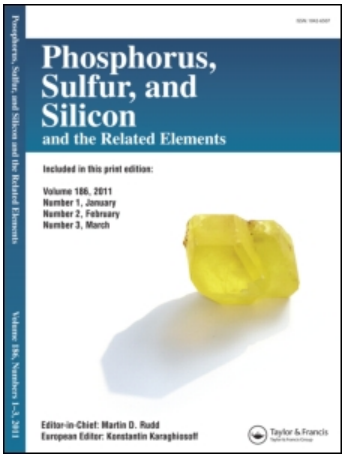

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Homolytic Cycloaddition: Novel Approach to the Construction of Sulfur-Containing Heterocycles and Crown Thioethers

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To cite this Article Troyansky, Emmanuil I.(1994) 'Homolytic Cycloaddition: Novel Approach to the Construction of Sulfur-Containing Heterocycles and Crown Thioethers', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 55 — 69
To link to this Article: DOI: 10.1080/10426509408034201
URL: http://dx.doi.org/10.1080/10426509408034201

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95-96, pp. 55-69
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HOMOLYTIC CYCLOADDITION: NOVEL APPROACH TO THE CONSTRUCTION OF SULFUR-CONTAINING HETEROCYCLES AND CROWN THIOETHERS

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A new general methodology for the construction of sulfur-containing heterocycles and crown thioethers based on facile, one-step 'assembling' of these molecules from α,ω-dithiols and alkynes via homolytic cycloaddition is developed.

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

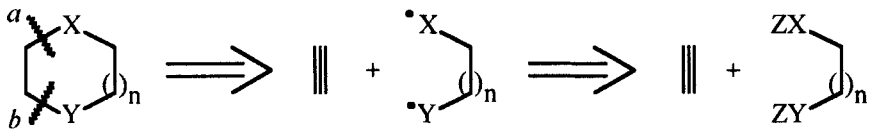
INTRODUCTION

Sulfur-hydrogen bond in thiols and other S-H substrates can be readily cleaved homolytically upon treatment with oxygen, peroxides, and other initiators of free radical reactions to produce thiyl and related sulfur-centered radicals which determines the extensive use of these reactions in the synthesis of organosulfur compounds. The most general method for the construction of new carbon-sulfur bonds is based on homolytic addition of compounds with thiolic S-H functions to multiple bonds of alkenes and alkynes.[1-3] Both intermolecular alkylation of sulfur atoms in thiols [1-3] and intramolecular homolytic cyclization of alkenthiols into saturated sulfur heterocycles (thiacyclanes) have been accomplished. [4] Only a few reactions of the latter type were published,[5] although the employment of free radical transformations of S-H compounds seems to be especially highly promising in the versatile synthesis of different sulfur-containing heterocycles.

HOMOLYTIC CYCLOADDITION - GENERAL CONCEPT

Retrosynthetic analysis enables to select the simplest synthetic routes and also to generalize the mechanisms of the known reactions, in particular of several free radical processes. [6]

In 1990 at the 14th International Symposium of Organic Chemistry of Sulfur (Lodz, Poland) we claimed for the first time that according to the retrosynthetic consideration each cyclic molecule can be 'cut' at two bonds marked (*a* and *b*) and alkynes correspondingly might be used as universal two-carbon synthons in cyclic system construction. The second reaction partner should possess two 'weak', readily homolizable X-Z and Y-Z bonds (Scheme 1).



SCHEME 1.

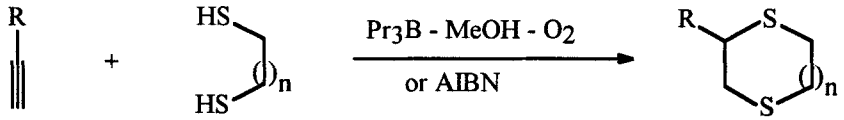
According to the proposed approach in **homolytic cycloaddition**, based on **intermolecular** free radical addition, preliminary synthesis of the precursor with suitable arrangement of the multiple bond and radical center is not necessary, which can be considered as a serious advantage as compared with **intramolecular** homolytic addition (cyclization).

The idea of homolytic cycloaddition was successfully realized in the synthesis of sulfur-containing heterocycles including crown thioethers.

SYNTHESIS OF 1,3- AND 1,4-DITHIACYCLANES

We have found that alkynes **1** react with 1,2- and 1,3-dithiols **2** in the presence of radical initiator to give 1,3- and 1,4-dithiacyclanes via heterocyclization. [7]

From the monosubstituted alkynes **1a-f**, bearing alkyl substituents at C≡C bond, and 1,2-ethanedithiol (**2** n=1) or 1,3-propanedithiol (**2** n=2) 2-substituted 1,4-dithianes (**3** n=1) or 1,4-dithiepanes (**3** n=2) were formed regiospecifically upon treatment with the system Pr_3B-MeOH-O_2 (oxygen was present, since the mixture was not exhaustively degassed) in benzene or THF (**1** : **2** : Pr_3B : MeOH =1:1:1:4) at ambient temperature or with AIBN in benzene (**1** : **2** : AIBN =1:1:0.15).



1 **2** **3**

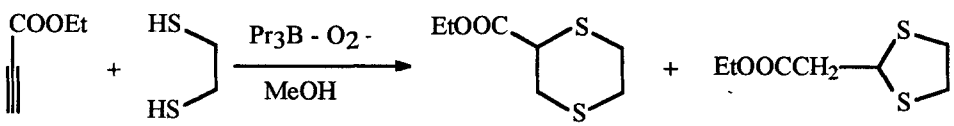
Yield 40 - 70%

1 R= C_4H_9 (**a**), C_6H_{13} (**b**), CH_2OH (**c**), CMe_2OH (**d**), CH_2OTHP (THP, tetrahydropyran-2-yl) (**e**), CH_2Cl (**f**).

