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First Synthesis of Macrocycles by Quadruple S$_{RN}$1 Reactions

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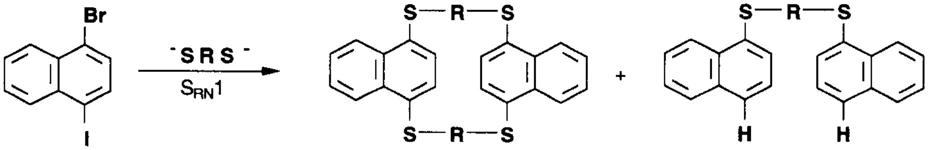
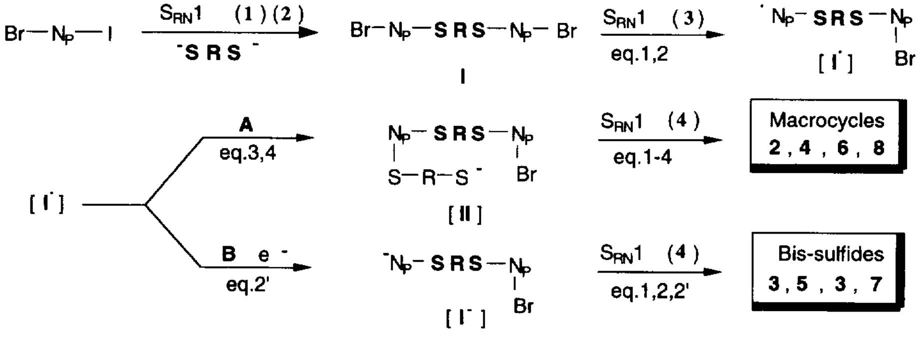
Abstract : 18, 20 or 22 membered heteromacrocycles are produced in one pot by quadruple S$_{RN}$1 photostimulated reactions between 1-iodo-4-bromo naphthalene and bidentate sulfanions $^-$SRS$^-$.

In reactions under S$_{RN}$1 conditions many thiolates $^-$SR are known to be efficient nucleophiles[1] whose behavior varies according to their structure and to that of the aryl halides used as substrates.[2] Among a great number of reactions, that of 1,2-diiodobenzene with $^-S(CH_2)_2S^-$ was reported[3] to give benzo-1,4-dithiane. The low yield of the double substitution leading to the cyclised product was ascribed to fragmentation reaction of the intermediate radical anion $[I\text{-}C_6H_4S\text{-}CH_2\text{-}CH_2\text{-}S^-]^{\bullet}$. The competition between this termination step and chain propagation leading to the expected product is known to occur for halobenzene but not for halonaphthalene substrates.[2] Thus, several *bis*-sulphides Np-**SRS**-Np have been obtained[4] from double S$_{RN}$1 reactions of 1- or 2-halonaphtalene with dithiolate anions $^-$**SRS**$^-$ and we report now reactions of *1,4-dihalonaphthalene* (Table).



1	R = $(CH_2)_3$	2	13% (dec.)	3	42% (68°)
	= $(CH_2)_4$	4	16% (175°-179°)	5	48% (73°)
	= $(CH_2)_2O(CH_2)_2$	6	16% (120°-124°)	7	45% (oil)
	= $(CH_2)_2S(CH_2)_2$	8	20% (164°-168°)	9	50% (oil)

Two series of products : macrocycles and *bis*-naphthalene sulfides were obtained[5] which resulted from S$_{RN}$1 reactions activated by light (no reaction in the dark). Their formation is rationalized on the Scheme.



The macrocycles **2**, **4**, **6**, **8** where four carbon-sulfur bonds are created clearly result from $S_{RN}1$ reactions (**1**) (**2**) (**3**) (**4**). Since I^- is a better leaving group than Br^-, one can guess that the first two reactions (**1**) (**2**) give the dibromo-*bis*-sulfide I and that the third reaction involving Br^- extrusion (eq 1, 2) gives rise to the radical [I$^\bullet$] from which two competitive pathways can take place.[6]

A Nucleophilic attack by $^-$**SRS**$^-$ leading to II (eq 3. 4) and therefrom to the macrocycles after ring closure by the fourth and ultimate $S_{RN}1$ reaction.

