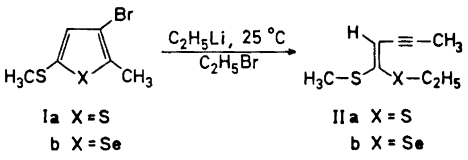
It has previously been demonstrated that certain 3-lithiothiophenes, and especially 3-lithioselenophenes, ring-open to give *Z*-1-butene-3-yne-1-thiolates and *Z*-1-butene-3-yne-1-selenolates.[1-4] These products are alkylated by the alkyl halides formed in the preparation of the lithio derivatives by halogen-metal exchange, or by alkyl halides intentionally added to the reaction mixture.

We have now found that this ring-opening reaction proceeds smoothly with 2-methylthio-4-thienyllithium, and especially with 2-methylthio-4-selenienyllithium derivatives, to give a type of organic compounds which as far as we could find have not been described before, namely acetylenic ketenethioacetals or mixed acetylenic ketenethio-seleno-acetals (*cf.* Formula scheme).

Thus the reaction of 3-bromo-2-methyl-5-methylthiothiophene (Ia) with ethereal ethyllithium at room temperature, followed by the addition of ethyl bromide, gave a mixture consisting of three components (VPC) in about 80 % yield. The main component (70 %), which was obtained pure by TLC, was shown by NMR, IR, and mass spectral data and by elemental analyses to be *Z*-1-ethylthio-1-methylthio-1-penten-3-yne. The two by-products, which were formed in 25 % and 5 % yields, both had molecular weight of 200, and judging from their fragmentation pattern, these compounds are most probably 1-methylthio-1-ethylthio-1-heptene-3-yne, formed by alkylation at the acetylenic methyl group, and 3-ethyl-2-methyl-5-methylthiothiophene, formed by Wurtz reaction between the initially formed 2-methyl-5-methylthio-3-thienyllithium and ethyl bromide. It should perhaps be stressed that if halogen-metal exchange between 2-methylthio-4-bromothiophenes is carried out at −70°, the 2-methylthio-4-thienyl-lithium derivatives are stable enough to allow the preparation of many different 4-substituted-2-methylthiothiophenes.[5,6]

3-Bromo-2-methyl-5-methylthioselenophene reacted more smoothly and gave an 85 % yield of 95 % pure *Z*-1-ethylseleno-1-methylthio-1-pentene-3-yne (IIb). (The structure proof is given in the experimental part.) It has been demonstrated that the ring-opening is stereospecific [2-4] (the acetylenic bond and the thiolate group being *cis*-situated), so the *Z*-structure is assigned to IIa and IIb. It was, however, observed that isomerization to a 50:50 mixture of *cis-trans* isomer occurred during attempts to prepare pure Ia by preparative VPC at 190°C. (For an investigation of barriers to rotation around the carbon-carbon double bond in 1,1-bisalkylthio-ethylenes, *cf.* Refs. 7 – 8.) Compound Ia was prepared from 2-methylthiophene by dibromination to give 3,5-dibromo-2-methylthiophene,[9] followed by halogen-metal exchange and reaction with dimethyldisulphide. 3,5-Dibromo-2-methylselenophene could not be prepared in a completely analogous way, as decomposition occurred upon attempted bromination of 2-methylselenophene under conditions used successfully in the thiophene series. However, by using *N*-bromosuccinimide, 2-methylselenophene [10] could be dibrominated in the 5- and 3-positions. Halogen-metal exchange and reaction with dimethyldisulphide, as in the thiophene series, gave compound Ib.



Ia X = S
b X = Se

IIa X = S
b X = Se

As mentioned above, compounds such as IIa and IIb have as far as we could find not been described in the literature. Addition of alkylthiolates or alkylselenolates to methyl-methylthiodiacetylenes occurs at the acetylenic carbon to which the methyl group is bonded, giving 2-methylthio-5-alkylthio-2-pentene-4-yne or the corresponding alkylseleno derivative, respectively.[11] It would perhaps be possible to apply the method used for the synthesis

of 1,1-dialkylthioethylenes,[12-14] consisting in the condensation of carbanions from active methylene derivatives with carbon disulphide, followed by alkylation. This method, has, as far as we are aware, not been applied to dialkylacetylenes, but even if it would be successful, it would certainly not be useful for the stereospecific synthesis of mixed ketenethioacetals or ketene thio-seleno acetals such as IIa and IIb.