SCHEME 2.

Heterocyclization to afford six-membered 1,4-dithianes (**3** n=1) proceeded more efficiently than similar reactions of the same alkynes to give seven-membered 1,4-dithiepanes (**3** n=2). In the 1,4-dithianes series the yields of heterocyclization products were markedly increased (from 48% to 67%) when 2-alkyl derivatives (**1a,b**) were replaced by hydroxyalkyl compounds (**1c-e**). Similar effect was also observed in the formation of 1,4-dithiepanes. The initators used (the Pr_3B-MeOH-O_2 system or AIBN) were equally effective in the heterocyclization. The Pr_3B-based system has the pronounced advantage since the reaction can be performed at ambient temperature, whereas AIBN requires boiling in benzene. The presence of Pr_3B is essential for the heterocyclization to proceed, because no 1,4-dithiane was formed on passing oxygen through a mixture of alkyne, 1,2-ethanedithiol, and methanol in benzene. The yields of **3** were slightly higher when THF was used as a solvent instead of benzene.

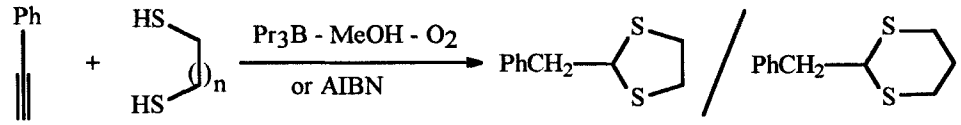
Functional substituents attached directly to triple bond critically affected the mode of addition to this bond and the structure of dithiacyclanes formed. Thus, in the reaction of (**2** n=2) with ethyl propiolate (**1g**) 1,2-addition to C≡C bond to give 2-ethoxycarbonyl-1,4-dithiane was only the minor reaction pathway and 1,1-addition to form isomeric 2-ethoxycarbonylmethyl-1,3-dithiolane prevailed, the ratio of competing 1,2- and 1,1-additions was 1:2.5 (Scheme 3).



1g **2** (n=2)

SCHEME 3.

The latter type of addition of thiyl radicals to the same terminal carbon occured with complete selectivity in the course of heterocyclization of dithiols with phenylacetylene. The reaction regiospecifically afforded 2-benzyl-1,3-dithiolane **4a** and 2-benzyl-1,3-dithiane **4b** (Scheme 4).

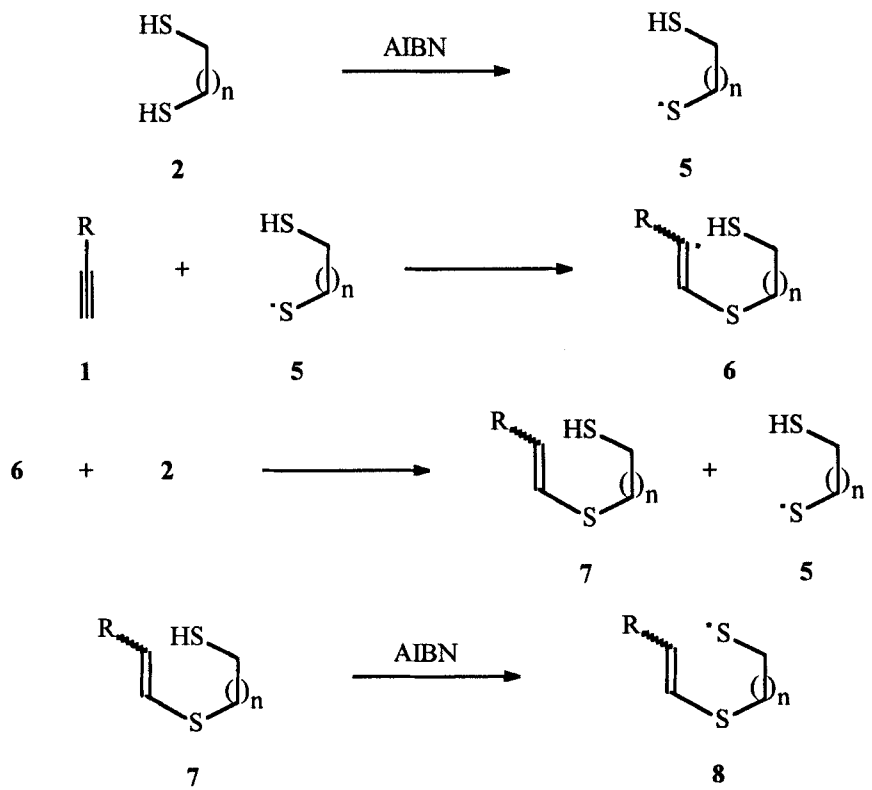


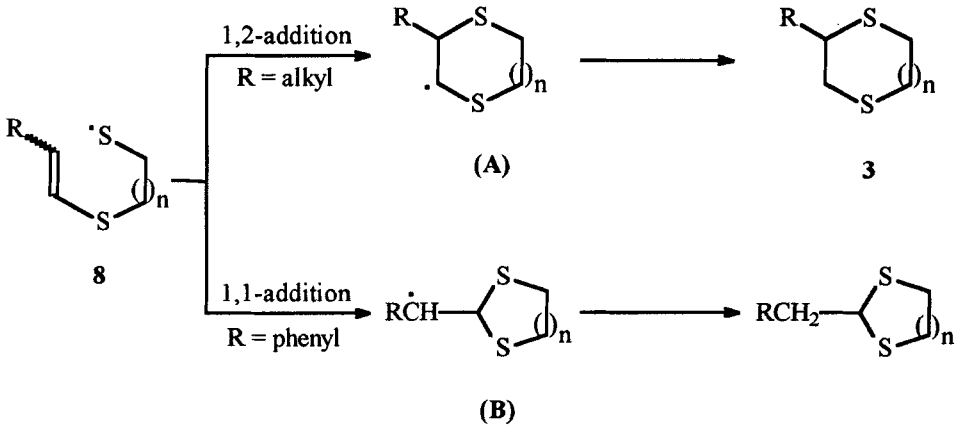
4a **4b**

SCHEME 4.

