Hypervalent Iodine Reagents **Very Important Paper**

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Structural Reevaluation of the Electrophilic Hypervalent Iodine Reagent for Trifluoromethylthiolation Supported by the Crystalline Sponge Method for X-ray Analysis**

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Abstract: *Hypervalent iodine* λ^3*-benziodoxoles are common electrophilic transfer reagents known for their enhanced stability compared to their non-cyclic analogues. Herein we present data showing that chlorobenziodoxole reacts with two different thiolate nucleophiles (thiocyanate and trifluoromethylthiolate), resulting in the formation of stable thioperoxy complexes rather than the expected benziodoxole derivatives. We further report a revised structure for the earlier described electrophilic trifluoromethylthiolation reagent (**1**), which was previously believed to contain the benziodoxole framework. Our findings, which are based on a combination of analytical techniques, including the recently introduced crystalline sponge method for X-ray analysis, unambiguously demonstrate that **1** is a thioperoxy compound both in solution and the solid state.*

Recently, Shen et al. introduced a new hypervalent iodine reagent for the transfer of an electrophilic trifluoromethylsulfur group (Figure 1, **1**).[1] Compound **1** was isolated as a colorless liquid and characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, as well as elemental analysis. Based on these data, Shen proposed that **1** contains the sulfur-bound hypervalent iodine motif, similar to all previously reported benziodoxole and benziodoxolone transfer reagents (Figure 1).[2–9]

As part of our work on the synthesis of aryl isocyanates,[10] we were interested in developing new reagents based on the benziodoxole motif for isocyanate and isothiocyanate group transfer chemistry. We anticipated that the ambidentate cyanate and thiocyanate nucleophiles could potentially react with reagent **3** at either the nitrogen or group 16 element (oxygen or sulfur) nucleophilic sites. Indeed, when **3** was treated with silver cyanate, a mixture of isomeric 1-cyanatobenziodoxoles was obtained, with the major product arising from reaction at the nitrogen atom (**4**; Scheme 1 a). In contrast, the reaction of **3** with silver thiocyanate yielded a single compound that did not contain the expected benziodoxole scaffold (**5**; Scheme 1 b). As shown in Scheme 1, the single crystal X-ray analysis of compound **5** revealed that the thiocyanate-group was S-bound to the oxygen atom of **2** rather than to the iodine.[11,12]

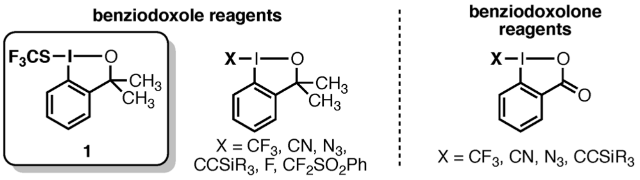
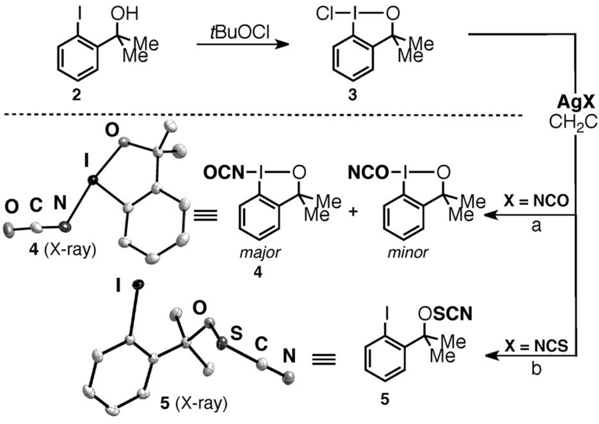


Figure 1. The reported structure of the reagent for electrophilic trifluoromethylthiolation (**1**) recently introduced by Shen et al., and representative examples of other reported benziodoxole-based hypervalent iodine transfer reagents.

Intrigued by this result, we conducted a brief comparison of the ^{1}H NMR spectra of the benziodoxoles and 2-iodobenzyl alcohol-derivatives that are shown in Figure 2. We found that the two compound classes (closed benziodoxole vs. open benzyl alcohol) generally display different characteristic signals in the aromatic region. Most notably, the aromatic protons that are *para* to the alkyl group (H_b) exhibited significant (0.5 ppm or greater) downfield shifts in the closed



Scheme 1. Synthesis of novel electrophilic transfer reagents and crystal structures of reagents **4** and **5**. Thermal ellipsoid plots are drawn at 50% probability, hydrogen atoms are omitted for clarity.

