Synthetic Methods

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An Electrophilic Reagent for the Direct Introduction of the $SCF_2PO(OEt)_2$ Group to Molecules

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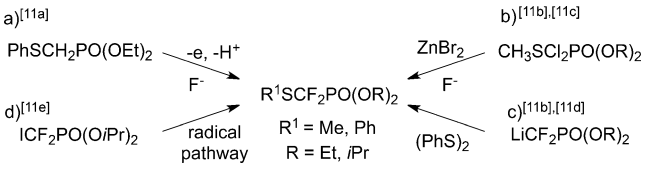
Abstract: *An unprecedented electrophilic difluoromethylthiolating reagent ($MesNHSCF_2PO(OEt)_2$) was designed. Under mild and metal-free conditions, this new reagent reacted with various nucleophiles, thus offering an efficient and operationally simple tool for the construction of C–$SCF_2PO(OR)_2$, N–$SCF_2PO(OR)_2$, and S–$SCF_2PO(OR)_2$ bonds. Finally, thanks to this new methodology, the synthesis of the non-stereoidal anti-inflammatory diflumidone was achieved.*

Because of the importance of the fluorine-containing molecules in pharmaceuticals and agrochemicals,[1] the organofluorine chemistry research field is continually and rapidly evolving.[2] Indeed, the presence of either a fluorine atom or a fluorinated group in molecules has a strong impact on their biological and physical properties.[3] Consequently, the design of new fluorinated groups is still a compelling challenge in this blooming field. Recently, SR_f-containing groups have appeared as key motifs and, among them, the SCF_3 and SCF_2H residues have attracted a strong interest from the scientific community thanks to their great features. Therefore, transformations to introduce the SCF_3[2a,4] and the SCF_2H[5] groups to molecules have been developed. Inspired by these recent advances, a promising approach relying on the design of original SCF_2-containing residues bearing an additional functional group (FG) has emerged. Indeed, by modulating the nature of the FG, the properties of the fluorinated residue could be fine-tuned at will. Taking into consideration the myriad of available fluorinated groups (CF_3, CF_2H, $CF_2PO(OR)_2$, CF_2SO_2Ph, C_nF_{2n+1}…), the synthesis of their sulfur-containing analogues would provide a new generation of fluorinated residues. This strategy has been recently illustrated by the contributions of the groups of Hu,[6] Gooßen,[7] Billard,[8] and others.[9] Indeed, various SCF_2FG-containing molecules (FG = SO_2Ph, R_f, SAr and COAr) were successfully synthesized using two main synthetic pathways: 1) the construction of a S–CF_2FG bond by reaction of a CF_2FG reagent with either thiols or disulfides, and 2) the direct introduction of a SCF_2FG group to molecules thanks to newly designed reagents. With these considerations in mind, we turned our attention to the $SCF_2PO(OR)_2$ group. We imagined that the original combination of a thioether with the $CF_2PO(OR)_2$ residue will be highly beneficial considering the intrinsic properties of both functional groups.[10]

To date, only a handful of reports have dealt with the synthesis of $SCF_2PO(OR)_2$-containing molecules. They relied on the difluorination of $PhSCH_2PO(OEt)_2$ by either an electrochemical pathway (Scheme 1 a)[11a] or by means of a halogen-exchange using $3\,HF{\cdot}NEt_3$ and $ZnBr_2$ starting from the corresponding chlorinated analogue (Scheme 1 b).[11b,c] Alternatively, either the nucleophilic addition of $LiCF_2PO(OR)_2$[11d] to diphenyl disulfide (Scheme 1 c)[11b,d] or the addition of a fluorinated radical, generated from $ICF_2PO(OiPr)_2$, to the Barton carbonate were reported by Lequeux (Scheme 1 d).[11e] It is worth mentioning that to date, there is no general and efficient access to $SCF_2PO(OEt)_2$-containing molecules and only a couple of products are available ($MeSCF_2PO(OR)_2$ and $PhSCF_2PO(OR)_2$).



Scheme 1. State of the art.

