Reviews

Homolytic addition of dithiols to alkynes: a new approach to the construction of dithiacyclanes and crown thioethers

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A novel general approach to the construction of sulfur-containing heterocyclic compounds and crown thioethers based on one-pot "assembling" of their molecules from α,ω-dithiols and alkynes *via* homolytic cycloaddition has been developed.

Key words: homolytic cycloaddition, homolytic macrocyclization, α,ω-dithiols, alkynes, dithiacyclanes, crown thioethers.

1. Introduction

The easy homolytic cleavage of S—H bonds in thiols by the action of oxygen, peroxides, and other initiators of radical reactions that results in the generation of highly reactive S-centered thiyl and related radicals accounts for the wide use of these processes in the synthesis of organosulfur compounds and is the cause of their importance in chemistry and biology.[1]

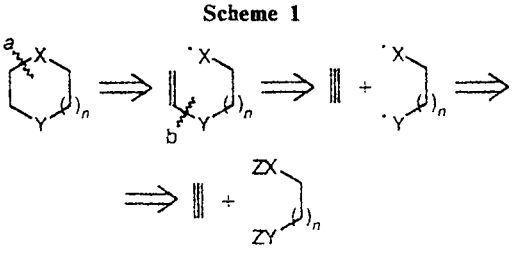
The homolytic addition of substrates with a thiol group to alkenes and alkynes has been studied most comprehensively. These reactions provided the basis for a general method for constructing new C—S bonds.[2—6] Reactions of this type have been used to carry out both intermolecular alkylation of the S atom in thiols[2,3] and intramolecular homolytic cyclization of alkenethiols to give sulfur-containing saturated heterocyclic derivatives, thiacyclanes.[7] In recent years, only a few new examples of reactions of this type have been reported,[8,9] despite the fact that transformations involving homolytic cleavage of the S—H bond appear quite promising for the synthesis of various sulfur-containing heterocyclic compounds.

2. Homolytic cycloaddition: general concept

Retrosynthetic analysis allows one to choose the simplest synthetic routes and to consider systematically the mechanisms of known reactions, in particular, of free radical processes.[10]

According to retrosynthetic analysis, any cyclic molecule can be "cut" at two designated bonds (*a* and *b*) and, hence, alkynes can be used as versatile two-carbon synthons for assembling cyclic systems.[11] The second reaction partner must contain two weak bonds, X—Z and Y—Z, that easily undergo homolytic cleavage (Scheme 1).

Scheme 1



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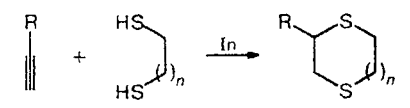
According to the proposed approach, *homolytic cycloaddition* based on *intermolecular free radical* addition does not require preliminary synthesis of a precursor in which the positions of the multiple bond and of the radical center are suitable for the subsequent cyclization. This can be regarded as a significant advantage over *intramolecular* homolytic addition (cyclization).

We have successfully implemented the idea of homolytic cycloaddition in the synthesis of sulfur-containing heterocyclic compounds and crown thioethers.

3. Synthesis of 1,3- and 1,4-dithiacyclanes

We found that alkynes **1** react with 1,2- and 1,3-dithiols **2** under conditions of radical initiation by azobis(isobutyronitrile) (AIBN)[2,3,5,6] or tripropylborane in the presence of oxygen[12,13] according to the heterocyclization pattern to give 1,3- and 1,4-dithiacyclanes.[14] The reaction of monosubstituted alkynes **1a—f** containing alkyl substituents at the C≡C bond with 1,2-ethanediol (**2a**, n = 1) or 1,3-propanedithiol (**2b**, n = 2) under the action of the Pr_3B—MeOH—O_2 system (oxygen is present, because exhaustive degassing has not been carried out) in benzene or THF (the ratio **1** : **2** : Pr_3B : MeOH = 1 : 1 : 1 : 1.4) at room temperature or in the presence of AIBN (the ratio **1** : **2** : AIBN = 1 : 1 : 0.15) with heating in benzene occurs regiospecifically to yield 2-substituted 1,4-dithianes **3a—f** (n = 1) or 1,4-dithiepanes **3g—i** (n = 2) (Scheme 2, Table 1).

Scheme 2



1a—f **2a**, n = 1; **2b**, n = 2 **3a—f**, n = 1; **3g—i**, n = 2

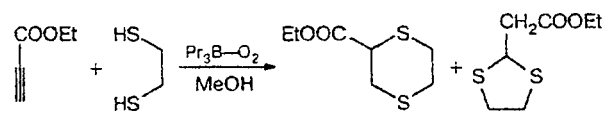
R = C_4H_9 (**a**,**g**), C_6H_{13} (**b**), CH_2OH (**c**,**h**), CMe_2OH (**d**,**i**), CH_2OTHP (THP = 2-tetrahydropyranyl) (**e**), CH_2Cl (**f**).

In = Pr_3B—O_2—MeOH or AIBN

The results obtained indicate that homolytic cycloaddition giving six-membered 1,4-dithianes **3a,b,d** is more efficient than similar reactions involving the same alkynes **1a,c,d**, and leading to seven-membered 1,4-dithiepanes **3g—i**. In the series of 1,4-dithianes, the yield of the product of heterocyclization markedly increases on going from 2-alkyl-substituted derivatives **3a,b** to 2-hydroxymethyl-1,4-dithiane **3c** and its analogs **3d,e**. A similar regularity is also observed in the case of 1,4-dithiepanes **3g—i**. Both initiators used in this reaction, the Pr_3B—O_2—MeOH system and AIBN, are virtually equally efficient in heterocyclization. An advantage of the system based on Pr_3B is that the reaction can be conducted at room temperature, whereas the reaction in the presence of AIBN requires refluxing in benzene at ~80 °C. The presence of Pr_3B is necessary for the reaction; when air is bubbled through a mixture of **1d**, **2a**, and MeOH in benzene, no 1,4-dithiane **3d** is formed. The yield of 1,4-dithianes increases somewhat when THF is used as the solvent instead of benzene.

