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PREPARATION OF DITHIOSELENIDES *VIA* A SELENIUM TRANSFER REAGENT

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Abstract: The addition of two moles of thiol to a unique selenium-transfer reagent, bis azole selenide **4**, results in very good isolated yields of dithioselenides (RS-Se-SR).

Selenium is essential in living systems; it is believed to be transported *in vivo* as a dithioselenide of glutathione or cysteine or coenzyme-A.[2] More recently, Block and Uden[3] have discovered this class in low concentration in garlic; the positive effects of selenium even in these small amounts in the diet, is of considerable interest.

The only synthetic preparation of bis(alkylthio)selenides (1) reported to date is that shown in Eq. (1).[2c] The mechanism of this reaction has been examined.[4]

$$4\,\text{R-SH} + \text{H}_2\text{SeO}_3 \text{ -----> } \underset{\mathbf{1}}{\text{R-S-Se-S-R}} + \text{R-S-S-R} + 3\,\text{H}_2\text{O} \qquad \text{(Eq. 1)}$$

Although this method gives moderate yields of two variants of **1**, the dithioselenides are strongly contaminated (*ca.* 30-65%) with a variety of other products which are hard to remove; the disulfide and thiosulfonate (RSO_2SR) are the major impurities.

Because sulfur transfer reagents have had a long and successful history,[5] we sought to develop a selenium analogue to facilitate the preparation of dithioselenides and related compounds. There have been a number of reports of useful selenium reagents in the literature;[6] N-phenylselenosuccinimide **2** and N-phenylselenophthalimide **3** have been prepared previously from two routes. We published the first preparation of a bis-azole selenide **4**[7] and now wish to report its ability to serve as a selenium transfer reagent.

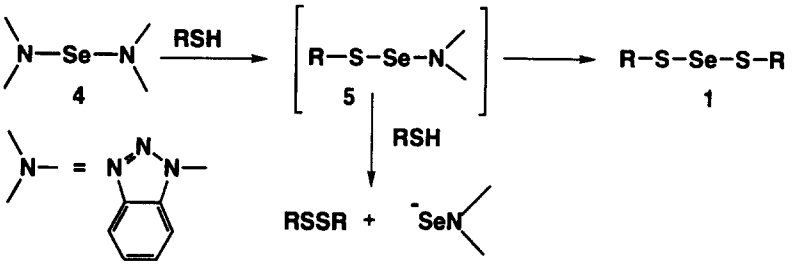
The preparation of reagent **4** was carried out as follows.[8] Two equiv. of N-chloro-benzotriazole were dissolved in 1 mL of dry CH_2Cl_2 under an argon atmosphere and cooled to -20 °C, whereupon the solute precipitate. One equiv. of diallyl selenide[7a] in 1 mL of CH_2Cl_2 was added dropwise *via* a syringe. The solution became homogeneous. This was allowed to warm to rt over 1 h, and a white precipitate was formed. The reaction mixture was stirred for 16 h and was triturated with 2 x 5 mL of dry hexanes with stirring. The

solid is very sensitive to moisture whereupon Se^o precipitates (mp 217 °C). Filtration affords the product in 25-50% yield.[7b]

In order to evaluate the reactivity of reagent **4**, various thiols were added dropwise to this suspension as solutions in dry solvents (hexanes, THF, CCl_4 CH_2Cl_2); the supernatant liquid turned yellow. The reaction mixture was stirred 2-3 h and filtered to remove the benzotriazole (nearly quantitative recovery). The resulting filtrate was condensed on 5g of silica gel and placed on top of a short silica column and eluted rapidly with hexane. Most of the reactions were carried out on 1-2 mmol scale or higher. The purity of the products was best when the reactions were carried out in CH_2Cl_2.

Recovery of the thiolate group (as the total of disulfide + dithioselenide) was nearly quantitative (*ca.* 98%). The yield of dithioselenide is given by its percentage composition in the mixture of disulfide with dithioselenide. Generally, high yields of dithioselenides were achieved, with very little disulfide produced; see the Table.

It is of interest to note that the greater the steric bulk of the thiol, the less the percentage of disulfide impurity. A working hypothesis is shown in the following Scheme. Dithioselenide **1** is clearly formed by consecutive thiol attacks on the selenium atom of **4** and subsequent intermediate **5**. The disulfide is produced by attack of thiol on the sulfur atom of intermediate **5**; from the relatively low yields of disulfide (1-5%) formed in most of the cases, the partitioning takes place by thiol reacting substantially with the selenium atom of **5** (Eq. 1). In the case of *n*-pentanethiol, a higher percentage of disulfide is formed.