The reaction of dithiols with alkynes provides therefore a general method for the synthesis of five-, six- and seven-membered 1,3- and 1,4-dithiacyclanes.

The mechanistic scheme of the reactions studied is presented in Scheme 5. For AIBN-initiated heterocyclization, usual homolytic mechanism involving successive inter- and intramolecular addition of thiyl radicals to the multiple bonds is supposed.





SCHEME 5.

The mode of cyclization is determined by the stability of the alternative primary reaction products, cyclic radicals (A) and (B). In fact, in the absence of any additional stabilizing factors, radicals A are considerably more stable as compared with B. For this reason 1,4-dithiacyclanes are formed if R is an alkyl substituent. On the contrary, in the case when R is phenyl, the corresponding benzyl-type radicals B are more stable and are transformed further into 1,3-dithiacyclanes. The reaction with R=ethoxycarbonyl represents an intermediate pattern.

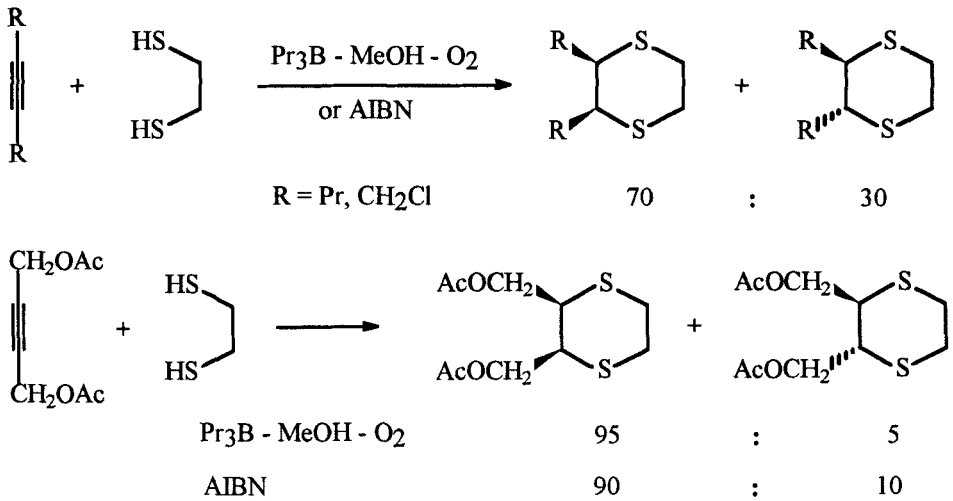
In the reactions induced by Pr_3B-MeOH-O_2, it is known that tripropylborane undergoes autooxidation extremely readily if even traces of oxygen are present, and propyl radicals are generated owing to homolytic substitution at boron atom. [8] Only these radicals induce the heterocyclization process (Scheme 6). The intermediate formation of organosulfurboron compounds is also quite probable. In particular case this suggestion was proved in a model reaction of 1,3,2-dithiaborolane with alkyne in the presence of O_2 and MeOH which afforded the corresponding dithiane. We consider this system, which only recently has been put to use more or less extensively for initiation of radical processes,[9] to be a universal mild initiator. Its employment in our studies enabled to supress significantly dimerization of thiyl radicals and to carry out all reactions unambiguously under kinetic control.

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

$$Pr\cdot + \mathbf{2} \longrightarrow PrH + HSCH_2(CH_2)_nS\cdot \quad \mathbf{5}$$

SCHEME 6.

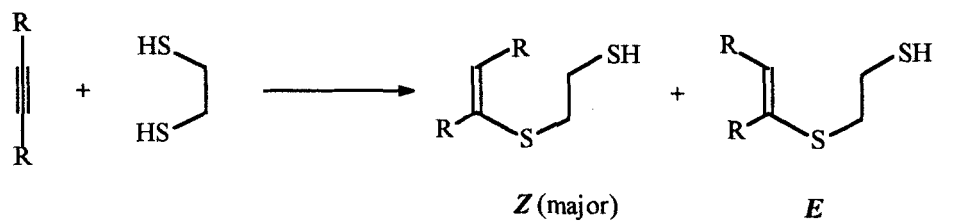
We found the homolytic heterocyclization reactions of α,ω-dithiols with disubstituted alkynes to be *cis*-stereoselective while the degree of stereoselectivity strongly increased on transition from 4-octyne and 1,4-dichloro-2-butyne to 1,4-butynediol diacetate (Scheme 7).[10] The ratio of diastereoisomers were practically independent of the initiator nature.