A functional group attached directly to the C≡C bond can exert crucial effects on the direction of the addition to this bond and on the structure of the resulting dithiacyclane. For example, when compound **2a** reacts with ethyl propiolate **1g** (R = CO_2Et) in the presence of the Pr_3B—O_2—MeOH system, 1,2-addition at the C≡C bond to give 2-ethoxycarbonyl-1,4-dithiane **3j** occurs in parallel with 1,1-addition, which yields isomeric 2-ethoxycarbonylmethyl-1,3-dithiolane; the ra-

Scheme 3



1g **2a** **3j**

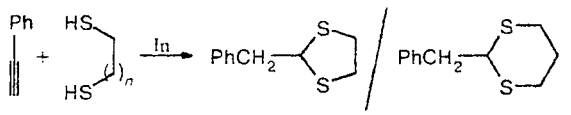
Table 1. Synthesis of 1,4-dithiacyclanes **3** [14]

Alkyne	R	Dithiol	n	Initiator	Solvent	Yield of **3** (%)
1a	C_4H_9	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3a**, 49
1b	C_6H_{13}	**2a**	1	AIBN	Benzene	**3b**, 47
1b	C_6H_{13}	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3b**, 55
1b	C_6H_{13}	**2a**	1	Pr_3B—O_2—MeOH	THF	**3b**, 71
1c	CH_2OH	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3c**, 51
1c	CH_2OH	**2a**	1	Pr_3B—O_2—MeOH	THF	**3c**, 67
1d	CMe_2OH	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3d**, 56
1d	CMe_2OH	**2a**	1	AIBN	Benzene	**3d**, 59
1d	CMe_2OH	**2a**	1	MeOH—O_2	Benzene	**3d**, 0
1e	CH_2OTHP	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3e**, 48
1e	CH_2Cl	**2a**	1	Pr_3B—O_2—MeOH	Benzene	**3f**, 50
1a	C_4H_9	**2b**	2	Pr_3B—O_2—MeOH	Benzene	**3g**, 41
1c	CH_2OH	**2b**	2	Pr_3B—O_2—MeOH	Benzene	**3h**, 56
1d	CMe_2OH	**2b**	2	Pr_3B—O_2—MeOH	Benzene	**3i**, 39

tio of the products of the competing 1,2- and 1,1-additions is 1 : 2.5 (Scheme 3).

This type of addition of thiyl radicals to the same terminal carbon atom occurs fully selectively in the heterocyclization of dithiols with phenylacetylene **1h**. The cycloaddition is regiospecific and affords 2-benzyl-1,3-dithiolane **4a** or 2-benzyl-1,3-dithiane **4b** in 30—40% yields (Scheme 4).

Scheme 4



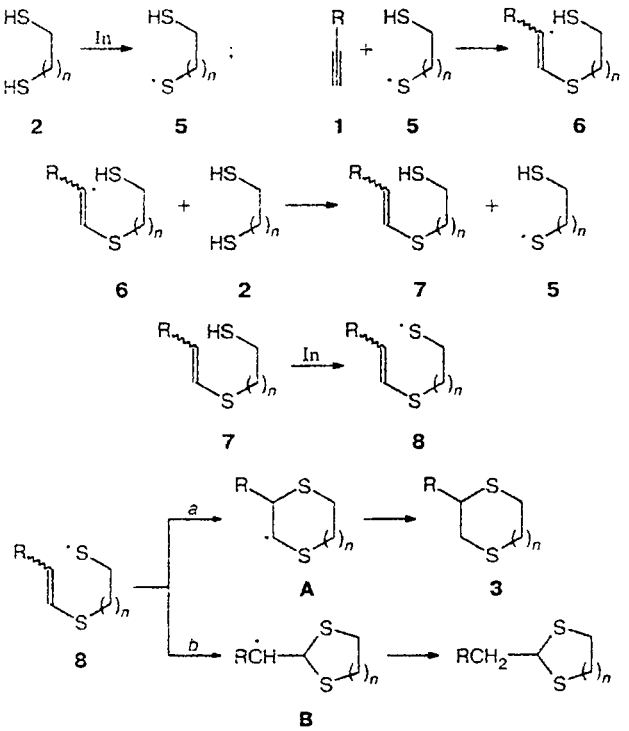
1h **2a/2b** **4a** **4b**

In = Pr_3B—O_2—MeOH or AIBN

Thus, free-radical reactions of dithiols with alkynes can serve as a general method for the synthesis of five-, six-, and seven-membered 1,4- and 1,3-dithiacyclanes.

The mechanism of the reactions studied is shown in Scheme 5. Heterocyclization initiated by AIBN is assumed to occur by the normal homolytic mechanism, which includes consecutive inter- and intramolecular addition of thiyl radicals to multiple bonds.

Scheme 5



In = AIBN
a — 1,2-addition, R = Alk
b — 1,1-addition, R = Ph

The pathway of cyclization of thiyl radicals **8** is determined by the relative stabilities of the alternative primary cyclic radicals, *viz.*, α-thioalkyl radicals **A** and β-thioalkyl radicals **B**. It is clear that in the absence of any additional stabilizing factors, radicals **A** are much more stable than radicals **B**; this apparently accounts for the fact that in the case where molecules **1a—f** incorporate alkyl substituents R, the reaction occurs selectively as 1,2-addition to give 1,4-dithiacyclanes **3**. Conversely, in the case of phenylacetylene **1h**, radicals **B** (R = Ph), precursors of 2-benzyl-1,3-dithiacyclanes resulting from 1,1-addition at the C≡C bond in **1h**, are more stable. The reaction of ethyl propiolate **1g** is an intermediate case: 1,2- and 1,1-additions occur as competing processes.

The above-considered scheme, which includes the intermediate formation of acyclic unsaturated thiols **7** preceded by radicals **6**, was confirmed by the identification of the corresponding enethiols in the reaction of **1h** with **2b**.

Cycloaddition of dithiols **2** to alkynes **1** initiated by the Pr_3B—O_2—MeOH system, which has been used previously in the addition of thiols to substrates with multiple bonds,[13] follows apparently a more complex pathway. Tripropylborane is known to be autooxidized extremely easily even when only traces of oxygen are present. As a result, propyl radicals are generated as a result of homolytic substitution at the boron atom.[12] It is these radicals that initiate heterocyclization by generating thiyl radicals (Scheme 6), which add subsequently to the C≡C bond of alkynes **1**.

Scheme 6

$$Pr_3B + O_2 \longrightarrow Pr_2BO{-}O^{\cdot} + Pr^{\cdot}$$

$$Pr^{\cdot} + \underset{\mathbf{2}}{HS(CH_2)_nCH_2SH} \longrightarrow PrH + \underset{\mathbf{5}}{HSCH_2(CH_2)_nS^{\cdot}}$$

Intermediate formation of organothioboron compounds *via* binding of the dithiol participating in the reaction, accompanied by generation of alkyl radicals, is also quite probable.[12,15] Subsequent methanolysis of compound **9** results in the liberation of dithiol **2**, which can again be involved in the reaction (Scheme 7).

