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Reductive Cleavage and Ring Expansion of Thiochromane and Benzodihydrothiophene

Theodore Cohen*, Fangping Chen, and Tomasz Kulinski

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Saverio Florio* and Vito Capriati

Dipartimento Farmaco-Chimico, Università di Bari, Via Orabona 4, 70125 - Bari, Italy

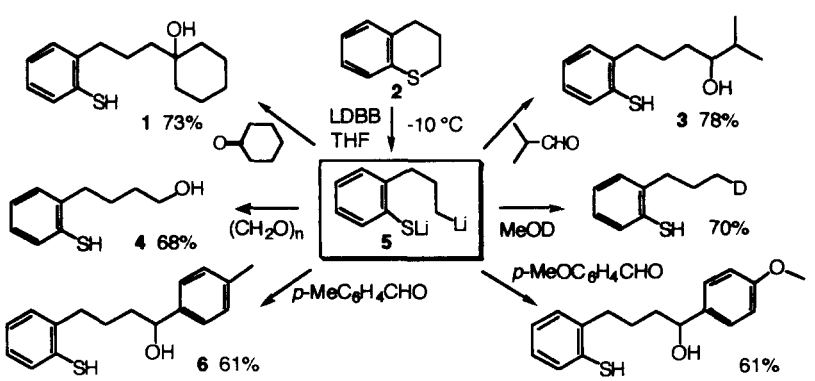
Abstract: Reductive ring cleavage of thiochromane and benzodihydrothiophene by the radical-anion 4,4'-di-*tert*-butylbiphenylide (LDBB) leads to organolithium compounds bearing a lithium arylthiolate group. The adducts of the latter with aldehydes and ketones undergo ring closure when treated under appropriate acidic conditions. The result is a two-pot one-carbon substitutive ring expansion of the original sulfur heterocycle.

The reductive cleavage of compounds bearing the phenylthio group by aromatic radical anions[1] is emerging as one of the most powerful methods known for the preparation of synthetically useful organolithium compounds (eq 1).[2] In this communication and in an accompanying one from these laboratories,[3] the first cases of ring cleavage of sulfur heterocycles by reductive lithiation are reported. The other deals with the reductive cleavage of benzo-1,3-thiazoline to generate α-aminocarbanions. The present communication reports the reductive cleavage of thiochromane (**2**) and benzodihydrothiophene (**13**) to yield ring-opened dianions and the ring closure of the latter to produce ring expanded versions of the starting heterocycles.

$$R\text{–}SPh \;+\; 2\,(ArH^{\bullet-}Li^{+}) \longrightarrow RLi \;+\; PhSLi \qquad (1)$$

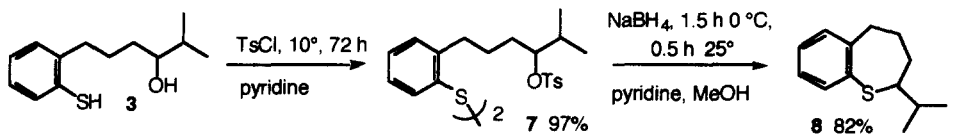
The reductive cleavage of thiochromane by lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[4] occurs in a fashion similar to that of the non-cyclic cases except that a considerably higher temperature than the -78° usually used is required for the thiochromane. Presumably, the requirement of a higher temperature is due to the difficulty that the rigid molecule has in attaining the proper stereoelectronic arrangement. The resulting dianion **5** was captured with deuteromethanol and by cyclohexanone and four different aldehydes, including formaldehyde, to yield alcohols bearing the arylthiol grouping in satisfactory yields (Scheme 1).

Scheme 1

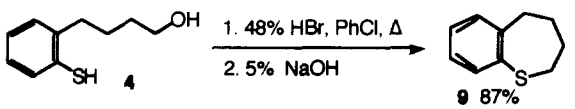


By transforming the hydroxyl group into a good leaving group, it was possible to cause its intramolecular displacement by sulfur to yield a benzothioepine. The first method tried was tosylation of the alcohol. Not surprisingly, the thiolate group also became tosylated and the benzenesulfinate group was displaced from the sulfur by another thiolate molecule leading to the disulfide **7** (Scheme 2). However it was not difficult to reductively cleave the disulfide with sodium borohydride leading to immediate ring closure to the benzothioepine **8** in good yield.