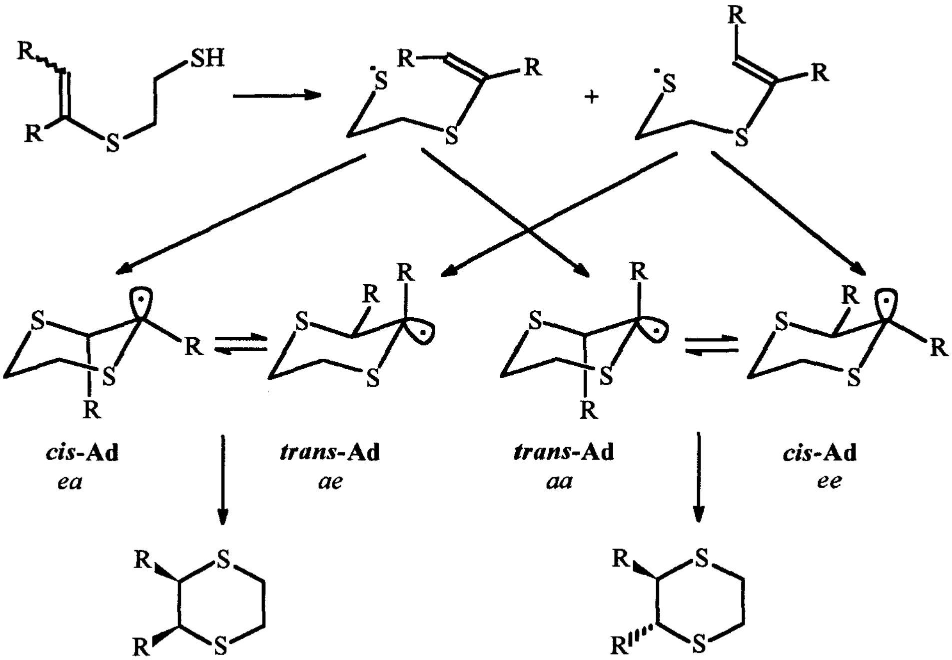
SCHEME 7.

Model experiments have shown that homolytic addition of dithiols to triple bonds proceeds predominantly as *trans* reaction and *Z* thiosubstituted olefinic products prevail. Conformational analysis of the transition state for intramolecular homolytic addition to double bond of these alkenes demonstrated the preference of *cis* reaction. Therefore, a combination of *trans* radical addition to triple bond and *cis* intramolecular radical addition determines the observed *cis*-stereoselectivity of homolytic heterocyclization (Scheme 8).

1. *trans* Radical Addition (*trans* Ad_R) to C≡C bond



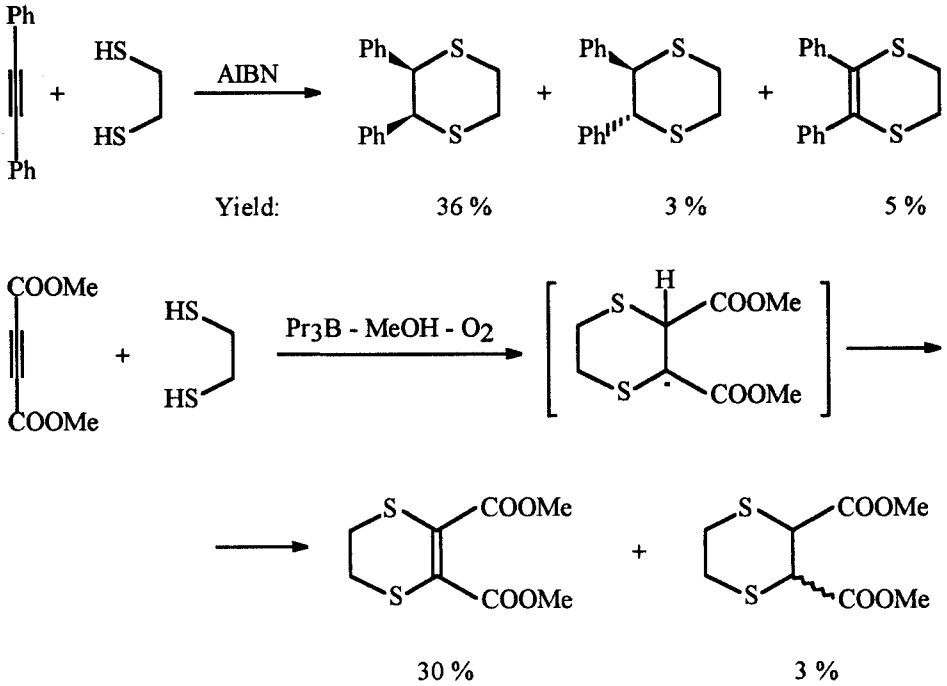
2. *cis* Radical Addition (*cis* Ad_R) to C=C bond



trans-Ad_R (C≡C) + *cis*-Ad_R (C=C) ⇒ *cis*-Heterocyclization

SCHEME 8.

Variation of substituents in disubstituted alkynes enabled to affect principally the type of heterocycle formed. With 1,2-diphenylacetylene the reaction yielded *cis* -2,3-diphenyl-1,4-dithiane with high stereospecificity, while unsaturated product, 5,6-diphenyl-2,3-dihydro-1,4-dithiin was isolated as a side-product. The situation changed dramatically on transition to dimethyl acetylenedicarboxylate. The main product of the reaction was 5,6-bis(methoxycarbonyl)-2,3-dihydro-1,4-dithiin, whereas its saturated analog was detected only as a minor component. We propose that the intermediate cyclic radical-adduct readily eliminates significantly mobile hydrogen atom due to captodative effects with the formation of 1,4-dithiin cycle (Scheme 9).



SCHEME 9.

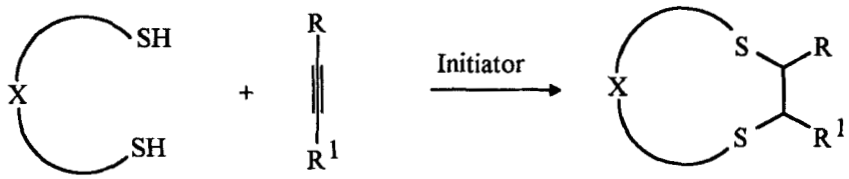
The detailed conformational analysis of 2-monosubstituted and 2,3-disubstituted 1,4-dithianes was performed by means of ^1H NMR spectroscopy and MMX calculations.[11,12]