Scheme 7

$$Pr_3B + \underset{\mathbf{2}}{HS(CH_2)_nCH_2SH} \longrightarrow \underset{\mathbf{9}}{Pr_2BS(CH_2)_nCH_2SH} + Pr^{\cdot}$$

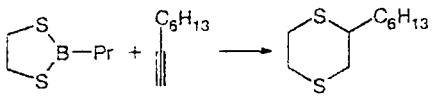
$$\mathbf{9} + MeOH \longrightarrow Pr_2BOMe + \underset{\mathbf{2}}{HS(CH_2)_nCH_2SH}$$

It was shown that the contribution of the pathway involving alcoholysis of the intermediate organothioboron compound is fairly large: the yield of **3b** in the reaction

of **1b** with **2a** in THF is 69% after 1.5 h and increases to 71% after 3 h, whereas in the absence of MeOH, the yield is equal to 43% after 1.5 h and does not increase further.[14]

In addition to these schemes, a certain contribution is probably made by the reaction pathway that involves intermediate formation of 1,3,2-dithiaboracyclanes from dithiols **2a,b** and tripropylborane. To confirm this assumption, we studied transformations of the model 2-propyl-1,3,2-dithiaborolane (**10**), which was specially synthesized from **2a** and Pr_3B, and found that **10** does react with an equimolar amount of **1b** in benzene at 20 °C to give compound **3b**, whose yield is 6% within 6 min after the beginning of the reaction and increases to 10—11% after 1.5—21 h (Scheme 8). When the reaction of **10** with **1b** is carried out in the presence of 4 equiv. of MeOH, the yield of **3b** is 17% after 0.1 h and increases to 43% after 21 h.[14]

Scheme 8



10 **1b** **3b**

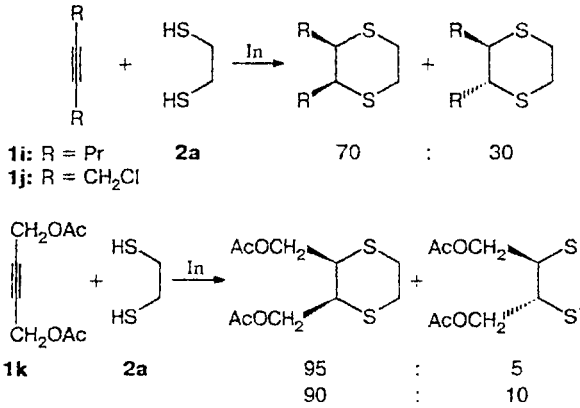
Thus, in reactions of dithiols **2** with alkynes **1**, the $Pr_3B—O_2—MeOH$ system and AIBN act as mild radical initiators, whose role is to generate ω-mercaptoalkylthiyl radicals **5** from dithiols; these radicals add subsequently to the C≡C bond in alkynes **1**. Dimerization and polymerization, which are quite typical of thiyl radicals including those generated from dithiols, are largely, although not completely, suppressed under the experimental conditions chosen; this ensures high selectivity of the formation of 1,4-dithiacyclanes under the conditions of kinetic control of the reaction.

4. Reaction of dithiols with disubstituted alkynes. Stereochemistry of homolytic cycloaddition

Heterocyclization of disubstituted alkynes **1i—k** containing alkyl type substituents at the C≡C bond with 1,2-ethanediol **2a** initiated by AIBN or tripropylborane in the presence of O_2 or MeOH occurs stereoselectively to give *cis*-2,3-disubstituted 1,4-dithianes as the major product.[16] The ratio of stereoisomers virtually does not depend on the way heterocyclization is initiated (Scheme 9).

The *cis*-stereoselective reaction between diphenylacetylene **1l** and **2a** initiated by AIBN affords unsaturated 5,6-diphenyl-2,3-dihydro-1,4-dithiin (**12**), along with *cis*- and *trans*-2,3-diphenyl-1,4-dithianes (**11a,b**); the **11a** : **11b** : **12** ratio is 20 : 2 : 1 (according to ^1H NMR spectra (250 MHz)), their overall yield is ~50% (Scheme 10).

Scheme 9

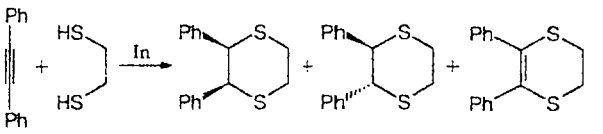


1i: R = Pr **2a** 70 : 30
1j: R = CH_2Cl

1k **2a** 95 : 5
90 : 10

In = $Pr_3B—O_2—MeOH$ (95 : 5) or AIBN (90 : 10)

Scheme 10

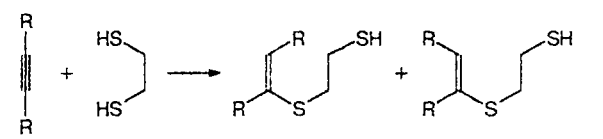


1l **2a** **11a** **11b** **12**

In = AIBN

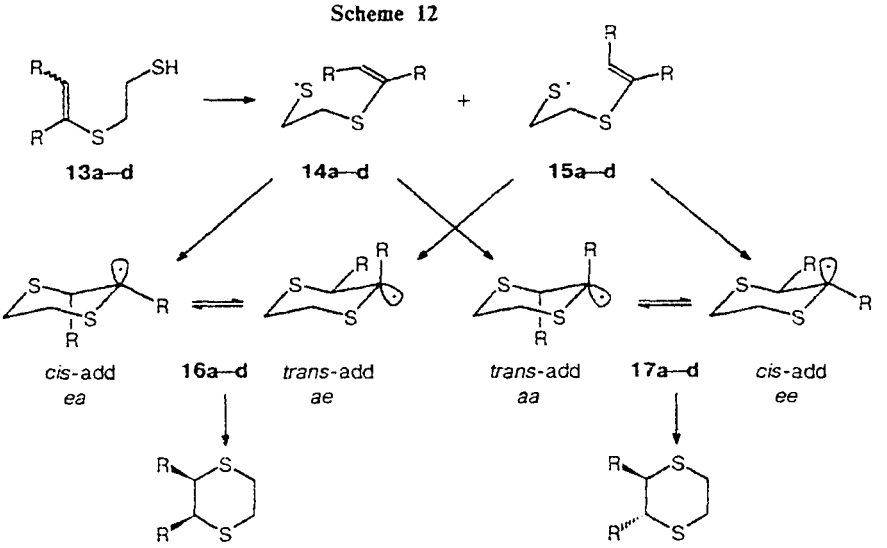
The stereochemistry of the addition of thiyl radicals to multiple bonds is known to depend on the substituents present in the molecules of the reacting unsaturated compounds and thiols, on the method of generation of the radicals, and on the reaction conditions.[2,3,13,17—19] Some reactions of this type are stereoselective; however, in general, there are no strict rules determining their stereochemistry. This is largely due to the fact that the addition of thiyl radicals is reversible.[2,3] Taking into account the foregoing, the mechanism of the reaction between **1i—l** and **2a** includes homolytic addition of 2-mercaptoethanethiyl radicals **5** (n = 1) to the triple bond in **1i—l** to give intermediate unsaturated thiols (*Z*)- and (*E*)-**13a—d**. Model experiments showed that the homolytic addition of dithiols to triple bonds occurs mostly as a *trans*-reaction and yields predominantly *Z*-thio-substituted alkenes (Scheme 11).

