

Studies on the Synthesis of Heterocyclic Compounds. VIII.

Action of Acyl Halides on 2,2-Di-*n*-butyl-1,3,2-benzoxathiastannole, 2-Chloro-1,3,2-benzoxathiaarsole and -stibole

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Received August 11, 1981

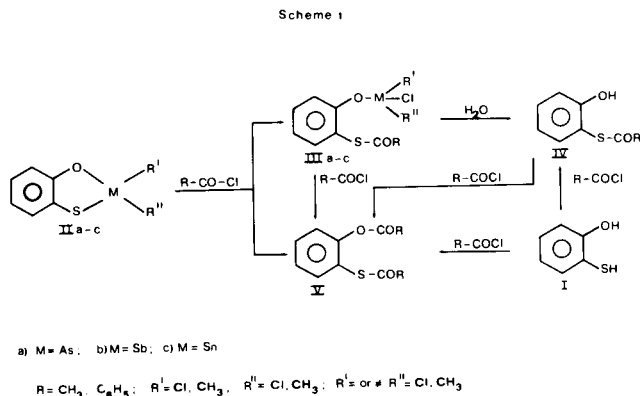
The cleavage reaction of some 1,3,2-benzoxathiastannole, -arsole and -stibole derivatives with acetyl and benzoyl chloride is described. The reactions were carried out refluxing in benzene or at room temperature. In all cases, the reaction occurs through the initial cleavage of the S-M linkage with formation of the respective *o*-acylthio derivatives. The structure of the prepared compounds was assigned on the basis of their analytical, physical and spectral data.

J. Heterocyclic Chem., **19**, 649 (1982).

The action of acyl halides on five-membered heterocyclic compounds containing the O-M-O (M = P, As, Sb, Sn) bond have been studied previously (1). The reaction always occurs with the cleavage of the O-M bond and leads, depending on reaction conditions, to formation of mono and diesters or of a mixture of both.

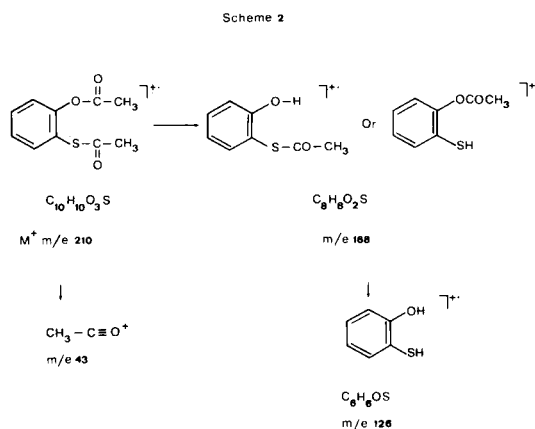
In this work we extend the research to derivatives of 1,3,2-benzoxathiastannoles, arsoles and stiboles in order to establish the relative ease of cleavage of O-M and S-M linkage by acyl halides, and to obtain monoesters with the acyl group linked to oxygen or sulphur atom.

Only a few examples of the synthesis of esters of this type has been described in literature (2). In this work 2,2-dimethyl-1,3,2-benzoxathiastannole (IIc), 2-chloro-1,3,2-benzoxathiaarsole (IIa) and -stibole (IIb) have been prepared starting from 2-hydroxythiophenol (I) and dimethyltin dichloride, or arsenic or antimony trichloride (3a-c), respectively. The cyclic structure of compounds IIa-c makes the oxygen and sulphur heteroatoms different in reactivity toward acyl halides giving symmetric and non-symmetric diesters.



It is apparent from the experimental results that the order of chemical reactivity with acetyl or benzoyl halide is the following: IIb > IIc > IIa (Scheme 1). This order suggests that the reactivity of the heterocyclic compounds

(IIa-c) was affected by the different electronic nature of the O and S atoms and by the chemical properties of M (As, Sb, Sn).



By reacting compounds IIa-c with 2.5 moles of acetyl or benzoyl chloride in refluxing benzene solution for certain periods, the corresponding diesters V were obtained in almost quantitative yields, together with dimethyltin dichloride, arsenic and antimony trichloride. In preliminary attempts, the opening of the heterocyclic ring involves, in the first step, cleavage of the S-M bond. This is the case also when the electronic factors favour the cleavage of the O-M bond (e.g. a methyl group at the *para* position with respect to the oxygen atom or the chlorine atom *para* to the sulphur atom). By reacting compounds IIa-b with a Grignard reagent (MeMg I) in benzene (at reflux as well as at room temperature) the cleavage of both the O-M and the S-M bond with formation of 2-hydroxythiophenol (I) was always observed. The benzene solution was hydrolyzed, washed with an aqueous solution of *N* sodium carbonate, 2*N*-sodium hydroxide, water and then dried. After evaporation of the solvent, the desired diesters were obtained in a high degree of purity. The structure of diesters V (R = CH₃, C₆H₅) have been determined by analytical and spectroscopic (ir, nmr, ms) data, and comparison with authentic samples obtained by different methods where possible.

