Homolytic Macrocyclization of Alkynes with Propane-1,3-dithiol as a Route to 14- and 21-Membered Crown Thioethers

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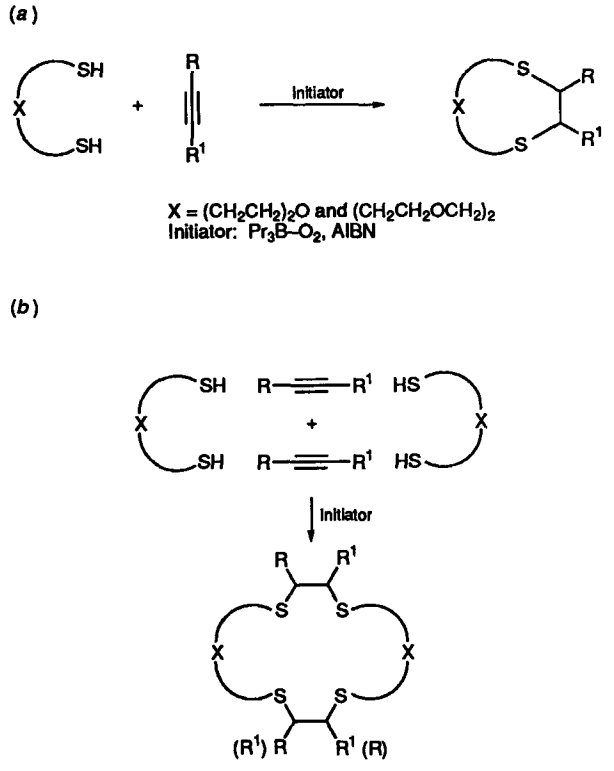
Crown thioethers, 1,4,8,11-tetrathiacyclotetradecanes and 1,4,8,11,15,18-hexathiaheneicosanes, have been synthesized as 2:2 and 3:3 cycloadducts in a 'one-pot' homolytic macrocyclization of alkynes with propane-1,3-dithiol.

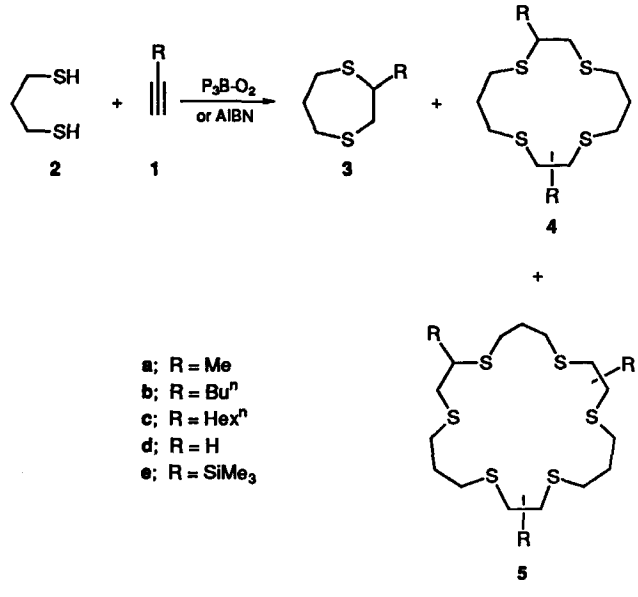
In the last few years studies on the chelating ability of crown thioethers as complexating agents of potential importance in analytical chemistry, environmental protection and medicine have been carried out quite intensively,[1,2] although their synthesis has been restricted to traditional 'assembling' from dithiols and α,ω-dihalides in the presence of cesium carbonate under high dilution conditions.[3]

Homolytic macrocyclization based on intramolecular free radical addition and successfully developed in the synthesis of some macrocycles[4,5] might be considered as a possible alternative to this traditional approach. However, this reaction usually requires the preliminary multistep synthesis of precursors with precisely located radical centres and multiple bonds, and this substantially reduces the utility of the reaction.

Recently we have found that our methods for construction of sulfur-containing heterocycles based on the homolytic cycloaddition of α,ω-dithiols with alkynes[6] can be successfully extended to the synthesis of 9-, 12- and 18-membered crown thioethers.[7,8] This approach has been applied to the 'assembling' of 12-membered (8-substituted 1,4-dioxa-7,10-dithiacyclododecane)[7] and 9-membered (5-substituted 1-oxa-4,7-dithiacyclononane)[8] crown thioethers as 1:1 cycloadducts [Scheme 1, path (*a*)] and 18-membered crown thioethers [5,14(15)-disubstituted 1,10-dioxa-4,7,13,16-tetrathiacyclooctadecanes][8] as 2:2 cycloadducts [Scheme 1, path (*b*)].