Scheme 11



1i—l **2a** ***Z*-13a—d** ***E*-13a—d**

Scheme 12



Note: *cis*-, *trans*-add — *cis*-, *trans*-addition.

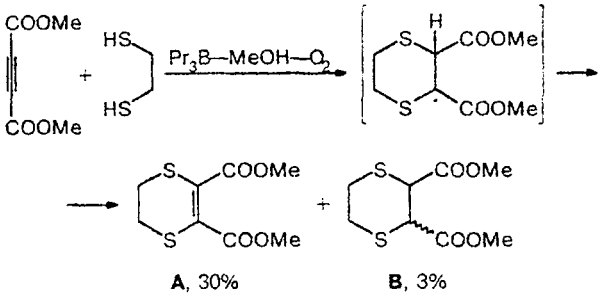
The subsequent intramolecular homolytic cyclization of **13a—d** *via* intermediate thiyl radicals **14a—d** and **15a—d** leads to stereoisomeric cyclic radicals **16a—d** and **17a—d**, precursors of *cis*- and *trans*-1,4-dithianes (Scheme 12).

It can be seen from this Scheme that in general, the stereochemistry of the process is determined by the following factors: the configuration of the double bond in unsaturated thiols **13a—d**, the direction of the attack of the S-centered radical on the C=C bond during the intramolecular cyclization of radicals **14a—d** and **15a—d**, and the relative stabilities of the conformers, including the possible interconversion of cyclic radicals **16** and **17** during the abstraction of hydrogen atoms by these radicals to give *cis*- and *trans*-2,3-disubstituted 1,4-dithianes.

In addition to the orientation of substituents, the orientation of the orbital occupied by the unpaired electron exerts a significant effect on the relative stabilities of radicals **16** and **17**. Anomeric n_S-σ orbital interaction should stabilize the axial arrangement of this orbital, similarly to the situation in compounds containing oxygen or nitrogen atoms in the ring.[20] It should be expected that the energy of the radicals would increase on going from radical *ee*-**17** to radicals *ea*-**16**, *ae*-**16**, and, finally, to the least stable *aa*-**17**. It is unknown whether the radicals have enough time during the reaction to undergo the conformational transitions marked in Scheme 12 by opposing arrows or if each of the radicals is converted independently into the final product. In principle, these transitions should not have an effect on the stereochemical outcome of the reaction. However, the set of transformations will be even more complex if the reversibility of the addition of thiyl radicals is manifested in this process.[2,3] In general, conformational analysis of the transition state for the intramolecular homolytic addition at the double bond in the intermediate alkenethiols **13** attests that the *cis*-reaction predominates. At the current stage of the study, it can be assumed that the observed *cis*-stereoselectivity of the cycloaddition of dithiols to disubstituted alkynes is determined by a combination of the *trans*-stereoselectivity of radical addition to the triple bond and the *cis*-stereoselectivity of intramolecular homolytic cyclization.

Functional substituents in disubstituted alkynes can have a determining effect on the type of heterocyclic compound formed. Thus the reaction of dimethyl acetylenedicarboxylate with 1,2-ethanethiol affords mostly 5,6-bis(methoxycarbonyl)-2,3-dihydro-1,4-dithiine (**A**), while its saturated analog (**B**) was detected only in a minor amount (Scheme 13).

Scheme 13



Detailed conformational analysis of 2-substituted and 2,3-disubstituted 1,4-dithianes has been carried out using ^{1}H NMR spectroscopy and MMX calculations.[21,22]

5. Homolytic macrocyclization: synthesis of crown thioethers

The approach developed has been used successfully to "assemble" various crown thioethers *via* homolytic cycloaddition of alkynes to appropriate dithiols. The crown thioethers thus synthesized differ in the size of the ring, the number and type of heteroatoms (sulfur, oxygen) in it, their mutual arrangement, and in the substituents.

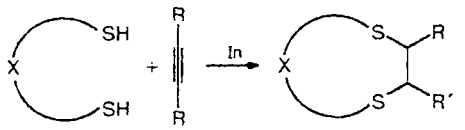
General aspects. Among the numerous free-radical processes used in modern organic synthesis (addition to multiple bonds, cyclization, oxidation, *etc.*),[23] cyclization, *i.e.*, intramolecular homolytic addition to multiple bonds, is apparently the most important, because of the unique prospects for the assembly of cyclic and polycyclic systems associated with this reaction.[24] Radical macrocyclization pioneered by Porter[25] has markedly extended the synthetic potential of free-radical processes and has been used extremely successfully in the syntheses of lopotoxin,[26a] cyclic systems of the taxan series,[26b] fused bicyclic systems,[26c] steroid structures,[26d] and derivatives of lysergic acid.[26e] However, to carry out homolytic macrocyclization, a preliminary multistep synthesis of precursors with exact positions of the radical center and the multiple bond is needed; it is clear that this restricts to a certain extent the scope of application of this reaction.

We found that radical cycloaddition—macrocyclization can be widely used for constructing crown thioethers according to two main reaction routes: as 1 : 1 adducts (Scheme 14, pathway 1) and/or as 2 : 2 cycloaddition products (Scheme 14, pathway 2); *i.e.*, the resulting crown thioethers incorporate either one or two units of both the starting dithiol and the alkyne, respectively. In some cases, products of the 3 : 3 cycloaddition have also been isolated. Crown thioethers (CTE) were prepared using the same initiators that we have used in the syntheses of dithianes and dithiepanes, *viz.*, the $Pr_3B—O_2—MeOH$ system or AIBN.

