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# Electrophilic (phenylsulfonyl)difluoromethylation of thiols with a hypervalent iodine(III)–$CF_2SO_2Ph$ reagent

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ABSTRACT

A hypervalent iodine(III)–$CF_2SO_2Ph$ compound (**3**) has been successfully prepared with selective nucleophilic reaction using $PhSO_2CF_2SiMe_3$ reagent, and this previously unkown compound **3** was found to act as a new electrophilic (phenylsulfonyl)difluoromethylation reagent for a variety of *S*-nucleophiles under very mild reaction conditions.

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As 'a small atom with a big ego',[1] fluorine plays increasingly important roles in many fields such as medicinal and pharmaceutical research and material science.[2] As a result, many endeavors have been drawn to develop new efficient synthetic methods for selective introduction of fluorinated moieties into organic molecules.[3] In the past four decades, nucleophilic and radical fluoroalkylations have been widely applied in organic synthesis.[3,4] However, the elctrophilic fluoroalkylation is much less generally used, partly as a result of the high cost and less availability of electrophilic fluoroalkylating reagents.[5] The currently known electrophilic fluoroalkylating reagents are mainly based on the structures of (fluoroalkyl)aryliodonium salts and (fluoroalkyl)arylchalcogen salts, which were developed by Yagupolskii,[6] Umemoto,[5,7] Shreeve,[8] Magnier,[9] Prakash,[10] among others.[11] Recently, Togni and co-workers reported several neutral compounds, 10-I-3 hypervalent iodine(III) compounds, as a new family of electrophilic trifluoromethylating agents.[12]

Previously, we had been interested in developing efficient methods for selective introduction of (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) into organic molecules, based on the fact that the $PhSO_2CF_2$ group is a versatile functionality that can be readily converted to other highly useful difluorinated moieties such as difluoromethyl ($CF_2H$), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) groups.[13] In this context, we have successfully applied $PhSO_2CF_2H$ (**1**) and $PhSO_2CF_2SiMe_3$ (**2**) as powerful *nucleophilic* (phenylsulfonyl)difluoromethylating reagents.[14] More recently, an efficient *radical* (phenylsulfonyl)difluoromethylation has also been developed by us using $PhSO_2CF_2I$ reagent.[15] However, *electrophilic* (phenylsulfonyl)difluoromethylation reaction has never been reported. Herein, we wish to report the first *electrophilic* (phenylsulfonyl)difluoromethylation with a hypervalent iodine(III)–$CF_2SO_2Ph$ reagent **3**.

In an attempt to prepare the hypervalent iodine(III)–$CF_2SO_2Ph$ reagent (**3**), we applied a one-pot protocol in which the ligand exchange reaction was carried out at the iodine(III) center (see Table 1).[16] Thus, the chloride substituent in **4** was replaced by an acetoxy group upon treatment with KOAc; after 1 h in dry acetonitrile, the insoluble salts were removed and the filtrate was evaporated under reduced pressure to afford the intermediate product **5**. Thereafter, the second reaction was carried out by a fluoride-mediated substitution of **5** with $PhSO_2CF_2SiMe_3$ (**2**), which corresponds to a formal umpolung of the $PhSO_2CF_2$ group from being in nucleophilic $PhSO_2CF_2SiMe_3$ to electrophilic in **3**. When acetonitrile was used as solvent and the molar ratio between **4** and $PhSO_2CF_2SiMe_3$ (**2**) was 1:2 (in the presence of catalytic tetrabutylammonium difluorotriphenylsilicate (TBAT)), only trace amount of product **3** was detected by $^{19}F$ NMR (Table 1, entry 1), with the major byproduct being $PhSO_2CF_2H$. When 2.0 equiv of starting material **4** was used, the yield increased to 74% in MeCN (entries 2 and 3). Similar results were also obtained when THF was used as solvent (entry 4), while the reaction in DMF gave better yields (entries 5–8). It was found that, by using 1.3 equiv of **4** and DMF as solvent at $-16\,^{\circ}C$ for 18 h, we were able to obtain the hypervalent iodine(III)–$CF_2SO_2Ph$ reagent **3** in 71% isolated yield (Table 1, entry 8). However, when $PhSO_2CF_2H$ (**1**)/LHMDS[14a] was used to replace $PhSO_2CF_2SiMe_3$ (**2**)/TBAT as a nucleophilic $PhSO_2CF_2$ transfer reagent, product **3** could only be obtained in low yield (18%).

