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COMMUNICATION

A direct and efficient preparation of 1-phenyltetrazol-5-yl sulfides from alcohols†

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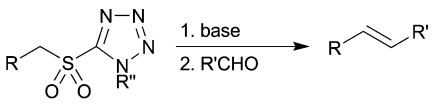
Treatment of primary or secondary alcohols with 1-phenyl-1(*H*)-tetrazole-5-thiol and $[Me_2NCHSEt]^+$ BF_4^- leads directly and cleanly to 1-phenyl-1(*H*)-tetrazol-5-yl sulfides.

The preparation of alkenes from aldehydes or ketones and α-sulfonyl carbanions, known as the Julia olefination reaction,[1] is a widely used process. In the original Julia protocol,[2] deprotonation of an alkyl aryl sulfone and addition to an aldehyde was followed by a separate reductive step to form the alkene.

A major advance in Julia olefination chemistry was the development of a number of modified procedures in which the reaction of an anion derived from an alkyl *hetero*aryl sulfone with an aldehyde led directly to an alkene as product, obviating the need for a second reductive step.[3] Foremost among these procedures is that of Kocieński, which uses alkyl tetrazol-5-yl sulfones **1** (Scheme 1).[4,5]



1 (R''=Ph or *t*-Bu)

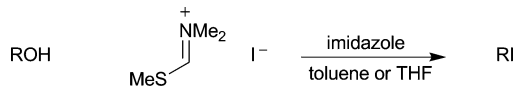
Scheme 1 The Julia–Kocienski olefination.

The sulfones **1** are invariably prepared by oxidation of the corresponding sulfides, which in turn are generally synthesised from alcohol precursors by one of two methods: either through the intermediacy of an activated alcohol such as a halide or a sulfonate, or by use of the Mitsunobu reaction with a tetrazole-5-thiol as the nucleophilic component.[4,6] The former method requires multiple operations, while the latter suffers from the production of an equimolar quantity of triphenylphosphine oxide, which can cause difficulties in purification.

A third method for the conversion of alcohols to tetrazolyl sulfides is by reaction with a *bis*-tetrazolyl dithiocarbonate. This method, however, is only applicable to allylic and benzylic alcohols.[7]

In this paper, we describe a new procedure for the direct conversion of alcohols into tetrazolyl sulfides, using an *S*-alkylated thioformamide salt as an activating reagent for alcohols. The by-products generated in the reaction are volatile and/or highly polar, facilitating work-up and product purification.

We recently reported that treatment of alcohols **2** with the methylsulfanyliminium iodide **3**, in the presence of imidazole, led to formation of alkyl iodides **4** (Scheme 2).[8]

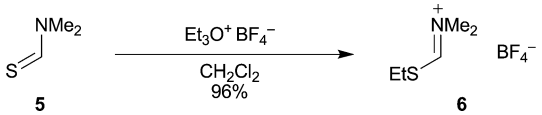


2 **3** **4**

Scheme 2 Iodination of alcohols with iminium salt **3**.

We reasoned that if the iodide counterion in **3** were replaced with a non-nucleophilic anion such as tetrafluoroborate, the resulting salt should still react with alcohols to afford an activated intermediate; in the absence of iodide, however, it should be possible to introduce other nucleophiles to displace the leaving group. 1-Phenyl-(1*H*)-tetrazole-5-thiol was selected as such a nucleophile.

To prepare the requisite activating reagent, *N*,*N*-dimethylthioformamide **5** was treated with triethyloxonium tetrafluoroborate in dichloromethane to afford the salt **6**, which precipitated as a crystalline solid on addition of the reaction mixture to diethyl ether (Scheme 3).‡



5 **6**

Scheme 3 Preparation of tetrafluoroborate salt **6**.

Initial investigations into sulfide formation were carried out with ethyl 6-hydroxyhexanoate **2a** as substrate. This alcohol was treated with 1-phenyl-(1*H*)-tetrazole-5-thiol **7** (1.2 equivalents), salt **6** (1.5 equivalents) and imidazole (0.5 equivalents) in a variety of solvents at elevated temperature (Table 1, entries 1–4).

In all cases, clean conversion of the alcohol to sulfide **8a** was observed. Of the solvents investigated, conversion was most rapid in toluene and acetonitrile, and toluene was chosen as the solvent for further optimisation.