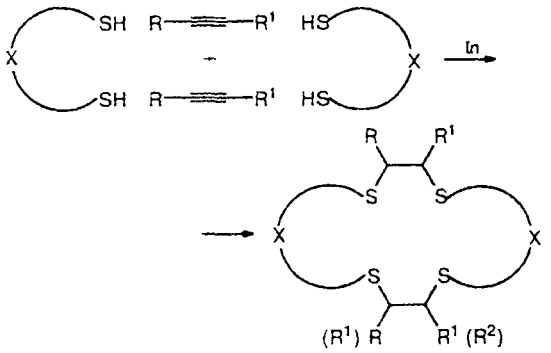
Twelve- and thirteen-membered crown thioethers.[27,28] Homolytic macrocyclization by pathway 1 made it possible to accomplish a convenient one-step synthesis of 12- and 13-membered crown thioethers and sulfur-

Scheme 14

***Pathway 1.* Design of CTE as products of homolytic 1 : 1 cycloaddition**



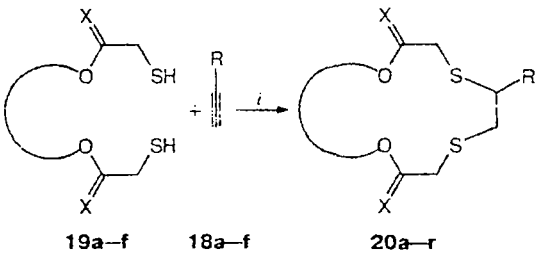
***Pathway 2.* Design of CTE as products of homolytic 2 : 2 cycloaddition**



X = $(CH_2)_n$, $(CH_2)_mQ(CH_2)_{n-m}$; Q = S, O

In = $Pr_3B—O_2—MeOH$ or AIBN.

Scheme 15



19a—f **18a—f** **20a—r**

i. $Pr_3B—O_2$, benzene—MeOH, 20 °C.

Table 2. Synthesis of 12- and 13-membered crown thioethers **20**

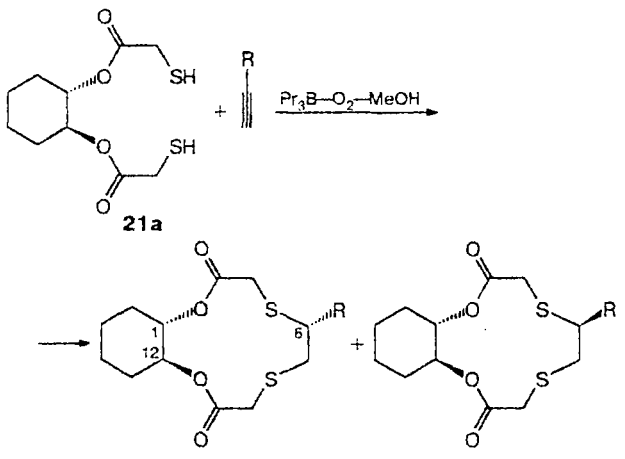
	X	19	R	18	20	Yield (%)
	H_2	19a	Me	18a	20a	30
			Bu	18b	20b	28
			CH_2OAc	18c	20c	21
			CH_2OMe	18d	20d	15
	O	19b	Me	18a	20e	48
			Bu	18b	20f	38
			CH_2OAc	18c	20g	35
			CMe_2OH	18e	20h	15
	O	19c	Me	18a	20i	32
			Bu	18b	20j	30
			CH_2OAc	18c	20k	21
			CH_2OMe	18e	20l	20
	O	19d	Bu	18b	20m	24
			CH_2OH	18l	20n	18
	O	19e	Me	18a	20o	27
			CH_2OMe	18d	20p	26
	O	19f	Bu	18b	20q	25
			CH_2OMe	18d	20r	42

containing macrocyclic lactones (Scheme 15, Table 2). By the reaction of alkynes **18** with 3,6-dioxaoctane-1,8-dithiol (**19a**), a readily available sulfur-containing analog of triethylene glycol, 12-membered crown thioethers **20a—d** were synthesized.[27,28] By using esters derived from mercaptoacetic acid and 1,2- and 1,3-diols as the "dithiol" component, 12- and 13-membered sulfur-containing lactones **20e—r** were prepared in yields of up to 48%.[28] The target products of macrocyclization were readily isolated by column chromatography. It should be emphasized that an attempt to initiate macrocyclization by AIBN did not result in the formation of crown thioethers. This suggests that the boron-containing intermediates arising during the reaction promoted by Pr_3B can act as a template that ensures the "assembly" of the macrocycle.

It is obvious that the mechanism of homolytic macrocyclization according to pathway 1 (see Scheme 14) is similar to that considered above for the homolytic cycloaddition giving 1,4-dithiacyclanes (Scheme 5).

Remote asymmetric induction in the synthesis of cyclohexano-fused 12-membered crown thiolactones.[29,30] The reaction under consideration not only provides a method for synthesizing a number of thiacrown compounds[27,28] but it also can be used in stereoselective synthesis. We found that cycloaddition of alkynes to *trans*-1,2-bis(mercaptoacetoxy)cyclohexane (**21a**) induced by the $Pr_3B—O_2—MeOH$ system occurs with an unexpectedly high diastereoselectivity and yields a mixture of stereoisomeric (1*S**,6*R**,12*S**)- and (1*S**,6*S**,12*S**)-*trans*-cyclohexano-fused 12-membered crown thiolactones **22a—c** and **23a—c**, the former markedly predominating[29,30] (Scheme 16).

Scheme 16



(1*S**,6*R**,12*S**)-**22a—c** (1*S**,6*S**,12*S**)-**23a—c**

Lactone	R	Ratio **22** : **23**	Overall yield **22+23**
a	Me	2.1 : 1	30%
b	Bu	2.4 : 1	23%
c	CH_2OMe	3.1 : 1	28%

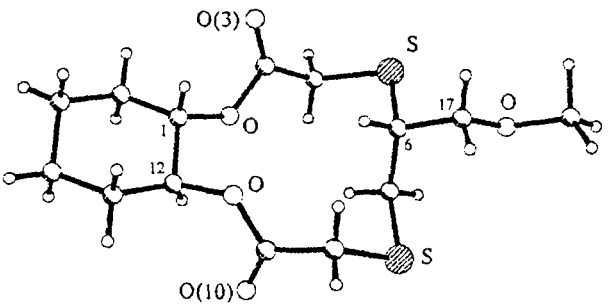
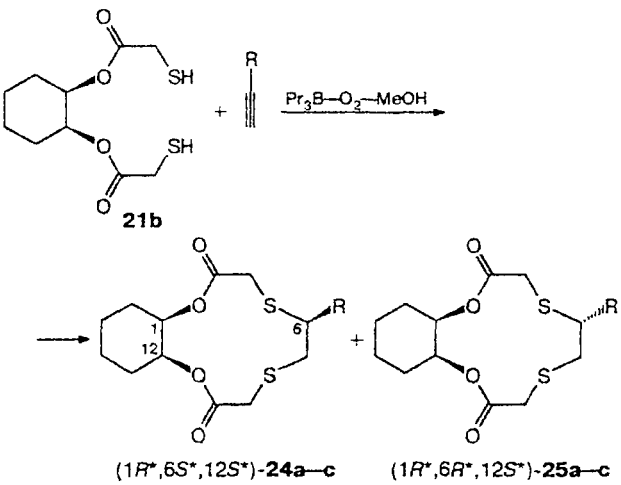


Fig. 1. Molecular structure of (1*S**,6*R**,12*S**)-**22c**.

