Removal of Thioacetal Protecting Groups by Benzeneseleninic Anhydride

By **Nigel J. Cussans** and **Steven V. Ley,*** Department of Chemistry, Imperial College, London SW7 2AY
Derek H. R. Barton, Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

A number of thioacetals were deprotected with benzeneseleninic anhydride in good yield. The reaction worked particularly well for hindered spiro-1,3-ditholans of 2,2,6-trimethylcyclohexanone and fenchone, and in examples where other literature methods had failed.

THE deprotection of thioacetals to the corresponding carbonyl compounds is an important synthetic transformation. While many procedures [1] are known to effect this transformation, new methodology is required particularly for examples which react poorly by these literature routes.

Here we report full details of the use of benzeneseleninic anhydride,[2] $[PhSe(O)]_2O$, as a suitable new reagent for the conversion of thioacetals (mainly 1,3-dithiolans) into carbonyl derivatives. A series of spiro-1,3-dithiolans (1)—(9), were prepared by standard methods [3] and separately treated with benzeneseleninic anhydride (1.1 equiv.) at room temperature. In the majority of cases the recovery of the corresponding carbonyl derivative was good. However for a number of the reactions studied additional comment is required.

RESULTS AND DISCUSSION

The results show that the anhydride is particularly efficient at removing hindered spiro-dithiolans, although slightly higher temperatures are usually needed. Thus at 50 °C both 2,2,6-trimethylcyclohexane- and fenchane-spiro-1,3-dithiolans [compounds (6) and (7)] readily afforded the parent ketones.

Also of special importance was the observation that the spiro-dithiolans (8) and (9) were equally easily deprotected with the anhydride, whereas all the literature methods we had tried failed. These failures were probably due to the high steric hindrance of the acetal moiety and to the extreme lability of the hydroxy-group in (9) towards dehydration. Some idea of the low reactivity of these particular acetals was indicated by the observation that (8) did not react at room temperature with methyl fluorosulphonate, normally an excellent reagent for deprotection of recalcitrant spiro-dithiolans. Only on warming to 40 °C did deprotection proceed. However concomitant aromatisation of ring B led to the formation of (10),[4] which was subsequently isolated in 37% yield.

For comparison we also studied the deprotection of a limited number of spiro-1,3-oxathiolans. Generally these reactions with the anhydride were faster, and phenylselenated by-products were also often isolated. Cholest-3-one-1,3-oxathiolan (11) for example gave, apart from a mixture of cholestanone and cholest-1-en-3-one, an additional product which was shown by its spectral characteristics to be (12); the formation of this has literature precedence. On the other hand the spiro-1,3-oxathiolan (13) gave 2-(phenylseleno)cyclohexanone (14) as one of the by-products.

In order to test whether benzeneseleninic anhydride would also be useful for the deprotection of spiro-dithians we showed that (15) afforded cholestanone (73%) at room temperature, although at a much slower rate than the spiro-dithiolan analogue.

The general deprotection reaction proceeds well in many different solvents, namely tetrahydrofuran, dichloro-, trichloro-, and tetrachloro-methane, benzene, and chlorobenzene. While pyridine is compatible with the reagent, other common nitrogen-containing solvents are less satisfactory. A hydrolytic work-up was not essential and the formation of the corresponding carbonyl derivative during the course of the reaction could be monitored by i.r. or n.m.r. spectroscopy. Titrimetric analysis of the reaction mixtures showed that all the oxidising power of the anhydride was consumed during the reactions.

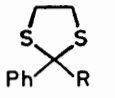
That initial reaction did not involve the conversion of a dithiolan sulphur atom into a sulphoxide by the anhydride was demonstrated as follows. First 2,2-diphenyl-1,3-dithiolan 1-oxide, and others, were inert towards the anhydride. Second, benzeneseleninic anhydride failed to transfer oxygen to simple sulphides and selenides such as diphenyl sulphide, diphenyl selenide, or dibenzyl sulphide even in boiling tetrahydrofuran over an extended period of time (1 week).

The diphenyl diselenide formed as the major by-product of the reactions could be easily isolated and re-oxidised to the anhydride.[6]

Examination of the reaction in an e.s.r. cavity failed to show the presence of radical species although we recognise they cannot be excluded as possible reaction intermediates. Unlike other methods of deprotecting dithioacetals the oxygen in the carbonyl group of the product does not come from water but from the reagent itself. Thorough drying of solvent and of reagents did not change the rate of reaction or the nature of the products.