SYNTHESIS OF CROWN THIOETHERS

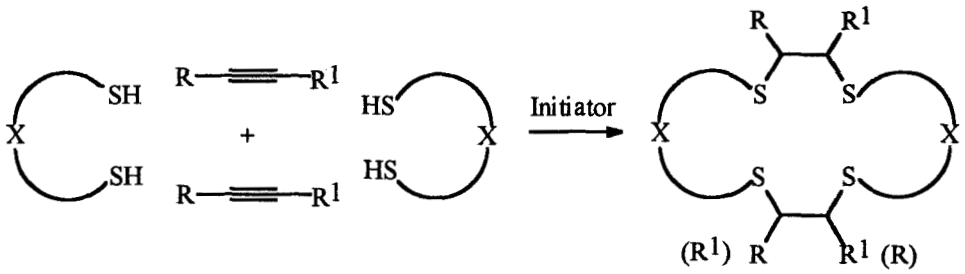
The approach developed was successfully extended to the 'assembling' of various crown thioethers via homolytic cycloaddition of alkynes with corresponding dithiols. Crown thioethers thus prepared differ in their ring size, number and type of heteroatoms (sulfur, oxygen, in some cases also nitrogen) and their mutual location, as well as in substituents.

General Aspects. [13] We have found that radical cycloaddition can be widely employed in the design of crown thioethers in two main ways, first, as 1:1 products (Scheme 10, path I) and/or second, as 2:2 products of cycloaddition (Scheme 10, path II), *i.e.*, crown thioethers produced contain one or two units of both starting dithiol and alkyne, respectively. In some cases, 3:3 products of cycloaddition were isolated as well. Actually, the same initiators, namely Pr_3B-O_2-MeOH and AIBN, we have used in the synthesis of dithianes and dithiepanes, promote the formation of crown thioethers.

Path I. ***Design of CTE as 1:1 products of homolytic cycloaddition***



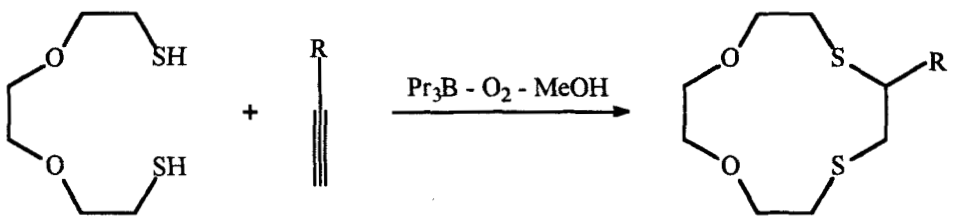
Path II. ***Design of CTE as 2:2 products of homolytic cycloaddition***



X= $(CH_2)_n$, $(CH_2)_mQ(CH_2)_{n-m}$, where Q = S, O, NH
Initiator: Pr_3B-O_2-MeOH, AIBN, *etc.*

SCHEME 10.

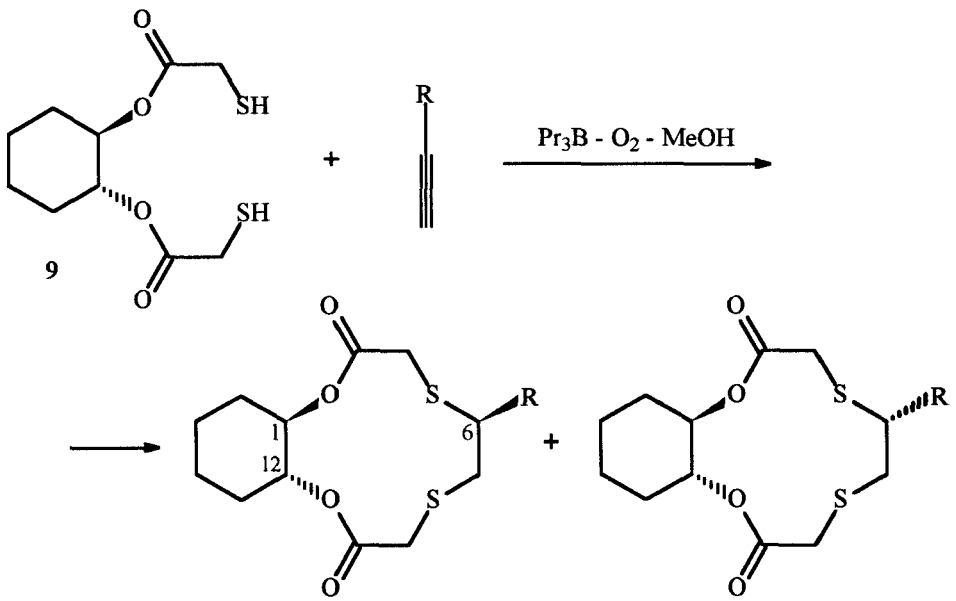
12-Membered Crown Thioethers. According to path I a concise and facile one-step synthesis of 12-membered crown thioethers was developed (Scheme 11).[14] The reaction proceeded readily and isolation of crown thioethers did not cause any problem. Starting dithiol as well as other dithiols, the reactions of which will be discussed further, belongs to readily available sulfur analogs of oligoethylene glycols. It should be specified that no crown thioethers were formed in reasonable amounts when we attempted to initiate macrocyclization with AIBN. It enables us to suggest that boron-containing species formed in the course of Pr_3B-promoted reaction could play the role of template to organize macrocycle 'assembling'.