B Electron transfer[6] leading to the anion $^-$Np-**SRS**-NpBr [I^-] (eq. 2'). The same process occuring once more in the ultimate $S_{RN}1$ reaction could explain the formation of *bis*-sulfides from [I$^\bullet$] .

Such a sequence of four $S_{RN}1$ reactions is unprecedented in the literature.[7] Further work is in progress to provide support to the mechanistic scheme and to explore the potential of the one-pot synthesis of 18, 20 or 22 membered ring compounds containing a various number of sulfur and oxygen heteroatoms.

References and Notes

1. Rossi, R.A.; de Rossi. R.H. Aromatic Substitution by the $S_{RN}1$ Mechanism. ACS Monograph 178, Washington DC, 1982.
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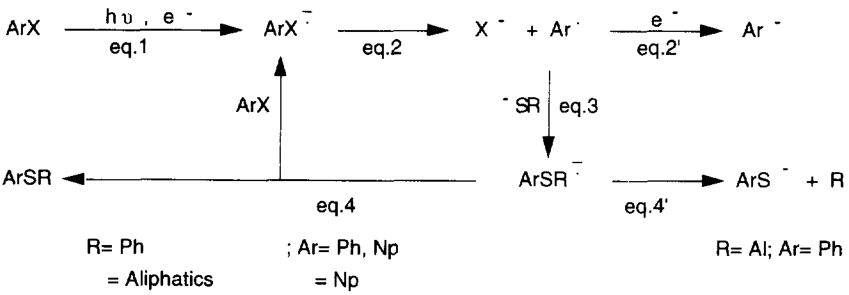
   The general mechanism in $S_{RN}1$ reactions with thiolates $^-$SR is described by eq.1 (Initiation) and eq 2-4 (chain propagation). The single product is the sulfide unless competitive reduction of Ar$^\bullet$ (eq. 2') or fragmentation of $ArSR^{\bullet-}$ (eq 4') occur, which are both termination steps leading to ArH or ArSH respectively.



3. Pierini, A.B., Baumgartner, M.T. and Rossi, R.A. *J. Org. Chem.*, **1987**, *52*, 1089-1092.
4. Beugelmans, R. and Ginsburg, H. *Tetrahedron Lett.*, **1987**, *28*, 413-414.
5. $S_{RN}1$ procedure. A solution of **1** (0.5 or 1 mmol) in liquid ammonia (25 ml) at -33°C, dithiol derivative and K-t-butoxide (2 or 4 mmol) is externaly illuminated by a 450 W Hanovia lamp through Pyrex for 180 min, under argon atmosphere. Quenching by NH_4Cl, water addition and extraction with CH_2Cl_2 followed by TLC purification give the products..

   Compounds **2**, **4**, **6**, **8**, **7**, **9** are new and have spectroscopic data (^1H, ^{13}C NMR, HRMS) in accordance with the structure. $SC\underline{H}_2$ typical ^1H NMR signals are observed for **2** (3,7, t, 8H, J = 6 Hz); **4** (2,85, m, 8H); **6** (3,41, t, 8H, J = 6 Hz); **8** (3,06, m, 8H). Bis- sulfides **3** and **5** are identical to samples of the previous study (Ref. 4). In all experiments, secondary products (oligomers ?) were observed, but are not yet characterized.
6. The electron involved in competitive reduction of Ar$^\bullet$ originates from the radical anion $ArX^{\bullet-}$ or $ArNu^{\bullet-}$. The fact that *bis*-sulfides are the major products might be due to intramolecular, and therefore very efficient electron transfer along pathway B.
7. Recent review : R.A. Rossi, A.B. Pierini and A.B. Penenory "Recent advances in the $S_{RN}1$ reaction of organic halides", Chap. 24 in Supplement D2 : The Chemistry of Halides, pseudo Halides and Azides (Ed. S. Patai and Z. Rappoport), J. Wiley and Sons, Chichester, 1995, p. 1395.

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