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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C8CC00921J

Journal Name

COMMUNICATION

An Electrophilic Reagent for the Synthesis of OCHFMe-Containing Molecules.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Herein the synthesis of a novel and bench stable electrophilic reagent to construct the OCFHMe motif from *O*-nucleophiles was described. This sulfonium salt, readily obtained in 5 steps, reacted with various phenols and alcohols. The resulting products, including complex molecules, were obtained in good yields. This reagent was also used for the functionalization of thiol derivatives.

The search for new bioactive molecules is a strategic research field and the contribution of organic chemists is of prime importance for the quest of new pharmaceuticals and agrochemicals.[1] In that context, organofluorine chemistry plays an indisputable role, mainly due to the intrinsic properties of the fluorine atom.[2,3] Hence, a plethora of drugs or agrochemicals, currently on the market, are fluorinated molecules.[4] Thus, the demand for this class of compounds, and particularly original molecules, is steadily increasing and the search for new fluorinated groups to discover bioactive molecules is an appealing and stimulating task. For instance, various promising motifs have recently attracted the attention of the scientific community such as the CF_2H,[5] the SCF_3[6] and the OCF_3[7] groups.

An efficient strategy to introduce or build up fluorinated motifs relies on the design of new reagents and particularly electrophilic ones as demonstrated by Togni's reagents[8] and various sulphur-based electrophilic reagents,[9] which have been used in a broad range of transformations. Among the latter, are the contributions from Umemoto,[10] Shibata,[11] Prakash[12] and Shen[13] for the introduction of the CF_3, CF_2H and CH_2F motifs by means of the design of sulfonium salts and ylide-based reagents. Despite these considerable advances further developments are still required to extend the current portfolio of electrophilic reagents to other fluorinated groups.

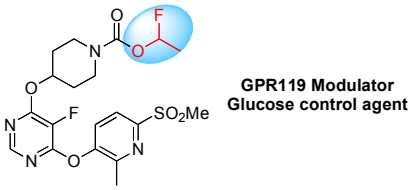
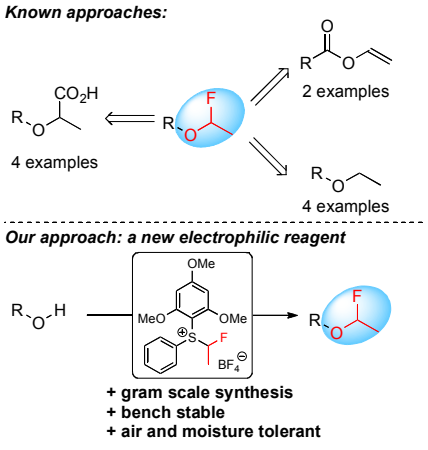


Figure 1 A bioactive molecule bearing a OCHFMe residue.

In that context, we designed a new electrophilic reagent to build up the OCHFMe group from phenols or alcohols. Although this motif is present in bioactive molecule (Figure 1),[14] only a handful of reports described preparative methods for the construction of this underexplored fluorinated residue. Indeed, the existing methods rely on 1) a bromo-fluorination/reduction sequence starting from enol ethers,[15] 2) the use of fluorine gas to oxidize ether functional group,[16] 3) the anodic oxidation of ethers or carbonates[17] and 4) the Mn-catalyzed decarboxylative fluorination.[18]



Scheme 1 State of the art and present work.

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and ^1H, ^{19}F and ^{13}C NMR spectra of the products. See DOI: 10.1039/x0xx00000x

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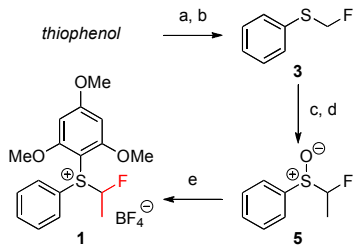
DOI: 10.1039/C8CC00921J



