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Short Communication

Heptafluoroisopropylthiolation of benzyl halides

Jiang-Pin Tan [a,b], Jin-Hong Lin [b,d], Fei Hao [b,c,*], Ji-Chang Xiao [a,b,*]

[a] College of Chemistry and Materials Science, Shanghai Normal University, 100 Guilin Road, Shanghai 200234, China
[b] Key Laboratory of Organofluorine Chemistry, Chinese Academy of Sciences, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[c] Shandong Provincial Key Laboratory of Molecular Engineering, Shandong Academy of Science, Qilu University of Technology, Ji'nan 250353, China
[d] Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China

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ABSTRACT

Heptafluoroisopropylthio group (-SCF(CF_3)$_2$) has bioactivities in insecticidal molecules, but the protocol for direct introduction of -SCF(CF_3)$_2$ is under-explored. Described here is a protocol on heptafluoroisopropylthiolation of benzyl halides with a hexafluoropropylene (HFP)/CsF/S_8 system. The reaction enables the rapid construction of a range of (CF_3)$_2$CFS-containing compounds from readily available materials. This protocol may find application in the synthesis of (CF_3)$_2$CFS-containing biologically active molecules.

1. Introduction

Due to strong electron-withdrawing effect and high lipophilicity, fluoroalkyl sulfides are of increasing importance in pharmaceuticals and agrichemicals [1]. Recently, CF_3S-containing and HCF_2S-containing compounds, such as Tiflorex (anorectic drug) [2], Toltrazuril (coccidiostatic drug) [2], Pyriprole (pesticide) [3], SSH-108 (herbicide)[3] have been developed (Fig. 1, top). As the large steric heptafluoroisopropyl group (CF(CF_3)$_2$) is also widely found in pharmaceuticals and agrochemicals (Fig. 1, middle) [4], we estimate that heptafluoroisopropylthio group (-SCF(CF_3)$_2$) may be effective for constructing bioactive molecules (Fig. 1, bottom). It is reported that (CF_3)$_2$CFS-containing phthalimide molecule with no cross-resistance is very suitable for the control of lepidopteran pests [5,6]. However, the lack of synthetic method is a major obstacle for exploring their application in bioactive compounds.

In 1962, Chambers obtained (CF_3)$_2$CFSSCF(CF_3)$_2$ by using Me_3SiCF(CF_3)$_2$ and S_8 [7]. Subsequently, Rosenberg used SF_4 to obtain [(CF_3)$_2$CF]$_2$$SF_2$ for the heptafluoroisopropylthiolations [8,9]. In the early stage, heptafluoroisopropylthio reagents [(CF_3)$_2$CFS] were needed in heptafluoroisopropylthiolations and thus various reagents, C_3F_7N=SF_2 [10–12], (CF_3)$_2$CFSCl [13], (CF_3)$_2$CFSC(CF_3)=CF_2 [14,15] and (CF_3)$_2$CFSSFC(CF_3)$_2$ [16–18] were developed (Scheme 1, (a)). Another approach to obtain heptafluoroisopropylation product is the usage of S-containing [S] substrates (Scheme 1, (b)). In 1981, Thoai proceeded heptafluoroisopropylation using benzyl thiocyanide (BnSCN) [19]. There are other [S] substrates like PhS^-, pH-SH or pH-SS-pH, reacting with C_3F_7I or $^-C_3F_7$ to build -SCF(CF_3)$_2$ [20–24]. It is worth noting that Petrov introduced -SCF(CF_3)$_2$ into tetracyclo[3.2.0.0^{2,7}.0^{4,6}] heptane in 3.6% yield using hexafluoropropene (HFP), KF and elemental sulfur (S_8) (Scheme 1, (c)) [25]. Although the heptafluoroisopropylthiolation product is a byproduct, it provides a new perspective for heptafluoroisopropylthiolation. While many advances in this area have been made, there are ongoing interests to develop effective heptafluoroisopropylthiolation protocols by using readily available and economic reagents.

2. Results and discussion

We have been interested in the synthesis of fluoro-containing compounds [26]. Previously, we have described that benzyl halides could undergo a trifluoromethylthiolation (-SCF_3) to afford CF_3S-containing molecules using $Ph_3P^+CF_2CO_2^-$as a fluoride and difluorocarbene source [27]. Herein we describe the heptafluoroisopropylthiolation of benzyl

* Corresponding authors at: College of Chemistry and Materials Science, Shanghai Normal University, 100 Guilin Road, Shanghai 200234, China.
E-mail addresses: haofei@qlu.edu.cn (F. Hao), jchxiao@sioc.ac.cn (J.-C. Xiao).