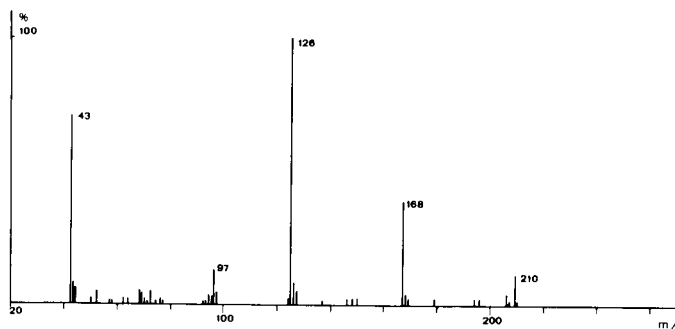


Figure 1 Mass spectrum of *o*-acetylthiophenyl acetate V (R=CH₃)

The infrared spectra of the diesters V (R = CH₃) exhibited the characteristic bands due to the O-C=O and S-C=O groups at 1760 and 1700 cm⁻¹, respectively. The ¹H nmr spectra of the diesters V showed signals at δ 7.58-7.10, δ 2.33 and δ 2.21 ppm, attributable to five aromatic protons, and to six methyl protons of S-CO-CH₃ and O-CO-CH₃ groups, respectively, while the spectra of the diesters V (R = C₆H₅) showed only aromatic signals, a multiplet at δ 8.10-7.30 ppm. These structures have been confirmed the ir and nmr spectra of the diesters V with those of phenyl acetate and phenylthio acetate (4a,b). The mass spectrum of *o*-acetylthiophenyl acetate V, presented in Figure 1 reveals some interesting fragmentation patterns.

By the injection of compounds V (R = CH₃) in the GS-MS spectrometer, a molecular ion at m/e 210, corresponding to the free *o*-acetylthiophenyl acetate was observed. The molecule fragments are shown in Scheme 2. The base peak in the spectrum occurs at m/e 126 corresponding to loss of the two neutral molecules of ketene from the parent ion and from the fragment at m/e 168 of relative abundance 11.4% and 39.3%, respectively.

It is significant that the ion at m/e 126 is the base peak in the spectrum of compound V (R = CH₃) indicating this ion to be relatively stable. The m/e 43 (CH₃-C≡O⁺) ion was observed in this compound and it is relatively abundant (71%) and it was formed by elimination of the radical C₆H₄O₂ from the parent ion. Furthermore the mass spectrum of phenyl acetate demonstrates the similarity in the fragmentation behaviour of the compounds V (R = CH₃) (8). In this compound the base peak occurs at m/e 94 corresponding, as expected, to loss of a neutral molecule of ketene by the parent ion. Others fragments are m/e 66, 65, 43 and 39 of relative abundance 14.3%, 11%, 5.6% and 10%, respectively.

The mass spectrum of phenylthio acetate differs from phenyl acetate by a calculation of their isotopic distribution (e.g. ³²S/³⁴S 25:1). The molecule easily cleaves losing the CH₂=C=O group and forming the base peak at m/e 110. The same approach can also be applied to the pre-

paration of non-symmetric diesters starting from the compounds IIa-c with consecutive addition of one mole of benzoyl chloride followed by one mole of acetyl chloride and then refluxing for a certain period in benzene. These non-symmetric diesters were identified by analytical and spectroscopic data. Repeating the reaction between the arsole and stannole derivatives and acyl chlorides in equimolar amounts, using benzene as the solvent, the monoesters IV (R = CH₃, C₆H₅) were obtained in 81-85% yields together with traces of the diesters. On the other hand, with a benzene suspension of 2-chloro-1,3,2-benzoxathiaastibole (IIb) and acyl chlorides (molar ratio of 1:1) after hydrolysis, only the diesters V were obtained and the unreacted starting compound IIb was always recovered. This apparently anomalous result is likely due to the poor solubility of 2-chloro-1,3,2-benzoxanthiaastibole (IIb) in the reaction solvent. The small amount of monoester which formed immediately went into solution and was converted into the corresponding diesters. Accordingly, if an excess of acyl halide was used thus increasing the solubility of the substrate, the diester V were obtained in quantitative yields at room temperature. Indeed, repeating the reaction in dimethylsulphoxyde solution at room temperature, the monoesters IV were obtained in excellent yields. The structure of the monoesters IV (R = CH₃, C₆H₅) which were synthesized have been assigned on the basis of their analytical, physical and spectral data.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer model 157G spectrophotometer. Samples were examined as potassium bromide pellets or as thin films in the case of liquids, absorption frequencies are quoted in reciprocal centimeters. The nmr spectra were determined on a Varian FT-80A spectrometer; chemical shifts were measured in ppm (δ) using TMS as the internal standard. The mass spectra of the liquid compounds were determined using a Hewlett-Packard 5992B combined gas chromatograph and quadrupole mass spectrometer, while the mass spectra of the solid compounds were determined on a Hitachi Perkin-Elmer RMU-6D spectrometer a 70 eV. Microanalyses for CHN were carried out on a Perkin-Elmer model 240 Elemental Analyzer.