On storage, the major stereoisomers **22a—c** crystallized spontaneously from their mixtures with **23a—c**. The (1*S**,6*R**,12*S**)-configuration of **22c** was established using X-ray diffraction data (Fig. 1). Based on the fact that the ^1H and ^{13}C NMR spectra of a mixture of stereoisomers **22c**, **23c** resemble closely the spectra of mixtures of **22a**, **23a** and **22b**, **23b**, and the fact that the spectra of **22c** are similar to those of the prevailing crystalline stereoisomers **22a** and **22b**, the same configuration, *viz.*, (1*S**,6*R**,12*S**), was attributed to the latter compounds.

Unlike the reactions involving *trans*-**21a**, cycloaddition of *cis*-thiol **21b** was not noticeably stereoselective, and the ratio of the resulting stereoisomers **24a—c** and **25a—c** was close to 1 : 1 (Scheme 17).

Scheme 17



(1*R**,6*S**,12*S**)-**24a—c** (1*R**,6*R**,12*S**)-**25a—c**

Compound	R	Ratio **24** : **25** (or **25** : **24**)	Overall yield **24+25** (%)
a	Me	1.20 : 1	18
b	Bu	1.15 : 1	30
c	CH_2OMe	1.05 : 1	21

Special control experiments have demonstrated that under the mild conditions of initiation of the addition by

the $Pr_3B—O_2—MeOH$ system, the configuration of the individual **22c** isolated from the mixture does not change, and neither does the ratio of steroisomers in the mixture of **22c** with **23c**.

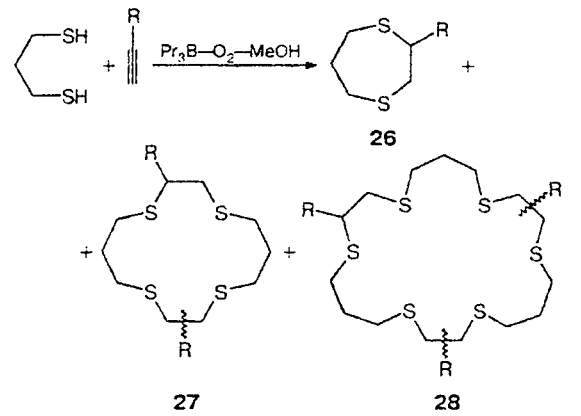
Therefore, the homolytic cycloaddition of *trans*-dithiol **21a** to alkynes is a truly stereoselective process and the degree of stereoselectivity is relatively high, despite the fairly large distance between the chiral center of *trans*-dithiol **21a** and the newly formed C-6 chiral center in **22a—c**. Based on molecular-mechanics calculations (MMX and PCMODEL programs), the observed diastereoselectivity can be explained by the fact that under the conditions of kinetic control, macrocyclization follows the route that is more favorable from the viewpoint of entropy.

Macrocyclization of **21** with alkynes can formally be regarded as remote 1,6-asymmetrical induction. Numerous examples of free-radical processes occurring with acyclic diastereofacial selectivity are known.[31] However, they mostly involve reactions with 1,2- and 1,4-asymmetrical induction, and only a few examples of free-radical reactions with remote asymmetrical induction of higher orders are known.[32]

Fourteen- and twenty-one-membered crown thioethers.[33] Additional consideration of the $Pr_3B—O_2—MeOH$-initiated reaction between 1,3-propanedithiol **2b** and alkynes regarding the possibility of macrocyclization has shown that, in addition to the 1 : 1 cycloadducts, *viz.*, 1,4-dithiepanes **26**, homolytic cycloaddition—macrocyclization (see Scheme 14, pathway 2) occurs to give crown thioethers as 2 : 2 cycloadducts — 14-membered 2,9(10)-disubstituted 1,4,8,11-tetrathiacyclotetradecanes (**27**) (in isolated yields of 3—9%) — and even 3 : 3 cycloadducts — 21-membered 2,9(10),16(17)-trisubstituted 1,4,8,11,15,18-hexathiacyclogeneicosanes (**28**) (in a yield of up to 5%) (Scheme 18). The contribution of macrocyclization to the overall process can be controlled to a certain extent by varying the concentrations of the initial dithiol and the alkynes. The ratio of the two types of crown thioethers formed also depends on the concentrations of the reagents, although this dependence is not regular.

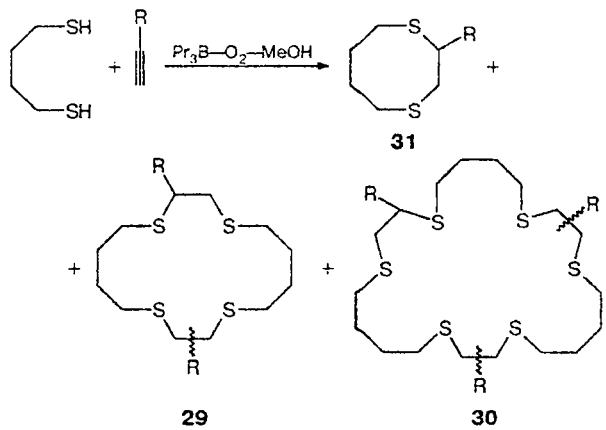
Sixteen- and twenty-four-membered crown thioethers.[34] A similar reaction of 1,4-butanedithiol with alkynes made it possible to prepare 2 : 2 and 3 : 3 adducts, *viz.*, the 16- and 24-membered crown thioethers, 2,10(11)-disubstituted 1,4,9,12-tetrathiacyclohexadecanes (**29**) and 2,10(11),18(19)-trisubstituted 1,4,9,12,17,20-hexathiacyclotetracosanes (**30**). It should be noted that, unlike the above-considered reaction of 1,3-propanedithiol, the eight-membered cyclic 1 : 1 adduct **31** is formed only in minor amounts (Scheme 19). This reflects the general problems in the construction of all types of eight-membered rings.[35,36] Intramolecular oxidative cyclization of the initial 1,4-dithiol to the corresponding six-membered 1,2-dithiane was the main un-

Scheme 18



[alkyne] = = [dithiol] /mol L^{-1}	R	Yield (%)		
		26	**27**	**28**
0.2	H	26	1	—
	Me	27	9	3
	C_4H_9	25	8	4
	C_6H_{13}	24	7	4
	$SiMe_3$	32	2	2
0.1	C_6H_{13}	50	3	1
0.4	C_4H_9	24	3	4
	C_6H_{13}	19	5	5