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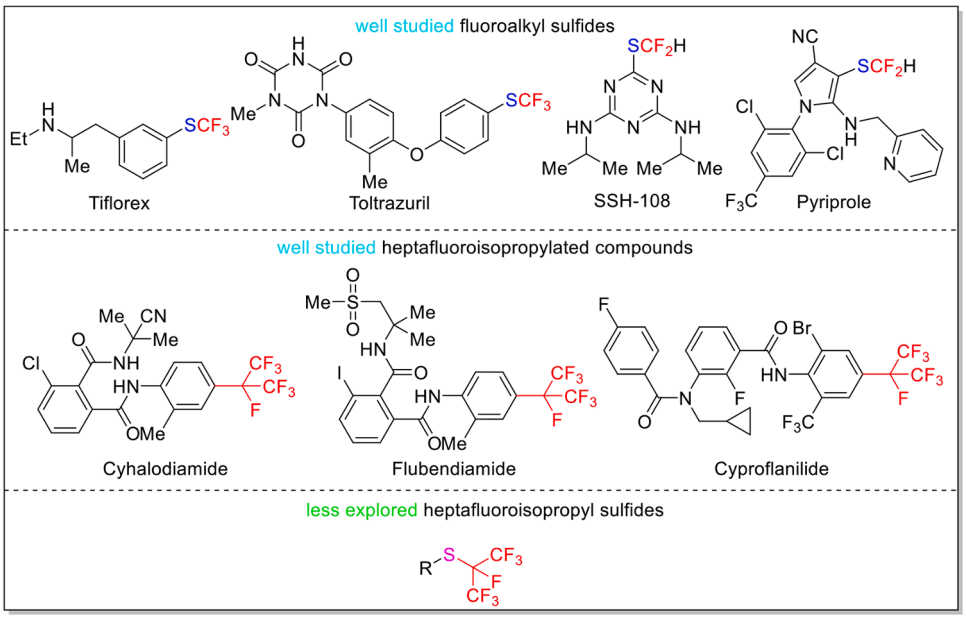


Fig. 1. Selected fluoroalkyl sulfides containing and heptafluoroisopropylated biologically active molecules.

halides using HFP/CsF/S_8 system. The protocol described herein can be used for the rapid synthesis of a wide variety of $(CF_3)_2$CFS-containing compounds in a safe and convenient manner (Scheme 1, (d)).

