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Electrophilic Hypervalent Trifluoromethylthio-Iodine(III) Reagent

Xiao-Guang Yang, Ke Zheng, and Chi Zhang*

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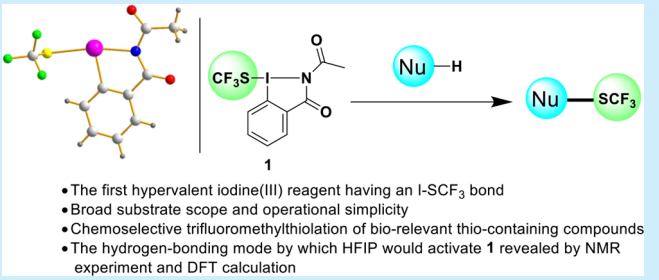
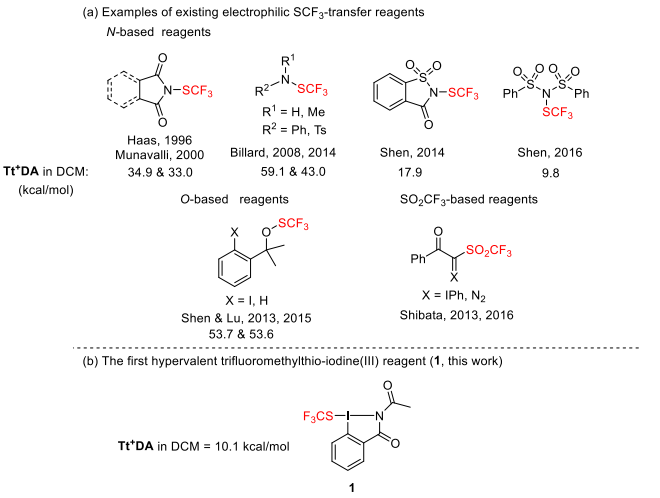
ABSTRACT: Herein we report the design and synthesis of hypervalent trifluoromethylthio-iodine(III) reagent **1** and the elucidation of its structure by NMR spectroscopy and X-ray crystallography. The trifluoromethylthiolation reactions of **1** with various nucleophiles were explored, and this compound was found to be a versatile electrophilic reagent for the transfer of a trifluoromethylthio group (−SCF_3). The hydrogen-bonding mode responsible for the activation of **1** by the solvent 1,1,1,3,3,3-hexafluoro-2-propanol was investigated both experimentally and computationally.



Hypervalent iodine reagents are multipurpose oxidizing agents, and their effectiveness as functional-group-transfer reagents is well-recognized.[1] For example, chlorine atoms and tosylate, cyano, and azide groups have been introduced into organic molecules by means of $ArICl_2$,[2] Koser's reagent,[3] Zhdankin's cyanoiodinane,[4] and azidoiodinane,[5] respectively. In addition, fluorine atoms and various fluorine-containing functional groups can also be efficiently incorporated into organic molecules by using hypervalent iodine(III) reagents. For example, $ArIF_2$ and fluoro-benziodoxole can transfer a fluorine atom,[6] Togni's reagent and its analogues can transfer a CF_3 group,[7] and perfluoroalkyl λ^3-iodane reagents can transfer their perfluoroalkyl groups.[8]

The trifluoromethylthiol group (−SCF_3), a heteroatomic fluorinated group, shows promise for medicinal chemistry applications because it can enhance the lipophilicity and metabolic stability of drugs as well as agrochemicals.[9] Therefore, considerable effort has been devoted to the development of SCF_3-transfer reagents.[10] In particular, the research groups of Haas,[11] Munavalli,[12] Billard,[13] Shen,[14] and Shibata[15] have contributed greatly to this field with their syntheses of novel electrophilic SCF_3-transfer reagents, which can be classified as N-based, O-based, or SO_2CF_3-based, depending on their structures (Scheme 1a). Of particular interest is Shibata's reagent, a unique trifluoromethanesulfonyl hypervalent iodonium ylide that acts as an efficient electrophilic SCF_3-transfer reagent in the presence of a copper(I) catalyst. However, Shibata's reagent does not contain an I(III)−S bond, and the SCF_3 group is generated by in situ reduction of an SO_2CF_3 moiety with intramolecular rearrangement.[15a] To the best of our knowledge, a hypervalent iodine(III) reagent bearing an SCF_3 group directly bonded to a λ^3-iodine atom remains unknown.[14a,16] In this study, we designed and synthesized the first *N*-acetylbenziodazole-based hypervalent trifluoromethylthio-iodine(III) reagent (**1**, Scheme 1b) and explored its ability to act as an electrophilic SCF_3-transfer reagent.