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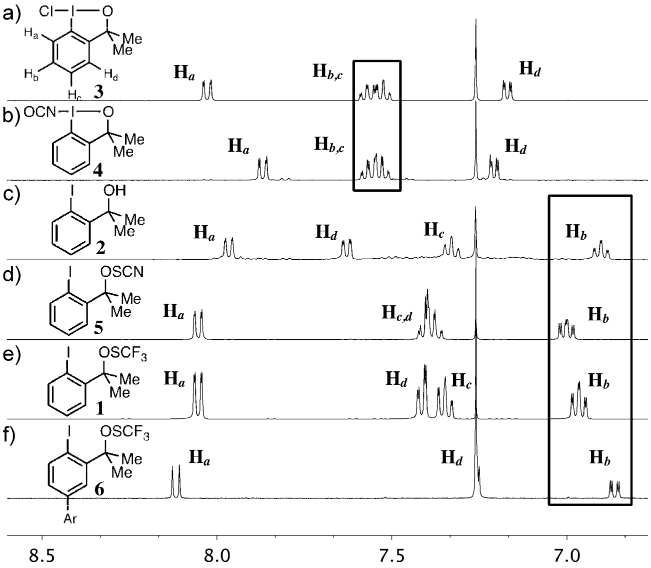
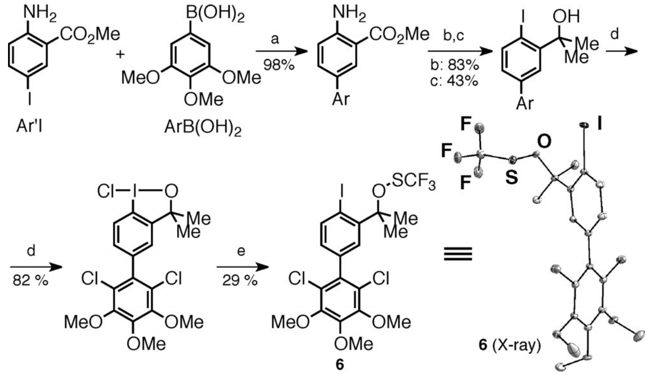


Figure 2. Comparison of the aromatic region of the ^{1}H NMR spectra of hypervalent-iodine-based transfer reagents and novel thioperoxide reagents.

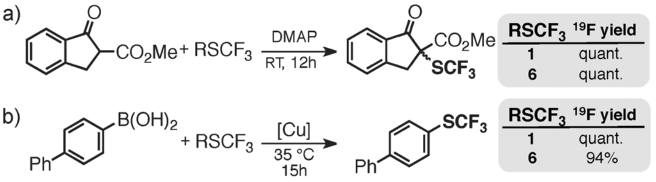


Scheme 2. Synthesis of a solid trifluoromethylthiolation reagent and the crystal structure of reagent **6**. Thermal ellipsoid plot is drawn at 50% probability, hydrogen atoms are omitted for clarity. Reaction conditions: a) Ar'I (1 equiv), ArB(OH)$_2$ (1.5 equiv), Pd(OAc)$_2$ (2 mol%), SPhos (4 mol%), K$_3$PO$_4$ (2 equiv), toluene, 110°C, 18 h; b) *p*TsOH (3 equiv), CH$_3$CN, then KI (2.5 equiv), NaNO$_2$ (2 equiv), H$_2$O, 5 h; c) MeMgBr (4 equiv), Et$_2$O, 40°C, 5 h; d) *t*BuOCl (4 equiv), THF/CH$_2$Cl$_2$ (2:1), 2 h; e) AgSCF$_3$ (1 equiv), THF, 50°C, 1 h. *p*TsOH = *para*-toluenesulfonic acid, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl.

compounds (Figure 2a,b) when compared to the open ones (Figure 2c,d). As described above, the sulfur-based nucleophile afforded the corresponding open compound (Figure 2d) with complete selectivity, which is in contrast to the reported benziodoxole structure of the related trifluoromethylthiolation reagent **1**. Compound **1** was synthesized according to the literature procedure[1a] and exhibited identical spectral properties to those reported. To our surprise, the ^{1}H NMR spectrum of **1** (Figure 2e) resembles those of the open-form compounds more closely than the spectra of the closed-form ones, suggesting that **1** could potentially exist as the open thioperoxy compound rather than the benziodoxole. The oxidation state of iodine in **1**, **5**, and **6** as $\mathrm{I^{I}}$ in solution was further corroborated by ^{13}C NMR spectroscopy, as outlined previously by Katritzky et al.[13]

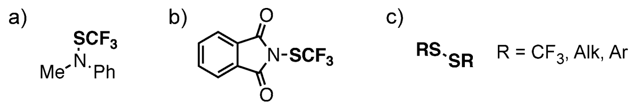
To further evaluate the structure of the Shen reagent, we undertook two parallel studies that would allow us to obtain X-ray crystallographic structural data.[14,15] We first sought to prepare a solid analogue of the trifluoromethylthio-transfer reagent. According to the route outlined in Scheme 2, we were able to construct a modified reagent **6** that contained the dichlorotrimethoxyphenyl substituent at C4 of the phenyl ring. This new reagent displayed the characteristic aromatic ^{1}H NMR signal that indicated a compound that did not contain the benziodoxole scaffold (Figure 2f). X-ray diffraction analysis of single crystals of **6** provided unequivocal structural evidence that the SCF$_3$ group is bound to oxygen rather than to iodine (Scheme 2).