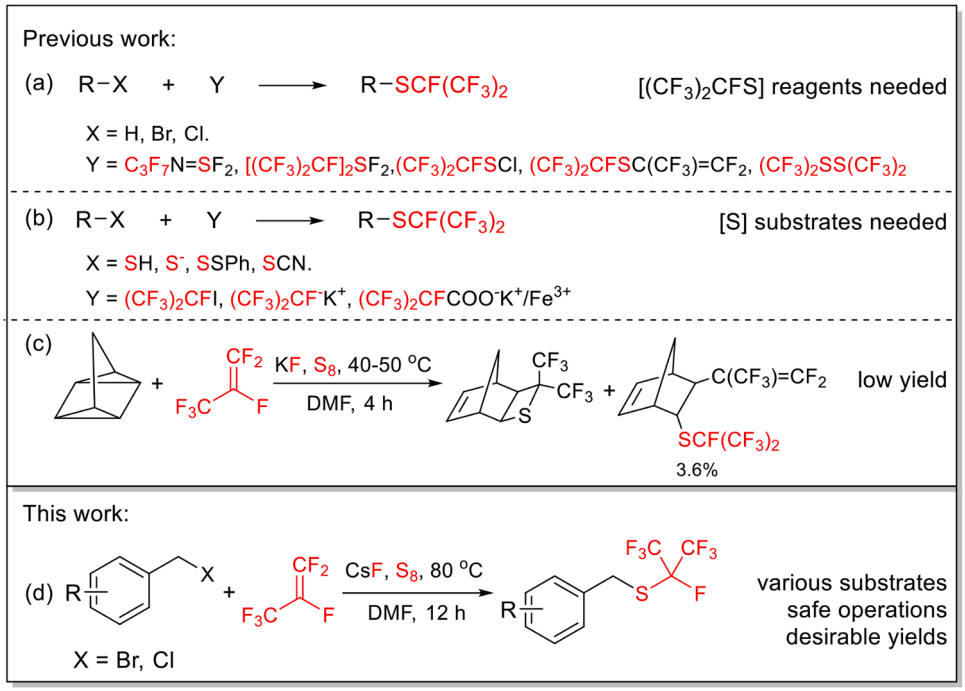
We used 4-phenylbenzyl bromide **1a** to establish the optimal reaction conditions. At initial, based on previous result [25], treatment of **1a** with 10 eq. HFP and 0.25eq S_8 in the presence of 1 eq. KF in 2 mL DMF at 80 °C for 12 h led to the desired heptafluoroisopropylthiolation product **2a** in 41% yield (Table 1, entry 1). In crude ^{19}F NMR spectrum, several signals were observed in the range of -C-CF_3 group, indicating the existence of side reactions. From GC–MS analysis, an ion peak at m/z = 429.2 suggest the probable produce of Ph-Bn-SCBr$(CF_3)_2$ by *in-situ* generated Br^- reacting with HFP. However, after chromatography, only **2a** was obtained. Then, our efforts have been devoted to improve the yield of **2a** by screening different variables. When CsF was screened, the yield was prompted to 56% (Table 1, entry 2). With CsF as the F^- source, a brief survey of the reaction solvents (Table 1, entry 3–7) revealed that DMF was a superior solvent (Table 1, entry 2). Changing the concentration of the reaction only gave the decrease in the yield (Table 1, entry 8,9). The screening of different loadings of S_8 and CsF respectively (Table 1, entry 10–14) revealed that a combination of 1 eq. S_8 and 1.7 eq. CsF led to an improvement in the product yield to above 99% (Table 1, entry 13). This may be because excessive CsF and S_8 would be reacted rapidly with HFP to generate -SCF$(CF_3)_2$ species with high efficiency.

With the optimized reaction conditions (Table 1, entry 13), the substrate scope for the heptafluoroisopropylthiolation was examined (Scheme 2). Electron-deficient, -neutral, -rich benzyl bromides could all be well converted into the desired products in 24 to 93% yields (2a-2p). Interestingly, a wide range of functional groups could be tolerated, such as ester, cyanide, alkene, aryl halides and heteroarenes. We next extended this protocol to heptafluoroisopropylthiolations of benzyl chlorides. Although the electrophilicity of benzyl chlorides is relatively weaker than benzyl bromides, the heptafluoroisopropylthiolation of benzyl chlorides could also proceed smoothly (2a, 2c, 2 m, 2o). Interestingly, different from 2a and 2c, 2 m and 2n were obtained in better yields from corresponding benzyl chlorides than benzyl bromides. Referring to crude ^{19}F NMR, when benzyl bromides 1 m and 1n were used as substrates, more side products were observed, which may be due to the higher reactivities of the corresponding benzyl bromides. It is worth noting that when propargyl bromide was used as substrate, the heptafluoroisopropylthiolation took place at the optimized reaction condition leading to corresponding heptafluoroisopropylthiolation products in a low yield (detected by ^{19}F NMR and GC–MS). Other substrates, such as secondary, alkyl, and allyl bromides, were not effective. This protocol was also demonstrated to be suitable for gram-scale synthesis as 2a obtained in 81% yield at ten times magnification.

On the basis of the above results and previous report [14], we propose the plausible reaction mechanism as shown in Scheme 3. HFP combines with F^-anion to generate $(CF_3)_2FC^-$anion, the latter reacts with S_8 to give S = $C(CF_3)_2$, which combines with F^- anion to form $(CF_3)_2CFS^-$anion. The $(CF_3)_2CFS^-$anion reacts with benzylic halides in a nucleophilic manner to give the desired product.

3. Conclusion

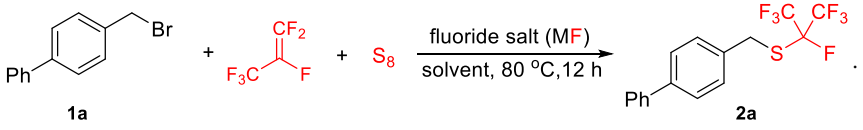
In summary, we have described the heptafluoroisopropylthiolation of benzyl halides by using HFP/CsF/S_8 system. The heptafluoroisopropylthiolation process occurred smoothly with electron-deficient, -neutral, -rich substrates under mild conditions. Since HFP is a readily available and economic industrial material, this protocol may find application in the synthesis of $(CF_3)_2$CFS-containing biologically active molecules.