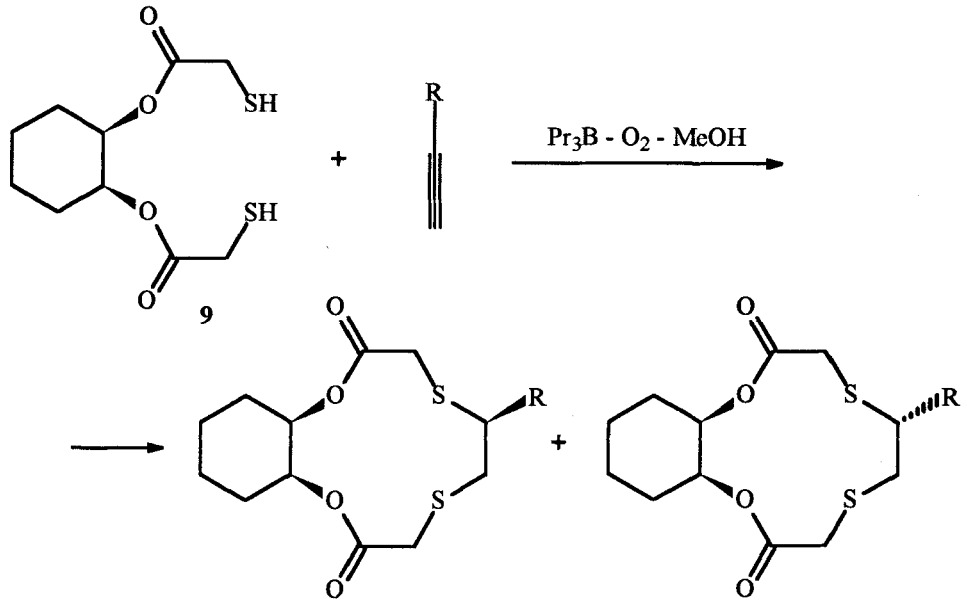
R = Me, Bu, CH_2OMe Yield 25-30%

SCHEME 11.

Remote Asymmetric Induction in the Synthesis of Cyclohexano-Fused 12-Membered Crown Thiolactones. This reaction was extended to the synthesis of the corresponding 12-membered crown thiolactones, and a family of lactones bearing functional substituents, important for further transformations, was synthesized. Cycloaddition of alkynes with diester of *trans*-1,2-cyclohexanediol **9** occured with unexpectedly high stereoselectivity to produce mixtures of (1*R**, 6*S**, 12*R**)- and (1*R**, 6*R**, 12*R**)-stereoisomers of bicyclic crown thiolactones **10** in the ratio 2 -3 : 1 (overall yields ~ 30%). The structure of major (1*R**, 6*S**, 12*R**)-steroisomers, which were isolated from these mixtures, were proved by X-ray analysis (Scheme 12.) It is interesting to note that no pronounced stereoselectivity was observed in cycloaddition of diester of *cis*-1,2-cyclohexanediol. The reasons which determine high level of remote asymmetric induction in free radical macrocyclization of **9** with alkynes are now under investigation.



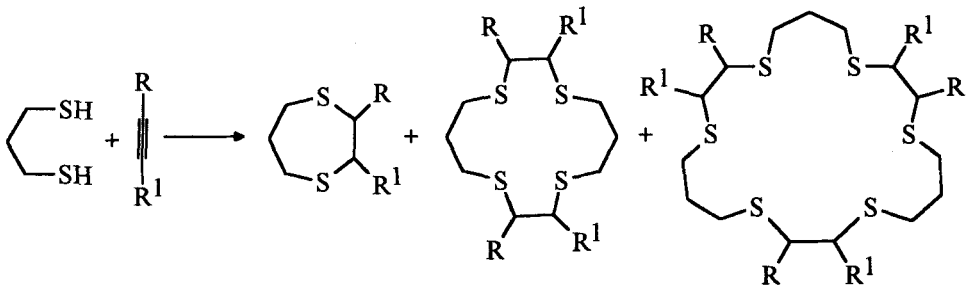
R	(1*R**, 6*S**, 12*R**)-**10**		(1*R**, 6*R**, 12*R**)-**10**
Me	2.1	:	1
Bu	2.3	:	1
CH_2OMe	3.1	:	1



R = Me, Bu, CH_2OMe ~ 1 : 1

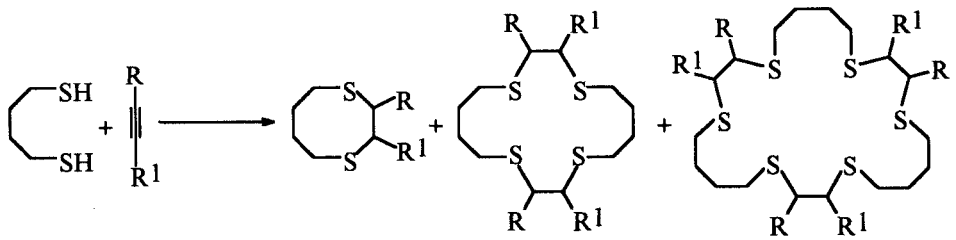
SCHEME 12.

14- and 21-Membered Crown Thioethers.[13] After additional consideration of the reaction of 1,3-propanedithiol with alkynes from the viewpoint of macrocyclization it was found that 14- (2:2 cycloadducts) (yield 3-9%) and even 21-membered crown thioethers (yield ~ 5%) (3:3 cycloadducts) can be synthesized together with 1,4-dithiepanes (1:1 cycloadducts). The process was controlled by alteration of concentration that provided an increase in macrocyclization contribution to the overall process. The ratios of both types of crown ethers formed also depended on the concentration of the starting reagents, however non-regularly (Scheme 13).



SCHEME 13.

