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Alkylation of thiols with trichloroacetimidates under neutral conditions

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Dedicated to the memory of Professor Harry Wasserman

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ABSTRACT

Trichloroacetimidates are displaced with thiols to form the corresponding sulfides without the need for an added acid or base by simply heating the reactants in refluxing THF. This operationally simple procedure provides the corresponding sulfides in excellent yields with only the formation of the neutral trichloroacetamide as the side product. The imidate may also be formed in situ, allowing for a direct method for the formation of sulfides from alcohols. This reaction provides a general method for the synthesis of a variety of sulfides from inexpensive and readily available alcohol starting materials.

The synthesis of sulfides is driven by the common nature of this functional group. Sulfides are present in molecules with diverse structures and functions, including pharmaceuticals,[1] secondary metabolites,[2a,b,1d,2c–e] enzyme cofactors,[3] and pesticides.[4] Sulfides are also valuable precursors to sulfones, which are useful reactants in olefination chemistry.[5] Synthetic chemists have developed a variety of methods to access sulfides. Classically sulfides are accessed through the alkylation of thiols with alkyl halides.[6] Mitsunobu conditions are effective in the synthesis of sulfides from unhindered alcohols, with the caveat that large amounts of waste (primarily phosphine oxides and reduced azodicarboxylates) are formed.[7] More recent approaches have focused on the direct synthesis of sulfides from unprotected alcohols. Because alcohols are less effective leaving groups than halides, these cases require the use of a Lewis acid, Brønsted acid, or metal catalyst to effect the sulfide formation.[8] These methods are often restricted to benzylic, allylic, and propargylic alcohols as they proceed though carbocation intermediates which preclude unactivated primary alcohols as substrates.

Based on some recent results from our laboratories in the displacement of trichloroacetimidates with carboxylic acids,[9] we hypothesized that trichloroacetimidates may be sufficiently basic to deprotonate a thiol directly. This would allow for the rapid displacement of the protonated imidate by the thiolate without the need for a Lewis or Brønsted acid catalyst. The displacement would generate trichloroacetamide as the only byproduct, which is significantly less acidic than the direct displacement of a halide resulting in the formation of a mineral acid side product that may destroy other sensitive functionality in complex molecules. In contrast, this method utilizing the imidate would provide a mild entry into sulfides under near neutral reaction conditions. Schmidt has pioneered the Lewis acid catalyzed addition of thiols to glycosidic trichloroacetimidates,[10] which has become an accepted method for the synthesis of thiosugars by the carbohydrate community,[11] but we were unable to find any examples of the displacement of glycosyl imidates without the addition of an acid catalyst (basic conditions have also been utilized to displace glycosyl trichloroacetimidates[12]). Only recently have trichloroacetimidates been used outside of the carbohydrate arena for sulfide formation but, as for glycosyl imidates, either a Lewis acid[13] or Brønsted acid catalyst[14] was utilized to facilitate the displacement of the imidate.

Initial studies (Table 1) were performed with diphenylmethyl (DPM) trichloroacetimidate (**2**) as the test substrate, since previous work on substitution reactions[9a,15] has shown that imidate **2** is highly reactive. While no reaction was observed at room temperature, heating 2-mercaptobenzothiazole **1** with diphenylmethyl imidate **2** in refluxing toluene gave a 76% yield of the sulfide product **3** (Table 1, entry 3), confirming our hypothesis that acidic thiols can be alkylated without the addition of a catalyst. A screen of different solvents and temperatures was then performed to further

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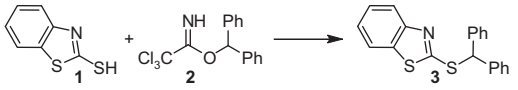
0040-4039/

Table 1
Reaction of thiol **1** with DPM trichloroacetimidate **2**[a]



Entry	Solvent[a]	Temperature	Yield[b] (%)
1	Toluene	23 °C	0
2	Toluene	65 °C	45
3	Toluene	Reflux (111 °C)	76
4	Dichloromethane	Reflux (40 °C)	48
5	THF	Reflux (66 °C)	88
6	2-Butanone	Reflux (80 °C)	Trace
7	Acetonitrile	Reflux (82 °C)	52
9	DMF	100 °C	18

[a] All reactions were performed at 0.1 M for 24 h.
[b] Isolated yields.

increase the yield of the alkylation. Both the reaction temperature and the solvent greatly influenced the yield of the sulfide product **3**, with more polar solvents like 2-butanone, acetonitrile, and DMF providing lower yields than the less polar solvents like toluene. THF emerged as the optimal solvent from this study, providing an 88% yield of sulfide product **3** after refluxing the reactants for 24 h.