To evaluate the potential steric and electronic effects that installation of the functionalized aromatic substituent could impart to the reagent, we compared the reactivity of **6** and **1** in previously reported SCF$_3$-transfer reactions. Under the optimized conditions reported by Shen et al. for β-ketoester- (Scheme 3a) or Cu-catalyzed arylboronic acid trifluoromethylthiolation (Scheme 3b),[1a] the two reagents displayed nearly identical reactivity profiles (Scheme 3).



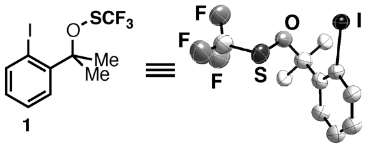
Scheme 3. Representative reactions of reagents **1** and **6** with β-ketoesters (a) and arylboronic acids (b). For detailed reaction conditions, see: Ref. [1a] and the Supporting Information. DMAP = *N*,*N*-dimethylaminopyridine.

Although it is possible that there exists a Curtin–Hammet scenario where both forms of the reagent exist in equilibrium in solution and the reactivity arises from the hypervalent iodine structure, no evidence for such an equilibrium was observed by ^{1}H or ^{19}F NMR spectroscopy, even at low temperatures (−80°C). Furthermore, the similarity of the thioperoxide structure to the previously reported nitrogen-based electrophilic trifluoromethylthiolation reagents by the groups of Billard[16] and Rueping[17] (Scheme 4a and b), as well as the disulfide reagents used for directed Cu-promoted sulfenylation of sp^{2} C—H bonds by Daugulis et al.[18] (Scheme 4c) supports the hypothesis that the observed reactivity[1a,c] could arise from the thioperoxide fragment itself.



Scheme 4. Trifluoromethylthiolation reagents reported by the goups of Billard (a), Rueping (b), and Daugulis (c).

Fujita recently introduced a new method for the structure determination of liquid compounds trapped in the pores of a host metal organic framework (MOF).[19] We were interested in applying this method to gain access to the X-ray structure of the parent reagent **1**. The MOF material was prepared by slow diffusion of a solution of ZnI_2 in methanol into the solution of 2,4,6-tri(4-pyridyl)-1,3,5-triazine in a mixture of nitrobenzene and methanol. Soaking the resulting crystals in cyclohexane at 50 °C for two weeks (used solvent was replaced by fresh solvent each day) allowed for the majority of nitrobenzene in the pores of the MOF to be exchanged with more labile cyclohexane molecules.[20] A consecutive soak of the crystals in the analyte provided X-ray quality crystals of the host–guest complex **1**@MOF. Subsequent structure determination using a variety of advanced refinement techniques[21] revealed the presence of 92 % of reagent **1** per asymmetric unit of the crystal structure of **1**@MOF, disordered over three crystallographically independent sites (see the Supporting Information for details). As shown in Scheme 5, the crystallographically-derived structure of **1** does not contain the benziodoxole fragment, and the SCF_3-group is bound to the oxygen atom.



Scheme 5. Crystal structure of the guest molecule **1** observed in the cavities of the MOF. Thermal ellipsoid plot is drawn at 50 % probability, hydrogen atoms are omitted for clarity.

In summary, we have discovered that the reaction of chlorobenziodoxole with two sulfur-containing nucleophiles leads to the formation of rearranged products containing stable thioperoxy groups. A combination of spectroscopic techniques, derivatization experiments, and the crystalline sponge method recently introduced by Fujita et al.,[19] allowed for unambiguous confirmation of the open form thioperoxide structure of the recently reported trifluoromethylthiolation reagent **1**, both in solution and in the solid state at room temperature. Importantly, whereas these results do not affect the chemical reactivity studies utilizing reagent **1**, as recently reported by Shen and co-workers,[1a] they do suggest that other mechanistic pathways for electrophilic trifluoromethylthiolation are possible.[1c]

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Keywords: crystalline sponge crystallography · host-guest systems · hypervalent compounds · thioperoxides · trifluoromethylthiolation

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