The following compounds were obtained according to literature procedures: 2-hydroxythiophenol (7), 2-chloro-1,3,2-benzoxathiaarsole (3a-b), 2-chloro-1,3,2-benzoxathiaastibole (3a-c), 2,2-dimethyl-1,3,2-benzoxathiaastannole (3a), phenylacetate (5).

All products were identified by comparison with authentic samples or by analytical and spectroscopic data.

General Procedures for the Preparation of Monoesters and diesters.

To a stirred solution of IIa-c (M = As, Sb, Sn) in dry benzene at room temperature a solution of acetyl or benzoyl chloride in dry benzene was added dropwise. The resulting mixture was stirred under reflux for several hours. After cooling, the benzene solution was washed with *N* sodium carbonate, the monoesters were isolated by extraction with aqueous sodium hydroxyde. The remaining benzene solution was dried and evaporated to give the crude diesters. The aqueous basic solution was acidified with hydrogen chloride and extracted with ether, dried and removed in a rotary evaporator to give the crude monoesters. The crude monoesters and diesters were purified by recrystallization or by distillation under reduced pressure or by column chromatography on silica gel.

o-Acetylthiophenyl Acetate V ($R = CH_3$).

Method A.

To a stirred solution of IIb (10 mmoles) in 15 ml of benzene at room temperature, a solution of acetyl chloride (25 mmoles) in 5 ml of benzene was added dropwise. The reaction mixture was stirred and refluxed for several hours, cooled and the solvent evaporated *in vacuo*. The crude residue of V was purified by eluting through a silica gel column using a 3:1 mixture of petroleum ether-diethyl ether as eluent to give a viscous pale yellow oil, yield 93%. The analytically pure sample was obtained by microdistillation *in vacuo* n_D^{20} 1.5668 (lit (2) bp 130° (2 mm); ir (film): 3040, 2920, 2840, 1760, 1710, 1590, 1570, 1460, 1440, 1360, 1260, 1180, 1100, 1060, 1030, 1000, 940, 900, 860, 810, 750, 710, 670, 660 cm^{-1} ; nmr (deuteriochloroform): δ 7.58-7.10 (m, 4H, arom), δ 2.33 (s, S-CO-CH₃, 3H), δ 2.21 ppm (s, O-CO-CH₃, 3H); ms: 210 (M⁺, 11), 168 (M - 42, 39), 126 (M - 84, 100), 43 (M - 167, 71).

Anal. Calcd. for C₁₀H₁₀O₃S: C, 57.14; H, 4.76. Found: C, 57.09; H, 4.80. The same procedure as for *o*-acetylthiophenyl acetate (V) ($R = CH_3$) was employed starting from IIa,c and acetyl chloride in benzene solution to give V in quantitative yield. Spectral data (ir, nmr, ms) and elemental analyses of this compound were identical to the products obtained from IIb.

Method B.

o-Acetylthiophenyl acetate V ($R = CH_3$) was also prepared by the method of Greenwood and Stevenson (2) starting from 2-hydroxythiophenol (I) (50 mmoles), acetyl chloride (115 mmoles), triethylamine (115 mmoles) and benzene (50 ml). The benzene solution was stirred a day at room temperature, washed with 2*N* sodium hydroxide, dried and evaporated to give V, yield 80%. Spectral data (ir, nmr, ms) and elemental analyses were identical with those of the product obtained by method A.

Phenyl Thioacetate.