Scheme 1. (a) Representative Existing Electrophilic SCF_3-Transfer Reagents and (b) New SCF_3-Transfer Reagent 1



In 2016, Schaefer and Zhang et al. showed that the benziodoxole-based SCF_3-transfer reagent would be unstable on the basis of computational results.[17] Therefore, we chose the *N*-acetylbenziodazole skeleton, which has been less investigated so far,[18] and the specific reasons are as follows. First, because intramolecular secondary I···O bonding is

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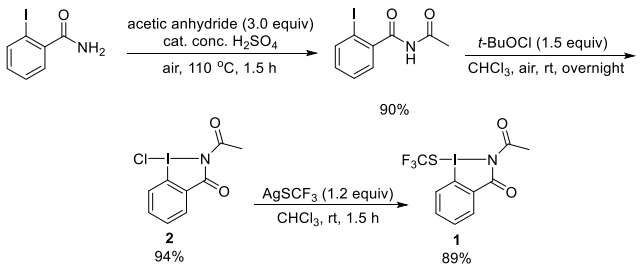
known to stabilize λ^3-iodanes, we hypothesized that the introduction of an acetyl group onto the benziodazole skeleton would stabilize the reagent via a secondary bonding interaction between the λ^3-iodine atom and the carbonyl oxygen of the acetyl group. Second, the mutual ligand interference (trans influence) plays an important role in the stability of λ^3-iodanes, and a principle is developed in which a λ^3-iodane with a strong trans-influencing ligand and a moderate trans-influencing ligand is stable.[19] Suresh et al. used the molecular electrostatic potential (MESP) minimum (V_{min}) as a measure to quantify the trans influence of ligands in λ^3-iodanes.[20] On the basis of their work, we classified the SCF_3 group and *N*-acetylbenzamido group (−N(PhCO)COMe) as moderate and strong trans-influencing ligands, respectively, by density functional theory (DFT) calculations. (See the SI for details.) In view of the previously mentioned reasons, we speculated that the combination of a SCF_3 ligand and an *N*-acetylbenziodazole skeleton would be favored and therefore tried to synthesize a hypervalent trifluoromethylthio-iodine(III) reagent.

Reagent **1** was readily synthesized via a three-step process (Scheme 2). First, 2-iodobenzamide was acetylated to afford

Scheme 2. Synthesis of Hypervalent Trifluoromethylthio-iodine(III) Reagent 1



N-acetyl-2-iodobenzamide, which was allowed to react with *t*-BuOCl to give hypervalent iodine(III) compound **2**. A ligand exchange reaction between **2** and $AgSCF_3$ generated hypervalent trifluoromethylthio-iodine(III) reagent **1** as a colorless solid in 75% overall yield. Reagent **1** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and high-resolution mass spectrometry. The ^{13}C NMR chemical shift of the C−I *ipso*-carbon (113.1 ppm) was in the typical region reported for hypervalent iodine(III) compounds. The ^{19}F NMR signal for the I(III)-SCF_3 moiety (−29.6 ppm) appeared at a markedly lower field than the signals for N−SCF_3 and O−SCF_3 fragments (which range from −47.3 to −53.3 ppm), owing to the strong deshielding effect of the λ^3-iodine atom. It is worth noting that **1** could be prepared on a large scale (25 mmol, 8.79 g) without diminishment of the yield.

Reagent **1** was air- and moisture-stable and could be stored in a freezer (−20 °C) for at least 4 months without decomposition. Thermogravimetry/differential thermal analysis showed that **1** decomposed at 137 °C to give a brown tar (Figure S1). The reagent showed good solubility in common organic solvents, including dichloromethane, chloroform, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP).

A single crystal of **1** was grown in dichloromethane/*n*-hexane at room temperature, and X-ray crystallography showed that the S1−I−N1 bond angle (169.33°) was <180° and that the C1−I−S1 and C1−I−N1 bond angles (92.97 and 76.47°, respectively) deviated from 90° (Figure 1). These results demonstrate that **1** has a distorted T-shaped structure that is

