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LETTERS

Functionalization of Thiocrown Ethers Containing the Thioacetal Unit

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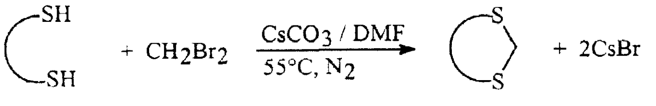
Abstract: Thiocrown ethers containing thioacetal units are readily prepared by reaction of the cesium salts of long chain dithiols with methylene dibromide. Preparation of the trimethylsilyl derivatives followed by condensation with aldehydes under basic conditions (Peterson reaction) leads to the expected macrocycles with exocyclic double bonds at the thioacetal carbon atom. © 1998 Elsevier Science Ltd. All rights reserved.

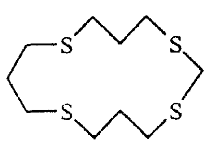
Many macrocyclic thioethers (thiocrown ethers) have now been prepared; the structural relationships between size, shape and complexing ability are becoming relatively clear.[1] Convenient syntheses of the requisite macrocycles can be accomplished by ring-closure using cesium thiolates in dimethylformamide (DMF).[2]

We have described the syntheses of thiocrown ethers provided with thioacetal linkages,[3] which should be appropriate points for functionalization if the chemistry of 1,3-dithiane is used as a model.[4-8] We report here a) an improved method for obtaining thiocrown ethers containing a thioacetal unit,[3] b) the use of this functionality in Peterson olefination reactions[4] and c) examples of further functionalization of the addition products.

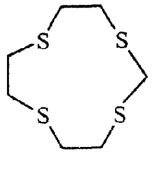
In our hands the cesium mediated, and twice repeated, nucleophilic substitution on methylene bromide shown in eq 1 provides easy access to the desired macrocycles. Examples of compounds prepared are **1-5**.[9]



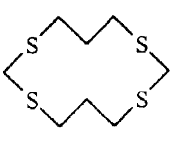
(**eq. 1**)



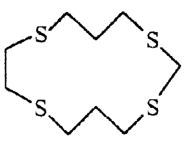
1 (75%)



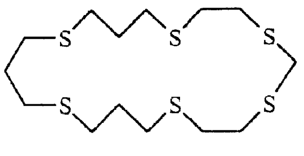
2 (67%)



3 (68%)



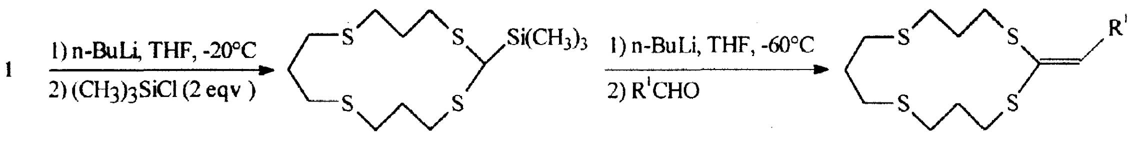
4 (54%)



5 (75%)

PII: S0040-4039(98)01308-2

In most instances **1** has been used for investigation of possibilities for functionalization. The Peterson reaction was carried out by initial silylation of **1** followed by purification of product **6**;[10] treatment with n-C$_4$H$_9$Li followed by aldehyde led to the formation of, as examples, **7a-f** (eq 2).[11]

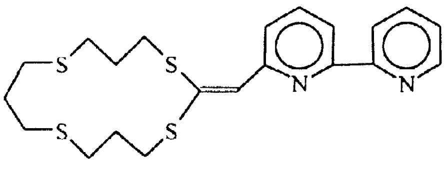


6 (70%)

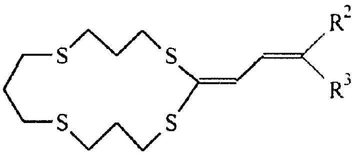
7

(eq. 2)

a) R^1 = C$_6$H$_5$ (53%)
b) R^1 = 2-thienyl (50%)
d) R^2 = C$_6$H$_5$, R^3 = H (75%)
e) R^2 = R^3 = CH$_3$ (23%)
f) R^2 = 4-CH$_3$OC$_6$H$_4$, R^3 = H (34%)



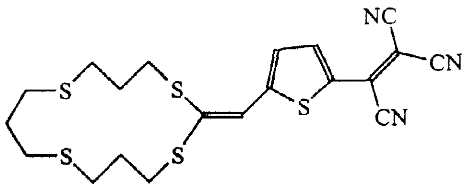
7c (13%)



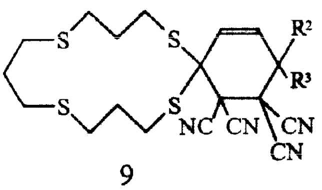
7d-f

In general these condensations with **1** (via **6**) compare well with analogous reactions with 1,3-dithiane, carried out for purposes of comparison. Condensations of **6** with ketones proceeded too sluggishly to be useful. Additions to α,β-unsaturated aldehydes (products **7d-f**) take place chiefly in a 1,2-fashion; 1,4-addition products were not isolated.