The departing sulphur residue in the spiro-1,3-dithiolan reactions was converted into a white insoluble polymer. This polymer could be isolated from the reaction of 2,2-dimethyl-1,3-dithiolan (16) with the anhydride. Elementary combustion analysis of the polymer suggested an empirical molecular formula between $C_2H_4S_2O$ and $C_2H_4S_2O_2$, the latter being closer to the found value, although difficulties in purification

were noted. The ^1H n.m.r. spectrum in [$^2H_5$]pyridine showed only a complex envelope at δ 3.21—2.79 and the i.r. spectrum showed absorptions at 1 320 (SO_2 symm) and 1 125 (SO_2 asymm) cm^{-1}. These data are consistent with the sulphide–sulphone polymer $(-SCH_2CH_2SO_2-)_n$. Indeed these parameters were very similar to the peracid oxidation product obtained from poly(ethylene disulphide).[7]

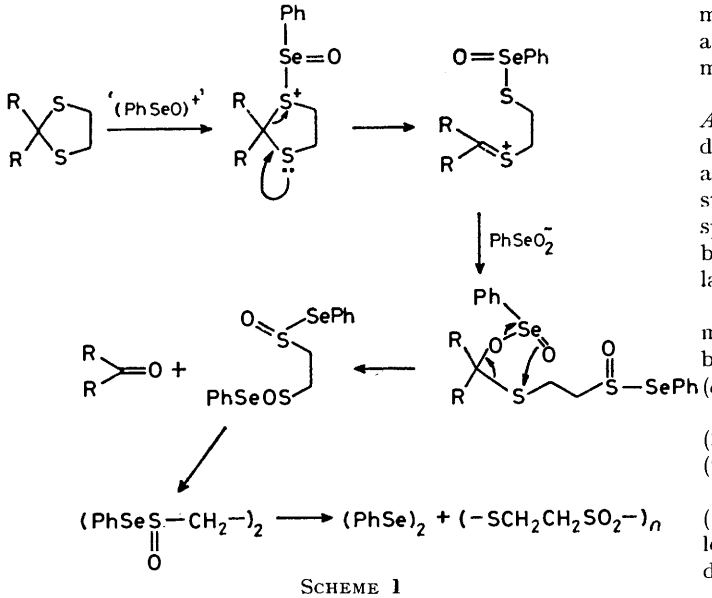


(16)

We suggest the mechanism outlined in Scheme 1 to account for these, and other, observations; this scheme is slightly different from our preliminary proposal.[2] We now postulate a rapid transfer of oxygen from selenium to sulphur in the reaction, [–S–Se(O)–Ph]⟶[–S(O)–Se–Ph]. This proposed rearrangement has a good driving force (S=O is stronger than Se=O) and may proceed through an intermediate (–S–O–SePh), the formation of which would be reversible. The fragmentation of $[PhSeS(O)CH_2]_2$ to give diphenyl diselenide and polymer may be a radical process. The –S(O)–Se– bond must be weak like that of –S(O)–S–. The overall driving force for the reaction is clearly the transfer of oxygen from selenium to sulphur.

Acyclic dithioacetals also react with the anhydride to afford the carbonyl derivative. However, the yield of recovered diphenyl diselenide can be as low as 20% due to the departing sulphur moiety containing a phenylseleno-residue. The dithioacetal (17) produces a 52% yield of cholestanone and a phenylselenated product later shown to be identical with that obtained from reaction of (18) with the anhydride. This phenyl-

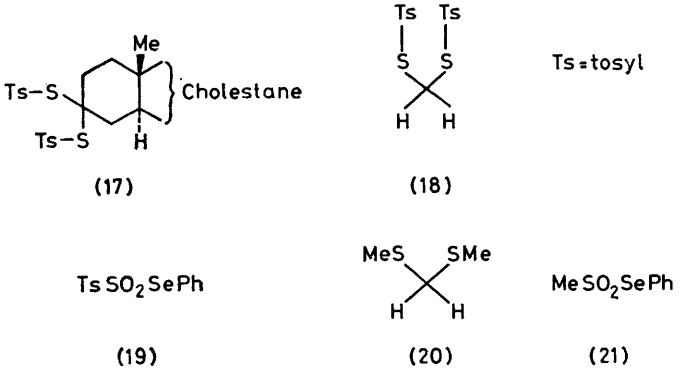
selenated product was assigned the structure (19) on the basis of its spectral and analytical data, and by comparison with an authentic sample.[8] In a similar fashion the dithioacetal (20) gave (21) on treatment with the anhydride.



SCHEME 1

The formation of these phenylselenated products is not entirely clear, although it is reasonable to speculate that a similar mechanism operates to that in the cyclic dithioacetals, *i.e.* initial reaction of the anhydride affords an intermediate which could break down to give (22). This compound could rearrange to (23) and finally by oxygen transfer, possibly from the anhydride, could lead to (19) (Scheme 2).

