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The "Thio-Arbuzov" Reaction of Sulfenate Esters with Sulfenyl Chlorides: Fate of the Thiosulfinate Product.§

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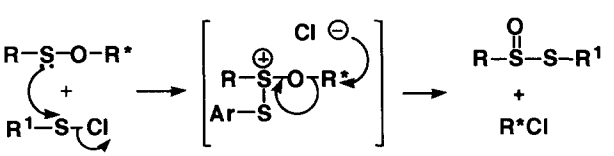
§ Dedicated to the memory of Zdenek Janousek.

Abstract: The further reaction of thiosulfinate esters (putative products of the "Thio-Arbuzov" reaction of sulfenate esters with sulfenyl chlorides) with sulfenyl chlorides and sulfenate esters has been studied. In the former case, sulfinyl chlorides and disulfides are formed. In the latter case sulfinate esters and disulfides are obtained.

Thiosulfinates have shown considerable biological activities,[1] these include anti-viral, and anti-bacterial properties.[2] Classically this interesting series of compounds has been isolated from crushed onions, garlic and leeks.[3] Two main methods of preparation are generally employed. The first utilises peracid oxidation, but is only useful for symmetrical thiosulfinates.[3a] Alternatively, condensation of a sulfinyl chloride with a thiol in the presence of a tertiary base, furnishes the thiosulfinate in excellent yield.[3b] A conceptually different approach would be to utilise the "Thio-Arbuzov" reaction.[4] If a sulfenate ester could be induced to follow this pathway, by interaction with a sulfenyl chloride (Scheme 1), the products should be the desired thiosulfinate and the corresponding haloalkane. Moore and O'Connor have fully investigated the preparation of alkyl sulfenate esters, and during this work claimed that thiosulfinate esters were formed as intermediates from the reaction of the sulfenates with sulfenyl chlorides.[5]

Scheme 1, The "Thio-Arbuzov" reaction.



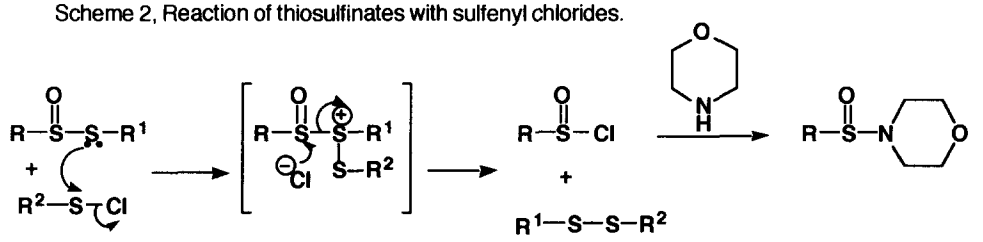
R = Aryl, R* = Menthyl, Me, R^1 = Aryl.

In practice on mixing equimolar amounts of a sulfenate ester and sulfenyl chloride a complex series of reactions ensues, ultimately yielding a sulfinate ester, disulfide and haloalkane. These complex "Thio-Arbuzov" reactions will be reported in full in due course. We felt that a likely explanation for the formation of the above products is the further reaction

of the labile thiosulfinate. In this communication we wish to report our findings on the reaction of thiosulfinates with both sulfenyl chlorides and sulfenate esters. Relatively few investigations into the chemistry of thiosulfinates have appeared in the literature, and mainly deal with their electrophilic properties. For example Kice *et al* have extensively studied nucleophilic attack on thiosulfinates, demonstrating two possible sites of attack for the nucleophile.[6]

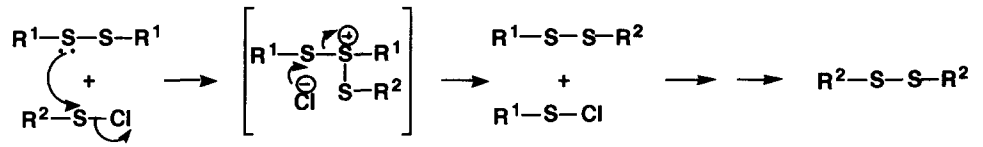
We chose firstly to study the reaction between thiosulfinates and sulfenyl chlorides.[7] Typically the thiosulfinate in $CDCl_3$ was added to the sulfenyl chloride (1eq) at -10°C, and the reaction monitored by ^1H NMR. When (S)-*p*-tolyl-*p*-toluenethiosulfinate was added to benzenesulfenyl chloride, the red colouration due to the sulfenyl chloride gradually dissipated. NMR analysis showed removal of the thiosulfinate tolyl peaks at 2.38 ppm (*p*-Tol-S(O)) and 2.33 ppm (*p*-Tol-S), and formation of singlets at 2.30 ppm and 2.40 ppm assigned to the disulfide and sulfinyl chloride espectively. The latter was trapped by addition of morpholine converting the sulfinyl chloride to the sulfinamide, see Scheme 2 and Table 1.

Scheme 2, Reaction of thiosulfinates with sulfenyl chlorides.



Interestingly in certain cases the disulfides were obtained as an approximately 1 : 2 : 1 mixture of the symmetrical (PhSSPh), unsymmetrical (PhSSTol), and symmetrical (TolSSTol) as illustrated in entries 1 and 3.[8,9] This can be explained by disulfide 'scrambling' reaction of the disulfide with sulfenyl chloride as shown in Scheme 3.[9] Entry 4 in Table 1 shows only one of the possible disulfides to be formed. This presumably reflects steric hindrance to attack at the *t*-BuS sulfur.

Scheme 3, disulfide scrambling.