Scheme 1. Heptafluoroisopropylthiolation strategies.

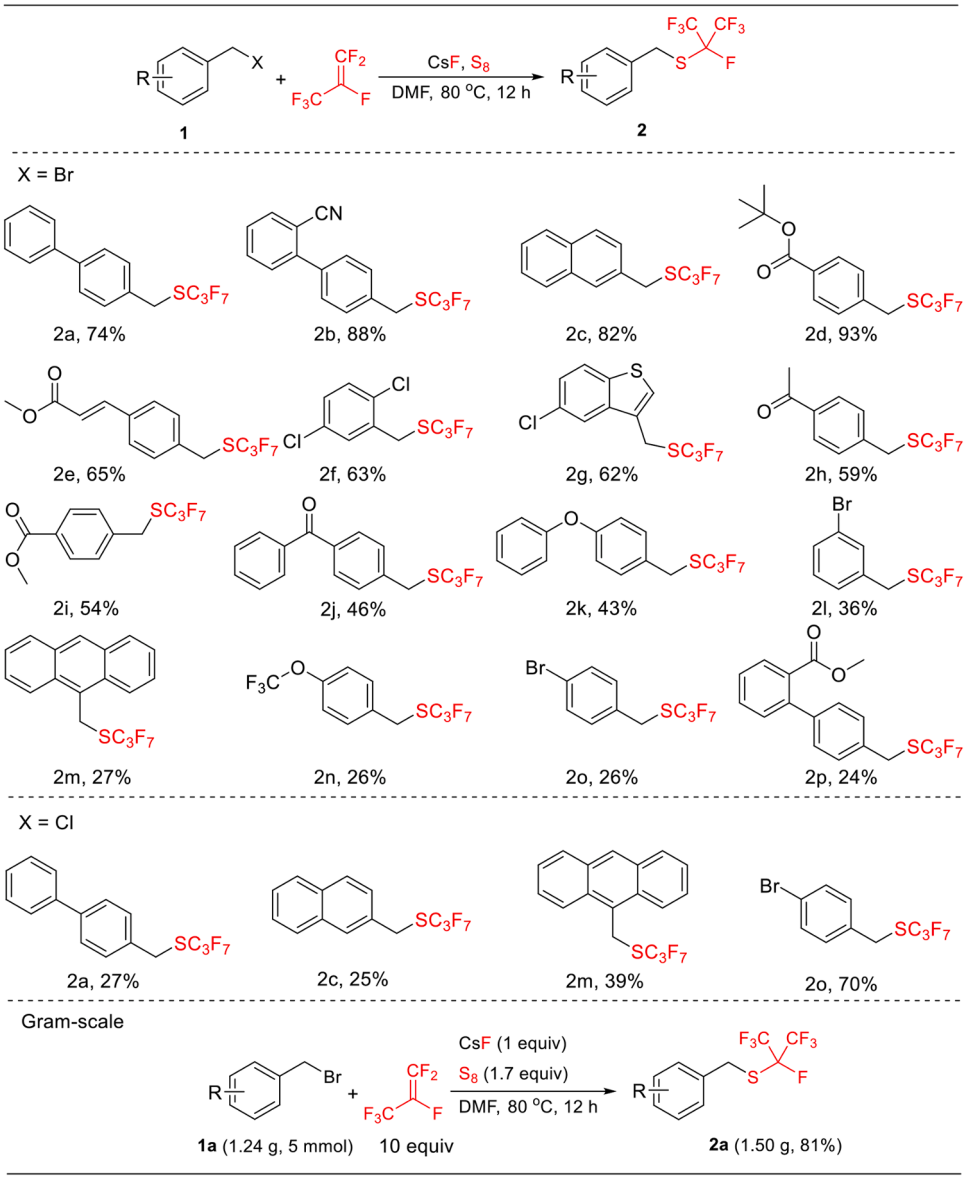
Table 1

The optimization of the reaction conditions.[a]