Scheme 19

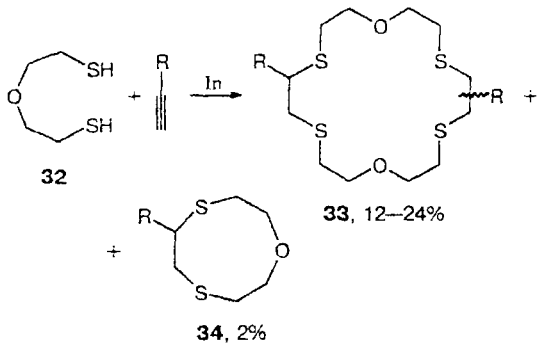


R	Yield (%)		
	31	**29**	**30**
CH_3	6	3	4
C_4H_9	2	9	2
C_6H_{13}	1	8	11
CH_2OH	3	9	3
CH_2OMe	2	6	2

desired side reaction that competed efficiently with the homolytic cycloaddition.

Nine- and eighteen-membered crown thioethers.[37] The mechanism of macrocyclization yielding the 2 : 2 cycloadduct as the major product (*i.e.*, occurring predominantly by pathway 2, Scheme 14) was studied in most detail in relation to the cycloaddition of 3-oxa-1,5-pentanedithiol (**32**) to alkynes. The reaction afforded the 18- and 9-membered crown thioethers, 1,10-dioxa-4,7,13,16-tetrathiacyclooctadecanes (**33**) and 1-oxa-4,7-dithiacyclononanes **34**; the 18-membered crown thioethers **33** (Scheme 20) substantially predominated. This should have been expected in view of the known difficulties associated with the synthesis of 9-membered cyclic compounds. Using ^1H NMR and ^{13}C NMR spectroscopy, it was found that 18-membered adducts **33** are formed as mixtures of four isomers (5,14- and 5,15-regioisomers differing in the mutual arrangement of the substituents R, each of them being a mixture of *cis*- and *trans*-forms).

Scheme 20

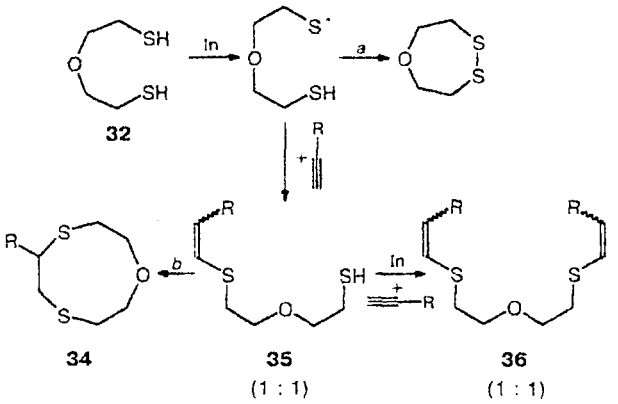


R = C_4H_9 (**a**), Me (**b**)
In = Pr_3B—O_2—MeOH or AIBN

The study of the reaction mechanism and the results of model experiments made it possible to propose the following sequence for the "assembly" of crown thioethers; in our opinion, this sequence is common to the formation of all the 2 : 2 adducts of macrocyclization (including 14-membered derivative **27** and 16-membered derivative **29** considered previously).

The first step of the reaction involves free-radical addition of thiyl radicals to the triple bonds and gives 1 : 1 adducts with an open chain (**35**), which are key precursors of both 9- and 18-membered crown thioethers. Direct homolytic cyclization of intermediate **35** leads to 9-membered crown thioethers **34**; on the other hand, adduct **35** can react with a second molecule of alkyne or with dithiol **32** to give two alternative products: the 1 : 2 adduct (**36**) and the 2 : 1 adduct (**37**) (Schemes 21 and 22). The corresponding 1 : 2 adduct (**36**, R = C_4H_9) was isolated from the products of the reaction of dithiol **32** with 1-hexyne.

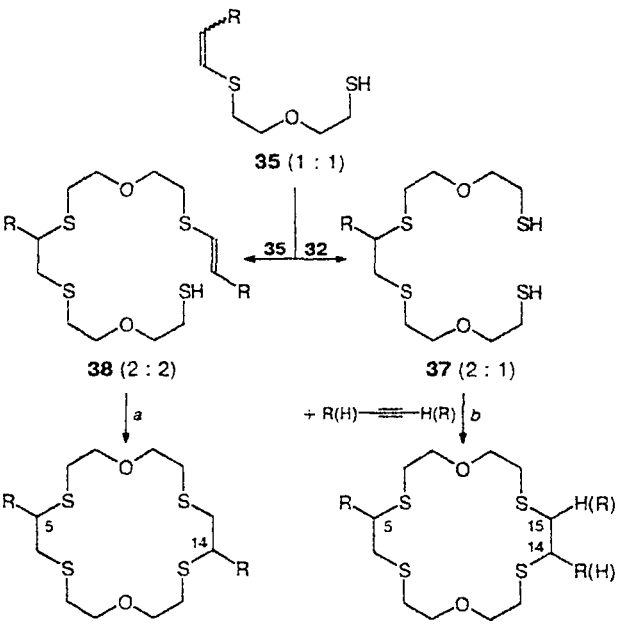
Scheme 21



In = Pr_3B—O_2—MeOH or AIBN
a. Cyclization.
b. Homolytic cyclization.

A model experiment showed that reaction of 1 : 2 adduct **36** (R = C_4H_9) with dithiol **32** in the presence of Pr_3B—O_2 yields no 18-membered crown thioether **33a**. This suggests that macrocyclization occurs most likely according to Scheme 22. The open-chain 1 : 1 adduct **35** adds a second molecule of dithiol **32** to give the intermediate 2 : 1 adduct (**37**). Subsequent homolytic

Scheme 22



a. Homolytic cyclization.
b. Homolytic cycloaddition.

cycloaddition of **37** to the initial alkyne results in the formation of crown thioethers **33** as mixtures of all of the (four) possible regio- and stereoisomers in approximately equal amounts. Unfortunately, exact determination of the structure of each of the resulting isomers is a very complicated task. 5,14-Dialkyl-substituted crown thioethers (5,14-**33**) can also be formed by homolytic cyclization of the 2 : 2 adduct (**38**), which is the intermediate resulting from homolytic addition of a molecule of unsaturated thiol **35** to another molecule of the same compound **35**.

From our viewpoint, the one-step synthesis of 12- and 13-membered crown thioethers from the corresponding 1,8- and 1,9-dithiols and alkynes that we carried out[27—30] is evidence supporting the above-considered mechanism of the "assembly" of 18-membered crown thioethers **33** from intermediate dithiol **37** and a second molecule of the alkyne.