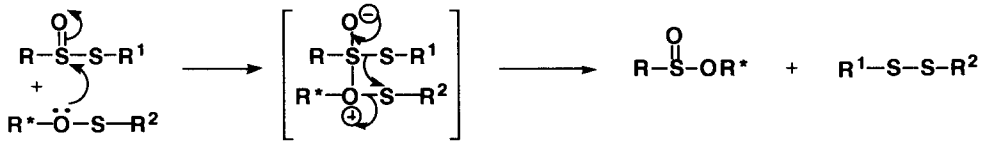
This method can therefore be used to prepare certain unsymmetrical disulfides. Numerous other methods have been described in the literature but all seem to suffer from various drawbacks.[9c,10] Clearly the method described here will only be of real benefit when the disulfide required has two R groups of sufficiently different steric requirements, as is illustrated in the last entry in the table, *e.g.* R^2 = Ph and R^1 = *t*-Bu.

Entry	Thiosulfinate	Sulfenyl Chloride	Sulfinyl Chloride (%)[a]	Sulfinamide (%)[b]	Disulfide RSSR (%)[c]
1	*p*-TolS(O)STol-*p*	PhSCl	*p*-TolS(O)Cl (95%)	*p*-TolS(O)morp (29%)	*p*-Tol-S-)$_2$ Ph-S-)$_2$ *p*-TolSSPh (95%)
2	*o*-TolS(O)SPh	PhSCl	*o*-TolS(O)Cl (95%)	*o*-TolS(O)morp (33%)	Ph-S-)$_2$ (95%)
3	*o*-TolS(O)STol-*o*	PhSCl	*o*-TolS(O)Cl (95%)	*o*-TolS(O)morp (34%)	*o*-Tol-S-)$_2$ Ph-S-)$_2$ *o*-TolSSPh (95%)
4	*p*-TolS(O)SBu-*t*	PhSCl	*p*-TolS(O)Cl (95%)	*p*-TolS(O)morp (30%)	*t*-BuSSPh (95%)

a = Not isolated, ^{1}H NMR yield. **b** = Isolated yield of pure product from column chromatography, the crude yields were greater than 75% by NMR. **c** = Isolated yield, confirmation of mixtures of disulfides was obtained by HPLC analysis. Morp = morpholine. All new compounds gave satifactory C,H,N analysis and spectroscopic data consistent with their stuctures.

Turning our attention to the sulfenate esters, Moore and O'Connor reported that these react with **alkyl** thiosulfinates to give a sulfinate ester and a disulfide.[5] We have shown that **aryl** thiosulfinates mirror this chemistry as highlighted in Scheme 4. The mechanism illustrated in Scheme 4 involves a similar process, namely attack of the hard oxygen on the hard sulfinyl sulfur, to that reported for the reaction of sulfenate esters with acid chlorides.[4]

Scheme 4, Reaction of thiosulfinates with sulfenate esters.



R = *p*-Tol, *o*-Tol R^1 = *p*-Tol, Ph R^2 = *p*-Tol, *o*-Tol, *m*-Tol R* = CH_3, menthyl

For example mixing menthyl *m*-toluenesulfenate and (S)-*p*-tolyl-*p*-toluenethiosulfinate in $CDCl_3$ at room temperature gave menthyl *p*-toluenesulfinate (94% yield) and the disulfide fraction (69% yield) as a mixture of *m*-TolSSTol-*m*, *p*-TolSSTol-*p* and *p*-TolSSTol-*m* as shown by ^{13}C NMR.[8] This reaction was complete after two hours. Likewise when (S)-p-tolyl *p*-toluenethiosulfinate and methyl *p*-toluenesulphenate in $CDCl_3$ were mixed a smooth transformation to the disulfide and sulfinate occurred. ^{1}H NMR indicated the reaction to have

gone to ~35% completion after 2 hours by formation of singlets at 3.40 (OCH_3 sulfinate ester), 2.45 (Tol-CH_3 sulfinate ester) and 2.25 (Tol-CH_3 disulfide). The reaction was shown to have gone to completion after 8 days. [*N B* this reaction is acid catalysed: the *o*-tolyl experiment when conducted in the presence of a catalytic amount of HCl was complete within one hour. This is in agreement with results obtained by Ciuffarin *et al.* [8]]

In summary, we have shown that thiosulfinate esters react with sulfenyl chlorides to give disulfides and sulfinyl chlorides (which were trapped as the sulfinamide). In certain cases unsymmetrical disulfides can be prepared although this procedure has little benefit over existing methods. The ready reaction of thiosulfinates with sulfenate esters has also been demonstrated. These reactions unfortunately, therefore preclude the use of the "Thio-Arbuzov" reaction as a preparative route to this interesting class of compounds.

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References and notes.

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9. Confirmation of the disulfide scrambling was achieved by HPLC using a Waters μBondpack C_{18} reverse phase analytical column; water : methanol (80 : 20) as the eluent, uv detection at 232 nm. Entry 3 (table 1), retention times; PhSSPh 6.33 mins (25%), PhSSTol-*o* 8.38 mins 50%), *o*-TolSSTol-*o* 11.24 mins (25%). See also a. Field, L., Chapter 7, p.362, *'The organic chemistry of Sulfur'*, Ed. S. Oae, Plenum, New York, **1977**. b. Parker, A. J.; Kharasch, N., *Chem. Rev.*, **1959**, *59*, 594. c. For a recent paper on disulfide synthesis see Leriverend, C.; Metzner, P., *Synthesis*, **1994**, 761 and references therein.
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