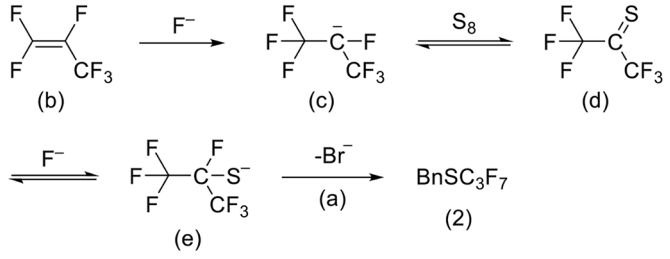


Entry	S_8 (eq.)	Fluoride salt (eq.)	Solvent	Yield (%)[b]
1	0.25	KF (1)	DMF	41
2	0.25	CsF (1)	DMF	56
3	0.25	CsF (1)	DMSO	N. D.[c]
4	0.25	CsF (1)	1,4-dioxane	N. D. [c]
5	0.25	CsF (1)	CH_3CN	18
6	0.25	CsF (1)	EtOAc	N. D. [c]
7	0.25	CsF (1)	THF	N. D. [c]
8[d]	0.25	CsF (1)	DMF	42
9[e]	0.25	CsF (1)	DMF	37
10	1	CsF (1)	DMF	63
11	1	CsF (1.1)	DMF	74
12	1	CsF (1.3)	DMF	79
13	1	CsF (1.7)	DMF	> 99
14	1	CsF (2)	DMF	> 99

[a] Reaction conditions: **1a**: HFP = 1:10, 80 °C, 12 h, 8 atm
[b] Determined by ^{19}F NMR with trifluoromethoxybenzene as internal standard
[c] N. D. = no desired product.
[d] 1 mL DMF.
[e] 3 mL DMF.



Scheme 2. Substrate scope of heptafluoroisopropylthiolation. Isolated yields. Reaction conditions: substrate 1 (0.5 mmol), HFP (10 eq.), S_8 (1 eq.), CsF (1.7 eq.), and DMF (2 mL) at 80 °C for 12 h.



Scheme 3. Proposed reaction mechanism.

Declaration of Competing Interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2022.109966.

References

[1] (a) V. Gouverneur, K. Müller, Fluorine in Pharmaceutical and Medicinal Chemistry, Imperial College Press, London, UK, 2012;

