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# Macrocyclization with Participation of Thiyl Radicals: Construction of 18- and 9-Membered Crown Thioethers

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A one-pot synthesis of crown thioethers, 1,10-dioxa-4,7,13,16-tetrathiacyclooctadecanes and 1-oxa-4,7-dithiacyclononanes, which are the 2:2 and 1:1 cycloadducts of the homolytic macrocyclization of alkynes with 3-oxapentane-1,5-dithiol, has been developed.

Free radical reactions have definitely entered the arsenal of modern organic chemistry. They play an especially important role in the construction of five- and six-membered carbo- and hetero-cycles, the synthesis of which is based mainly on intramolecular homolytic addition to multiple bonds.[1–3] In the last few years this principle has also been successfully used in the synthesis of macrocyclic compounds.[4,5]

Another approach to the synthesis of cyclic compounds is based on homolytic cycloaddition. Thus, a radical reaction of α,ω-dithiols with alkynes leads selectively to five-, six- and seven-membered 1,3- and 1,4-dithiacyclanes.[6]

In the present work, as a development of this approach, we have accomplished the homolytic macrocyclization of alkynes **1a,b** with 3-oxapentane-1,5-dithiol **2** induced by tripropylborane in the presence of oxygen or azobisisobutyronitrile (AIBN) which results in the formation of 18-membered and 9-membered crown thioethers 5,14(15)-dialkyl-1,10-dioxa-4,7,13,16-tetrathiacyclooctadecanes **3a,b** and 5-alkyl-1-oxa-4,7-dithiacyclononanes **4a,b** (Scheme 1). In addition to these products 1-oxa-4,5-dithiacycloheptane **5** is formed ( ~ 3%) in both reactions. In the reaction of **2** with hex-1-yne **1b** bis(3-thianon-4-enyl) ether **6**, an open-chain 1:2 adduct of **2** with **1b**, was also produced.

The structures of all the preparatively isolated products **3a,b–6** were established on the basis of $^{1}$H and $^{13}$C NMR as well as mass spectra (electron impact and chemical ionization) data. The 18-membered crown ethers **3a,b** are formed as mixtures of regioisomers which differ in the mutual location of two substituents [at C(5) and C(14) or C(5) and C(15)]. Each of these

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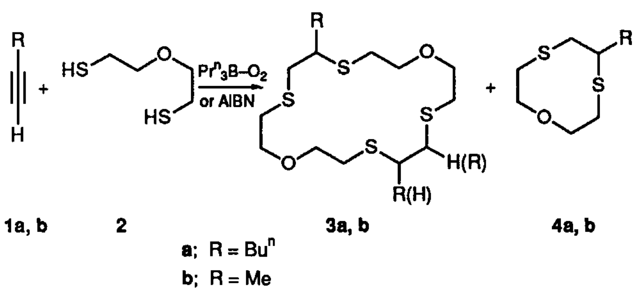


Scheme 1

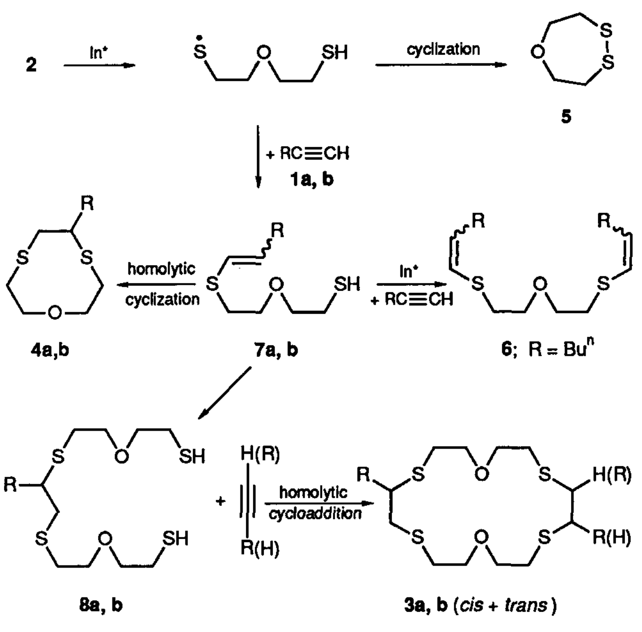
regiosiomeric crown thioethers is formed as a mixture of *cis*- and *trans*-isomers. This conclusion is based on the presence in the $^{13}$C NMR spectra of separated and purified individual **3a** and **3b** (the molecular weights of which are 356 and 440, respectively, according to the chemical ionization mass spectra, of eight signals in the $OCH_2$-group resonance region (δ 72.5–73.0). This is in accord with the number of such signals calculated for a mixture of four different isomers (regio- and stereo-) taking into account the presence of symmetry elements in each of these isomers. It should be mentioned that all four isomers of **3a** as well as of **3b** are formed in practically equal amounts. Unfortunately, at the present time it is impossible to accomplish exact assignments of the signals in the NMR spectra to each of the regio- and stereo-isomers.

It was found in a special experiment that under conditions of $Pr^n_3B–O_2$-initiated free radical addition of **2** to **6** the corresponding 18-membered crown thioether **3b** was not formed.

