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Reactions of allyl alcohols and boronic acids with trifluoromethanesulfonyl hypervalent iodonium ylide under copper-catalysis

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Trifluoromethylsulfinyl and trifluoromethylthio groups are both important substituents for pharmaceuticals, agrochemicals and herein functional materials. We report the trifluoromethylthiolation of allyl alcohols 2 with trifluoromethanesulfonyl hypervalent iodonium ylide 1 under copper catalysis to provide trifluoromethylsulfinyl compounds 3. Trifluoromethylthiolation of boronic acids 4 with 1 furnished trifluoromethylthio compounds 5.

In recent decades, there has been tremendous interest in organofluorine compounds due to their great achievements as pharmaceuticals, agrochemicals and functional materials.¹ The vast majority of successful works reported in this area have dealt with fluorinated and trifluoromethylated compounds, and a huge number of effective methods have been developed for the synthesis of these fluorinated molecules.² Our group has also contributed to this area by developing shelf-stable reagents for fluorination³ and trifluoromethylation reactions.⁴ In 2013, we reported a novel reagent, trifluoromethanesulfonyl hypervalent iodonium ylide 1, for the electrophilic trifluoromethylthiolation reaction.⁵ Trifluoromethylthio (SCF₃) compounds are becoming rather attractive after fluorinated and trifluoromethylated compounds in the same research fields, since the introduction of SCF₃ entities into the target compounds greatly changes or improves the lipophilicity of parent molecules⁶ without altering the original framework much; and this effect is higher than that by the trifluoromethyl substitution. In contrast to trifluoromethyl compounds, SCF₃ compounds can be further elaborated to exhibit more suitable lipophilic profiles by the stepwise oxidation into corresponding sulfoxides (S(O)CF₃) and sulfones (SO₂CF₃, triflones). In this context, the synthesis of SCF₃ compounds has received great attention.⁷ In particular, the development of electrophilic trifluoromethylthiolation reagents⁸ is going to be prevalent in the next several years, because it should be a key to realizing late-stage

medicinal significance. The trifluoromethanesulfonyl hypervalent iodonium ylide **1** we developed is useful for the trifluoromethylthiolation of enamines, indoles, β -keto esters,⁵ pyrroles,⁹ arylamines,¹⁰ allylsilanes and silyl enol ethers.¹¹ Reagent **1** is very stable, and crucial for the fact that the trifluoromethylthiolation by 1 is the in-situ activation of 1 under copper catalysis to a carbene intermediate. Our interest in the utility of 1 prompted us to investigate the reactions of other substrates, allyl alcohols 2 and boronic acids 4. We demonstrate herein that the reaction of allyl alcohols 2 with 1 under copper catalysis can furnish allylic trifluoromethyl sulfoxides¹² 3. instead of trifluoromethylthio compounds in good yields via a [2,3]sigmatropic rearrangement.¹³ The reaction of boronic acids¹⁴ **4** with 1 under the same copper catalysis provided cross coupling trifluoromethylthio compounds 5 in moderate yields (Scheme 1). Previous works



Scheme 1 Utilization of trifluoromethanesulfonyl hypervalent iodonium ylide 1.

Results and Discussion

We first examined the reaction of 1-phenyl-2-propen-1-ol (2a) with 1 as a model substrate to optimize the reaction conditions by a [2,3]-sigmatropic rearrangement to provide S(O)CF₃-product **3a** instead of regular SCF₃-products. The reaction was initially

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examined under similar conditions for the trifluoromethylthiolation of allylsilanes and silyl enol ethers in our previous work¹¹ (Table 1, runs 1-2). The desired $S(O)CF_3$ -product **3a** was obtained in 67% yield. A longer reaction time gave **3a** in higher yield (72%, Table 1, run 2). When it comes to screening solvents, amide solvents (NMP, DMF) gave **3a** in comparatively favorable yields (43-58%, runs 3-4), but a halogenated solvent (CH₂Cl₂), an ether solvent (THF), an ester solvent (AcOEt) and other polar solvents (MeCN, DMSO, EtOH) were not suitable for this transformation (runs 5-10). We next optimized the copper catalysts (runs 11-16). The use of Cu (II) species was found to be better than Cu (I) species (CuCl vs CuCl₂, CuOAc vs Cu(OAc)₂), but no improvement was observed. A higher reaction temperature did not improve the yield of **3a** (run 17). The reaction did not proceed in the absence of CuF₂ (run 18).

Table 1Optimization of transformation of 1-phenyl-2-propen-1-ol(2a) into 3a.^a

OH Ph 2a	Ph IPh 1 (2.0 eq CuX (20 m solvent, terr	SO ₂ CF ₃	SCF3	Ph 3:	∽_CF₃ ⊔ 0
run	CuX	solvent	temp	time (h)	yield
			(°C)		(%) [»]
1	CuF ₂	DMAc	rt	10	67
2	CuF ₂	DMAc	rt	24	72
3	CuF ₂	NMP	rt	24	58
4	CuF ₂	DMF	rt	24	43
5	CuF ₂	CH_2CI_2	rt	24	trace
6	CuF ₂	THF	rt	24	0
7	CuF ₂	MeCN	rt	24	23
8	CuF ₂	DMSO	rt	24	0
9	CuF ₂	EtOH	rt	24	0
10	CuF ₂	AcOEt	rt	24	trace
11	CuCl	DMAc	rt	24	0
12	CuCl ₂	DMAc	rt	24	6
13	CuBr ₂	DMAc	rt	24	36
14	CuOAc	DMAc	rt	24	12
15	Cu(OAc) ₂	DMAc	rt	24	50
16	Cu(OTf) ₂	DMAc	rt	24	13
17	CuF ₂	DMAc	50	24	54
18	-	DMAc	rt	24	0

^{*a*} The reactions were carried out with **2a** (0.25 mmol), **1** (0.50 mmol) and CuX (0.05 mmol) in each solvent (1.25 ml). ^{*b*} ¹⁹F NMR yields with PhF (0.75 mmol) as an internal standard.