(b) R.D. Chambers, Fluorine in Organic Chemistry, Blackwell Publishing Ltd, Oxford, UK, 2004;
(c) P. Kirsch, Modern Fluoro Organic Chemistry, Wiley-VCH, Weinheim, DE, 2004.
[2] X.H. Xu, K. Matsuzaki, N. Shibata, Synthetic methods for compounds having CF_3-S units on carbon by trifluoromethylation, trifluoromethylthiolation, triflylation, and related reactions, Chem. Rev. 115 (2015) 731–764.
[3] N.M. Niyaz, N. Garizi, Y. Zhang, T.K. Trullinger, R. Hunter, A.M. Buysse, A. Kubota, P.R. Leplae, D Knueppel, C.T. Lowe, D. Pernich, D.A. Demeter, T.C. Johnson, Pesticidal compositions and processes related to their preparation and use, (to Dow Agrosciences LLC) WO Pat. 2,013,062,981. (2013).
[4] D. Voeste, L. Brahm, Insecticides for increasing the crop yield, (to BASF SE) WO Pat. 2,009,024,546. (2009).
[5] K. Yoshida, T. Wakita, H. Katsuta, A. Kai, Y. Hiba, K. Takahashi, H. Kato, N. Kawahara, M. Nomura, H. Daido, J. Maki, S. Banba, Amide derivatives, process for production of the same, and method for application thereof as insecticide, (to Mitsui Chemicals INC) EP Pat. 1,714,958. (2006).
[6] Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, Current contributions of organofluorine compounds to the agrochemical industry, iScience 23 (9) (2020), 101467.
[7] R.D. Chambers, W.K.R. Musgrave, J. Savory, Organometallic and metalloid compounds made from heptafluoro-2-iodopropane, and their properties, J. Chem. Soc. (1962) 1993–1999 (resumed).
[8] R.M. Rosenberg, E.L. Muetterties, Preparation and properties of tetracoördinate sulfur(IV) fluorides, Inorg. Chem. 1 (4) (1962) 756–762.
[9] C.T. Ratcliffe, J.N. Shreeve, Some perfluoroalkylsulfinyl halides $R_fS(O)X$. New preparations of trifluoromethylsulfur trifluoride, J. Am. Chem. Soc. 90 (20) (1968) 5403–5408.
[10] T. Kitazume, J.M. Shreeve, Some partially fluorinated cyclic and acyclic compounds of sulphur (II) and (IV) and partially fluorinated cyclic compounds of phosphorus (III) and (V), J. Fluor. Chem. 8 (5) (1976) 437–445.
[11] R.D. Dresdner, J.S. Johar, J. Merritt, C.S. Patterso, *N*-perfluoroalkyl *S*-perfluoroisopropyl iminosulfur monofluorides, Inorg. Chem. 4 (5) (1965) 678–681.
[12] J.S. Johar, R.D. Dresdner, Some new fluorocarbon-sulfur systems, Inorg. Chem. 7 (4) (1968) 683–686.
[13] J.F. Harris, Free-radical reactions of fluoroalkanesulfenyl halides. 3. Reactions of fluoroalkanesulfenyl and chlorofluoroalkanesulfenyl chlorides with hydrocarbons, J. Org. Chem. 44 (4) (1979) 563–569.
[14] D.C. England, Synthesis and chemistry of a perfluoroacylketene and related compounds containing a perfluoroisopropyl sulfide group, J. Org. Chem. 46 (1) (1981) 153–157.
[15] D.C. England, J.C. Piecara, Reactions of amines with a dimer of hexafluoropropene and with a perfluorovinyl sulfide prepared with hexafluoropropene, J. Fluor. Chem. 17 (3) (1981) 265–288.
[16] S.A. Postovoi, I.M. Volpin, N.I. Delyagina, M.V. Galakhov, Y.V. Zeifman, L. S. German, S^- anions from 2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane and their reactions, Bull. Acad. Sci. USSR Div. Chem. Sci. 38 (6) (1989) 1261–1264.
[17] W.J. Middleton, W.H. Sharkey, Fluorothiocarbonyl Compounds. II. Reactions of hexafluorothioacetone, J. Org. Chem. 30 (5) (1965) 1384–1390.
[18] W. Bludssus, R. Mews, O. Glemser, G.G. Alange, The reaction of thiazylfluoride with hexafluoropropene, Isr. J. Chem. 17 (1–2) (1978) 137–140.
[19] T. Nguyen, M. Rubinstein, C. Wakselman, Reaction of perfluoroalkyl carbanions with thiocyanates. Synthesis of fluorinated sulfides and sulfenyl chlorides, J. Org. Chem. 46 (9) (1981) 1938–1940.
[20] B. Exner, B. Bayarmagnai, C. Matheis, L.J. Goossen, Synthesis of perfluoroalkyl thioethers from aromatic thiocyanates by iron-catalysed decarboxylative perfluoroalkylation, J. Fluor. Chem. 198 (2017) 89–93.
[21] N. Roques, Nucleophilic perfluoroalkylation of diaryldisulfides with perfluorocarboxylate salts, J. Fluor. Chem. 107 (2) (2001) 311–314.
[22] A.E. Feiring, Perfluoroalkylation of thiols. Evidence for a radical chain process, J. Fluor. Chem. 24 (2) (1984) 191–203.
[23] S. Munavalli, A. Hassner, D.I. Rossman, S. Singh, D.K. Rohrbaugh, C.P. Ferguson, Novel reactions of perfluoroalkylphenyl sulfides with organolithium reagents, J. Fluor. Chem. 73 (1) (1995) 7–11.
[24] V.I. Popov, V.N. Boiko, L.M. Yagupolskii, Phase transfer-catalyzed ion-radical perfluoroalkylation of thiols, J. Fluor. Chem. 21 (3) (1982) 365–369.
[25] V.A. Petrov, C.G. Krespan, W. Marshall, Reaction of quadricyclane with fluorinated sulfur-containing compounds, J. Fluor. Chem. 126 (9–10) (2005) 1332–1341.
[26] J.H. Lin, J.C. Xiao, Fluorinated ylides/carbenes and related intermediates from phosphonium/sulfonium salts, Acc. Chem. Res. 53 (8) (2020) 1498–1510.
[27] Z. Liu, J. Long, X. Xiao, J.H. Lin, X. Zheng, J.C. Xiao, Y.C. Cao, $Ph_3P^+CF_2CO_2^-$ as an F^- and:CF_2 source for trifluoromethylthiolation of aryl halides, Chin. Chem. Lett. 30 (3) (2019) 714–716.