The scope of this ring-opening route to acetylenic ketene mercaptals appears to be broad. It should be possible to use different alkylthio or arylthio groups in the thiophenes and selenophenes. It is also feasible to alkylate the thiolate or selenolate functionality formed in the ring-opening with a variety of reagents, if the halogen-metal exchange is carried out with phenyllithium followed by any alkylating agent.[15] We are currently persuing these aspects of the ring-opening reaction.

Experimental. 3,5-Dibromo-2-methylselenophene. To a stirred solution of 9.6 g (0.066 mol) of 2-methylselenophene in 70 ml of acetic acid, 25.8 g (0.145 mol) of *N*-bromosuccinimide was added in portions at room temperature. When the addition was complete, the mixture was stirred for 30 min and poured into water. The mixture was extracted several times with ether and the combined ether phases washed with sodium hydrogen carbonate solution and water to neutral reaction. The ether phase was dried and fractionated to yield 11.0 g (55 %) of 2,4-dibromo-5-methylselenophene, b.p. 81–82°/1 mmHg. NMR (CCl_4): $\delta_{CH_3}=2.35$ ppm; $\delta_4=6.96$ ppm. [Found: C 19.86; H 1.28; Br 52.87; Se 26.07. Calc. for $C_5H_4Br_2Se$ (302.84): C 19.83; H 1.33; Br 52.77; Se 26.07].

3-Bromo-2-methyl-5-methylthioselenophene. To a stirred solution of 7.74 g (0.0256 mol) of 3,5-dibromo-2-methylselenophene at −70°, 16.0 ml of 1.6 N butyllithium in hexane was added at −70°. After 10 min the reaction mixture was pressed into 2.45 g (0.0260 mol) of dimethyldisulphide in 25 ml of anhydrous ether and the mixture stirred for 3 h and then hydrolyzed with water. The ether phase was washed with dilute sodium hydroxide solution and water, dried and fractionated to yield 4.42 g (64 %) of the title compound, b.p. 89–93°/0.8 mmHg. NMR (CCl_4): $\delta_{SCH_3}=2.86$ ppm, $\delta_{CH_3}=2.82$ ppm, $\delta_4=7.55$ ppm. [Found: C 26.60; H 2.55; Br 29.56; S 11.78; Se 29.40. Calc. for C_6H_7BrSSe (270.05): C 26.69; H 2.61; Br 29.59; S 11.87; Se 29.24].

3-Bromo-2-methyl-5-methylthiothiophene. From 36.0 g (0.141 mol) of 3,5-dibromo-2-methylthiophene [9] in 100 ml of anhydrous ether, 81.5 ml of 1.6 N butyllithium in hexane and 14.1 g (0.150 mol) of dimethyldisulphide, 22.2 g (70 %) of the title compound, b.p. 79–81°/1.4 mmHg was obtained, following the procedure described above. NMR (CCl_4) δ_{SCH_3}, $\delta_{CH_3}=2.29$ and 2.36 ppm, $\delta_4=6.78$ ppm. [Found: C 32.22; H 3.19; Br 35.80; S 28.80; Calc. for $C_6H_7BrS_2$ (223.15): C 32.29; H 3.16. Br 35.81; S 28.71].

Z-1-Ethylseleno-1-methylthio-1-pentene-3-yne. To a stirred solution of 2.70 g (0.0100 mol) of 3-bromo-2-methyl-5-methylthioselenophene in 50 ml of anhydrous ether, 15.8 ml of 0.7 N ethereal ethyllithium was added, and the mixture stirred for 15 min. Then 7.6 g (0.070 mol) of ethyl bromide was added and the mixture stirred for 4 h. Water was added, the ether phase separated, washed with water and dried. The ether was evaporated, and VPC (OV 17 (5 %), 2 m × 3 mm, 170°) showed that the crude product (1.85 g; 84 %) consisted to 95 % (area %) of the title compound. Distillation yielded 1.2 g (55 %) of pure *Z*-1-ethylseleno-1-methylthio-1-pentene-3-yne, b.p. 66–67°/5×10^{-3} mmHg. IR: 2205 cm^{-1} (C≡C), 1530 cm^{-1} (C=C). NMR (CCl_4): $\delta_{CCH_3}=1.95$ ppm; $\delta_2=5.68$ ppm; $\delta_{SCH_3}=2.16$ ppm; $\delta_{Se-CH_2}=2.84$ ppm; $\delta_{CH_2-CH_3}=1.37$ ppm; $J_{CCH_3-H}=2.40$ Hz; $J_{CH_2-CH_3}=7.0$ Hz. Mass spectrum: M^+; $m/e=220$. Calc. for $C_8H_{12}S^{80}Se$ $m/e=220$. [Found: C 43.78; H 5.52; S 14.58; Se 36.21. Calc. for $C_8H_{12}SSe$ (219.21): C 43.83; H 5.52; S 14.63; Se 36.02].