By increasing the loading of imidazole and thiol in the reaction, and lowering the amount of solvent, complete conversion of **2a** to

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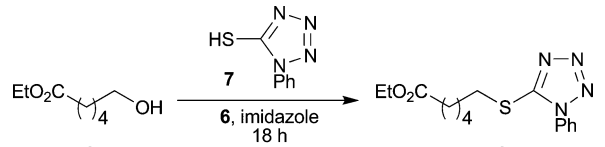
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and ^1H and ^{13}C NMR spectra for compounds **6**, **8a–k** and **9**. See DOI: 10.1039/c0ob00863j

Table 1 Optimisation of sulfide formation[a]



entry	solvent	T/°C	conversion/%
1	toluene	90	91
2	THF	reflux	52
3	MeCN	reflux	83
4	DMF	90	57
5	toluene	90	100[b]

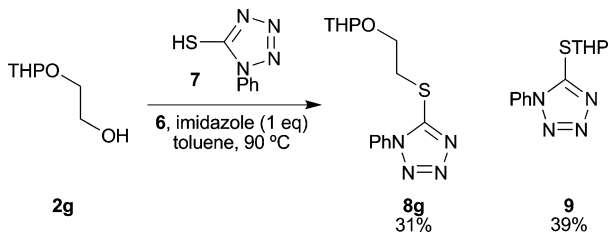
[a] 0.2 M alcohol **2a**, 0.5 equiv. imidazole, 1.5 equiv. **6**, 1.2 equiv. **7**. [b] 0.5 M alcohol **2a**, 1.0 equiv. imidazole, 1.5 equiv. **6**, 2.0 equiv. **7**.

8a could be achieved in 18 h, and **8a** could be isolated in 76% yield (Table 1, entry 5 and Table 2, entry 1).

The scope of the reaction was next explored with a range of alcohols. For both primary (Table 2, entries 1–4) and secondary alcohols (entry 5) good yields of the desired sulfides were obtained.

In some cases, incomplete reaction was observed under the standard reaction conditions, but it was found that complete conversion could be achieved by addition of further imidazole – for example, with alcohol **2f** (entry 6), two equivalents of imidazole were required; under these conditions an isolated yield of 88% was obtained.

When THP-protected diol **2g** was subjected to the standard reaction conditions, only a low yield of the expected sulfide **8g** was obtained, with the remainder of the isolated material being the THP-protected thiol **9** (Scheme 4). This product was presumed to arise from initial deprotection of **2g** under the slightly acidic conditions, and reaction of the resulting tetrahydropyranyl cation with **7**. By increasing the amount of imidazole in the reaction mixture to 5 equivalents, formation of **9** could be suppressed, and **8g** could be isolated in 80% yield (Table 2, entry 7). These modified reaction conditions were also used successfully with an acid-sensitive Boc-protected aminoalcohol substrate **2h** (entry 8). Surprisingly, the use of a TBS-protected diol **2i** gave a sulfide product **8i** from which the silyl protecting group had been cleaved (entry 9).

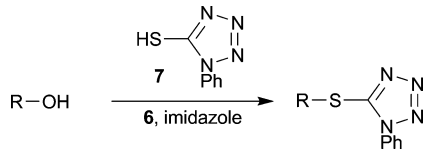


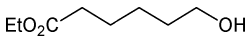
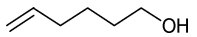
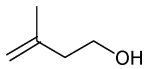
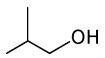
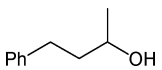
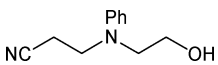
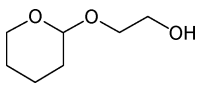
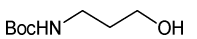
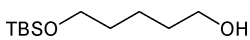
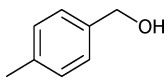
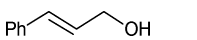
Scheme 4 Reaction of THP-protected alcohol **2g**.

Benzylic and allylic alcohols **2j** and **2k** underwent rapid reaction, with conversion to the corresponding sulfides complete within 1 h (entries 10 and 11); for these reactive alcohols, only 1.2 equivalents of thiol **7** rather than the usual 2 equivalents was used.