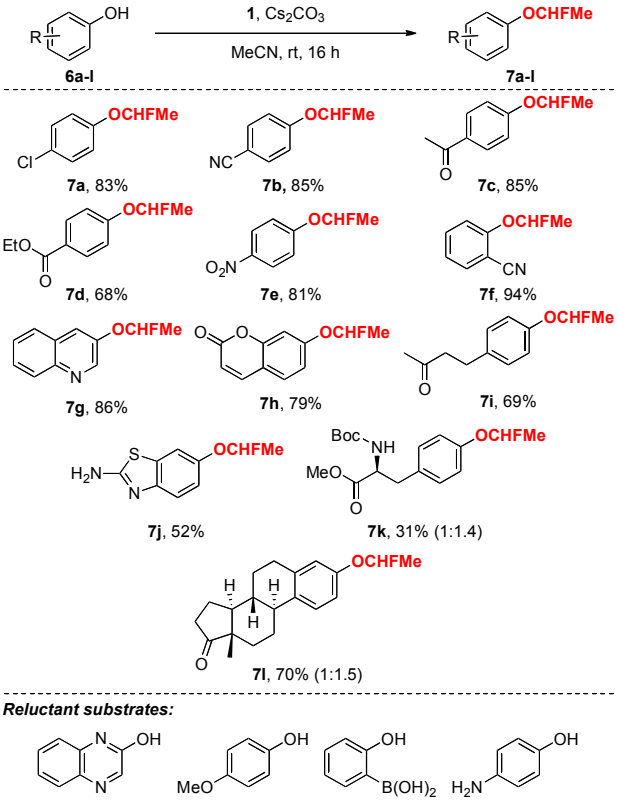
Scheme 2 Synthesis of the reagent **1**. a) $(CH_2O)_n$, toluene/HCl, 50 °C to rt, 95%. b) KF, 18-crown-6, MeCN, 90°C, 98%. c) *m*CPBA, DCM, 0 °C, 63%. d) LiHMDS, MeI, THF/HMPA, - 98 °C, 79%. e) Tf_2O, TMB, Et_2O, 0 °C, 67%, d.r. = 3:1. TMB = 1,3,5-trimethoxybenzene.

These methods either proceed under harsh conditions or use toxic reagents. Moreover, these approaches suffer from poor functional groups tolerance and limited substrates scope (Scheme 1).

Thus, the design of a sulfonium salt as an electrophilic reagent enabling the formation of a O-CHFMe bond appeared as a straightforward approach. Herein, the efficient synthesis of the first electrophilic CHFMe-source and its application with *O*-nucleophiles were depicted.

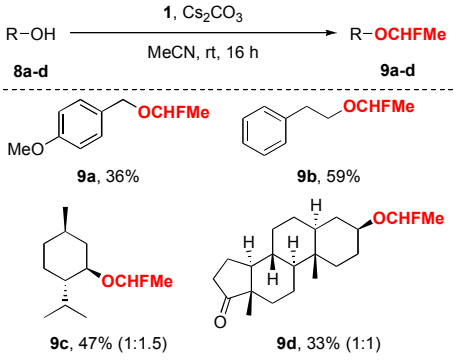
The sulfonium **1** was readily synthesized from thiophenol in five steps (Scheme 2). First, the chloromethylation of thiophenol, followed by the halogen exchange furnished the fluoromethylsulfane **3** in an excellent yield,[19] without purification. Then, the oxidation of the sulfane and a subsequent alkylation reaction gave the sulfoxide **5** in 50% yield over two steps. Finally, **5** was converted into the sulfonium salt **1** in 67% yield, as a 3:1 mixture of diastereoisomers on a gram scale.[20] The reagent **1** is a bench stable solid and is air and moisture tolerant.

Having this reagent in hands, we first explored its reactivity toward phenol derivatives (Scheme 3). The reaction of *para*-chlorophenol with **1** in the presence of Cs_2CO_3 in MeCN at room temperature gave the desired product **7a** in a good 83% yield. The transformation was tolerant to several functional groups since phenols bearing a cyano, ketone, ester and nitro group, furnished the corresponding OCFHMe-containing derivatives **7b-f** in good to excellent yields (68%-94%). Note that the substitution pattern did not have any impact on the outcome of the transformation since the *ortho*-cyanophenol afforded **7f** in 94% yield. To our delight, 3-hydroxyquinoline **6g** reacted smoothly to deliver **7g** in a decent 86% yield. This example demonstrated the possible functionalization of heterocyclic derivatives, which are of high importance in pharmaceutical and agrochemical research. Then, the reagent **1** was used to functionalize relevant molecules as the coumarin **6h** and the raspberry ketone **6i**. The corresponding OCFHMe derivatives **7h** and **7i** were isolated in 79% and 69%, respectively. Then, the Riluzole analogue **7j** was obtained in 52% yield, starting from 2-amino-6-hydroxybenzothiazole **6j**. Finally, *N*-Boc-tyrosine methyl ester **6k** and estrone **6l** were converted into the corresponding compounds **7k** and **7l** in 31% and 70% yields, respectively. Note that both compounds were



