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RING EXPANSION REACTIONS OF 1,3-DITHIOLANS AND 1,3-DITHIANS. A NEW SYNTHESIS OF DIHYDRO-1,4-DITHIINS AND DIHYDRO-1,4-DITHIEPINS

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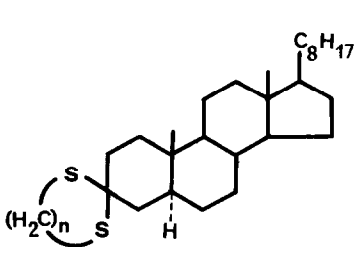
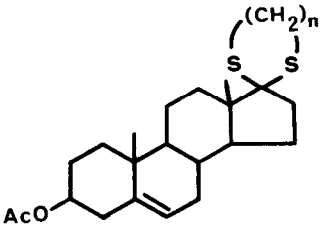
Summary: A mild and convenient method for ring expansion of 1,3-dithiolans and 1,3-dithians to dihydro-1,4-dithiins and dihydro-1,4-dithiepins, respectively, using phenyl selenenyl chloride in methylene chloride is described. A mechanism involving sulphenyl chloride derivatives as intermediates is proposed.

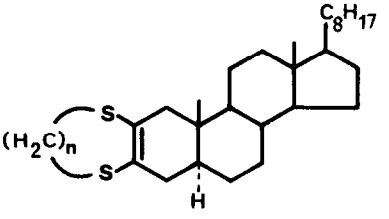
The synthetic methods available for the synthesis of dihydro-1,4-dithiins starting from 1,3-dithiolans are limited to i) neutral or acid-catalyzed thermal rearrangements[1,2] of 1,3-dithiolan-1-oxides, prepared by selective oxidation of ethylenethioketals, and ii) reaction of 1,3-dithiolans with ethyl N-chlorocarbamate.[3] In addition, a survey of the existent literature indicates only one precedent for ring-expansion of 1,3-dithians to dihydro-1,4-dithiepins, in low yield.[2]



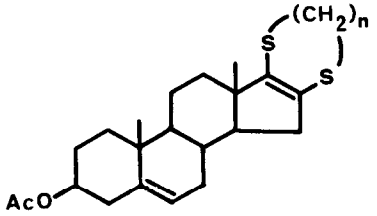
1a,b



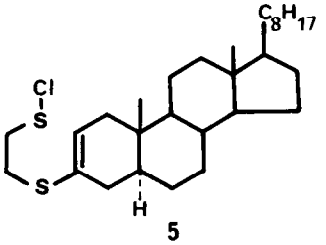
2a,b



3a,b



4a,b



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a n = 2
b n = 3

In view of the synthetic value of these transformations we wish to report a novel one-step synthesis of steroidal dihydro-1,4-dithiins and dihydro-1,4-dithiepins by reaction of ethylenethioketals and propylenethioketals with phenyl selenenyl chloride.

Results are shown in Table,[4] and a typical experiment is described as follows: to a cold solution (0 °C) of 1,3-dithiolan (1a) (1 mmol) in methylene chloride (30 ml) was added dropwise while stirring phenyl selenenyl chloride (2.1 mmol) in methylene chloride (13 ml) for 15 min. The solution was then stirred for 10 min., poured into aqueous sodium hydrogen carbonate and extracted with methylene chloride. Silica gel column chromatography of the residue (eluant n-hexane:benzene, 8:2) gave the dihydro-1,4-dithiin (3a) in 74% yield.

The reactions summarized in the Table proceed smoothly in high yield and they are eventually applicable to complex molecules, being compatible with the presence of a wide variety of functional groups. The sole by-product isolated is the corresponding ketone in the case of 1,3-dithians (entries IV and VI). Also, it should be noted that two moles of phenyl selenenyl chloride per mole of thioketal are needed in order to complete the reaction (compare entries I and II).

The dihydro-1,4-dithiepin (4b) was also synthesized, but in lower yield (35%), starting from (2b) by the known[1] two-step sequence that begins with the oxidation of (2b) (MCPBA), followed by the acid-catalyzed thermolysis of the resulting monosulphoxide (PTSA in benzene).

The mechanism of this new ring expansion reaction can be rationalized in terms of the formation of a sulphenyl chloride intermediate B (Scheme). Indeed, the sulphenyl chloride (5) was obtained when the 1,3-dithiolan (1a) was allowed to react with phenyl selenenyl chloride in milder conditions (entry III). The double bond in (5) is located between C-2 and C-3, as inferred by the shape of the signal of the vinylic proton in its ^{1}H NMR spectrum (m, $W_{1/2}$ 16 Hz at δ 5.70).[5] Compound (5) is thermically stable (reflux in cyclohexane for 12 h), but in the presence of hydrogen chloride[6] at 0 °C gave smoothly a 2:3 mixture of (3a) and (1a). The dihydro-1,4-dithiin (3a) is exclusively formed when the treatment with hydrogen chloride is performed in the presence of diphenyl diselenide (1 mol-eq.).