Thus, the design of a bench-stable reagent to directly introduce an $SCF_2PO(OEt)_2$ residue will enlarge the current toolbox of fluorinated groups and open new routes for functionalizing complex molecules. Herein, we disclosed a simple and straightforward synthesis of the first electrophilic $SCF_2PO(OEt)_2$ source and its broad application in various transformations. Inspired by the recent studies from Gooßen and co-workers,[5a,b,12] and taking advantage of our own expertise for the preparation of N-(cyanosulfanyl)aniline derivatives,[13] we hypothesized that the synthesis of the electrophilic $SCF_2PO(OEt)_2$ reagent might be realized in two steps from the corresponding and readily available aniline and $TMSCF_2PO(OEt)_2$. Indeed, the N-(cyanosulfanyl)aniline derivative **1**, prepared in 66% yield (on 10 mmol scale) from 2,4,6-trimethylaniline and NaSCN,[13,14] was engaged in a nucleophilic cyanide–$CF_2PO(OEt)_2$ substitution with in situ generated $CuCF_2PO(OEt)_2$.[15] With this approach, the electrophilic $SCF_2PO(OEt)_2$ source **2** was prepared in 71% yield on 0.25 mmol scale (Scheme 2). Its synthesis was conveniently scalable and the bench-stable reagent[16] **2** was obtained in 60% yield on 4.4 mmol scale.

Then, to showcase the potential of this reagent, we first studied the electrophilic (diethyl phosphono)difluoromethylthiolation reaction of electron-rich (hetero)arenes (Scheme 3). With exposure to air, a large variety of indole derivatives were functionalized, in the presence of TsOH, to

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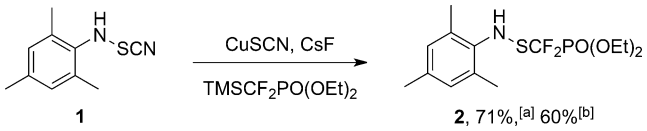
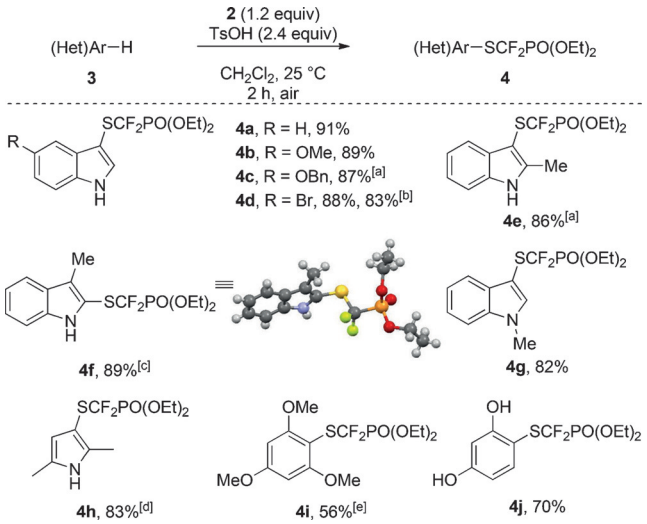


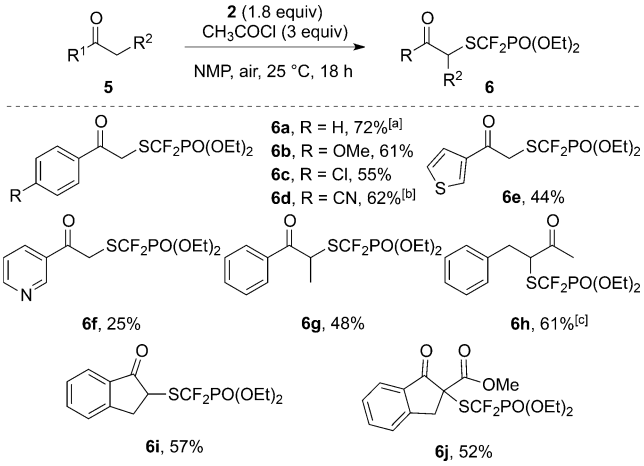
Scheme 2. Synthesis of the electrophilic $SCF_2PO(OEt)_2$ reagent **2**. [a] Reaction performed on 0.25 mmol scale. [b] Reaction performed on 4.4 mmol scale. TMS = trimethylsilyl.