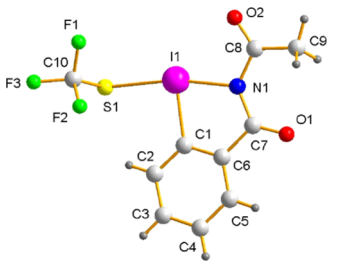
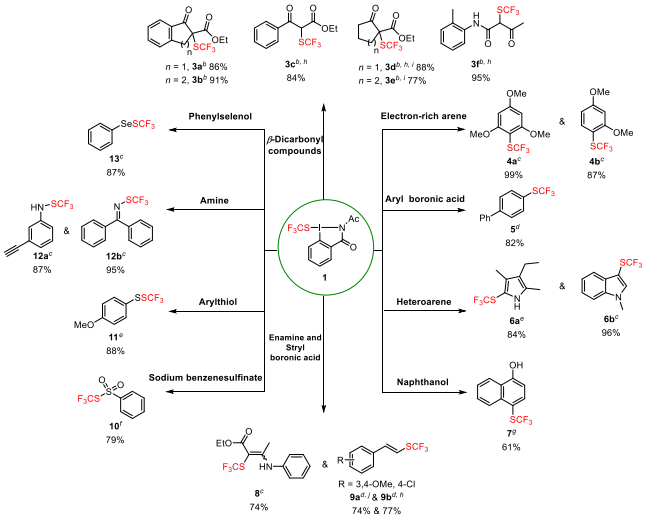


Figure 1. Single-crystal X-ray structure of **1**.

typical of λ^3-iodanes. The I1···O2 distance (2.966 Å) was considerably shorter than the sum of the van der Waals radii of the two atoms (3.50 Å),[21] indicating the presence of secondary bonding. Notably, this is the first observation of an I(III)−SCF_3 bond, which has a bond length of 2.566 Å.

With hypervalent trifluoromethylthio-iodine(III) reagent **1** in hand, we explored its synthetic utility for the trifluoromethylthiolation of nucleophiles (Scheme 3). We found that

Scheme 3. Direct Electrophilic Trifluoromethylthiolation of Various Nucleophiles with 1[a]



[a]Isolated yields are reported. [b]Reaction conditions, unless otherwise noted: β-dicarbonyl compound (0.2 mmol), **1** (0.3 mmol), triethylamine (0.22 mmol), MeCN (2 mL), rt. [c]Substrate (0.2 mmol), **1** (0.24−0.30 mmol), HFIP (2 mL), rt. [d]Reaction conditions, unless otherwise noted: boronic acid (0.1 mmol), **1** (0.15 mmol), CuI (5 mmol %), 1,10-phenanthroline (10 mmol %), K_2CO_3 (0.2 mmol), MeCN (2 mL), 65 °C. [e]Substrate (0.2 mmol), **1** (0.24 mmol), dichloromethane (2 mL), 0 °C. [f]Sodium benzenesulfinate (0.3 mmol), **1** (0.2 mmol), HOAc (2 mL), rt. [g]1-Naphthanol (0.2 mmol), **1** (0.3 mmol), $CHCl_3$ (2 mL), rt. [h]Reaction was performed at 0 °C. [i]C_2H_5ONa (3.0 equiv) was used as a base. [j]Reaction was performed at rt.

cyclic and acyclic β-dicarbonyl compounds, including β-ketoesters and a β-ketoamide, reacted with **1** in the presence of a base under mild conditions to give the corresponding α-trifluoromethylthiolated products (**3a**−**f**) in good to excellent yield. Because SCF_3-substituted arenes and heteroarenes are important structural motifs in pharmaceuticals and agrochemicals,[9a] we also evaluated reactions of these types of substrates and found that electron-rich arenes and heteroarenes (a pyrrole and an indole) could be transformed into the corresponding trifluoromethylthiolated products (**4a**, **4b**, **6a**,