Scheme 3 Scope of the reaction between **1** and phenols. Reaction conditions: **1** (0.2 mmol), **6** (0.24 mmol), Cs_2CO_3 (0.24 mmol), MeCN, rt, 16 h. Isolated yields are given. Diastereoisomeric ratios are reported into parenthesis.

obtained as a mixture of diastereoisomers. Unfortunately, some phenol derivatives were reluctant under our reaction conditions, like the 2-hydroxyquinoxaline, the *para*-guaiacol, the 2-hydroxyphenylboronic acid and the 4-hydroxyaniline. Then, we sought to explore the reactivity of **1** with alcohols (Scheme 4). Under the same reaction conditions, *para*-methoxybenzylic alcohol **8a** and homobenzylic alcohol **8b** were converted into the OCFHMe derivatives **9a** and **9b** in 30% and 59% yields. Pleasingly, complex secondary alcohols, namely the (–)-menthol **8c** and the *trans*-androsterone **8d**, were



Scheme 4 Scope of the reaction between **1** and alcohols. Reaction conditions: **1** (0.2 mmol), **8** (0.24 mmol), Cs_2CO_3 (0.24 mmol), MeCN, rt, 16 h. Isolated yields are given. Diastereoisomeric ratios are reported into parenthesis.

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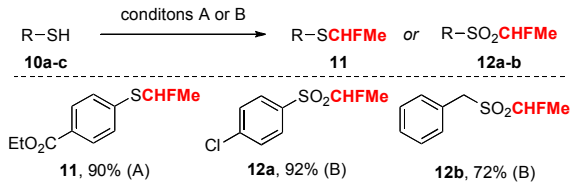

Scheme 5 Functionalization of thiols with **1**. Reaction conditions A: **1** (0.2 mmol), **10** (0.24 mmol), Cs_2CO_3 (0.24 mmol), MeCN, rt, 16 h. Reaction conditions B: *i*. **1** (0.2 mmol), **10** (0.24 mmol), Cs_2CO_3 (0.24mmol), DCM, rt, 16 h. *ii*. *m*CPBA (71%, 1.2 mmol), DCM, rt, 2 h. Isolated yields are given.

suitable substrates giving the corresponding products **9c** and **9d** as a mixture of diastereoisomers in moderate yields (47% and 33%). Finally, as sulfur-containing fluorinated motifs are important in drug discovery,[4c,6,21] we took advantage of the reactivity of **1** to extend the reaction to thiol derivatives to construct the SCHFMe motif (Scheme 5).[22] First, the ethyl *para*-mercaptobenzoate **10a** was converted into **11** in an excellent 90% isolated yield. Regarding the reaction of the *para*-chlorothiophenol **10b** and the benzylmercaptan **10c**, an additional oxidation step of the sulfane intermediate was required to isolate the corresponding sulfones **12a** and **12b** in excellent yields over two steps, 92% and 72% yields, respectively.[23]

In summary, we reported the straightforward synthesis of a new electrophilic reagent for the synthesis of OCHFMe derivatives. This sulfonium salt broadens the current toolbox of electrophilic reagents and was applied to the functionalization of a broad range of substrates including phenols, alcohols and thiols. The resulting products were obtained in moderate to excellent yields under simple and practical reaction conditions. This new methodology allows an easy access to the underdeveloped OCHFMe motif. Thus, we believe that this reagent will be useful to the discovery of new bioactive molecules bearing the OCHFMe motif.