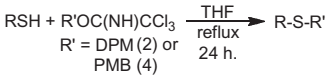
A study on the generality of this alkylation with respect to the thiol nucleophile was next undertaken (Table 2). This analysis was performed in the context of evaluating the installation of protecting groups on the thiol, and so two imidates that can be used to install common thiol protecting groups, diphenylmethyl trichloroacetimidate **2** (DPM imidate) and 4-methoxybenzyl-2,2,2-trichloroacetimidate **4** (PMB imidate), were chosen as the alkylation reagents. In general yields were higher with DPM imidate **2**, likely due to the enhanced electrophilicity of this system. Aromatic thiols proved to be excellent substrates for the alkylation reactions, providing the sulfide products in excellent yields. Alkyl thiols provided more moderate yields of the sulfide products. We suspect the lower acidity of alkyl thiols leads to a slower proton transfer to the imidate nitrogen, resulting in a less rapid displacement of the imidate with these thiols.

Interestingly, when washing the reaction mixtures with 2 M NaOH to remove unreacted thiol, it was noticed that the trichloroacetamide byproduct was also removed. As trichloroacetamide is insoluble in water, this is most likely due to the deprotonation of the acetamide (trichloroacetamide has pK_a of 12), with the deprotonated acetamide being water soluble and removed via the aqueous washing. This discovery provides a convenient method for the removal of the major byproduct of the alkylation, further enhancing the usefulness of this process. Attention was then turned to the variation of the imidate alkylating reagent (Table 3).

The experiments in Table 3 were performed in THF at reflux with 1-phenyl-1*H*-tetrazole-5-thiol **18**, as this thiol has found common use in the preparation of sulfones for the Julia–Lygothe olefination reaction.[16,5d,b,c] Table 3 depicts the wide range of trichloroacetimidates used with thiol **18**, including benzylic, allylic, propargyl, and alkyl trichloroacetimidate electrophiles with consistently respectable yields. Benzylic trichloroacetimidates with both electron donating and electron withdrawing substituents on the aromatic ring provided excellent yields of the sulfide product. Allylic and propargylic trichloroacetimidates also provide high yields with thiol **18** when compared to benzylic trichloroacetimidates (entries 9–15, Table 3). No products of S_N2' addition were observed in entries 10–13 in Table 3, and no isomerization of the alkene was observed for the geraniol and nerol substrates **28** and **29**. The phthalimidomethyl system also proved a capable reaction partner, providing sulfide **32** in 78% yield. Unhindered methyl and ethyl trichloroacetimidates provided the corresponding sulfides in good yields (75% and 81%, respectively). No reaction was observed with the isopropyl imidate in refluxing THF, but switching to toluene as the solvent to access a higher reaction temperature provided a 38% yield of the isopropyl sulfide **34**. The yield of **34** could be increased to 51% by using 5 equiv of the imidate.

Reaction of 1-phenyl-1*H*-tetrazole-5-thiol **18** with *tert*-butyl imidate did not provide the expected sulfide product, but instead gave the tetrazolothione **36** as the major product in 32% yield (Scheme 1). The yield of **36** could be increased to 55% by using an excess (5 equiv) of the imidate. In the case of the *t*-butyl imidate, steric interactions between the bulky *t*-butyl group and the adjacent *N*-phenyl ring may favor alkylation of the nitrogen,

Table 2
Protection of thiols with DPM imidate **2** or PMB imidate **4**



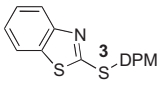
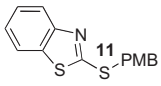
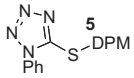
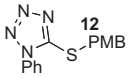
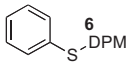
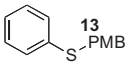
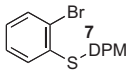
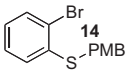
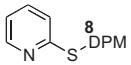
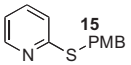
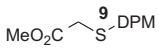
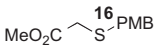
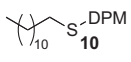
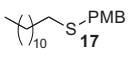
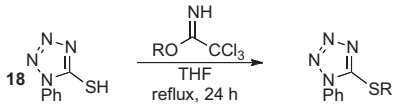
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		88	8		89
2		94	9		84
3		78	10		79
4		71	11		59
5		85	12		81
6		65	13		52
7		64	14		40

