CHEMISTRY LETTERS, pp. 1517-1520, 1988.

A Novel Method for the Generation of Thial S-Sulfides from 2,4,6-Trisubstituted 5,6-Dihydro-1,3,5-dithiazines[1)]

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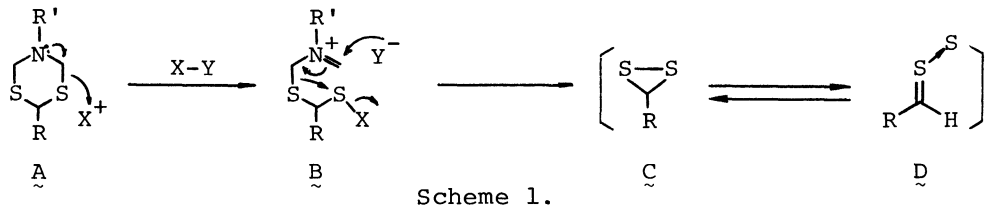
Treatment of 2,4,6-trisubstituted 5,6-dihydro-1,3,5-dithiazines with NCS or NBS afforded highly reactive thial S-sulfides, which underwent dimerization to give the corresponding 1,2,4,5-tetrathianes. The products were also selectively converted into naturally-occurring cyclic polysulfides, 1,2,4-trithiolanes and 1,2,3,5,6-pentathiepanes, by treatment with Ph_3P, KCN, or Na_2S_4.

Thiosulfine(thial S-sulfide) D is one of the highly reactive heterocumulenes having C=S=S functionality,[2)] and several methods for the transient generation of thiosulfines D or the isomeric dithiiranes C have been investigated.[3,4)] Those methods are roughly classified into (a) thiation of sulfinyl functionality by using P_2S_5 or its analogues, (b) polysulfurization of active methylene compounds by polysulfur dichlorides, and (c) decomposition of some functionalized disulfides. However, to date, no studies on stabilized thial S-sulfides have been made because of the difficulty of substrate preparation and occurrence of undesired reactions by the reagents. During course of our studies on the reactive heterocumulenes containing sulfur, we found that some heterocyclic compounds behave as new sources of reactive intermediates.[5)] From such a standpoint, oxidative fragmentation of 5,6-dihydro-1,3,5-dithiazine ring A initiated by some soft oxidative electrophiles X^+ would be expected to provide a new route for thiosulfines D or their chemical equivalents C as shown in Scheme 1. In this paper we would like to describe a



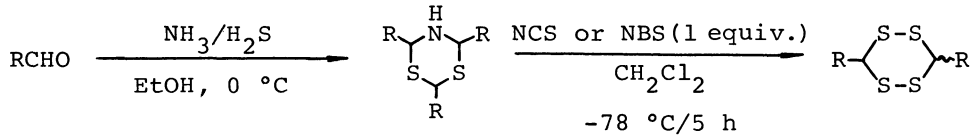
Scheme 1.

novel and convenient method for the conversion of 5,6-dihydro-1,3,5-dithiazines A into the corresponding 1,2,4,5-tetrathianes by the in-situ dimerization of thial S-sulfides D, which were generated by the oxidative fragmentation of A using NCS or NBS.

2,4,6-Trisubstituted 5,6-dihydro-1,3,5-dithiazines 2 used for this study were prepared from aliphatic and aromatic aldehydes 1, NH_3, and H_2S according to Kira's

method,[6] and the substrates 2 were then treated with NCS or NBS in CH_2Cl_2 at -78 °C to afford tetrathianes 3 in good yields as mixtures of cis and trans isomers. These results were shown in Table 1. Only when 3 possessed aromatic substituents,

Table 1. Preparation of 2,4,6-Trisubstituted 5,6-Dihydro-1,3,5-Dithiazines 2 and Conversion of 2 to 3,6-Disubstituted 1,2,4,5-Tetrathianes 3



1 2 3

RCHO		Yield/% of 2	NXS	Yield/% of 3	Cis/Trans
C_6H_5CHO	(1a)	61	NCS	72	3/2
C_6H_5CHO	(1a)	61	NBS[a]	29	3/2
C_6H_5CHO	(1a)	61	NBS	81	3/2
$4\text{-}CH_3OC_6H_4CHO$	(1b)	56	NBS	62	3/2
$4\text{-}CH_3C_6H_4CHO$	(1c)	61	NBS	75	4/3
$4\text{-}ClC_6H_4CHO$	(1d)	73	NBS	55	7/4
CH_3CHO	(1e)	32	NBS	30	-[b]