Scheme 3. Electrophilic substitution of electron-rich arenes and heterorenes. Reaction performed on 0.15 mmol scale. Yields of isolated products are given. [a] 4 h. [b] Reaction performed on 2 mmol scale. [c] 8 h. [d] 1 h. [e] 12 h. TsOH = *p*-toluenesulfonic acid.

the corresponding products **4** in high yields at room temperature. Pleasingly, when the reaction of **3a** with **2** was carried out, the (diethyl phosphono)difluoromethylthiolated indole **4a** was obtained in 91% yield. Several indoles substituted with electron-donating groups (**4b** and **4c**) and a halogen (**4d**) were selectively functionalized at C3.[14] A reaction was performed on a 2 mmol scale and **4d** was obtained in 83% yield showcasing the synthetic utility of **2**. Note that 2- and 3-methyl-substituted indoles (**3e** and **3f**) were suitable substrates, thus affording **4e** and **4f**, respectively, in good yields and the structure of **4f** was further confirmed by X-ray analysis.[17] Even the N-methyl indole **3g** and the pyrrole **3h** were efficiently converted into the (diethyl phosphono)difluoromethylthiolated products **4g** (82%) and **4h** (83%), respectively. Anisole and phenol derivatives (**3i** and **3j**) were also compatible and the corresponding products (**4i** and **4j**) were obtained in somewhat lower yields (56% and 70%, respectively).

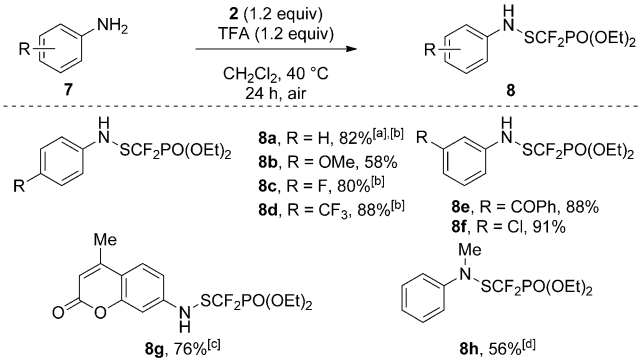
Aimed at demonstrating further the synthetic utility of **2**, we explored the functionalization of cyclic and acyclic ketones (Scheme 4). With the assistance of acetyl chloride as recently developed by the group of Cao,[18] the (diethyl phosphono)difluoromethylthiolation reaction of acetophenone (**5a**) was successfully achieved at room temperature, thus leading to **6a** in 72% yield. The methodology was extended to acetophenone derivatives bearing electron-donating (**6b**) and electron-withdrawing groups (**6c**, **6d**). In



Scheme 4. (Diethyl phosphono)difluoromethylthiolation of ketones and β-ketoester. Reaction performed on 0.2 mmol scale. Yields of isolated products are given. [a] 1.5 equiv of **2** were used. [b] 3 equiv of **2** were used, 20 h. [c] 16 h. NMP = *N*-methylmorpholine-N-oxide.

all cases, the expected α-substituted ketones were synthesized in good yields. Ketones substituted by a heteroaromatic substituent such as thienyl and pyridyl groups afforded the products **6e** and **6f** in 44% and 25% yields, respectively. The functionalization on a methylene at the α-position of a carbonyl group was also evaluated, thus furnishing **6g** in 48% yield. Interestingly, the reaction proved to be selective for the secondary C–H bond as demonstrated with **6h**, which was isolated in 61% yield. The scope of this reaction was further extended to the cyclic ketone and β-ketoester (**5i** and **5j**). Worth mentioning is that in all these cases, only the selective monofunctionalization was observed, and it is highly desirable for late-stage functionalization.