We have shown that benzeneseleninic anhydride is a suitable new reagent for the deprotection of thioacetals, particularly those in hindered environments, and also in some cases when conventional methods failed. Recent



(17) (18) (19) (20) (21)

work has also shown that the anhydride will deprotect diselenoacetals more efficiently than other methods.[9]

EXPERIMENTAL

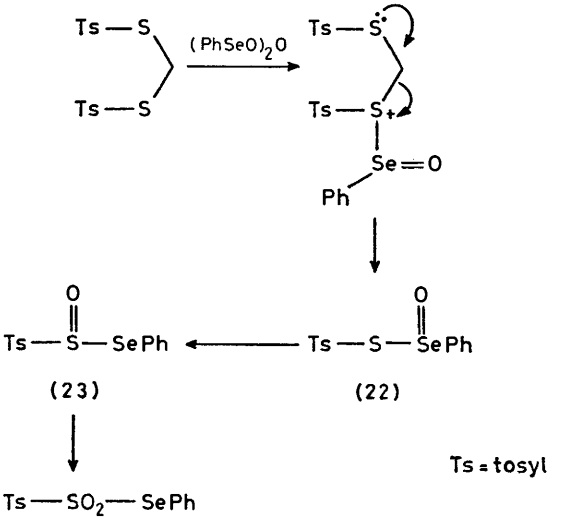
M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were obtained for solutions in $CDCl_3$ ($SiMe_4$ as internal standard) at 60 MHz. Thin layer and preparative layer chromatography were carried out on silica gel (Merck GF_{254} Type 60). Light petroleum refers to the fraction of b.p. 40—60 °C. Solutions were dried over magnesium sulphate, and solvents by standard techniques. Benzeneseleninic anhydride was prepared by the literature method.[6] The thioacetals were prepared by standard methods.[3] All the carbonyl products were compared with authentic samples, usually by ^{1}H n.m.r., i.r., t.l.c., g.l.c., and m.p. where appropriate.

General Procedure for the Reaction of Benzeneseleninic Anhydride (BSA) with Thioacetals.—The thioacetal was dissolved in dry tetrahydrofuran and benzeneseleninic anhydride (1.1 mol equiv.) added in one portion to the stirred reaction mixture maintained under an inert atmosphere at room temperature. The reaction was monitored by t.l.c. and the products worked up, usually by preparative layer chromatography (p.l.c.).

Reaction of (1). Compound (1) (80 mg) with BSA (174 mg) in THF (3 ml) after 40 min gave benzaldehyde; (*a*) 34% by p.l.c., (*b*) 78% as the 2,4-dinitrophenol derivative, and (*c*) 92% by g.l.c.

Reaction of (2). Compound (2) (152.6 mg) with BSA (234.4 mg) in THF (15 ml) after 2 h gave benzophenone (99.9 mg, 93%).

Reaction of (3). Compound (3) (81.8 mg) with BSA (146 mg, 0.41 mmol) in THF (3 ml) after 30 min gave tetralone; (*a*) 25% by p.l.c., (*b*) 65% as the 2,4-dinitrophenol derivative, and (*c*) 70% by g.l.c.



SCHEME 2

Reaction of (4). Compound (4) (182.1 mg) with BSA (378 mg) after 18 h gave cyclohexanone, 59% by g.l.c.

Reaction of (5). Compound (5) (115 mg) with BSA (98.2 mg) in CH_2Cl_2 (3 ml) after 1 h gave 5α-cholestan-3-one (69.1 mg, 72%).

Reaction of (6). Compound (6) (54.6 mg) with BSA (91 mg) after 18 h at 50 °C gave 2,2,6-trimethylcyclohexanone, 63% by g.l.c.

Reaction of (7). Compound (7) (57 mg) with BSA (90 mg) after 18 h at 50 °C gave fenchone, 78% by g.l.c.

Reaction of (8). Compound (8) [10,11] (63.3 mg) with BSA (60 mg) in CH_2Cl_2 (2 ml) after 3.5 h gave 6aα,12aα-dihydro-1-phenylnaphthaceno[1,12-*bc*]furan-6,12(7*H*)-dione (23 mg, 63%), m.p. 225 °C (decomp.) (lit.,[4] 234—235 °C), $\nu_{max.}$ 1 700

cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 260 (ε 42 300), 275 (sh) (29 600), 280 (sh) (26 100), 295 (24 200), 305 (sh) (20 500), and 360 nm (17 800); δ 8.0—7.2 (12 H, m), 4.78 (1 H, d, *J* 7 Hz), and 4.1—3.1 (3 H, m).

Reaction of (9). Compound (9) † (17.5 mg) with BSA (17.6 mg) in CH_2Cl_2 (1 ml) containing pyridine (3 drops) after 5 h gave 6,6aα,7,12aα-tetrahydro-6β-hydroxy-6α-methyl-1-phenylnaphthaceno[1,12-*bc*]furan-12-one (7.4 mg, 51%), m.p. 180—182 °C (lit.,[13] 180—183 °C); $\nu_{max.}$ 3 400 and 1 680 cm^{-1}; $\lambda_{max.}$ 245 (ε 23 300), 298 (sh) (25 900), 311 (28 200), and 325 (sh) nm (16 300); δ 8.0—7.2 (12 H, m), 4.42 (1 H, d, *J* 5 Hz), 3.4—3.2 (2 H, m), 2.8 (1 H, m), and 1.75 (3 H, s).