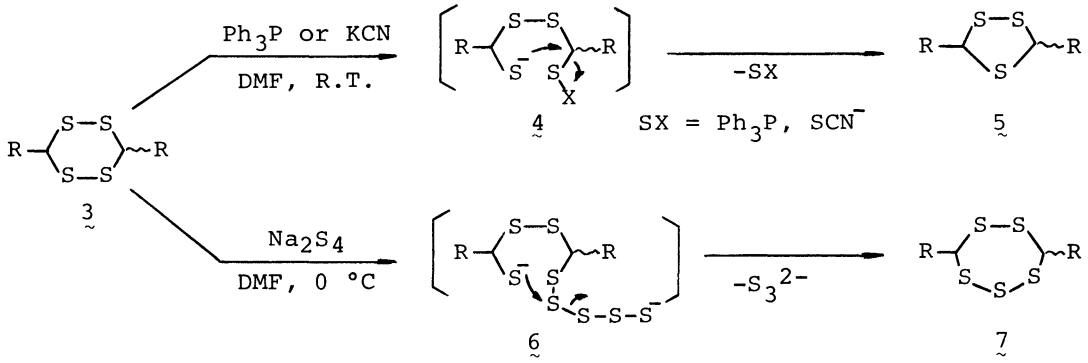
a) When 0.5 equiv. of NBS was used, 31% of 2a was recovered. b) Not determined.

isomers of 3a-d and 3a'-d' could be separated by SiO_2 column chromatography and the subsequent fractional recrystallization. However, surprisingly, isomers of 3a-d with lower melting points had a trend to undergo isomerization into the other isomers without exception during storage in the dark at room temperature. Structures of the products were confirmed not only ^1H NMR, IR, MS, and elemental analyses[7] but also by the comparision of their physical properties with those reported for 1,2,4,5-tetrathianes 3.[8,9] Furthermore, for the structual confirmation of 3, conversion of 3 into several naturally-occurring cyclic polysulfides attained as shown below was attempted.

Whenever cis/trans mixtures of 3a(R=Ph) and 3e($R=CH_3$) were treated with 1.1 equiv. of thiophilic reagents(Ph_3P or KCN), unseparable cis/trans mixtures of the corresponding 1,2,4-trithiolanes, 5a and 5e, respectively, were obtained in good yields along with $Ph_3P=S$ or SCN^-. One isomer of 5a(R=Ph) was identical with trithiolaniacin(cis-3,5-diphenyl-1,2,4-trithiolane) isolated from the root of *petiveria alliacea*[10] on the basis of ^1H NMR data, and the physical properties of both isomers 5e($R=CH_3$) were also identical in all respects with those reported for 1,2,4-trithiolane either isolated as a component of meat flavor[11] or synthesized.[12]

Next, 3f(R=H) was treated with 10 equiv. of Na_2S_4 in DMF at room temperature. 1,2,3,5,6-Pentathiepane 7f was isolated in 30% yield as colorless needles after separation by SiO_2 column chromatography. All physical data of 7f including ^1H NMR, IR, MS, and melting point were completely identical with those of naturally-occurring lenthionine isolated as an odorous substance of edible Shiitake mushroom(*Lentinus edodes*),[13] an antibiotic component from a red alga(*Chondria Californica*),[14] and of synthesized one reported by Still.[15] Ring expansion reaction also proceeded by the treatment of 3a(R=Ph) with Na_2S_4 to afford new

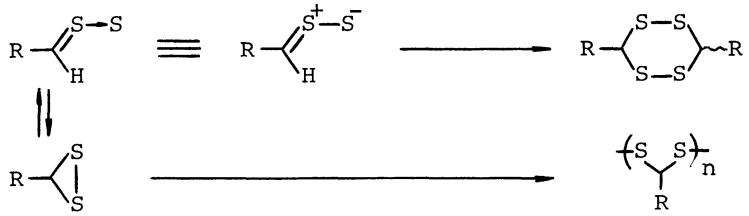
compounds assigned as cis/trans mixtures of 4,7-diphenyl-1,2,3,5,6-pentathiepane 7a in 18% yield along with 5a in 15% yield. The results of the both conversions indicate that 3 has a 1,2,4,5-tetrathiane ring system. These reactions may proceed through a pathway involving S-S bond cleavage of tetrathiane 3 by the thiophilic attack of nucleophiles as shown in Scheme 2.



Scheme 2.

It was already mentioned by several authors that thiosulfines effectively undergo dimerization to give 1,2,4,5-tetrathianes.[16] So our results might be explained by the transient existence of thial S-sulfides generated in the reaction system. Unfortunately attempts at the in-situ trapping of the intermediates with some olefins or acetylenes were not successful and 3 were isolated as the sole products in every case.

