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Preparation and Reactions of Perfluoroalkanesulfenyl Chlorides

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Several perfluoroalkanesulfenyl chlorides were prepared from the corresponding perfluoroalkanesulfenic acids in high yields, and their reactions with thiol, amine, arene and alkene were studied. A series of perfluoroalkyl-containing disulfides, sulfonamides, aryl sulfides and α-chlorosulfides were synthesized under mild conditions.

Keywords perfluoroalkanesulfenyl chloride, perfluoroalkanesulfenyl acid, substitution, disulfide, addition

Introduction

Sulfenic acids and their derivatives have been known as key intermediates in many biological activities and the related researches are still very attractive.[1] Generally, sulfur containing substrates in organisms, such as thiol, sulfide and disulfide, are firstly oxidized to sulfenic acids and then the sulfur could be involved in biological activities.[1,2] It is well known that sulfenic acid is highly reactive and generally the self-condense reaction is very easy to occur.[3] Therefore, great efforts have been made to obtain stable sulfenic acids.[4] As one of important derivatives of sulfenic acids, sulfenyl halides are more stable and regarded as key intermediates for further transformation of sulfenic acids in organisms. Because of the R—S—Cl (R=alkyl or aryl) connectivity, sulfenyl chlorides are also very reactive and behave as sources of RS^+. For these reasons, the chemistry of sulfenyl chloride was studied much more than the acid.[1,5]

Recently, a series of perfluoroalkanesulfenic acids was successfully synthesized in our laboratory.[6] Due to the high electron-withdrawing effect of perfluoroalkyl groups, these fluorinated sulfenic acids were quite stable and could exist in solution for months. In further studies on their properties and synthetic applications, it was found that perfluoroalkanesulfenyl chlorides could be obtained from them under mild conditions. Although there are some reports about the reaction of trifluoromethanesulfenyl chloride,[7] in consideration of the unique properties of perfluoroalkyl group, the reactivity of perfluoroalkanesulfenyl chloride is worth exploring. Therefore, we further investigated the reaction of perfluoroalkanesulfenyl chlorides with different reagents. The results are reported in this paper.

Experimental

General procedure for the synthesis of perfluoroalkanesulfenyl chlorides (2)

To a solution of perfluoroalkanesulfenic acids **1** (0.4 mmol) in toluene (5 mL) was added saturated Et_2O•HCl (5.0 equiv.) in darkness under nitrogen. The reaction mixture was stirred at room temperature for 30 min. The corresponding sulfenyl chlorides **2** were obtained in more than 95% yields as determined by ^{19}F NMR using C_6F_6 as internal standard.

General procedure for the reaction of 2 and thiol

In darkness, to a solution of **2b** (0.4 mmol) in toluene (5 mL) was added the solution of phenyl thiol (0.4 mmol in 5 mL of toluene) slowly at room temperature. Then the mixture was stirred at room temperature for 3 h. After the reaction was completed (monitored by ^{19}F NMR), the solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane) to give product **3b** in 77% yield.

General procedure for the reaction of 2 and amine

In darkness, to a solution of **2b** (0.4 mmol) in toluene (5 mL) was slowly added the solution of aniline (10.0 equiv. in 5 mL of DCM) at 0—5 ℃. After addition, the mixture was stirred for 1 h. Then saturated $NaHCO_3$ was dropwisely added to reach the pH=7—8.

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Dedicated to Professor Xikui Jiang on the occasion of his 90th birthday.

The aqueous phase was extracted with ethyl acetate (10.0 mL×3), and the combined organic phase was dried over anhydrous Na_2SO_4. After being concentrated, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to give sulfenamide **5a** in 86% yield.

General procedure for the reaction of 2 and arene

In darkness, to a solution of **2b** (0.4 mmol) in toluene (5 mL) was slowly added the solution of indol (10.0 equiv. in 5 mL of DCM) at room temperature. After the reaction was completed (monitored by ^{19}F NMR), the mixture was concentrated and the residue was purified by column chromatography on silica gel (hexane) to give product **6d** in 94% yield.

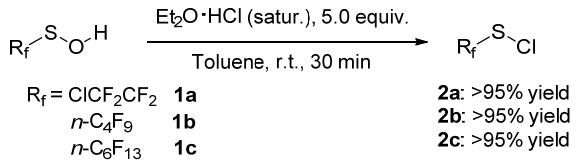
General procedure for the reaction of 2 and alkene

In darkness, to a solution of **2b** (0.4 mmol) in toluene (5 mL) was slowly added the solution of 1-octene (10.0 equiv. in 5 mL of DCM). The mixture was stirred at 55 ℃ for 7.5 h (monitored by ^{19}F NMR). After reaction, the mixture was concentrated and the residue was purified by column chromatography on silica gel (hexane) to give product **7a** and **7a'** in 88% total yield with a ratio of 1.0∶0.3.