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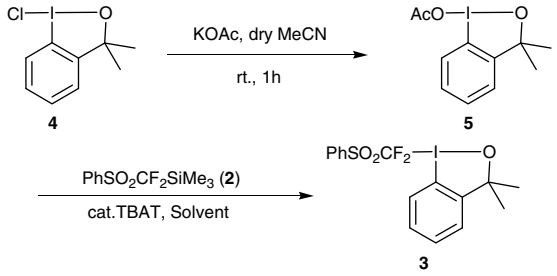
**Table 1**
One-pot synthesis of reagent **3**



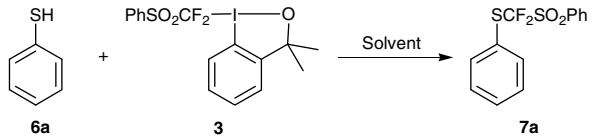

| Entry | Solvent | Ratio (**4**:**2**) | Time (h) | Temp (°C) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 1:2 | 18 | −16 | Trace |
| 2 | $CH_3CN$ | 2:1 | 5 | −45 | 75 |
| 3 | $CH_3CN$ | 2:1 | 12 | −16 | 74 |
| 4 | THF | 2:1 | 5 | −16 | 69 |
| 5 | DMF | 2:1 | 5 | −16 | 88 |
| 6 | DMF | 2:1 | 5 | −45 | 86 |
| 7 | DMF | 2:1 | 18 | −16 | 86 |
| 8 | DMF | 1.3:1 | 18 | −16 | 87 (71[b]) |

[a] The yield was determined by $^{19}F$ NMR based on the ratio of product **3** and by-product $PhSO_2CF_2H$ (**1**).
[b] Isolated yield.

It should be noted that the above-obtained product **3** was found to be more stable than Togni's hypervalent iodine(III)–$CF_3$ compound.[12] Compound **3** can be purified by silica gel column chromatography and stored in a refrigerator for months without any detectable decomposition, while Togni's reagent can only be exposed to and manipulated in moist air for a much shorter period of time.[12] Thus, starting from easily accessible materials, we were able to synthesize I(III)–$CF_2SO_2Ph$ reagent **3** in one-pot with reasonably good yield, and this method also facilitated a scale-up to multigram quantities.

With the electrophilic compound **3** in hand, next we explored its reactivity with sulfur-nucleophiles by using thiophenol (**6a**) as a model compound.[17] As shown in Table 2, the reactions were carried out in $CH_2Cl_2$, DMF, or $CH_3OH$ to give the product **7a** in 66–77% yields (entries 1, 3–4 and 6–9), while in THF or MeCN much lower yields were observed (entries 2 and 5). Additionally, the reaction temperature did not affect the yields significantly (entries 1 and 3). An optimal product yield (75%) was observed when the reaction proceeded in $CH_2Cl_2$ at −78 °C for 3 h with 1.2 equiv thiophenol being used (Table 2, entry 7). Similar to Togni's trifluoromethylation,[12] the present electrophilic (phenylsulfonyl)difluoromethylation reaction does not require extra base, because a stoichiometric amount of alkoxide is formed upon formal '$PhSO_2CF_2^+$' transfer, and 2-(2-iodophenyl)propan-2-ol is found as a by-product which is the starting material for preparation of reagent **4**.

**Table 2**
Survey of reaction conditions

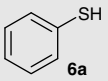
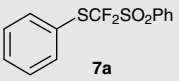
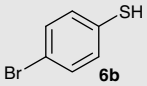
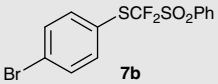
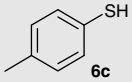
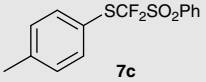
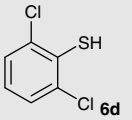
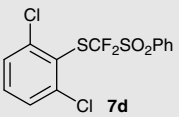
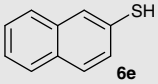
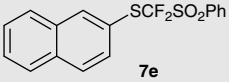
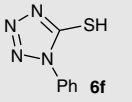
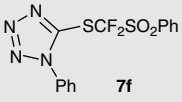
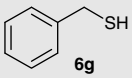
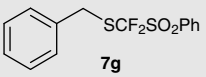
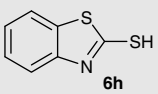
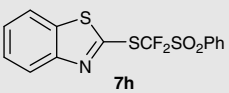
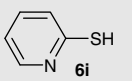
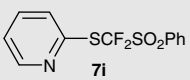
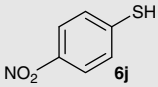
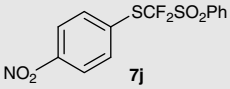
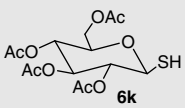
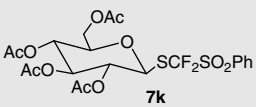