Table 3
Alkylation of thiol **18** with various imidates



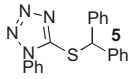
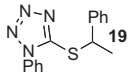
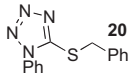
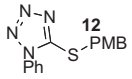
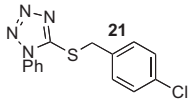
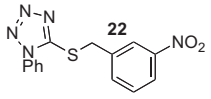
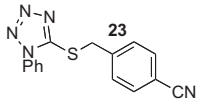
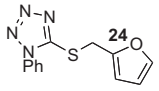
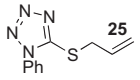
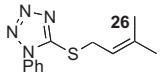
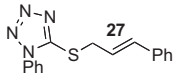
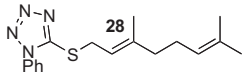
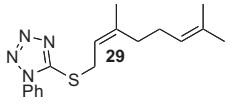
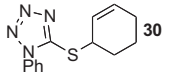
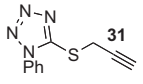
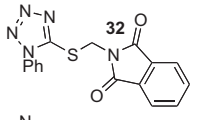
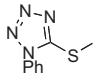
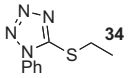
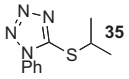
Entry	Product	Yield (%)
1	 **5**	94
2	 **19**	87
3	 **20**	87
4	 **12** PMB	84
5	 **21**	88
6	 **22**	80
7	 **23**	72
8	 **24**	69
9	 **25**	96
10	 **26**	98
11	 **27**	95
12	 **28**	83
13	 **29**	88
14	 **30**	91
15	 **31**	96
16	 **32**	78
17	 **33**	75

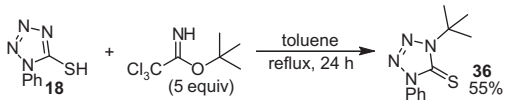
Table 3 (*continued*)

Entry	Product	Yield (%)
18	 **34**	81
19	 **35**	38[a,b]

[a] The reaction was performed in toluene at reflux.
[b] A 51% isolated yield of **35** was obtained when 5 equiv of imidate was used in toluene at reflux.

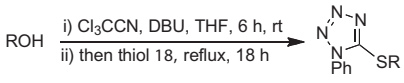
leading directly to the tetrazolothione **36**, while other alkylations lead to the tetrazole sulfide. Recently Wu et al. showed that tetrazole sulfides may be rearranged to the thermodynamically favored tetrazolothiones by heating in DCE with catalytic $Ga(OTf)_3$,[17] so it is also possible that after initial S-alkylation the *t*-butyl group rapidly migrates to the nitrogen.

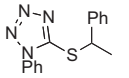
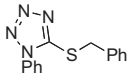
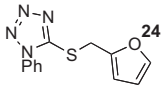
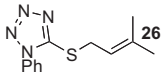
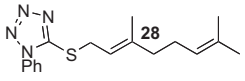
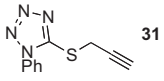
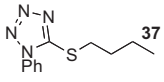
While addition of the thiol to the trichloroacetimidate provides a powerful method for the formation of new sulfides under mild conditions, one must still prepare and isolate the trichloroacetimidate from the alcohol before substitution. Attempts were therefore made to streamline the process into a single flask procedure by forming the trichloroacetimidate in situ followed addition of the thiol and heating to effect a direct displacement. In situ



Scheme 1.

Table 4
Single flask procedure for the conversion of alcohols to sulfides

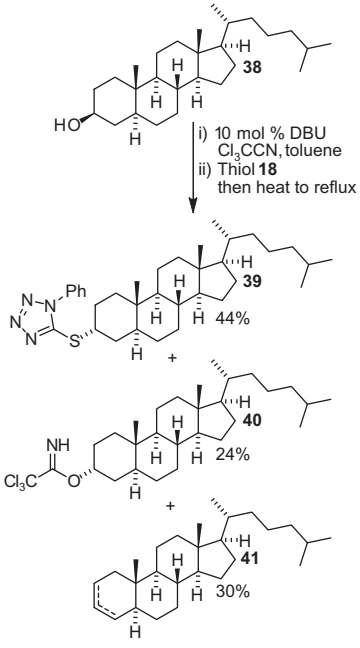


Entry	Product	Yield (%)
1	 **19**	64
2	 **20**	78
3	 **24**	67
4	 **26**	82
5	 **28**	79
6	 **31**	77
7	 **37**	63

formation of the imidate is a well-known process often used in allylic trichloroacetimidates before Overman rearrangement.[18] A series of alcohols were first subjected to imidate formation conditions in anhydrous THF followed by addition of the thiol and simple heating. While the yields for this two-step procedure are slightly lower than for the substitution reaction itself (Table 4) the advantage of substitution without the need for isolation of the trichloroacetimidate is clear.