Scheme 1 Path (*a*), design of crown thioethers as 1:1 adducts of homolytic cycloddition; path (*b*), design of crown thioethers as 2:2 adducts of homolytic cycloaddition



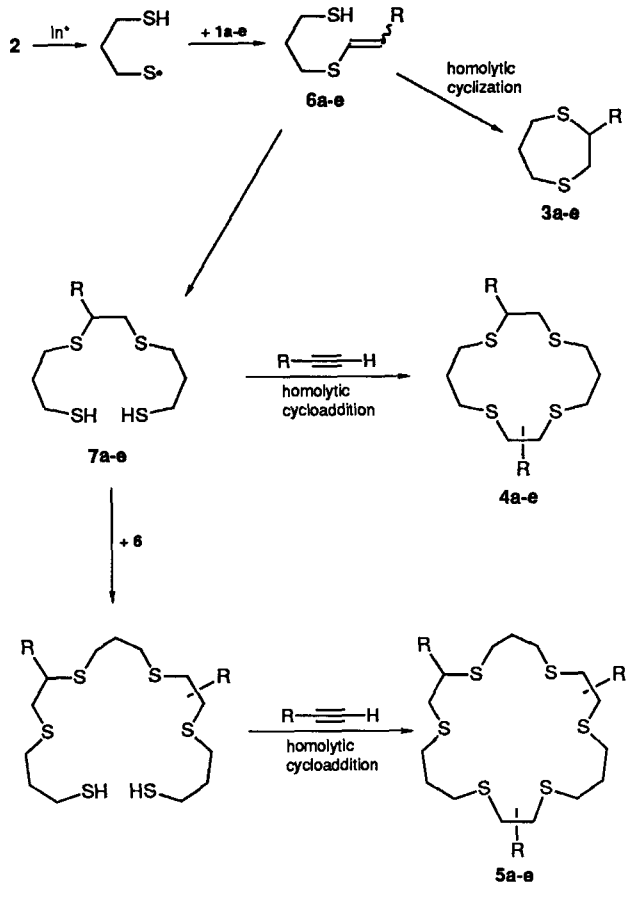
Scheme 2

In developing this approach in the present work we have found that when alkynes **1a–e** interact with propane-1,3-dithiol **2**, induced by free radical initiators [tripropylborane in the presence of oxygen or azobis(isobutyronitrile), AIBN], together with homolytic cycloaddition leading simultaneously to 1:1 cycloadducts (1,4-dithiepanes **3a–e**), the homolytic macrocyclization reactions proceed with formation of crown thioethers: 14-membered 2,9(10)-disubstituted 1,4,8,11-tetrathiacyclotetradecanes **4a–e** as 2:2 cycloadducts and even 21-membered 2,9(10),16(17)-trisubstituted 1,4,8,11,15,18-hexathiacycloheneicosanes **5a–c**, **3e** as 3:3 cycloadducts, Scheme 2. The yields of preparatively-isolated cyclic adducts **3–5** are presented in Table 1. These data demonstrate that an increase in the concentration of **1a–e** and **2** from 0.1 to 0.2 mol dm^{-3} significantly facilitates macrocyclization with formation of crown thioethers **4** and **5**, the yield of which, however, changes little on further increase of starting component concentrations to 0.4 mol dm^{-3}. Thus, on reaction of **1c** with **2** it has been shown that yields of 7-membered 1:1 cycloadduct **3c** decrease (*ca.* 2 fold) with **1c**

Table 1 Homolytic cyclization of alkynes with propane-1,3-dithiol induced by tripropylborane

Alkyne	R	Concentration/mol dm^{-3}		Products and their yields(%)		
		Alkyne	Dithiol			
1a	Me	0.2	0.2	**3a**, 27	**4a**, 9	**5a**, 3
1b	Bu	0.2	0.2	**3b**, 25	**4b**, 8	**5b**, 4
1b[a]	Bu	0.2	0.2	**3b**, 26	**4b**, 5	**5b**, —
1c	C_6H_{13}	0.2	0.2	**3c**, 24	**4c**, 7	**5c**, 4
1d	H	0.2	0.2	**3d**, 26	**4d**, 1	**5d**, —
1e	$SiMe_3$	0.2	0.2	**3e**, 32	**4e**, 2	**5e**, 2
1c	C_6H_{13}	0.1	0.1	**3c**, 50	**4c**, 3	**5c**, 1
1b	Bu	0.4	0.4	**3b**, 24	**4b**, 3	**5b**, 4
1c	C_6H_{13}	0.4	0.4	**3c**, 19	**4c**, 5	**5c**, 5

[a] Initiator, AIBN.