| Entry | Solvent | Ratio (**6a**:**3**) | Time (h) | Temp (°C) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 2:1 | 3 | −78 | 76 |
| 2 | THF | 2:1 | 3 | −78 | 39 |
| 3 | $CH_2Cl_2$ | 2:1 | 3 | −45 | 66 |
| 4 | DMF | 2:1 | 3 | −45 | 77 |
| 5 | $CH_3CN$ | 2:1 | 3 | −45 | 58 |
| 6 | $CH_3OH$ | 2:1 | 3 | −78 | 74 |
| 7 | $CH_2Cl_2$ | 1.2:1 | 3 | −78 | 75 |
| 8 | $CH_2Cl_2$ | 2:1 | 7 | −78 | 67 |
| 9 | $CH_2Cl_2$ | 0.8:1 | 3 | −78 | 66 |

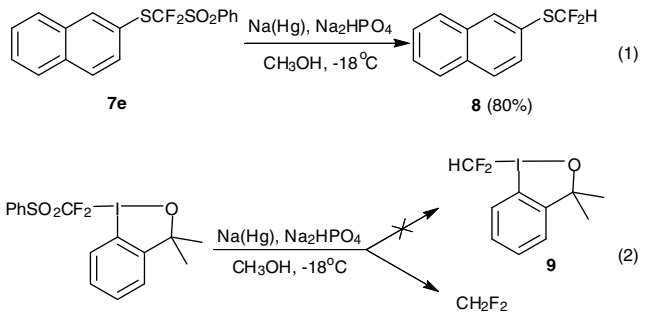
[a] Yields were determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.

Having established the optimized reaction conditions with reagent **3**, we studied the scope of the current electrophilic (phenylsulfonyl)difluoromethylation chemistry with a range of sulfur-nucleophiles. The results are summarized in Table 3. It was found that a variety of structurally diverse thiophenol derivatives showed high reactivity with reagent **3** at low temperature (−78 °C), and the corresponding (phenylsulfonyl)difluoromethylated products **7** were obtained in good yields (68–85%, see Table 3, entries 1–5 and 10). Furthermore, 1-phenyl-1,2,3,4-tetrazole-5-thiol (**6f**), phenylmethanethiol (**6g**), 2-benzothiazolethiol (**6h**), and pyridine-2-

**Table 3**
Electrophilic (phenylsulfonyl)difluoromethylation of thiols **6** with compound **3**

| Entry | Substrate | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  **6a** |  **7a** | 75 |
| 2 |  **6b** |  **7b** | 68 |
| 3 |  **6c** |  **7c** | 72 |
| 4 |  **6d** |  **7d** | 77 |
| 5 |  **6e** |  **7e** | 85 |
| 6[b] |  **6f** |  **7f** | 80 |
| 7 |  **6g** |  **7g** | 87 |
| 8[b] |  **6h** |  **7h** | 82 |
| 9[b] |  **6i** |  **7i** | 80 |
| 10 |  **6j** |  **7j** | 83[c] |
| 11 |  **6k** |  **7k** | 78 |

[a] Isolated yield.
[b] The reaction was carried in $CH_2Cl_2$–EtOH (2:1, v/v).
[c] Determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.




**Scheme 1.**

thiol (**6i**) were all able to be efficiently (phenylsulfonyl)difluoromethylated by reagent **3** with 80–87% product yields (entries 6–9), while in some cases EtOH was required to dissolve the substrates (Table 3, entries 6, 8 and 9). It is particularly remarkable that with reagent **3**, the (phenylsulfonyl)difluoromethylation of pyranose derivative **6k** could also be accomplished with good yield (78%) under very mild reaction conditions (Table 3, entry 11). On the other hand, we found that simple aliphatic thiols did not show reactivity toward compound **3** under the similar reaction conditions. Moreover, the current electrophilic (phenylsulfonyl)difluoromethylation reaction failed to transfer $CF_2SO_2Ph$ group to many carbon nucleophiles we examined.