An understanding of the mechanism of this one-pot, homolytic macrocyclization reaction leading to 18-membered **3a,b** and cyclic 2:2 adducts of **1a,b** with **2** is principally important.

Taking into consideration: (*i*) the formation of four isomers of **3a,b** in the reaction of **1a,b** with **2**; (*ii*) the higher reactivity of the carbon≡carbon triple bond in comparison with a double bond towards addition of radicals[7] and, in particular, of thiyl radicals; (*iii*) a comparatively easy recombination of the latter with S—S bond formation;[8] and (*iv*) the absence of **3b** in the products of the reaction of **2** with **6**, we suggest that crown thioethers **3a,b** are formed from **7a,b**, the 1:1 adducts of alkynes **1a,b** with dithiol **2**, and also from **8a,b**, the 1:2 adducts, according to the mechanism of Scheme 2, which also explains the formation of the other products **4a,b–6**.

We recently confirmed the possibility of a cycloaddition like the reaction of **1a,b** with **8a,b** by homolytic cycloaddition of 3,6-dioxaoctane-1,8-dithiol to alkynes to form 12-membered crown thioethers (8-substituted 1,4-dioxa-7,10-dithiacyclododecanes).[9]



In* = $Pr^n_3B–O_2$ or AIBN

Scheme 2

Thus, homolytic cycloaddition of alkynes **1a,b** with 2:1 adducts of dithiol **2** with **1a,b** is the main reaction pathway for 'assembling' the 5,14- and 5,15-dialkylsubstituted crown thioethers **3a,b**.

The yields of the 18-membered crown thioethers **3** (12–24%) in this one-pot homolytic reaction exceed those of the predecessor of this series, the unsubstituted 1,10-dioxa-4,7,13,16-tetrathiacyclooctadecane (4–10%) achieved by heterolytic condensation.[10,11]

The results of conformational analysis of the 9-membered crown thioethers **4a,b** by NMR spectroscopy and molecular mechanics (MMX), together with studies of the complexing properties of the 18- and 9-membered crown thioethers **3** and **4** will be published in future full papers.

A typical procedure was as follows. A 250 ml 3-necked flask equipped with two funnels and a magnetic stirrer was charged under an argon atmosphere with 4 ml of a 1 mol $dm^{-3}$ solution (4 mmol) of tripropylborane in hexane and 100 ml of benzene. A solution of 0.55 g (4 mmol) of 3-oxa-1,5-pentanedithiol **2**, 0.65 ml of anhydrous MeOH in 30 ml of benzene and a solution of 0.33 g (0.46 ml, 4 mmol) of hex-1-yne **1b** in 30 ml of benzene were added dropwise and synchronously. The reaction mixture was stirred at ambient temperature for 24 h, then treated with 25 ml of a 1 mol $dm^{-3}$ solution of $NH_4Cl$. The aqueous phase was extracted with EtOAc (3 × 15 ml), the extract was combined with the organic layer, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on a column with $SiO_2$ ($CH_2Cl_2$ was used as an eluent) and 60 mg (yield 10%) of bis(3-thianon-4-enyl) ether **6**, $R_f$ 0.94 ($CH_2Cl_2$, Silufol); 18 mg (yield 2%) of 5-butyl-1-oxa-4,7-dithiacyclononane **4b**, $R_f$ 0.43; 106 mg (yield 12%) 5,14- and 5,15-dibutyl-1,10-dioxa-4,7,13,16-tetrathiacyclooctadecane **3b**, $R_f$ 0.29, were collected. In addition to these products 1-oxa-4,5-dithiacyclohexane **5** (~3%) was identified in the mixture by means of GLC, GC–MS and $^1$H NMR spectroscopy.†

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† *Spectroscopic data* for preparatively isolated crown thioethers: **3b**: $^1$H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, 6H), 1.20–1.60 (m, 10H), 1.88 (m, 2H), 2.55–3.20 (m, 14H), 3.68 (m, 8H); $^{13}$C NMR (62.7 MHz, $CDCl_3$) δ 13.8 (Me), 22.3, 28.6–28.7 and 32.6–32.8 [$(CH_2)_3Me$], 30.0–30.1, 31.1–31.2 and 38.2–38.3 ($SCH_2$), 45.3–45.5 (SCH), 71.2–71.3 ($OCH_2$); MS (electron impact) *m/z* 440 ($M^+$, 100%), 143 (98), 161 (95), 61 (93), 83 (67), 129 (65), 221 (58), 117 (51), 103 (47), 220 (42), 89 (42).

**4b**: $^1$H NMR (250 MHz, $CDCl_3$) δ 0.82 (t, 3H), 1.20–1.40 (m, 4H), 1.45 (m, 2H), 2.60–2.95 (m, 5H), 3.10–3.17 (m, 2H), 3.78 (m, 2H), 4.10 (m, 2H); $^{13}$C NMR (62.7 MHz, $CDCl_3$) δ 14.44(q), 23.33(t), 30.52(t), 32.89(t), 33.51(t), 36.19(t), 40.24(t), 49.91(d), 74.52(t), 75.04(t); MS (chemical ionization) *m/z* 220 ($M^+$).