Scheme 3

and **2** concentration increase from 0.1 to 0.2 mol dm^{-3}, obviously due to an acceleration of intermolecular homolytic addition leading to the formation of oligomeric adducts with open chains. It should also be mentioned that the ratio of 2:2 and 3:3 cycloadducts **4** and **5** decreases with dithiol **2** and corresponding alkyne **1** concentration growth. Substituent R affects somewhat the yields of crown thioethers **4** and **5** (*cf.* reactions of **1a–c** and **1d,e**); however, the origin of this effect is not yet clear.

Analogous to the mechanism considered in detail in ref. 8, we suppose that the reaction studied proceeds according to Scheme 3.

Homolytic macrocyclization of this type proceeds sufficiently only with monosubstituted alkynes. From but-2-yne with an internal triple bond the corresponding 14-membered crown thioether 2,3,9,10-tetramethyl-1,4,8,11-tetrathiacyclotetradecane was formed in a yield of only 0.5% while in the reactions of **2** with oct-4-yne and butyne-1,4-diol diacetate the corresponding macrocyclic compounds have not been detected.

The known heterolytic methods of synthesis of unsubstituted 1,4,8,11-tetrathiacyclotetradecane **4d** are based on the condensation of the specially-synthesized precursor 3,7-dithianonane-1,9-dithiol **7d** with 1,3-dibromopropane. Thereby the total yield of **4d** increases from 3% to 24% on transition from metallic sodium[9] as a condensation agent to caesium carbonate.[10] In the last case caesium ions act as a template. The introduction of the latter in free radical reaction of alkynes with 1,3-propanedithiol leads to the complete inhibition of crown thioether **4** and **5** formation.

The results obtained demonstrate the abilities of homolytic cycloaddition–macrocyclization in the construction of 14- and 21-membered crown thioethers.

Typical preparative procedure was as follows. A solution (4 ml, 1 mol dm^{-3}) of tripropylborane (4 mmol) in hexane was added to a solution of propane-1,3-dithiol **2** (0.44 g, 4 mmol), alkyne **1** (4 mmol) and anhydrous MeOH (0.65 ml, 0.4 g, 16 mmol) in benzene (15 ml) under an argon atmosphere. The reaction of **1b** with **2** induced by AIBN (5 mol % from **1b** and **2**) was carried out in benzene under reflux. All experiments were performed under TLC and GLC control. After complete consumption of dithiol **2** the reaction mixture was washed with an aqueous solution of NaOH (1 g in 20 ml water) and the benzene layer was separated. The aqueous layer was extracted with ether (3 × 30 ml), the extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was combined with the benzene layer and reaction products were isolated by chromatography on a column with SiO_2. In the case of reactions of **2** with **1a-d**, hexane–ether (12:1) was used as eluent. To isolate the products of reaction of **2** with **1d** the systems benzene–pentane 1:5 (250 ml) and benzene–pentane–ether 33:166:1 (200 ml) were used successively as eluents. The structures of preparatively-isolated 1,4-dithiepanes **3** and 14- and 21-membered crown thioethers **4** and **5** were established on the basis of ^1H and ^{13}C NMR spectroscopy and mass spectrometric data.†

† *Spectroscopic data* for preparatively isolated reaction products: **3e**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.99 (m, 2H), 2.18 (dd, 1H), 2.67 (dd, 1H), 2.90–3.18 (m, 5H); MS (electron impact) *m/z* 73(100%), 35 (71), 206 (M^+, 58), 100 (48), 63 (47), 85 (47), 78 (38), 67 (20), 40 (28), 45 (24), 117 (24).

4a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 6H), 1.92 (m, 4H), 2.44–2.80 (m, 10H), 2.92 (m, 4H); MS (electron impact) *m/z* 106 (100%), 41, (51), 45 (33), 296 (M^+, 28), 107 (22), 44 (22), 74 (21), 73 (17), 46 (16), 108 (15), 120 (14), 75 (13), 147 (12).