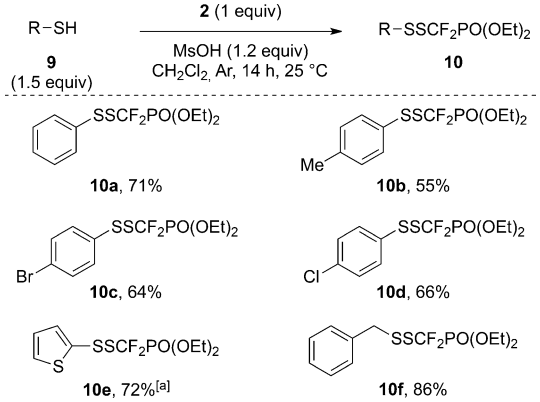
Encouraged by these results, we turned our attention to the synthesis of (diethyl phosphono)difluoromethanesulfenamides, as sulfenamide-containing molecules are important compounds in various fields of chemistry.[19] Pleasingly, the transfer of the $SCF_2PO(OEt)_2$ from the sterically hindered **2** to various anilines was successfully achieved in a metal-free process (Scheme 5). A panel of difluoromethylthiolated



Scheme 5. Reaction of the aniline derivatives **7** with **2** to produce the sulfenamides **8**. Reaction performed on 0.2 mmol scale. Yields of isolated products are given. [a] 25 °C, 0.15 mmol scale. [b] 18 h. [c] 42 h. [d] 72 h, 50 °C. TFA = trifluoroacetic acid.

sulfenamides (**8**) was synthesized in good to high yields (56–91 % yields) in the presence of trifluoroacetic acid. We were delighted to find that the transformation demonstrated a good functional-group tolerance as anilines bearing an electron-donating substituent such as methoxy (**8b**) or electron-withdrawing groups (halogen, CF_3 and ketone, **8c–f**) were functionalized in high yields (up to 91 % yield). The versatility of the method was further illustrated through the synthesis of $SCF_2PO(OEt)_2$-containing analogues of biorelevant molecules such as triflumidate and the diflumidone (**8e**) as well as the coumarin 120 (**8g**). Interestingly, the secondary amine **7h** was functionalized in 56 % yield, albeit a longer reaction time and an increase of the temperature to 50 °C were needed.[20]

We next found that thiol derivatives were also suitable nucleophiles (Scheme 6), thus offering an efficient access to the otherwise difficult-to-synthesize unsymmetrical fluorinated disulfides. The reaction proceeded smoothly at room

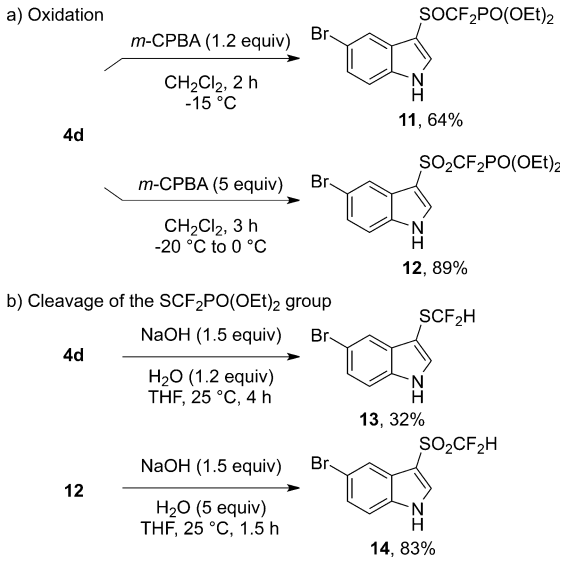


Scheme 6. Synthesis of unsymmetrical fluorinated disulfides **8**. Reaction performed on 0.2 mmol scale of **2**. Yields of isolated products are given based on **2**. [a] 1.7 equiv of **9e** was used, 18 h. MsOH = methanesulfonic acid.