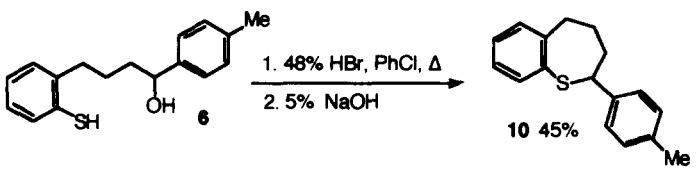
Scheme 2



We then sought a ring expansion which was more efficient than the three-pot one described above. This was accomplished using two different procedures depending on the structure of the ring opened alcohol. In the case of **4** and **6**, treatment with concentrated hydrobromic acid converted the alcohol to an alkyl bromide (not isolated) which partially ring closed without further treatment. However, the addition of aqueous sodium hydroxide completed the process and allowed high yield ring closures (eq 2 and 3).

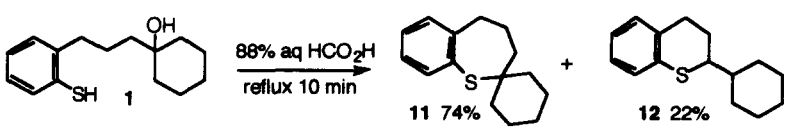


(2)



(3)

In the case of the tertiary alcohol **1**, ring closure was accomplished by heating at reflux for a short time in concentrated formic acid (eq 4). The minor product **12** from this ring closure is presumably formed by protonation of the exo elimination product. Protonation to form the tertiary cation, that would lead to **11**, is undoubtedly favored but the less stable secondary carbocation, formed upon the other mode of protonation, must ring close far faster.

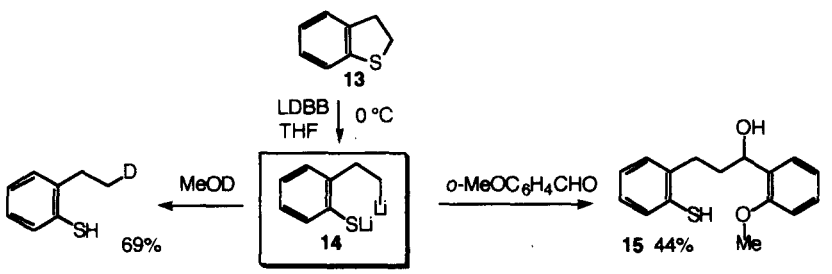


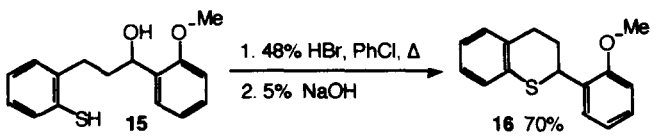
(4)

The reductive cleavage of benzodihydrothiophene **13** required a somewhat higher temperature than that of the thiochromane as expected by the greater rigidity of the system. The final result, however, was similar. Quenching of the resulting dianion **14** with deuteromethanol provided a 69% yield of deuteriated 2-

ethylthiophenol (Scheme 3). The dianion could also be captured with *o*-anisaldehyde. The adduct **15** can be ring closed using the hydrobromic acid treatment (eq 5).

Scheme 3





(5)

It is thus clear that organolithiums bearing adjacent arenethiolate groups can be prepared by reductive cleavage of thiochromane and benzodihydrothiophene. These dianions can be captured by aldehydes and ketones and the resulting adducts undergo ring closure under appropriate acidic conditions. Thus, compounds **9-11** and **16** are the results of a two-pot ring expansion[5] of the sulfur heterocycle fused to a benzene ring. Since the starting materials **2** and **13** are readily available,[6,7] these ring expansions should be attractive as methods for the synthesis of the larger rings. Thiochromanes and benzothioepins have been reported to possess biological activity[8] and both are difficult to prepare.[9,10]