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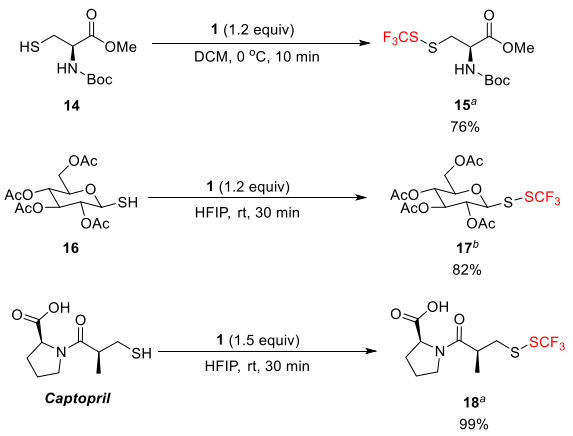
and **6b**) by reaction with **1** in high to excellent yield. Gratifyingly, even an unactivated arene could be efficiently trifluoromethylthiolated: Compound **5** was obtained when the corresponding aryl boronic acid was used as the substrate and CuI was included as a catalyst. 1-Naphthanol was also a good substrate, affording 4-trifluoromethylthiolated-1-naphthanol (**7**) in a synthetically useful yield. The reaction of an enamine with **1** afforded C(sp^2)−H trifluoromethylthiolation product **8** in 74% yield when HFIP was used as a solvent. In addition, trifluoromethylthiostyrenes **9a** and **9b** were obtained from the corresponding styryl boronic acids in the presence of a catalytic amount of CuI. Notably, this transformation was stereospecific: Only the E product was observed by ^{19}F NMR spectroscopy. Heteroatoms could also undergo trifluoromethylthiolation. Specifically, the SCF_3 moiety could be efficiently introduced onto the S (−2, +4), N, and Se atoms of *p*-methoxybenzenethiol, sodium benzenesulfinate, diphenylmethanimine, 3-ethynylaniline, and phenylselenol upon reaction with **1**. It is worth noting that the reduction product *N*-acetyl-2-iodobenzamide of **1** could be easily recovered (93%) after the reactions to regenerate **1** by oxidation and ligand exchange.

Encouraged by the utility of **1** for the trifluoromethylthiolation of the arylthiol, we examined the reactivity of **1** with three biologically relevant compounds bearing thiol groups (Scheme 4). Both protected cysteine derivative **14** and 1-

Scheme 4. Trifluoromethylthiolation of Biologically Relevant Thiol-Containing Compounds

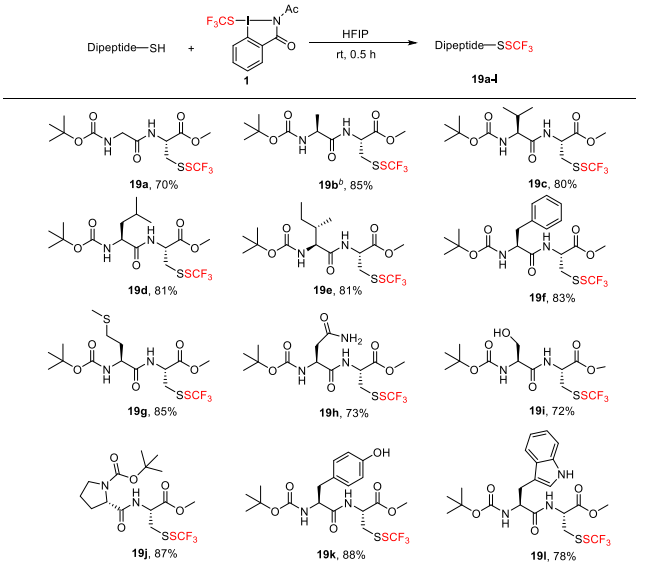


[a]Isolated yield. [b]Yield determined by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard.

thioglucose derivative **16** reacted with **1** under mild conditions to give the corresponding trifluoromethyl disulfides in high yield. It is worth noting that captopril, a widely used antihypertension drug, was successfully trifluoromethylthiolated by using **1**, affording the desired product **18** in 99% yield, and the free carboxylic acid group did not hamper the reaction. Previous literature has shown that trifluoromethyl disulfides are valuable precursors to prepare biologically active trifluoromethyl thiosulfonates.[22]

The modification of peptides and proteins is a powerful strategy for modulating their biological functions,[23] and numerous methods for the modification of peptides or proteins at cysteine residues have been reported.[24] In this study, we used the protocol described herein to carry out the trifluoromethylthiolation of dipeptides at their cysteine residues (Scheme 5). Specifically, the treatment of various

Scheme 5. Trifluoromethylthiolation of Cysteine Residues of Dipeptides[a]



[a]Isolated yields are reported. Reaction conditions, unless otherwise noted: dipeptide (0.1 mmol), **1** (0.12 mmol), HFIP (2 mL), rt, 0.5 h. [b]Reaction time was 2 h.

dipeptides containing nonpolar natural amino acids (Ala, Gly, Ile, Leu, Phe, and Val) with **1** in HFIP at room temperature generated the corresponding trifluoromethyl disulfides in good to high yield. This reaction showed excellent chemoselectivity; cysteine residues could be selectively trifluoromethylthiolated in the presence of other nucleophilic functional groups. For example, dipeptides containing asparagine, proline, and tryptophan residues all smoothly afforded the corresponding dipeptides with trifluoromethylthiolated cysteine residues. Notably, readily oxidized groups such as the methylthio group of methionine, the hydroxyl group of serine, and the phenolic group of tyrosine were also tolerated. Previous works mainly focused on the trifluoromethylthioation of simple thiols;[25] as far as we know, this is the first systematic study on the trifluoromethylthioation of cysteine-containing dipeptides.