When a concentrated solution of any of the thiols in CH_2Cl_2 was added to the reaction mixture, the precipitate disappeared rapidly after approximately one third of the thiol had been added; the solution then became yellow. After complete addition and stirring for 10 min, most of the solvent was removed and the concentrate chromatographed with hexanes on a short silica column. The resulting product mixture contained greater amounts of disulfides than when the solutions were more dilute. Ratios of RSSeSR/RSSR were highest at concentrations of thiol in CH_2Cl_2 of *ca.* 0.5.

With the azole sulfides the first step is faster than the second, permitting the preparation of unsymmetrical trisulfides;[3a] however, when one equivalent of an aliphatic thiol is added to **4** followed later by a different thiol, the resulting product mixture consists of *ca.* 43% RSSeSR, 12% RSSeSR', 42% R'SSeSR'. This indicates that the second step is faster than the first one, consuming all the thiol, and not permitting an accumulation of **4**. This contrasted with the results of adding a combined solution of two thiols in a competition experiment. As expected, a nearly statistical product mixture resulted (1:2:1), with some partitioning between the symmetrical products. The presence of unsymmetrical product may indicate some exchange with the free thiol of an intermediate.

The bis(alkylthio)selenides **1** were reacted with triphenylphosphine effecting the removal of the selenium atom; a small amount (5%) of triphenylphosphine sulfide was also detected. Parallel results[9] were found when trisulfides were reacted with triphenylphosphine; the central chalcogen (sulfur) is removed (*ca.* 95%).

The bis(alkylthio)selenides **1** also lost selenium on standing if any benzotriazole remained in the products. The least stable of the products were where R = *n*-pentyl and *i*-butyl which lost selenium gradually over several weeks; in contrast, the *t*-butyl isomer was very stable, eventually crystallizing (mp 34-35 °C). Minimization of the amount of disulfide present is important since it is impossible to purify the bis(alkylthio)selenides even by analytical HPLC. Distillation is possible for the lower boiling products, however, this was not possible for the cyclohexyl derivative. While the alkyl series of products may be passed through a column, the aryl series could not; elemental selenium was rapidly lost.

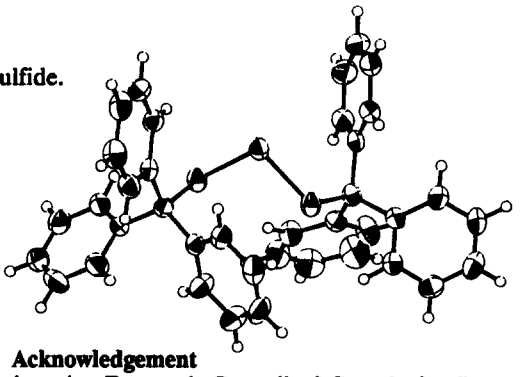
Table 1 Yields and Spectroscopic Data for RSSeSR' Products.[10]

R/R'	% Yield[b]	^{77}Se	M+(^{80}Se)[c]
t-butyl[a,b]	98	555	258
s-butyl[d]	96	595.7/595.3	
i-butyl[d]	90	715	
n-pentyl[d]	80	687	286
n-butyl[d]		687	
cyclohexyl[d]	92	601	310
t-butyl/*s*-butyl		576	
t-butyl/*n*-pentyl		620	
p-CH_3O-phenyl[e]	75	931	
phenyl[d]	92	867	298
trityl	90	695	

[a] mp 32.5-34.5 °C; λ_{max} 277 nm (log ϵ 3.2); [b] yields represent pure **1** appropriately adjusted with GC response factors; [c] the mass spectra for these compounds displayed the characteristic selenium cluster patterns.

The dithioselenide products were characterized by ^{77}Se, ^{13}C and ^{1}H NMR, mass spectrometry, GLC (3% ov101 cap. column, 80 to 230° C at 20°/min. using FID), and UV (k_{max} *ca.* 275 nm). These results are summarized in Table 1. In addition, the ditritylthioselenide was crystallized and its structure (first of this class of compound) determined by X-ray crystallography. Although in principle the molecule has an axis of symmetry about the selenium atom, crystal packing forces result in non-equivalent dihedral angles for the sulfur-selenium bonds; these are 100.3° and 86.3°. The C-S (1.893 Å) and S- Se (2.185Å) bond lengths as well as the C-S-Se (106.3°) bond angles also show slight asymmetry, however these are within the margins of error. The S-Se-S bond angle is 108.3° (Fig. 1).

Figure 1. Ortep plot of Dirityl-2-selenatrisulfide.



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