With the optimized reaction conditions in our hand (Table 1, run 2), we next investigated the substrate scope of allyl alcohols (Scheme 2). Applying the reaction of **2** having naphthyl or alkyl substituted phenyl groups, the desired trifluoromethyl sulfinyl products **3b-d** were obtained in good to high yields (61-85%, Scheme 2). The electron-donating group (OMe) could be applied without a high steric effect in the reaction (**3e-g**). Phenyl allyl alcohols substituted with electron-withdrawing groups (Cl, CF₃) gave the desired products **3h-i** in modest to high yield (44-75%). Additionally, hetero aromatic allyl alcohols **3j-k** were also relevant in this transformation, providing the corresponding trifluoromethyl sulfinates without any functionalization of the heteroaryl moieties. It is interesting to note that even when alkyl and branched allyl

alcohols **21-n** were applied, the reaction proceeded to the sulfinates, although in moderate yields (15-42%).^{10.1039/C5DT02214B}



Scheme 2 Transformation of allyl alcohols 2a-n into 3a-n (isolation yields, reaction conditions: 2 (0.25 mmol), 1 (0.50 mmol) and CuF_2 (0.05 mmol) in DMAc (1.25 ml), rt, 24 h under N₂).

 a The reaction time was 5 h. b E/Z =22/3. c d.r. = 3/2. d The reaction time was 2 h.

We next attempted the cross coupling trifluoromethylthiolation reaction of boronic acids 4 with 1. 4-Phenoxy-phenyl boronic acid (4a) was first examined in the reaction with 1 under the same conditions as in scheme 2, i.e., with a catalytic amount of CuF₂ in DMAC. The reaction did not proceed at rt, but 13% of the desired SCF₃ cross coupling product 5a was obtained at 80 °C using a higher amount of CuF₂ (1.2 equiv.) (runs 1-2, Table 1S, ESI). When Cu(OAc)₂ (1.2 equiv.) was used, the yield of 5a improved to 47% (run 7, Table 1S, ESI). The substrate scope was next examined for the trifluoromethylthiolation reaction of aryl- and vinylboronic acids (Scheme 3). Although the yields were moderate, various boronic acids were applicable in the cross coupling reaction. Simple arylboronic acid **4b-c** were converted into the desired trifluoromethylthiolated products 5b-c in modest yields (25-29%). The electron-donating and -withdrawing substituted arylboronic acids **4d-e** were also transformed into **5d-e** in 27-38% yield. Furthermore, hetero arylboronic acid 4f-g were applied to the trifluoromethylthiolation reaction, although the yield of 5f-g was low (12-15%). Both arylboronic acids and vinylboronic acids 4h-i also could be transformed into the F₃CS-products 5h-i in good yields (45-55%).



 $\label{eq:scheme 3} \begin{array}{l} \mbox{Trifluoromethylthiolation of boronic acids $4a$-i (isolation yields, reaction conditions: 4 (0.25 mmol), 1 (0.50 mmol) and $Cu(OAc)_2$ (0.30 mmol) in DMAc (1.25 ml), $80 °C, 10 h under N_2). \end{array}$

Conclusions

We have succeeded synthesis both in the of trifluoromethylsulfinyl and trifluoromethylthio compounds using trifluoromethanesulfonyl hypervalent iodonium ylide 1 under copper catalysis. The reaction of various allyl alcohols 2 with 1 in the presence of a catalytic amount of CuF2 furnished trifluoromethylsulfinyl compounds instead of trifluoromethylthio compounds via a [2,3]-sigmatropic rearrangement. On the other hand, trifluoromethylthiolation of boronic acids 4 with 1 under reaction conditions similar using Cu(OAc)₂ provided trifluoromethylthio compounds in moderate yields via a cross coupling reaction. Although the same reactions providing 3 and 5 have been reported using "other trifluoromethylthiolation reagents" under different conditions, these "trifluoromethylthiolation reagents" themselves should be prepared in advance by "trifluoromethylthiolation or related trifluoromethylation". On the other hand, our reagent 1 can be prepared form ubiquitous CF₃SO₂ CF₃SO₂Na, any compounds such as without using trifluoromethylthiolation reagent. These results show the further expansion of the scope and utility of reagent 1 for trifluoromethylthiolations. A separate study will focus on this aspect of the chemistry of 1 as well as further applications to accommodate a broader range of reactions.

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Trifluoromethylsulfinyl ${\bf 3}$ and trifluoromethylthio ${\bf 5}$ compounds are independently obtained by the sulfone-type reagent ${\bf 1}$ under Cu catalysis.