Compound **7b** on treatment with tetracyanoethene was converted, although in poor isolated yield, to **8**, which is interesting in conjunction with potential nonlinear optical properties.[12,13] Compounds **7d-f** underwent Diels-Alder cycloaddition with tetracyanoethene in quantitative crude yield to provide **9a-c**, which have been characterized by NMR spectroscopy and by mass spectra. Owing to problems of purification analytically pure materials have not been obtained. Reactions with diethyl azodicarboxylate are fast but complex mixtures are obtained. Reactions with other dienophiles failed. From the ^{1}H and ^{13}C NMR spectra it was clear that 4 + 2 (Diels-Alder) rather than 2 + 2 cycloaddition had occurred as concluded from observation of two rather than one vinylic hydrogen and carbon atoms.



8 (10%)



9

a) $R^2 = C_6H_5$, $R^3 = H$ (75%)
b) $R^2 = R^3 = CH_3$ (23%)
c) $R^2 = 4\text{-}CH_3OC_6H_4$, $R^3 = H$ (34%)

The chemistry of these new systems is being explored with particular emphasis on the possibilities for modification of derivatives **7**.

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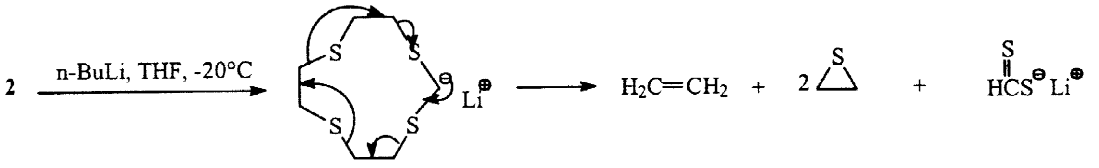
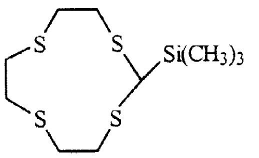
9. Spectra of all new compounds were in accord with expectation; unless otherwise stated satisfactory analytical data and/or exact mass spectral data were obtained for all new compounds. The synthesis of compound 1 is representative. A dry, 1L, three-necked, round-bottomed flask was fitted with a thermometer, a 250 mL addition funnel, a reflux condenser and a magnetic stirring bar. The whole apparatus was kept

under a nitrogen atmosphere. The flask was charged with 450 mL of DMF and 3.26g (10 mmol) of Cs_2CO_3. The mixture was stirred and heated to 55-60°C. A solution of 1,5,9,13-tetrathiatridecane (2.56g, 10 mmol) and methylene bromide (1.74g, 10 mmol) in 250 mL of DMF was added over a period of 8-12 h. After the addition was complete, the reaction mixture was cooled to room temperature. The DMF was distilled off as thoroughly as possible under reduced pressure. The residue was purified by column chromatography over Al_2O_3 (active, neutral) with toluene as eluent. There was obtained 2.03g (7.6 mmol, 76% yield) of 1,3,7,11-tetrathio-cyclotetradecane (**1**) as a white, crystalline solid, mp. 69.5-70.5°C; ^{1}H NMR($CDCl_3$, 200 MHz): 1.89(m, 6H), 2.64 (t, 8H), 2.76 (t, 4H), 3.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 28.6 (t), 29.2 (t), 30.2 (t), 30.4 (t), 36.3 (t); HRMS m/e (M^+) calcd. 268.045, obsd. 268.045.

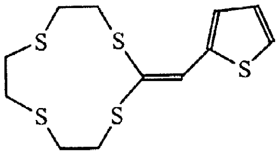
10. Silylation of compounds with *dimethylene* bridges, for example **2**, under these conditions failed and virtually complete decomposition occurred likely for the reason illustrated in eq. i. This type of process is known to occur with 1,3-dithiolane.[8] The problem can be avoided by carrying out the reactions at -100°C; the silyl derivative (shown) is readily obtained and condensations with, for example, 2-thiophene aldehyde proceed cleanly under these conditions.



(eq.i)



(86%)



(85%)

11. Compounds **7a-f** were obtained in 23 to 75 % yields by this approach. Some modifications to the established procedure[7,8] were made. The macrocycle **1** dissolved in sodium dried THF was cooled to about -20°C just above the point that precipitation began. Lithiation with n-BuLi was carried out at that temperature and the solution was cooled to -60°C and *two equivalents* $(CH_3)_3SiCl$ were added. The silyl derivatives were isolated and purified by vacuum distillation. The silylated derivatives were again deprotonated with n-BuLi at -60°C and then one equivalent of aldehyde was added. The olefinic products were obtained on work-up. In some cases heavy oils were formed that were difficult to purify.

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