Z-1-Ethylthio-1-methylthio-1-pentene-3-yne. When 10.0 g (0.0448 mol) of 3-bromo-2-methyl-5-methylthiothiophene in 150 ml of ether was treated with 75 ml of 0.6 N ethyllithium and then with 23.4 g (0.150 mol) of ethyl iodide and worked up as above, 7.5 g of product was obtained which according to VPC (BDS (10 %); 2 m × 3 mm; 130–190°, 16°/min) and combined VPC-mass spectrometry showed three components (in order of increasing retention time) with the area percentage 5 (m/e 200), 70 ($m/e=172$, the title compound), and 25 ($m/e=200$). The crude product was distilled at 91–94°/1.2 mmHg and pure *Z*-1-ethylthio-1-methylthio-1-pentene-3-yne was obtained through preparative thin layer chromatography (1 mm silica gel; hexane:ether 10:1). IR: 2205 cm^{-1} (C≡C); 1540 cm^{-1} (C=C). NMR (CCl_4): $\delta_{CCH_3}=2.00$ ppm; $\delta_2=5.58$ ppm; $\delta_{SCH_3}=2.28$ ppm; $\delta_{SCH_3}=2.86$ ppm; $\delta_{CH_2-CH_3}=1.28$ ppm; $J_{CCH_3-H}=2.40$ Hz; $J_{CH_2-CH_3}=7.0$ Hz. [Found: C 55.7; H 7.04; S 36.4. Calc. for

$C_8H_{12}S_2$ (172.32): C 55.76; H 7.02; S 37.22]. VPC analyses were performed on a Perkin Elmer 900 Gas Chromatograph. IR spectra were recorded on a Perkin Elmer 257 Grating Infrared Spectrophotometer, NMR spectra on a Varian A-60 spectrometer and mass spectra on an LKB 9000 mass spectrometer.

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Reactivation of Phosphorylated Cholinesterase by Some Imidazole-substituted Oximes

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Nucleophilic agents such as oximes have been employed in restoring the activity of cholinesterase (ChE) which has been inactivated by organophosphorus compounds. Methyl-quaternized pyridinium aldoximes have been found particularly effective.[1] By a suitable modification of the substituent on the nitrogen, an increase in the reactivation rate was obtained.[2] Our intention has been to study the effect of an imidazole substituent in the pyridine aldoxime.

There is strong evidence that imidazole is part of the active site of ChE.[3] Furthermore, imidazole has a well documented catalytic capacity, *e.g.* for ester hydrolysis, both as a nucleophile itself and as a catalyst in a general acid-base catalyzed reaction.[3] Thus it would be of interest to study the effect on the reactivation process of a properly spaced imidazole group.

Moreover, imidazole-substituted oximes may participate in the degradation of organophosphorus compounds before they reach the active site of the enzyme.

The syntheses were performed by reacting 4(5)-chloromethylimidazole hydrochloride or 4(5)-(2-bromoethyl)imidazole hydrobromide with the appropriate pyridine aldoxime in dimethylformamide. However, it was not possible to obtain the 2-aldoxime of *N*-(imidazolylethyl)pyridinium bromide by this procedure. The difficulties with quaternization of 2-pyridine aldoximes have been pointed out previously by Poziomek *et al.*[4]

The reactivator potency against BuChE inhibited by methylisopropoxyphosphoryl fluoride (Sarin) is illustrated in Table 1. It is evident that I and II are slightly more active than 2-(hydroxyimino)-methylpyridinium methanesulphonate (P2S), a compound used as an antidote in nerve gas poisoning and as a standard in reactivation experiments. None of the compounds I – V is able to reactivate the enzyme after inhibition with dimethylamidoethoxy-