Reaction of (11). Compound (11) (282.8 mg) with BSA (251.3 mg) in THF (5 ml) after 23 h gave: (*a*) 2-(*phenylseleno*)*cholest*-1-*en*-3-*one* (12) (69.8 mg), m.p. 128—129 °C (from light petroleum); $\nu_{max.}$ 2 900, 2 850, 1 665, 1 590, 1 440, and 1 030 cm^{-1}; $\lambda_{max.}$ 215 (ε 9 500), 235 (sh) (4 070), 265 (2 300), and 320 nm (750); *m/e* 540 (M^+), and 383, *m** 272 (calc. for 540→383: *m**, 271.65); $[\alpha]_D$ −5.5° (Found: C, 73.1; H, 9.15. $C_{33}H_{48}OSe$ requires C, 73.4; H, 9.0%): and (*b*) a mixture of 5α-cholestan-3-one and cholest-1-en-3-one (30.4 mg) by ^{1}H n.m.r. and i.r. comparison with authentic samples.

Reaction of (13). Compound (13) (159.7 mg) with BSA (364 mg) after 7.5 h gave cyclohexanone, 55% by g.l.c. In a separate experiment compound (13) (534 mg, 3.37 mmol) with BSA (1.224 g, 3.4 mmol) in THF (8 ml) after 1 h gave, as well as cyclohexanone and diphenyl diselenide, 2-(phenylseleno)cyclohexanone (14) (340 mg, 40%); $\nu_{max.}$ 1 700 cm^{-1}; δ 7.67—7.13 (5 H, m), 3.9 (1 H, t, *J* 5 Hz), and 2.7—1.5 (8 H, m).

Reaction of (15). Compound (15) (255 mg) with BSA (213 mg) in THF (7 ml) after 16 h gave 5-α-cholestan-3-one (150.6 mg, 73%), m.p. 128 °C.

Reaction of (16). Compound (16) (533.2 mg) was treated with BSA (1.435 g) in THF (6 ml). After 45 min evaporation of the solvent (and acetone produced) gave a yellow oil. Treatment with Et_2O–light petroleum gave a yellow solution and an insoluble powder (319 mg); $\nu_{max.}$ (KBr disc) 1 320 and 1 125 cm^{-1}, δ([$^2H_5$]pyridine) 3.21—2.79 (complex CH_2 resonances). The yellow solution yielded diphenyl diselenide (1.154 g, 93%), m.p. 61—62 °C.

Reaction of (17). Compound (17) (258 mg) with BSA (161.5 mg) in THF (10 ml) after 2 h and 18.5 h at 40 °C gave (*a*) compound (19) (see later) and (*b*) 5α-cholestan-3-one (161 mg, 52%), m.p. 128 °C.

Reaction of (18). Compound (18) (2.178 g) with BSA (3.03 g) in THF (10 ml) at 55 °C for 16.5 h gave *p*-tolyl phenylselenenyl sulphone (19) (1.42 g, 55%), m.p. 78—79 °C (lit.,[8] 77—78 °C); $\nu_{max.}$ (KBr disc) 1 590, 1 080, and 1 135 cm^{-1}; δ 7.5—7.0 (9 H, m) and 2.32 (3 H, s); *m/e* 312 (M^+), 247, 232, 157, 139, and 91 (Found: C, 50.4; H, 3.8; S, 11.6. Calc. for $C_{13}H_{12}O_2SSe$: C, 50.15; H, 3.9; S, 10.3%).

Reaction of (20). Compound (20) (338.2 mg) with BSA (933.5 mg) in THF (6 ml) after 17 h gave methyl phenylselenenyl sulphone (21) (573.5 mg, 78%) which on crystallisation (benzene–light petroleum) gave pure (21) (325 mg), m.p. 84—85 °C; $\nu_{max.}$ (KBr disc) 1 470, 1 435, 1 400, 1 300, 1 180, 1 120, 1 060, 1 020, 1 000, 955, 915, 750, 740, 700, and 665 cm^{-1}; δ 7.9—7.68 (2 H, m), 7.57—7.33 (3 H, m), and 3.27 (3 H, s), *m/e* 236 (M^+), 173, 171, 157, 117, 115, 77, and 64 (Found: C, 35.75; H, 3.4. $C_7H_8O_2SSe$ requires C, 35.75; H, 3.4%).

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† Prepared by addition of methyl-lithium to (8).

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