TABLE. Ring expansion of thioketals with PhSeCl

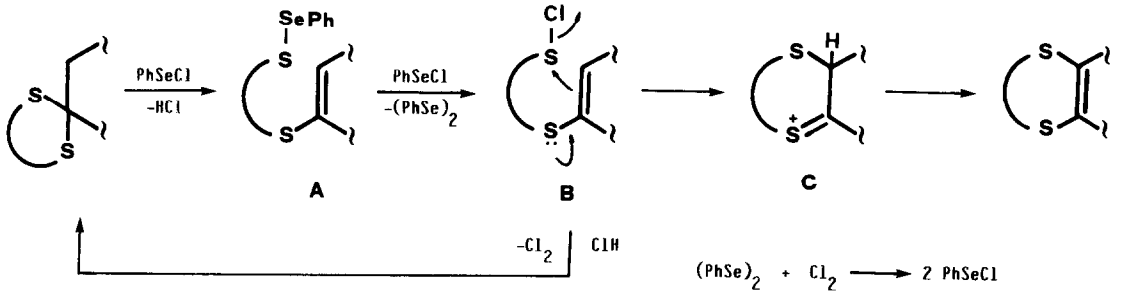
Entry	Thioketal	Mol-eq. of PhSeCl	Conditions Temp.(°C); Time (min.)	Product (yield%)
I	1a	2.1	0 ; 25	3a (74)
II	1a	1.1	0 ; 60	3a (35); 1a (50)
III	1a	1.3	-80 ; 50	5 (33); 1a (30)
IV	1b	2.1	0 ; 60	3b (56)[a]
V	2a	2.1	0 ; 45	4a (81)
VI	2b	2.1	0 ; 45	4b (90)[b]

a) Cholestan-3-one (27%) is also obtained.

b) Androst-5-en-17-one-3β-yl acetate (6%) is also obtained.

All these results are in agreement with the proposed mechanism shown in the Scheme.

Scheme



Reaction of the thioketal with PhSeCl leads to the sulphenyl selenide A[7] which reacts further with a second molecule of PhSeCl to produce the sulphenyl chloride B. The subsequent intramolecular interaction of the sulphenyl chloride and the olefinic carbons takes place in two ways: i) to form the starting thioketal and chlorine which in situ reoxidizes the diphenyl diselenide allowing the reaction to go to completion,[8] and ii) to produce the ring-expansion product by acid-catalyzed electrophilic addition[9] through the sulphur-stabilized cationic intermediate C.

Acknowledgements

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4. Compound (3a): m.p. 174-5 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 0.64 (3H, s, 13-Me), 0.80 (3H, s, 10-Me), 0.85 (6H, d, J 7 Hz, 25-Me), 3.16 (4H, s, -CH_2-S-); ^{13}C NMR ($CDCl_3$) δ 118.55, 118.1 (2-C, 3-C); MS m/z 460 (M^+, 100%).

   Compound (3b): m.p. 118-120 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 0.62 (3H, s, 13-Me), 0.72 (3H, s, 10-Me), 0.84 (6H, d, J 7 Hz, 25-Me), 0.87 (3H, d, J 7 Hz, 20-Me), 2.67, 2.77 (total 2H, each m, $W_{1/2}$ 10 Hz, -CH_2-S-), 3.70 (2H, m, $W_{1/2}$ 35 Hz, -CH_2-S-); ^{13}C NMR ($CDCl_3$)δ 127.65, 127.04 (2-C, 3-C); MS m/z 474 (M^+, 100%).

Compound (4a): m.p. 189-191 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, s, 13-Me), 1.00 (3H, s, 10-Me), 1.99 (3H, s, OAc), 3.09 (4H, s, -CH_2-S-), 4.6 (1H, m, $W_{1/2}$ 30 Hz, 3-H), 5.3 (1H, m, $W_{1/2}$ 15 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ 120.36 (16-C, 17-C), 122.3 (6-C), 140.2 (5-C); MS m/z 404 (M^+, 100%), 389 (M^+-Me, 60%).

Compound (4b): m.p. 225-7 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s, 13-Me), 0.99 (3H, s, 10-Me), 1.99 (3H, s, OAc), 2.3 (4H, m, $W_{1/2}$ 40 Hz, -CH_2-S-), 4.6 (1H, m, $W_{1/2}$ 30 Hz, 3-H), 5.3 (1H, m, $W_{1/2}$ 15 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ 128.7, 142.05 (16-C, 17-C), 122.3 (6-C), 140.2 (5-C); MS m/z 418 (M^+, 30%), 403 (M^+-Me, 100%).

Compound (5): m.p. 112-4 °C (n-pentane/acetone); ^{1}H NMR ($CDCl_3$) δ 0.63 (3H, s, 13-Me), 0.71 (3H, s, 10-Me), 0.83 (6H, d, J 7 Hz, 25-Me), 0.87 (3H, d, J 7 Hz, 20-Me), 2.8 (4H, m, $W_{1/2}$ 40 Hz, -CH_2-S-), 5.70 (1H, m, $W_{1/2}$, 16 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ 125.8 (2-C), 129.15 (3-C); MS m/z 462 (100%), 460 (40%).

5. The assigned disposition of the sulphur atoms in compounds (3a) and (3b) is consistent with the structure of the sulphenyl chloride intermediate (5).

6. A solution of compound (5) (1 mmol) in methylene chloride (50 ml) was treated at 0 °C with a saturated solution of hydrogen chloride in methylene chloride (5 ml) for 1 h.

7. In the experiment corresponding to entry III, an unstable third compound was also obtained in 10% yield. Its H NMR spectrum is consistent with a structure of type A δ 5.60 (1H, m, $W_{1/2}$ 16 Hz, 2-H) and 7.2, 7.6 (total 5H, each m, Ph) .

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