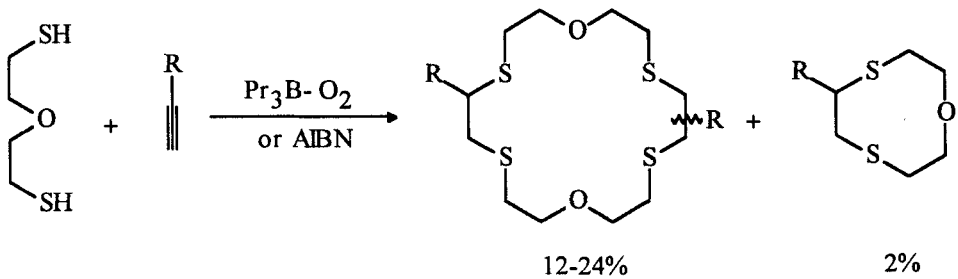
16- and 24-Membered Crown Thioethers. A similar reaction of 1,4-butanedithiol offered a way to 16- and 24-membered crown thioethers (Scheme 14). It may be noted that in contrast to the previous reaction of 1,3-propanedithiol 8-membered 1:1 adduct was formed in a very low amount if at all. It reflects common disadvantage and problems in construction of 8-membered rings of all types. The main undesirable side-reaction, which competed effectively with homolytic cycloaddition, was intramolecular oxidation (oxidative self-cyclocondensation) of the starting 1,4-dithiol into the corresponding 6-membered 1,2-dithiane.



R, R^1 = Me, Bu, C_6H_{13}, CH_2OH, CH_2OMe.	Yield ~ 1 - 4 %	6 - 12 %	7 - 17 %

SCHEME 14.

9- and 18-Membered Crown Thioethers.[15] The next macrocyclization reaction, which was probably the most extensively studied by us, is the cycloaddition of 3-oxa-1,5-pentanedithiol with alkynes. This afforded 18- and 9-membered crown thioethers, and the former strongly predominated among the reaction products (Scheme 15). This result is predictable, since as it was discussed above, is determined by common difficulties in the synthesis of 9-membered cyclic compounds.



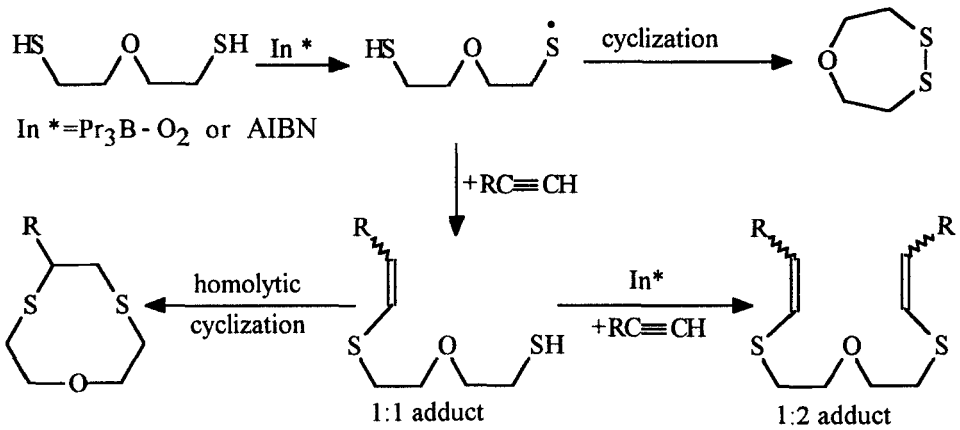
12-24% 2%

SCHEME 15.

Examination of the reaction mechanism and a number of special experiments carried out with model compounds allowed one to suggest the following reaction

schemes for the 'assembling' of crown thioethers, which we believe are also valid for other related processes.

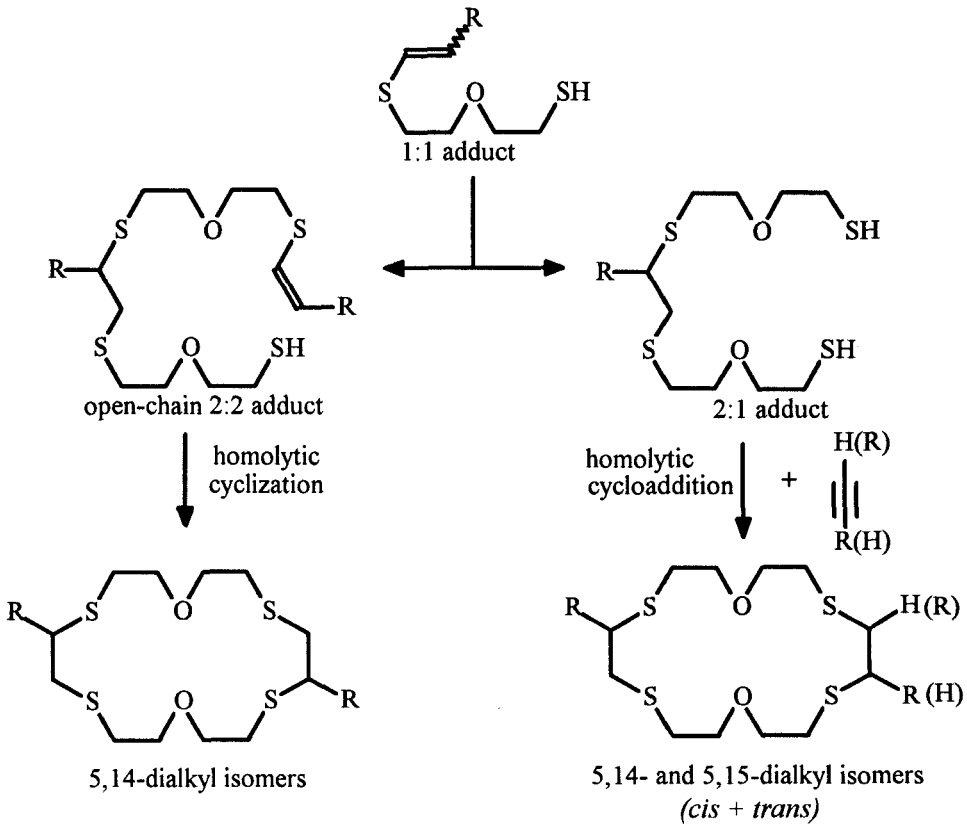
First of all, free radical addition of thiyl radicals to triple bond leads to open-chain 1:1 adduct, which serves as a key precursor in the formation of both 9- and 18-membered crown thioethers. In fact, upon homolytic cyclization 1:1 adduct transforms into 9-membered crown ether and, on the other hand, it may react with the second molecule of dithiol or alkyne giving two alternative 2:1 and 1:2 adducts (Scheme 16).