Work-up of the reactions proved very straightforward – no aqueous work-up was required, and the crude reaction mixture

Table 2 Scope of sulfide formation[a]



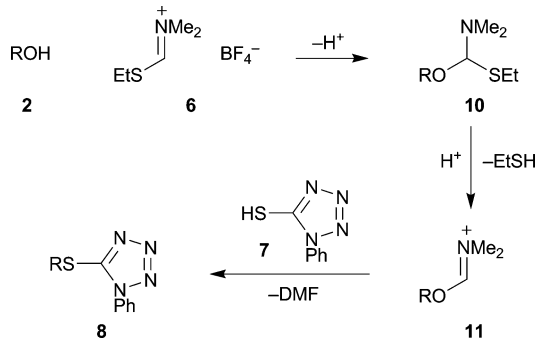
entry	alcohol		time/h	yield/%
1	**2a**		18	76
2	**2b**		18	70
3	**2c**		18	67
4	**2d**		6	75
5	**2e**		18	83
6	**2f**		18	88[b]
7	**2g**		18	80[c]
8	**2h**		24	76[c]
9	**2i**		18	62[c,d]
10	**2j**		1	91[e]
11	**2k**		1	90[e]

[a] 0.4–0.5 M alcohol **2**, 1.0 equiv. imidazole, 1.5 equiv. **6**, 2.0 equiv. **7**, toluene, 90 °C. [b] 2.0 equiv. imidazole. [c] 5.0 equiv. imidazole. [d] Isolated product was the desilylated material $HO(CH_2)_5S(CN_4Ph)$. [e] 1.2 equiv. thiol **7**.

was simply concentrated *in vacuo*. Furthermore, purification of the sulfides was straightforward as all of the reaction by-products – dimethylformamide, ethanethiol and imidazolium tetrafluoroborate – are either volatile or highly polar.

A plausible mechanism for the formation of tetrazolyl sulfides **8** is depicted in Scheme 5 – this is closely related to the mechanism which was proposed for iodide formation (Scheme 2).[8,9] Addition of alcohol **2** to salt **6** leads, after loss of a proton, to orthoester-type intermediate **10**. Protonation of the sulfur and loss of ethanethiol then affords the key activated intermediate **11**, from which S_N2 displacement of DMF by **7** (or its conjugate base) leads to the observed sulfide product.

In conclusion, we have developed a method for the direct conversion of alcohols to 1-phenyl-(1*H*)-tetrazolyl sulfides by treatment with the appropriate thiol and a thioiminium salt which is readily prepared and shelf-stable. The method is tolerant of a wide variety of functional groups, including acid-sensitive protecting groups, and the products are readily isolated.



Scheme 5 Mechanism of sulfide formation.

Experimental section

N-(Ethylsulfanylmethylene)-*N*,*N*-dimethylammonium tetrafluoroborate (6)

To a solution of triethyloxonium tetrafluoroborate (5.57 g, 29.3 mmol) in CH_2Cl_2 (50 mL) was added *N*,*N*-dimethylthioformamide **5** (2.3 mL, 26.7 mmol) and the solution stirred at room temperature for 18 h. The mixture was concentrated *in vacuo* to approximately half of its original volume and then added dropwise to stirred Et_2O (100 mL); the solution was then placed in a refrigerator for 2 h. The resulting precipitate was collected by filtration under argon, washed with cold Et_2O (2 × 25 mL) and dried *in vacuo* for 10 min to give salt **6** (5.26 g, 96%) as a white crystalline solid which was stored at –25 °C under argon.

General procedure for preparation of 1-phenyl-1(*H*)-tetrazol-5-yl sulfides

To a solution of alcohol **2** in toluene (0.4–0.5 M) were added salt **6** (1.5 equiv.), imidazole (1.0 to 5.0 equiv) and 1-phenyl-1(*H*)-tetrazole-5-thiol **7** (1.2 to 2.0 equiv.), and the mixture heated to 90 °C. Upon completion of the reaction (monitored by TLC or ^{1}H NMR analysis), the solvent was removed *in vacuo*. Purification by flash chromatography afforded pure sulfide **8**.

Acknowledgements

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Notes and references

‡ The *S*-methyl analogue of **6** was also prepared using trimethyloxonium tetrafluoroborate, and tested in the sulfide-forming reaction; however, no significant difference in reactivity was observed when this salt was used and so the less expensive salt **6** was employed in all subsequent reactions.

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