Phenyl thioacetate was obtained according to the procedure of Ralston and Wilkinson (6), bp 110-113° (8 mm), n_D^{20} 1.5706; ir (film): 3380, 3040, 2910, 1705, 1580, 1470, 1440, 1350, 1320, 1300, 1260, 1210, 1190, 1110, 1080, 1060, 1020, 990, 940, 860, 830, 740, 700, 680 cm^{-1} ; nmr (deuteriochloroform): δ 7.33-7.15 (m, 5H arom), δ 2.33 (s, S-CO-CH₃, 3H) ppm; ms: 152 (M⁺, 29), 110 (M - 42, 100), 109 (M - 43, 30), 43 (M - 109, 29).

Anal. Calcd. for C₈H₈OS: C, 63.15; H, 5.26. Found: C, 63.09; H, 5.25.

o-Benzoylthiophenyl Benzoate V ($R = C_6H_5$).

Method A.

This compound was prepared by the same procedure described for V ($R = CH_3$) starting from IIa-c (30 mmoles), benzoyl chloride (65 mmoles) and 20 ml of benzene. The benzene solution was heated for some hours and worked as above for *o*-acetylthiophenyl acetate (V). The resulting crude residue was recrystallized from ethanol to give V ($R = C_6H_5$) as white plates; quantitative yield, mp 65° (lit (2) mp 68°); ir (potassium bromide): 3050, 1740, 1680, 1570, 1470, 1440, 1310, 1270, 1260, 1200, 1170, 1070, 1050, 1020, 880, 750, 700, 670, 640, cm^{-1} ; the nmr spectrum (deuteriochloroform) contained only aromatic signals at δ 8.10-7.30 ppm; ms: 334 (M⁺, 28), 258 (M - 76, 13), 214 (M - 120, 33), 105 (M - 229, 100).

Anal. Calcd. for C₂₀H₁₄O₃S: C, 71.85; H, 4.19. Found: C, 71.63; H, 4.16.

Method B.

Analogously to method B as described for *o*-acetylthiophenyl acetate V ($R = CH_3$), V ($R = C_6H_5$), was prepared, yield 80%, mp 68° mixed mp unaltered by method A. Spectral data (ir, nmr, ms) and elemental analyses coincided well with those of authentic samples obtained by method A and literature procedures (2).

o-Acetylthiophenol IV ($R = CH_3$).

Method A.

To a stirred solution of IIa-c (10 mmoles) in 15 ml of benzene was added dropwise a solution of acetyl chloride (10 mmoles) in 5 ml of benzene. The reaction was allowed to stir for several hours at room temperature

and was then heated at reflux for 1 hour. After cooling, the reaction mixture was poured into 15 ml of an aqueous solution of sodium carbonate and the organic layer was washed with 3 × 10 ml of 2*N* sodium hydroxide, then water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel using petroleum ether 40-70°-diethyl ether (3:1) as solvent. The material was identified as *o*-acetylthiophenyl acetate V ($R = CH_3$) by ir, nmr and ms spectroscopy and these data compared with those of an authentic sample as obtained above. The product was obtained in a yield of 11-13%. The aqueous basic solution, after acidification with dilute hydrochloric acid was extracted with diethyl ether. The ethereal solution was dried over sodium sulfate and evaporated to dryness. The oily residue was chromatographed on a silica gel column using petroleum ether 40-70°-diethyl ether (3:1) as eluent to give IV ($R = CH_3$) in yields of 81-85%. An analytical sample was prepared by microdistillation *in vacuo* bp 122-125° (10 mm), n_D^{20} 1.6097; ir (film): 3470, 3040, 2960, 2920, 1700, 1560, 1470, 1440, 1330, 1280, 1260, 1210, 1150, 1120, 1050, 1030, 920, 830, 730, 670 cm^{-1} ; nmr (deuteriochloroform): δ 7.49-6.68 (m, 4H arom); δ 6.66 (s, 1H, OH, deuterium oxide exchanged), δ 2.16 ppm (s, S-CO-CH₃, 3H); ms: 168 (M⁺, 43), 126 (M - 42, 99), 43 (M - 125, 100).

Anal. Calcd. for C₈H₈O₂S: C, 57.14; H, 4.76. Found: C, 57.06; H, 4.73.

Method B.

This material was prepared by the same procedure described for *o*-acetylthiophenyl acetate, starting with a solution of 2-hydroxythiophenol (I) (30 mmoles), acetylchloride (30 mmoles), triethylamine (30 mmoles) and benzene (20 ml). The benzene solution was stirred at room temperature for 2 hours and filtered. The benzene extracts were washed successively with *N* sodium carbonate, 2*N* sodium hydroxide, water and dried over anhydrous sodium sulfate. After removed of the benzene, the resulting residue was chromatographed on a silica gel column (elution with petroleum ether 40-70°-diethyl ether 3:1) to give *o*-acetylthiophenyl acetate V ($R = CH_3$), yield 26%. This material was identified by bp, tlc, ir, nmr and ms spectroscopy with an authentic sample. The aqueous solution was worked up as described by method A giving *o*-acetylthiophenol (IV) ($R = CH_3$), yield 30%. Spectral data (ir, nmr, ms) and elemental analyses were identical with those of the product obtained from method A.

o-Benzoylthiophenol IV ($R = C_6H_5$).