Notice that the yields achieved for 18-membered crown ethers **33** (12—24%) are higher than the yields (4—10%) of the first representative of this series, unsubstituted 1,10-dioxa-4,7,13,16-tetrathiacyclooctadecane synthesized by heterolytic condensation.[38,39]

A comparison of the yields of heterocycles of various sizes prepared within the framework of our approach indicates that the tendency of compounds to form 1 : 1 adducts in homolytic cycloaddition decreases in the order: 6-membered 1,4-dithianes > 7-membered 1,4-dithiepanes > 8-membered oxathiocanes > 9-membered crown thioethers and then increases on going to 12- and 13-membered crown thioethers. The tendency to form 2 : 2 adducts, *viz.*, 14-, 16-, and 18-membered crown thioethers, becomes more pronounced on going from 1,3- and 1,4-dithiols to 1,5-dithiols. From the products of reactions leading to 14- and 16-membered rings, the corresponding 21- and 24-membered crown thioethers were also isolated. Unlike macrocyclization giving 1 : 1 adducts, *viz.*, 12- and 13-membered crown thioethers, which is initiated only by the $Pr_3B—O_2$ system, homolytic cycloaddition yielding larger rings, 2 : 2 and 3 : 3 adducts, *viz.*, 14-, 16-, 18-, 21-, and 24- membered crown thioethers, can be initiated both by the $Pr_3B—O_2$ system and by AIBN, *i.e.*, these rings can also be "assembled" in the absence of the assumed template effect of the intermediate organoboron compounds.

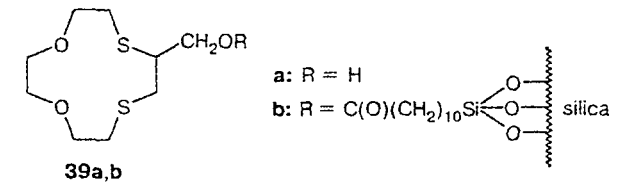
6. Complex-forming ability of 1,4-dithiacyclanes and crown thioethers

The extensive development of the chemistry of crown thioethers over the past two decades[40] has largely been caused by the interest in these compounds as ligands, whose complexes with metals exhibit unusual properties in biological[41] and chemical systems.[42] Crown thioethers are also regarded as compounds that are of fundamental interest for medical applications.[43] They are widely used as reagents for selective extraction, ionophores for ion-selective electrodes, and modifiers for chromatographic sorbents in various branches of analytical chemistry.[44] However, general methods for the synthesis of crown thioethers are usually limited to their traditional "assembly" from dithiols and α,ω-dihalides under conditions of high dilution[45] or on a solid support.[46]

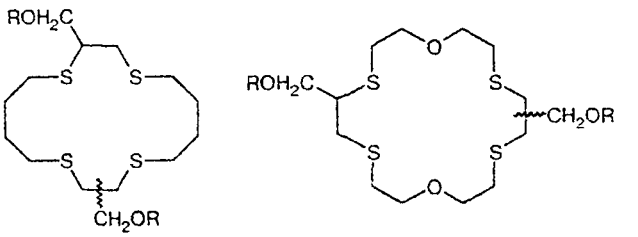
We studied the complex-forming ability of a number of heterocyclic compounds immobilized on a silica gel matrix and containing an SCH_2CH_2S fragment that were obtained using the methodology of homolytic cycloaddition.[47]

Immobilized reagents are insoluble in water and stable in solutions with low pH; they rapidly form insoluble complexes with metal ions. The analytical properties of macrocyclic compounds can be markedly improved by immobilizing them on the surface of appropriate organic or inorganic supports.[40,44,48—50] The properties of immobilized oxygen- and nitrogen-containing crown ethers have been studied fairly comprehensively, whereas the data on the synthesis and complex-forming properties of immobilized crown thioethers are quite scarce.[51]

Immobilization of hydroxymethyl-substituted 12-, 16-, and 18-membered crown thioethers **39a—41a** (which were prepared by homolytic cycloaddition of the corresponding α,ω-dithiols to propargyl alcohol) by covalent binding to a silica gel matrix "covered" with COOH groups (by treatment with trimethylsilyl 11-(triethoxysilyl)undecanoate) led to immobilized reagents **39b—41b**.



39a,b



40a,b **41a,b**

All the immobilized crown thioethers and 1,4-dithiacyclanes studied possessed substantial adsorption capacities with respect to Ag^{I}, Au^{III}, and Hg^{II} ions. However, reagents **39b—41b** exhibited no marked affinity for Ni^{II}, Co^{II}, Cd^{II}, Ge^{III}, Mg^{II}, and Ca^{II} ions. Among the reagents studied, **41b** containing a "grafted" 18-membered crown-thioether fragment proved to be the most efficient for removal and concentration of Ag^{I} and Au^{III} ions; for example, treatment of a test solution with reagent **41b** resulted in the removal of more than 90% of the Au^{III} ions. This makes it possible to regard **41b** as

well as **39b** and **40b** as promising reagents for concentrating gold from sea water.

This conclusion was confirmed by a study of the interaction of the transition metal ions Ag^{I}, Au^{III}, Hg^{II}, Cu^{II}, and Pd^{II} with composite carbon-paste electrodes chemically modified by the addition of **39b—41b**, carried out by cyclic voltammetry. These electrodes made it possible to improve markedly the voltammetric parameters of the redox behavior of Ag^{I} and Au^{III} ions under hydrodynamic conditions. It was found that these parameters depend substantially on the number of electron-donating sulfur atoms in the molecules of crown thioethers **39a—41a** fixed on the hydrophobic silica gel matrix incorporated in the electrode; the effect of crown thioethers as ligands on the electroreduction of Ag^{I}, Au^{III}, and other transition metal ions correlates well with the sorption properties of modifiers **39b—41b** with respect to these metals. A composite carbon-paste electrode containing **41b** (18-membered crown thioether deposited on a silica gel matrix) ensured the best conditions for the determination of gold and iron ions by flow injection analysis, which allows one to regard it as a quite promising electrode for the development of electrochemical sensor systems for detecting these ions.

* * *

We believe that our approach to homolytic macrocyclization is fairly general for the chemistry of free-radical processes and the chemistry of heterocyclic compounds, because it has already been used successfully in a one-pot synthesis of 1,4-dithiacyclanes and crown thioethers. However, a comprehensive study of all the possible fields of application of this approach and its limitations is probably a task for the future.

If it is possible to extend the methodology developed for S-centered radicals to C-centered radicals (*cf.* Scheme 1), this would mean the development of a free-radical alternative to the Diels—Alder cycloaddition reaction.

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