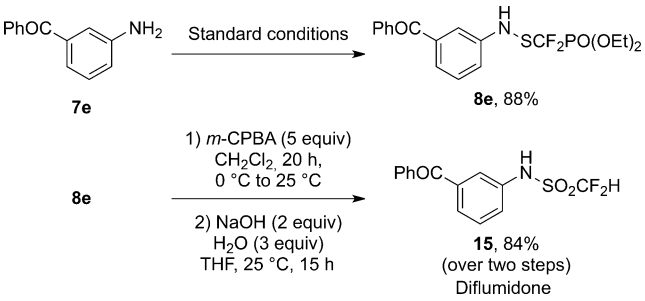
temperature with thiophenol derivatives bearing either an electron-donating substituent (**10b**) or an electron-withdrawing group (**10c** and **10d**). Finally, the functionalizations of heteroaromatic (**9e**) and benzyl (**9f**) thiols was efficiently achieved, thus affording the corresponding products **10e** and **10f** in high yields (72 % and 86 %, respectively).

Further exploration of the potential of the $SCF_2PO(OEt)_2$ group led to its conversion into the corresponding sulfoxide **11** and sulfone **12** in good yields, thus affording straightforward access to other high-value added fluorinated groups (Scheme 7a). As the SCF_2H group is considered as an emergent fluorinated group,[5] we investigated the possibility of converting the $S(O)_nCF_2PO(OEt)_2$ residue ($n = 0$ or 2) into the corresponding $S(O)_nCF_2H$ group.[21] After intensive investigations, it turned out that under basic conditions (NaOH) and using water as an additive, the CF_2–P bond cleavage occurred, thus leading to **13** and **14** in 32 and 83 % yield, respectively (Scheme 7b).

With all these synthetic tools in hand, we applied them to the synthesis of Diflumidone (**15**), a non-stereoidal anti-inflammatory compound.[22] Indeed, we succeeded in a straightforward access to **15** in a three-step/two-purification



Scheme 7. Post-functionalization reactions. *m*-CPBA = *meta*-chloroperbenzoic acid, THF = tetrahydrofuran.



Scheme 8. Synthesis of Diflumidone.

sequence from the commercially available 3-aminobenzophenone (**7e**) in 74 % overall yield (Scheme 8). Worth mentioning is that the previous approach provided **15** from **7e** in a low yield (28 %)[23] by employing the rather expensive difluoromethanesulfonyl chloride,[24] and it required a two-step synthesis using the ozone-depleting HCF_2Cl.

In conclusion, the electrophilic reagent **2** was successfully synthesized as a unique bench-stable and easy-to-handle $SCF_2PO(OEt)_2$ source. It was efficiently applied to the functionalization of $C(sp^2)$ and $C(sp^3)$ centers. In addition, nucleophiles such as primary and secondary amines as well as aromatic and aliphatic thiols were efficiently functionalized. Furthermore, access to sulfoxide and sulfone derivatives was achieved after a simple oxidation step, and is particularly interesting from a synthetic point of view. The conversion of the $SCF_2PO(OEt)_2$ residue into SCF_2H and SO_2CF_2H groups illustrated the versatility of this fluorinated group. Moreover, the synthesis of a biorelevant molecule, Diflumidone, was achieved in high yield. The selective introduction of the $SCF_2PO(OEt)_2$ group to a panel of molecules considerably extended the scope of the $SCF_2PO(OEt)_2$-containing derivatives and we believe that the design of this electrophilic reagent will open new avenues towards further investigations regarding the potential of the $SCF_2PO(OEt)_2$ residue.

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[16] The reagent **2** can be stored for three months at room temperature under air without any loss of efficiency (see the Supporting Information).

[17] CCDC 1494845 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[20] Unfortunately, when the more nucleophilic aliphatic amines were engaged with **2** in CH_2Cl_2 in the absence of TFA, no reaction occurred. Indeed, **2** was recovered untouched despite longer reaction time, increased reaction temperature, and the presence or not of another additive such as BF_3OEt_2, TMSCl in replacement of TFA.

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