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Synthesis of Sulfonium Salts by Sulfide Alkylation; an Alternative Approach

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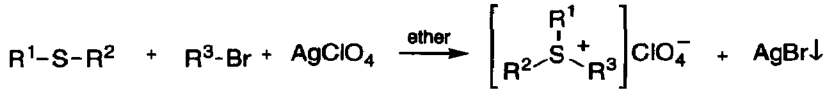
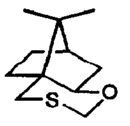
Abstract: Sulfonium salts may be synthesised easily and in good yield by alkylation of the corresponding sulfide using alkyl bromides in the presence of sodium salts in acetone.

Chiral sulfur ylides can be used for efficient asymmetric epoxidation of carbonyl compounds.[1-6] They are obtained by deprotonation of the corresponding sulfonium salts which themselves are prepared by alkylation of chiral sulfides.[7] Sulfonium salts with one or more different groups attached to sulfur are not usually made by simply treating a sulfide with an alkylating agent, as the reaction is reversible and can lead to the formation of mixed sulfonium salts.[8] The solution to this problem is to prevent reversibility by exchanging the liberated nucleophilic counterion for a non-nucleophilic counterion during the course of the reaction and this is commonly achieved by using silver perchlorate as shown in Scheme 1. The nucleophilic halide is removed by precipitation as its silver salt and the sulfonium perchlorate salt thus obtained.

Scheme 1



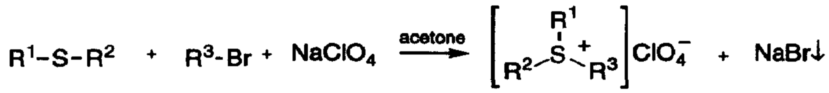
During the course of our studies on asymmetric epoxidation,[9,10] we wanted to benzylate sulfide (**1**), but were unable to purify the corresponding sulfonium salt using the above method. It seemed that residual silver salts were inhibiting further purification, a problem noted by others.[3]



(1)

We therefore needed an alternative, non-silver mediated, method for sulfide alkylation. Cognisant of the Finkelstein reaction[11] in which soluble sodium iodide displaces a bromide but the reverse reaction is prevented by the formation of insoluble sodium bromide, we asked whether sodium perchlorate could render alkylation of a sulfide irreversible when carried out in acetone, as shown in Scheme 2.

Scheme 2



We were pleased to find that this reaction was successful[12] and consequently tested its scope using different sulfides, alkylating agents and sodium salts. The results are summarised in Table 1.

Table 1

Entry	Alkylating Agent	Sulfide	Salt	Yield
1	$PhCH_2Br$	Me_2S	$NaClO_4$	83%
2	$PhCH_2Br$	Tetrahydrothiophene	$NaClO_4$	90%
3	$PhCH_2Br$	Tetrahydrothiophene	$NaBF_4$	86%
4	$PhCH_2Br$	Tetrahydrothiophene	$NaBPh_4$	89%
5	CH_3CH_2Br	Tetrahydrothiophene	$NaClO_4$	58%
6	$PhCH_2Br$	(1)	$NaClO_4$	41%
7	$PhCH_2Br$	(1)	$AgClO_4$	0%

Several points are worthy of note. It was found that sodium perchlorate, sodium tetraphenylborate and sodium tetrafluoroborate promoted alkylation of sulfides, (entries 2-4), although sodium perchlorate was superior due to its higher solubility in acetone. Sodium perchlorate also promoted alkylation of unactivated alkyl bromides (entry 5).[13] Finally, the benzyl perchlorate salt of sulfide (**1**) was obtained as a single diastereoisomer.

This method of sulfide alkylation has several advantages over the standard accepted procedure using silver salts;
(i) Our method is more economical.
(ii) As the range of available sodium salts is greater than the range of silver salts, our method allows for the preparation sulfonium salts with a wider range of counterions.
(iii) Yields are competitive and the products are cleaner and easier to isolate.

In summary, this method of sulfonium salt synthesis provides a useful alternative to current procedures.

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(12) Sulfide (2.0 mmol), alkyl bromide (2.0 mmol) and sodium salt (2.0 mmol) were stirred in minimum acetone at room temperature until no further sulfide remained. The mixture was filtered, evaporated under reduced pressure and triturated with pentane to give the required sulfonium salt.

(13) Alkylation of tetrahydrothiophene with 2-bromopropane was unsuccessful using this method.

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