In conclusion, reactive thial S-sulfides were generated by the treatment of 5,6-dihydro-1,3,5-dithiazine ring 2 with NCS or NBS, and the intermediates underwent dimerization to give the corresponding 1,2,4,5-tetrathianes 3 in good yields by the route as shown in Scheme 3. This is the first example of non-stabilized aliphatic



Scheme 3.

and aromatic thial S-sulfides. In addition, selective transformation of 1,2,4,5-tetrathianes 3 into 1,2,4-trithiolanes 5 and 1,2,3,5,6-pentathiepanes 7 were achieved under mild reaction conditions. Some of these heterocycles are found as the components of meat flavors such as thialdine 2e, 3,6-dimethyl-1,2,4,5-tetrathiane 3e, 3,5-dimethyl-1,2,4-trithiolane 5e, and lenthionine 7f.[11,17,18]

Reactions of other oxidative electrophiles with 5,6-dihydro-1,3,5-dithiazines 2 for further transformations are now in progress.

References

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7) 3a(R=Ph): colorless needles, mp 178-179 °C, IR(KBr);700 cm^{-1}, ^1H NMR($CDCl_3$);δ 5.40(2H, s), 7.28-7.50(10H, m). 3a'(R=Ph): colorless solid, mp 103-104 °C, IR (KBr);700 cm^{-1}, ^1H NMR($CDCl_3$);δ 5.40(2H, s), 7.28-7.50(10H, m). 3b(R=4-$CH_3OC_6H_4$) : colorless needles, mp 184-185 °C, MS(m/e);368(M^+), 152(b.p.), IR(KBr);1250, 740, 680 cm^{-1}, ^1H NMR($CDCl_3$);δ 3.76(6H, s), 5.33(2H, s), 6.81(4H, d, J=8.0 Hz), 7.50(4H, d, J=8.0 Hz), Found: C, 51.87, H, 4.30%, Calcd for $C_{16}H_{16}O_2S_4$: C, 52.17, H, 4.35%. 3b'(R=4-$CH_3OC_6H_4$): colorless solid, mp 94-95 °C, MS(m/e);368(M^+), 152 (b.p.), IR(KBr);1250, 740, 680 cm^{-1}, ^1H NMR($CDCl_3$);δ 3.76(6H, s), 5.33(2H, s), 6.81(4H, d, J=8.0 Hz), 7.38(4H, d, J=8.0 Hz), Found: C, 51.79, H, 4.78%, Calcd for $C_{16}H_{16}O_2S_4$: C, 52.17, H, 4.35%. 3c(R=4-$CH_3C_6H_4$): colorless needles, mp 202-203 °C, ^1H NMR($CDCl_3$);δ 2.34(6H, s), 5.36(2H, s), 7.23(4H, d, J=8.0 Hz), 7.36 (4H, d, J=8.0 Hz). 3c'(R=4-$CH_3C_6H_4$): colorless solid, mp 83-84 °C, ^1H NMR($CDCl_3$) ;δ 2.34(6H, s), 5.36(2H, s), 7.23(4H, d, J=8.0 Hz), 7.50(4H, d, J=8.0 Hz). 3d (R=4-ClC_6H_4): colorless needles, mp 187-188 °C, ^1H NMR($CDCl_3$);δ 5.38(2H, s), 7.20-7.55(8H, m). 3d'(R=4-ClC_6H_4): colorless solid, mp 63-64 °C, ^1H NMR($CDCl_3$): δ 5.38(2H, s), 7.20-7.55(8H, m). 3e, 3e'(R=CH_3): colorless oil, MS(m/e);184(M^+), 59(b.p.), IR(oil);665 cm^{-1}, ^1H NMR($CDCl_3$);δ 1.66 and 1.67(6H, d, J=7.5 Hz), 4.41 and 4.61(2H, q, J=7.5 Hz). 3f(R=H): colorless needles, mp 125-127 °C, MS(m/e); 156(M^+, b.p.), IR(KBr);1350, 825, 690 cm^{-1}, ^1H NMR($CDCl_3$);δ 3.10-5.00(4H, m).
Relative stereochemistry of tetrathianes 3 bearing aromatic substituents could not be determined by the physical data noted above. From the analogy of α- and β-isomers of substituted 1,3,5-trithianes and by the difference of their thermodynamic stability, isomers 4a-d with higher melting points are assumed to be trans. But there is no evidence to support our assumption about the stereochemistry of 3 and 3'.
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(Received June 13, 1988)