This work was partially supported by INSA Rouen, Rouen University, CNRS, EFRD, LabexSynOrg (ANR-11-LABX-0029), Région Normandie (Crunch Network) and the IUF (Institut Universitaire de France). E.C. thanks the LabexSynOrg (ANR-11-LABX-0029) for a doctoral fellowship.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 K. C. Nicolaou, *Angew. Chem. Int. Ed.*, 2014, **53**, 9128–9140.
2 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
3 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330. (*b*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359. (*c*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637–643.
4 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506. (*b*) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Chem. Educ.*, 2013, **90**, 1403–1405. (*c*) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842.
5 (*a*) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797–804. (*b*) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang and S. J. Lippard, *J. Am. Chem. Soc.*, 2017, **139**, 9325–9332. (*c*) M.-C. Belhomme, T. Poisson and X. Pannecoucke, *J. Org. Chem.*, 2014, **79**, 7205–7211.
6 (*a*) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, **2014**, 2415–2428. (*b*) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731–764. (*c*) S. Barata-Vallejo, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 7150–7182.
7 (*a*) T. Besset, P. Jubault, X. Pannecoucke and T. Poisson, *Org. Chem. Front.*, 2016, **3**, 1004–1010. (*b*) A. Tlili, F. Toulgoat and T. Billard, *Angew. Chem. Int. Ed.*, 2016, **55**, 11726–11735.
8 J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682.
9 C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765–825.
10 (*a*) T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757–1778. (*b*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156–2164.
11 (*a*) A. Matsnev, S. Noritake, Y. Nomura, E. Tokunaga, S. Nakamura and N. Shibata, *Angew. Chem. Int. Ed.*, 2010, **49**, 572–576. (*b*) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga and N. Shibata, *Org. Lett.*, 2011, **13**, 3596–3599. (*c*) G. Liu, X. Wang, X.-H. Xu, X. Lu, E. Tokunaga, S. Tsuzuki and N. Shibata, *Org. Lett.*, 2013, **15**, 1044–1047. (*d*) X. Wang, G. Liu, X.-H. Xu, N. Shibata, E. Tokunaga and N. Shibata, *Angew. Chem. Int. Ed.*, 2014, **53**, 1827–1831. (*e*) S. Arimori and N. Shibata, *Org. Lett.*, 2015, **17**, 1632–1635. (*f*) Y. Nomura, E. Tokunaga and N. Shibata, *Angew. Chem. Int. Ed.*, 2011, **50**, 1885–1889.
12 (*a*) G. K. S. Prakash, S. Krishnamoorthy, S. K. Ganesh, A. Kulkarni, R. Haiges and G. A. Olah, *Org. Lett.*, 2014, **16**, 54–57. (*b*) G. K. S. Prakash, I. Ledneczki, S. Chacko and G. A. Olah, *Org. Lett.*, 2008, **10**, 557–560. (*c*) G. K. S. Prakash, C. Wéber, S. Chacko and G. A. Olah, *Org. Lett.*, 2007, **9**, 1863–1866. (*d*) E. Carbonnel, T. Besset, T. Poisson, D. Labar, X. Pannecoucke and P. Jubault, *Chem. Commun.*, 2017, **53**, 5706–5709. (*e*) P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. Eur. J.*, 2014, **20**, 9514–9518.
13 (*a*) Y. Liu, X. Shao, P. Zhang, L. Lu and Q. Shen, *Org. Lett.*, 2015, **17**, 2752–2755. (*b*) J. Zhu, Y. Liu and Q. Shen, *Angew. Chem. Int. Ed.*, 2016, **55**, 9050–9054. (*c*) Y. Liu, L. Lu and Q. Shen, *Angew. Chem. Int. Ed.*, 2017, **56**, 9930–9934.
14 D. J. Buzard, S. H. Kim, J. Lehmann, S. Han, I. Calderon, A. Wong, A. Kawasaki, S. Narayanan, R. Bhat, T. Gharbaoui, L. Lopez, D. Yue, K. Whelan, H. Al-Shamma, D. J. Unett, H.-H. Shu, S.-F. Tung, S. Chang, C.-F. Chuang, M. Morgan, A. Sadeque, Z.-L. Chu, J. N. Leonard and R. M. Jones, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4332–4335
15 D. Limat, G. Guggisberg and M. Schlosser, *Liebigs Ann.* 1995, 849-853.
16 H.-D. Quan, M. Tamura, J. Murata, R.-X. Gao and A. Sekiya, *J. Fluorine Chem.* 2000, **106**, 121-125.
17 M. Hasegawa, H. Ishii, Y. Cao and T. Fuchigami, *J. Electrochem. Soc.*, 2006, **153**, D162.
18 X. Huang, W. Liu, J. M. Hooker and J. T. Groves, *Angew. Chem. Int. Ed.*, 2015, **54**, 5241–5245.
19 Note that **3** can be prepared in one step from the commercially available thioanisole, see: T. Umemoto and G. Tomizawa, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3625-3629.

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20 Compound **1** is bench-stable and can be stored at -20 °C for months without traces of decomposition.
21 H.-Y. Xiong, X. Pannecoucke and T. Besset, *Chem. Eur. J.*, 2016, **22**, 16734–16749.
22 For selected examples, see: (*a*) M. Fujita, M. Suzuki, K. Ogata and K. Ogura, *Tetrahedron Lett.* 1991, **32**, 1463-1466. (*b*) T. Fuchigami, A. Konno, K. Nakagawa and M. Shimojo, *J. Org. Chem.* 1994, **59**, 5937-5941. (*c*) A. Konno, K. Nakagawa and T. Fuchigami, *J. Chem. Soc., Chem. Commun.*, 1991, 1027.
23 Note that, in these cases, the SCFHMe derivatives decomposed upon purification.