4b: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 6H), 1.20–1.51 (m, 10H), 1.70–1.96 (m, 6H), 2.50–2.90 (m, 14H); MS (electron impact) *m/z* 189 (100%), 106 (20), 190 (16), 107 (15), 150 (13), 380 (M^+, 13), 55 (10), 191 (9), 73 (9), 57 (9), 83 (8).

4c: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 6H), 1.29 (br s., 12H), 1.40–1.60 (m, 6H), 1.74–1.85 (m, 2H), 1.86–2.05 (m, 4H), 2.50–3.15 (m, 14H); MS (chemical ionization) *m/z*: 107 (100%), 219 (98), 325 (72), 217 (70), 148 (70), 437 (MH^+, 65), 220 (65), 106 (63), 137 (63), 436 (M^+, 61), 133 (61), 438 (58), 136 (51), 108 (51), 109 (47), 69 (44).

4d: ^1H NMR (300 MHz, $CDCl_3$) δ 1.90–2.06 (m, 4H), 2.63–2.88 (m, 16H); MS (electron impact) *m/z* 106 (100%), 135 (45), 134 (40), 107 (40), 268 (M^+, 40), 73 (28), 72 (26), 61 (21), 105 (20), 108 (15), 87 (15), 136 (10), 120 (10), 119 (10), 101 (10).

4e: ^1H NMR (300MHz, $CDCl_3$) δ 0.14 (s, 18H), 1.86–2.10 (m, 6H), 2.66–2.90 (m, 10H), 2.94–3.05 (m, 2H); MS (electron impact) *m/z* 206 (100%), 339 (80), 119 (79), 28 (73), 83 (71), 73 (58), 100 (56), 106 (54), 133 (51), 101 (49), 101 (47), 132 (46), 180 (43), 85 (42), 59 (41), 107 (39), 193 (37), 205 (30), 341 (27), 162 (26), 236 (23), 340 (21), 237 (18), 323 (17).

5a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, 9H), 1.90 (m, 6H), 2.50–2.75 (m, 15H), 2.80–3.00 (m, 6H); MS (electron impact) *m/z* 44 (100%), 106 (68), 41 (33), 46 (21), 73 (19), 74 (18), 45 (17), 60 (16), 57(16), 43 (16), 143 (15), 147 (14), 55 (14), 107 (12), 39 (12), 149 (11), 71 (11), 81 (11), 42 (10), 444 (M^+, 19), 256 (7), 296 (3).

5b: ^1H NMR (300) MHz, $CDCl_3$ δ 0.92 (t, 9H), 1.24–1.57 (m, 15H), 1.73–1.82 (m, 3H), 1.83–1.95 (m, 6H), 2.60–2.79 (m, 18H), 2.80–2.88 (m, 3H); MS (electron impact) *m/z* 106 (100%), 107 (97), 189 (90), 191 (86), 108 (47), 55 (43), 296 (36), 190 (34), 73 (33), 149 (31), 83 (31), 297 (29), 74 (29), 57 (28), 138 (25), 115 (24), 120 (24), 117 (23), 221 (19), 137, (19), 133 (18), 119 (17), 157 (16), 222 (14), 175 (13), 486 (9), 570 (M^+, 7).

5c: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 9H), 1.30 (br s., 18H), 1.48 (m, 9H), 1.78 (m, 3H), 1.88 (m, 6H), 2.60–2.90 (m, 21H); MS (electron impact) *m/z* 106 (100%), 217 (91), 219 (73), 107 (67), 69 (39), 218 (36), 324 (33), 108 (28), 105 (23), 120 (22), 147 (18), 325 (18), 143 (16), 249 (13), 145 (12), 138 (12), 185 (12), 654 (M^+, 12), 326 (11), 189 (9), 203 (8), 165 (8), 149 (8)

5e: ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 27H), 1.82–1.97 (m, 6H), 1.98–2.10 (m, 3H), 2.63–2.89 (m, 15H), 2.93–3.04 (m, 3H); MS (electron impact) *m/z* 206 (100%), 193 (98), 279 (89), 179 (88), 223 (87), 106 (83), 101 (81), 191 (79), 73 (74), 147 (56), 618 (M^+, 55), 207 (55), 205 (53), 252 (17), 305 (16), 518 (4), 442 (3).

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