Method A.

This compound was prepared by the same procedure described above for *o*-acetylthiophenol IV ($R = CH_3$), starting from IIa-c (10 mmoles), benzoyl chloride (10 mmoles) and 20 ml of benzene. The above workup afforded a mixture of compounds which were purified by crystallization. *o*-Benzoylthiophenol (IV) ($R = C_6H_5$), after crystallization from petroleum ether 40-70°, was obtained in 76-79% yields, mp 119° (lit (2) mp 122°); ir (potassium bromide): 3470, 3400, 3040, 1690, 1600, 1580, 1450, 1420, 1320, 1290, 1200, 1170, 1120, 1070, 1020, 930, 800, 750, 680, 660 cm^{-1} ; nmr (deuteriochloroform): δ 8.12-7.38 (m, 9H arom) and δ 7.33 (s, 1H, OH deuterium oxide exchanged); ms: molecular ion, *m/e* 230 (Calcd. 230).

Anal. Calcd. for C₁₃H₁₀O₂S: C, 67.82; H, 4.34. Found: C, 67.93; H, 4.30.

o-Benzoylthiophenyl benzoate V ($R = C_6H_5$) was obtained in 15-17% yield by crystallization of ethanol.

Method B.

o-Benzoylthiophenol IV ($R = C_6H_5$) was also prepared from I (50 mmoles), benzoyl chloride (50 mmoles) and benzene (50 ml) according to the literature procedure (2) until evolution of hydrogen chloride had almost ceased (2 days). In contrast with published data (2) a mixture of compounds of IV and V was obtained with yields of 8% and 6.6%, respectively. Spectral data (ir, nmr, ms) and elemental analyses were identical with those of the product obtained by method A.

o-Benzoylthiophenyl Acetate V ($R = CH_3$ and C_6H_5).

Method A.

To a stirred solution of IIa-c (10 mmoles) and benzene (10 ml) was added dropwise a solution of benzoyl chloride (10 mmoles) in 2 ml of benzene. After heating several hours, to the reaction mixture was added dropwise a solution of acetyl chloride (10 mmoles) in 2 ml of benzene and reflux was continued for several hours. The benzene solution, after washing with aqueous sodium carbonate and water, was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on a silica gel column using petroleum ether 40-70°-diethyl ether (1:1) as an eluent to give V (R = CH₃ and C₆H₅), yield 72%, mp 101-103°; ir (potassium bromide): 3060, 2920, 2840, 1740, 1710, 1680, 1600, 1580, 1470, 1440, 1370, 1310, 1250, 1200, 1100, 1060, 1040, 1020, 940, 900, 840, 820, 780, 750, 700, 680, 640, cm⁻¹; nmr (deuteriochloroform): δ 7.94-7.37 (m, 9H arom.) and δ 2.30 ppm (s, O-CO-CH₃, 3H); ms, molecular ion, m/e 272 (Calcd. 272).

Anal. Calcd. for C₁₅H₁₂O₃S: C, 66.17; H, 4.41. Found: C, 66.22; H, 4.38.

Method B.

A mixture of *o*-benzoylthiophenol IV (30 mmoles), triethylamine (30 mmoles) and acetyl chloride (30 mmoles) in 10 ml of benzene was stirred for several hours at room temperature. The reaction mixture was then filtered and the benzene solution washed with aqueous sodium carbonate and water then dried over anhydrous sodium sulfate. After removal of the solvent, the resulting residue was purified as above, yield 63%, mp mixed mp 101°; ir, nmr and ms are identical with those of a sample prepared by method A.

Reaction of IIa-b with Methylmagnesium Iodide.

To a stirred solution of methylmagnesium iodide (30 mmoles) in 10 ml of dry diethyl ether, a solution of IIa-b (10 mmoles) in 10 ml of benzene was added dropwise under an atmosphere of nitrogen at room

temperature. When the addition was completed, the mixture was stirred under reflux for 2 hours. After cooling, the mixture was hydrolyzed with water and the organic layer dried over anhydrous sodium sulfate. After removal of the solvent, the resulting residue was distilled under reduced pressure to give 2-hydroxythiophenol (I) in excellent yield, bp 105-107° (15 mm) lit (7) bp 113 (13 mm).

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