As a strong hydrogen-bond donor,[26] HFIP markedly activates hypervalent iodine(III) reagents and existing SCF_3-transfer reagents via the hydrogen-bonding interaction.[27] In many of the reactions previously described, we observed that using HFIP as a solvent facilitated the transfer of SCF_3. To gain insight into the mechanism by which HFIP activated **1**, we performed a ^1H NMR spectroscopy study (Figure 2) and density functional theory (DFT) calculations. The ^1H NMR spectrum of a 1:2 mixture of **1** and HFIP (Figure 2c) showed a downfield shift of the OH signal of HFIP relative to that in the absence of **1** (Figure 2a). The DFT calculations indicated that HFIP formed hydrogen bonds with the two carbonyl oxygen atoms of **1**, and thus the nitrogen and sulfur atoms in the hydrogen-bonded adduct were more electron-deficient than those in isolated **1**. (The charge distributions were −0.010 vs 0.191 and 0.117 vs 0.348, respectively; see the SI for details.) On the basis of these experimental and theoretical results, we reasoned that hydrogen bonding between **1** and HFIP activated **1** by polarizing the hypervalent iodine bond. HFIP may also have stabilized the trifluoromethylthio cation (CF_3S^+).

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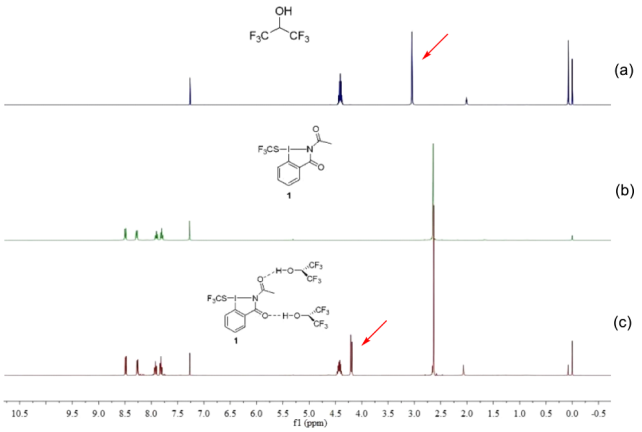

Figure 2. ^{1}H NMR spectra of (a) HFIP, (b) **1**, and (c) a 1:2 mixture of **1** and HFIP. The red arrow indicates the OH signal of interest, which was deshielded in the adduct.

In addition, we calculated the trifluoromethylthio-cation-donating ability (Tt^+DA) of **1** on the quantitative scale established by Cheng and Xue's group[28] for electrophilic SCF_3-transfer reagents. This calculation revealed the Tt^+DA value for **1** was 10.1 kcal·mol^{-1}, confirming it to be a powerful electrophilic SCF_3-transfer reagent.

In conclusion, we designed and synthesized the first hypervalent trifluoromethylthio-iodine(III) reagent **1**. Reagent **1**, which has a typical λ^3-iodane structure, was characterized by NMR spectroscopy and X-ray crystallography. We found that **1** could be used as an electrophilic SCF_3-transfer reagent for the trifluoromethylthiolation of various nucleophiles under mild conditions. In particular, by using **1**, we were able to accomplish selective trifluoromethylthiolation of dipeptides at cysteine residues with good tolerance for other functional groups. Our findings reveal **1** to be an attractive tool for the incorporation of SCF_3 into molecules. Furthermore, we used experimental and computational techniques to determine the hydrogen-bonding mode by which HFIP activated **1**. Further study of the unique reactivity of **1** is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00405.

Experimental details, analytical data, and NMR spectra (PDF)

Accession Codes

CCDC 1914324 and 1914326 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Chi Zhang − *State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, College of Chemistry, Nankai University, Tianjin 300071, China;* orcid.org/0000-0001-9050-076X; Email: zhangchi@nankai.edu.cn

Authors

Xiao-Guang Yang − *State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, College of Chemistry, Nankai University, Tianjin 300071, China*

Ke Zheng − *State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, College of Chemistry, Nankai University, Tianjin 300071, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00405

Notes

The authors declare no competing financial interest.

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