As demonstrated earlier,[13,14] the phenylsulfonyl group in the final products can be readily removed via a reductive desulfonylation procedure. As shown in Scheme 1, the product **7e** was converted to difluoromethylated sulfide product in high yield (80%, see Scheme 1, Eq. 1). However, when we tried to remove the phenylsulfonyl group in the reagent **3** under the similar conditions to obtain a desired direct electrophilic difluoromethylating reagent **9**, the reaction failed and compound **3** was converted to difluoromethane ($CH_2F_2$), which was detected by $^{19}F$ NMR spectroscopy ($\delta = -144.8$ (t), $^2J_{H,F} = 51.1$ Hz) (Scheme 1, Eq. 2).[18]

In conclusion, we have successfully prepared a hypervalent iodine(III)–$CF_2SO_2Ph$ compound (**3**) with $PhSO_2CF_2SiMe_3$ reagent (**2**). This reagent can be used as a useful electrophilic (phenylsulfonyl)difluoro-methylation reagent for a variety of *S*-nucleophiles under very mild reaction conditions. The phenylsulfonyl group in the final products can be readily removed via a reductive desulfonylation procedure, so that reagent **3** can be considered as a useful electrophilic difluoromethylating reagent. Further investigation of this chemistry is currently underway in our laboratory.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.064.

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16. Preparation of the hypervalent iodine(III)–$CF_2SO_2Ph$ reagent **3**: Under $N_2$ atmosphere, the compound **4** (0.925 g, 3.1 mmol) and dry KOAc (0.520 g, 5.3 mmol) were stirred in dry MeCN (18 ml) for 1.5 h at ambient temperature. After filtration in air, the filtrate was transferred to another 50-mL three-neck flask protected by $N_2$ atmosphere, and then the solvent was evaporated under reduced pressure to get the in situ generation of compound **5**, to which dry DMF (18 ml) was added. The solution was cooled to −16 °C and $PhSO_2CF_2SiMe_3$ **2** (0.634 g, 2.4 mmol, dissolved in 5 mL of DMF) was added via a needle, followed by addition of catalytic tetrabutylammonium triphenyldifluorosilicate (TBAT). After stirring for 18 h at −16 °C, the reaction was quenched by adding excess amount of $H_2O$, followed by extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:5, v/v) as eluent to give product **3** (0.770 g, 1.7 mmol, yield: 71%) as a white solid. Mp: 89–90 °C. IR (film): 2971, 1448, 1332, 1159, 1106, 1052, 770, 566 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.93 (d, $J$ = 6.9 Hz, 2H), 7.81 (d, $J$ = 8.4 Hz, 1H), 7.72 (t, $J$ = 7.8 Hz, 1H), 7.57 (t, $J$ = 7.8 Hz, 2H), 7.45 (t, $J$ = 7.2 Hz, 1H), 7.33–7.39 (m, 1H), 7.26–7.29 (m, 1H), 1.44 (s, 6H). $^{19}F$ NMR: $\delta$ −84.2 (s, 2F). $^{13}C$ NMR: $\delta$ 150.0, 135.5, 131.5, 130.5, 129.8, 129.5, 129.4, 127.1 120.5 (t, $J$ = 370.9 Hz), 111.7, 77.6, 30.6. MS (ESI): $m/z$ 453 ($M+H^+$). Anal. Calcd for $C_{16}H_{15}F_2IO_3S$: C, 42.49; H, 3.34. Found: C, 42.74; H, 3.58.
17. Typical procedure for electrophilic (phenylsulfonyl)difluoro-methylation of thiols **6** with compound **3**: Under $N_2$ atmosphere, the compound **3** (0.096 g, 0.21 mmol) and thiophenol (**6a**) (0.028 g, 0.25 mmol) were stirred in dry $CH_2Cl_2$ (3 ml) for 3 h at −78 °C. Then, the reaction was quenched by adding excess amount of $H_2O$, followed by extraction with $CH_2Cl_2$. The organic phase was washed successively with NaOH (5%) and brine, and then dried over anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:50, v/v) as eluent to give product **7a** (0.047 g, 0.16 mmol, yield: 75%) as a colorless liquid. $^1H$ NMR: $\delta$ 7.87–7.92 (m, 2H), 7.48–7.71 (m, 5H), 7.28–7.40 (m, 3H). $^{19}F$ NMR: $\delta$ 79.0 (s, 2F). MS (EI, $m/z$, %): 300 ($M^+$, 0.26), 159 (100.00). The characterization data was consistent with the previous report, see: Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53.
18. Although difluoromethane ($CH_2F_2$) is a gaseous compound (bp −51.6 °C), it dissolves in the reaction solvent (methanol) and thus enables us to characterize it by $^{19}F$ NMR. Our characterization data for $CH_2F_2$ was consistent with the previous report, see: Weigert, F. J. *J. Org. Chem.* **1980**, *45*, 3476–3483.