SCHEME 16.

Model experiments have shown that no 18-membered crown thioethers are formed via the second path, *i.e.*, via the reaction of 1:2 adduct with dithiol. The most probable mechanism of the reaction is depicted in Scheme 17. As regards 18-membered cycle formation, an open-chain 1:1 adduct adds the second molecule of the starting dithiol. Subsequent homolytic cycloaddition to the intermediate 2:1 adduct gives crown ethers as mixtures of all (four) possible regio- and stereoisomers, usually in approximately equal amounts.

The exact determination of the structure of each isomer formed and complete assignment of the signals in NMR spectra is very difficult, although it remains one of our main goals. It should be noted especially that even a mixture of stereoisomers of dibutyl substituted crown ethers exhibited quantitative selectivity toward a mixture of mercury and silver ions, which allows one to achieve complete selectivity in separation of mercury ions from silver ions. A number of studies on complexation ability and other properties of synthesized crown thioethers are now in progress.



SCHEME 17.

Comparison of yields of heterocycles of different size thus prepared demonstrates that the tendency to form 1:1 adducts of homolytic cycloaddition decreases in the series: 6-membered 1,4-dithianes > 7-membered 1,4-dithiepanes > 8-membered oxathiocanes > 9-membered crown thioethers with subsequent increase in the case of 12-membered crown thioethers. The tendency to give 2:2 adducts becomes much more pronounced on transition from 1,3- and 1,4-dithiols to 1,5-dithiols, the 14-, 16- and 18-membered crowns are formed. In addition to 14- and 16-membered cycles corresponding 21- and 24-membered thiocrown ethers are also isolated.

We believe that approach presented above to homolytic macrocyclization is of general significance since a number of families of crown thioethers has been already synthesized. However we realize that complete determination of the scope and limitations of this approach still could require great efforts.

In the event the methodology widely developed for S-centered radicals can be extended to C-centered analogs (*cf.* Scheme 1), it could mean a creation of free radical alternative of Diels-Alder cycloaddition.

ACKNOWLEDGEMENT

I am indebted to all members of my research team and other collaborators who actively participated in the accomplishment of this work.

REFERENCES

1. F.W.STACEY and J.F.HARRIS, JR., in Organic Reactions (John Wiley & Sons, Inc., New York - London, 1963), **13**, 150 - 376.
2. K.GRIESBAUM, Angew.Chem., Int. Ed., **9**, 273-287 (1973); O.ITO and M.D.C.M.FLEMING, J. Chem. Soc. Perkin Trans. II, 689-693 (1989).
3. L. BENATI, P.C.MONTEVECCHI, and P.SPAGNOLO, J. Chem. Soc. Perkin Trans. I, 2103 - 2109 (1991).
4. J.-M.SURZUR, in Reactive Intermediates, edited by R.A.Abramovitch (Plenum Press, New York, 1982), vol. 2, 121 - 295.
5. D. HARROWVEN, Tetrahedron Lett., **34**,5653-5656 (1993).
6. D.P.CURRAN, SynLett, 63-72 (1991).
7. D.V.DEMCHUK, A.I.LUTSENKO, E.I.TROYANSKY, and G.I.NIKISHIN. Bull. Acad. Sci. USSR. Div. Chem. Sci. (Engl. Translation), **39**, 2542-2550 (1990).
8. B.M.MIKHAILOV and YU.N.BUBNOV, Izvestia AN SSSR. Ser.Khim., 2248 (1964).
9. Y.ISHINOSE, K.MAKAMATSU, K.NOZAKI, J.-L.BIRBAUM, K.OSHIMA, and K.UTIMOTO, Chem. Lett., 1647- 1650 (1987).
10. E.I.TROYANSKY, YU.A.STRELENKO, D.V.DEMCHUK, V.V.SAMOSHIN, A.I.LUTSENKO, and G.I.NIKISHIN, Bull. Acad. Sci. USSR. Div. Chem. Sci. (Engl. Translation), **40**, 1629-1636 (1991).
11. YU.A.STRELENKO, V.V.SAMOSHIN, E.I.TROYANSKY, D.V.DEMCHUK, G.I.NIKISHIN, and N.S.ZEFIROV, Tetrahedron, **47**, 9455-9462 (1991).
12. YU.A.STRELENKO, V.V.SAMOSHIN, E.I.TROYANSKY, D.V.DEMCHUK, D.E.DMITRIYEV, G.I.NIKISHIN, and N.S.ZEFIROV, Tetrahedron, **50**, in press (1994).
13. E.I.TROYANSKY, D.V.DEMCHUK, R.F.ISMAGILOV, M.I.LAZAREVA, YU.A.STRELENKO, and G.I.NIKISHIN, Mendeleev Commun., 112-114 (1993).
14. E.I.TROYANSKY, M.I.LAZAREVA, D.V.DEMCHUK, V.V.SAMOSHIN, YU.A.STRELENKO, and G.I.NIKISHIN, SynLett, 233 - 234 (1992).
15. E.I.TROYANSKY, D.V.DEMCHUK, M.I.LAZAREVA, V.V.SAMOSHIN, YU.A.STRELENKO, and G.I.NIKISHIN, Mendeleev Commun., 48-49 (1992).