We hypothesized that the more moderate yield of the sulfide products in the case of the isopropyl sulfide **35** may be due to competing elimination reactions to from the volatile alkene as a side product, as the substitution reaction in these cases may be sluggish due to sterics. To explore this idea the single flask substitution procedure was performed on dihydrocholesterol **38** with thiol **18**, as the alkene byproduct in this case should not be volatile (Scheme 2). Exposing steroid **38** to the in situ substitution reaction in refluxing THF did not give product, returning the imidate **40** instead. This result is consistent with the reactions of isopropyl trichloroacetimidate, which required heating in toluene to form sulfide **35**. Formation of the imidate of **38** in toluene followed by addition of thiol **18** and heating to reflux gave a much faster reaction, and lead to the isolation of sulfide **39** in 44% yield. None of the β-isomer was observed in the crude ^{1}H NMR, with the balance of the material being unreacted trichloroacetimidate **40** (24%) and a mixture of alkenes **41** (30%).

Given the results described above the direct displacement of trichloroacetimidates with thiols seems to proceed under either a S_N^2 or S_N^1 mechanism. Supporting an S_N^2 mechanism, the methyl trichloroacetimidate provided good yield of methyl sulfide **36**. Additionally, the displacement of the chiral alcohol **39** proceeded with inversion, as none of the other diastereomers could be detected in the crude ^{1}H NMR. Support for an S_N^1 type mechanism comes from the ability to form sulfide **33** from diphenylmethyl trichloroacetimidate, as substitution at this center typically proceeds through an S_N^1 pathway. Therefore we propose that the substitution reaction can proceed under either an S_N^2 or S_N^1 manifold (Fig. 1) depending on the structure of the electrophile. This is different mechanistically than previous uncatalyzed substitution reactions



Scheme 2.

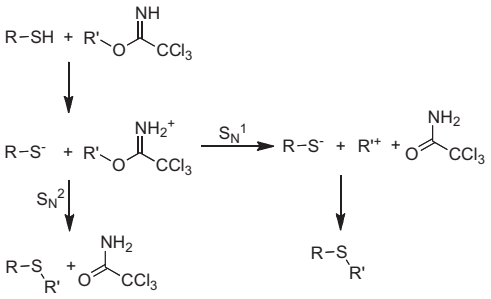


Figure 1. Mechanistic possibilites.

with carboxylic acids,[9] that appeared to go through carbocation intermediates.

In summary, a new methodology for alkylating thiols under neutral conditions without the need of an acid, base, or metal catalyst by utilizing a trichloroacetimidate as an electrophile has been demonstrated. No precedence has shown that this displacement can be performed solely under thermal conditions without an added catalyst. The scope and optimal conditions of these trichloroacetimidate displacements to generate sulfides have been investigated. Aromatic thiols provide better conversions than alkyl thiols, likely due to their greater acidity. Using tetrazole thiol **18** as the test substrate, we have shown that the reaction tolerates considerable variation of substrate with alkyl, allylic, propargylic, and benzylic trichloroacetimidates (with both electron donating and electron withdrawing groups) all participating in the substitution reactions. Reactions with more sterically hindered trichloroacetimidates tended to provide lower yields than less hindered substrates, and in the case of the *tert*-butyl imidate lead to the tetrazolothione product instead of the sulfide. Conditions have also been developed to directly convert primary alcohols to their corresponding sulfides in a single flask procedure going through a transiently formed trichloroacetimidate intermediate. These conditions are notable as many other methods for the direct conversion of alcohols to sulfides are dependent on pathways that proceed through carbocation intermediates, and therefore do not allow for the use of unactivated primary and secondary alcohols. Based on the available information, it is likely that the displacement of the imidate under these conditions may proceed through either an S_N^1 or S_N^2 pathway depending on the structure of the electrophile. The major byproduct of the reaction, trichloroacetamide, can be conveniently removed by washing with aqueous NaOH solutions. Additionally, trichloroacetonitrile is quite inexpensive, especially when purchased in quantity, making this new protocol economical. This method may find wide application in the synthesis of sulfides from alcohols, a common functional group transformation.

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Supplementary data

Supplementary data (detailed experimental procedures and NMR data (^{1}H and ^{13}C spectra)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.042.

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