Typical Procedures

Reductive lithiation of 2 and capture of the carbanion with formaldehyde: To a preformed solution of LDBB (1.0 mmol)[4a] at -10 °C, thiochromane (65 mg, 0.43 mmol, in 2 mL of THF) was added dropwise. The reaction mixture was stirred at -15 to -10 °C for 15 min. The color of the solution changed from dark blue to dark red. The reaction mixture was cooled to -78 °C and paraformaldehyde (35 mg, 1.1 mmol, in 2 mL of THF; dried under high vacuum overnight) was added. The mixture was allowed to warm to 0 °C in an ice bath and worked up by equilibration between ether and water followed by evaporation of the dried extract. Flash chromatography (5% - 10% EtOAc/hexanes) gave recovered DBB and the product **4** (158 mg, 73%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.29-7.04 (m, 4 H, Ar), 3.71 (t, J = 6.4, 3 H, C*H*OH), 3.32 (s, 1 H, SH), 2.71 (t, J = 7.2 Hz, 2 H, benzylic), 1.77-1.62 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 142.1, 130.69, 130.30, 129.57, 126.65, 126.04, 62.62, 34.21, 32.33, 25.75.

Ring closure of primary alcohol 4: Chlorobenzene (2 mL), **4** (23 mg, 0.126 mmol) and 0.5 mL of 48% aq. HBr were mixed and heated to reflux for 20 hr. According to TLC, all of the **4** reacted and there were two spots. One may be the bromide, and the other the cyclized product **5**. The reaction mixture was treated with 5 mL of 5% aq. NaOH and 2 mL of ether was added. After the reaction mixture had been stirred at 25 °C for 15 min, the more polar spot disappeared on TLC. The reaction mixture was extracted with ether and the organic layer was dried over $MgSO_4$. The solvent was removed by rotory evaporation. Flash chromatography (hexanes) gave the product (18 mg, 87%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.54 (d, J = 7.2, 1 H, Ar), 7.27-7.01 (m, 3 H, Ar), 3.04 (m, 2 H, C*H*$_2$SAr), 2.75 (m, 2 H, benzylic), 2.11 (m, 2 H), 1.71 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 147.62, 137.10, 133.00, 129.79, 127.79, 126.07, 36.81, 34.43, 32.66, 27.41; HRMS: calc. for $C_{10}H_{12}S$ M^+ 164.0660, found 164.0659.

Ring closure of tertiary alcohol 1: Alcohol 1 (50 mg, 0.20 mmol) was mixed with 5 mL of 88% formic acid. After the reaction mixture had been stirred at 25 °C for about 30 min, some of **1** was still unreacted. The solution was heated to reflux under argon for 10 min. The reaction mixture was extracted with ether. The organic layer was washed by 5% aq. NaOH and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation. Flash chromatography (hexane) gave **11** (37mg, 74%) as a white solid and **12** (11mg, 22%) as a light yellow oil. **11**: ^1H NMR ($CDCl_3$): δ 7.49 (d, J = 7.8, 1 H, Ar), 7.23-7.08 (m, 3 H, Ar), 2.98 (m, 2 H, benzylic), 1.91-0.84 (m, 14 H); ^{13}C NMR ($CDCl_3$): δ 148.26, 134.80, 133.15, 129.04, 128.11, 126.17, 49.17, 46.23, 36.43, 26.20, 22.67, 21.57; HRMS: calc. for $C_{15}H_{20}S$ M^+ 232.1286, found 232.1272. **12**: ^1H NMR ($CDCl_3$): δ 7.22-6.93 (m, 4 H, Ar), 3.17 (m, 1 H, CHSAr), 2.91-2.71 (m, 2 H, benzylic), 2.22 (m, 1 H, methinyl of cyclohexane), 2.00-0.86 (m, 12 H); ^{13}C NMR ($CDCl_3$): δ 129.43, 126.65, 126.42, 123.80, 48.62, 42.84, 30.21, 26.79, 26.56, 26.43, 26.37; HRMS: calc. for $C_{15}H_{20}S$ M^+ 232.1286, found 232.1316.

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