Results and Discussion

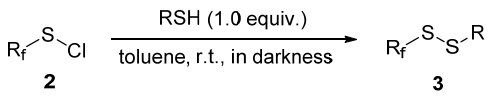
As shown in Scheme 1, perfluoroalkanesulfenyl chlorides **2a**—**2c** were easily prepared from the reaction of perfluoroalkanesulfenic acids **1a**—**1c** with Et_2O•HCl (5.0 equiv.) at room temperature. More than 95% yields could be obtained as determined by ^{19}F NMR with C_6F_6 as internal standard.

Scheme 1 The synthesis of perfluoroalkanesulfenyl chlorides



Disulfides are very important functional groups in organism and the formation of S—S bond in organism always involves the reactions of sulfenic acid derivatives and thiols.[1,2] In our initial experiments, we studied the reaction of **2** with various thiols. It was found that perfluoroalkanesulfenyl chlorides were photo-sensitive and converted completely to perfluoroalkyl disulfides within 30 min under visible light. Therefore, all reactions were carried out in darkness. As shown in Table 1, perfluoroalkanesulfenyl chlorides **2a**—**2c** could react with phenyl thiol readily at room temperature. There was no obvious difference in yields of perfluoroalkyl phenyl disulfides (**3a**—**3c**) (Table 1, Entries 1—3, 73%—77%). Further investigation found that thiols with electron donating groups in the phenyl ring also gave the corresponding disulfides **3d**—**3e** in good isolated yields (Entries 4—5, 75%—77%). However, the strong electron withdrawing NO_2 group in thiol made the yield decrease to 45%, and disulfide ClC_2F_4-S-S-C_2F_4Cl was formed as the major byproduct (Entry 6). It is worthy to mention that benzylthiol could also react with **2** to give the corresponding disulfide in good yield (Entry 7).

Table 1 The reactions of perfluoroalkanesulfenyl chlorides with thiols

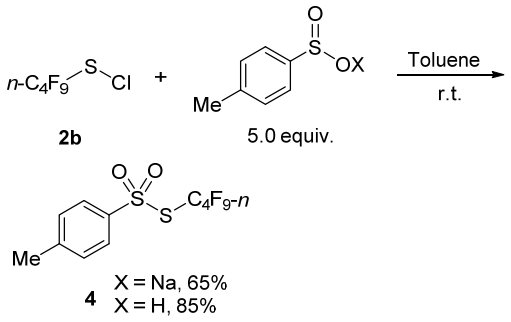


Entry[a]	2/R_f	R	3, Yield[b]/%
1	**2a**/CF_2CF_2Cl	C_6H_5	**3a**, 76
2	**2b**/*n*-C_4F_9	C_6H_5	**3b,** 77
3	**2c**/*n*-C_6F_{13}	C_6H_5	**3c,** 73
4	**2a**/CF_2CF_2Cl	*p*-MeO-C_6H_4	**3d,** 77
5	**2a**/CF_2CF_2Cl	*o*-MeO-C_6H_4	**3e,** 75
6	**2a**/CF_2CF_2Cl	*p*-O_2N-C_6H_4	**3f,** 45
7	**2a**/CF_2CF_2Cl	$C_6H_5CH_2$	**3g,** 75

[a] Reaction conditions: **2** (0.4 mmol), thiol (0.4 mmol), toluene (10 mL), r.t., in darkness. [b] Isolated yield.

Under similar conditions, the reaction of sodium *p*-toluenesulfinate with sulfenyl chloride **2b** was also tested, and product **4** was obtained in 65% yield. When *p*-toluenesulfinic acid, which is more soluble, was used instead of the salt, the yield could be improved to 85% (Scheme 2).

Scheme 2 The reaction of **2b** and *p*-toluenesulfinic acid (salt)



Sulfenamides have been proposed for many practical applications.[1,8] For example, they are very important rubber additives, and of great technical interest as fungecides and microbicides. Furthermore, they are also very useful in the protection of functional groups.[1a] Thus, we further explored the reactions of sulfenyl chloride **2b** with a series of amines. As shown in Table 2, both primary amines and secondary amines could react with **2b** under mild conditions to give the corresponding sulfenamides in moderate to high yields. Arylamines bearing methoxyl or nitro substituent at *p*-position af-

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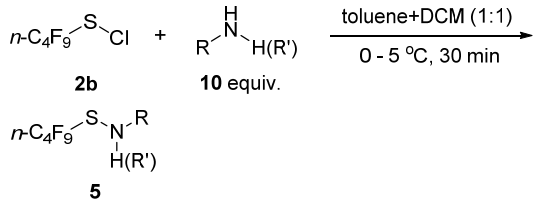
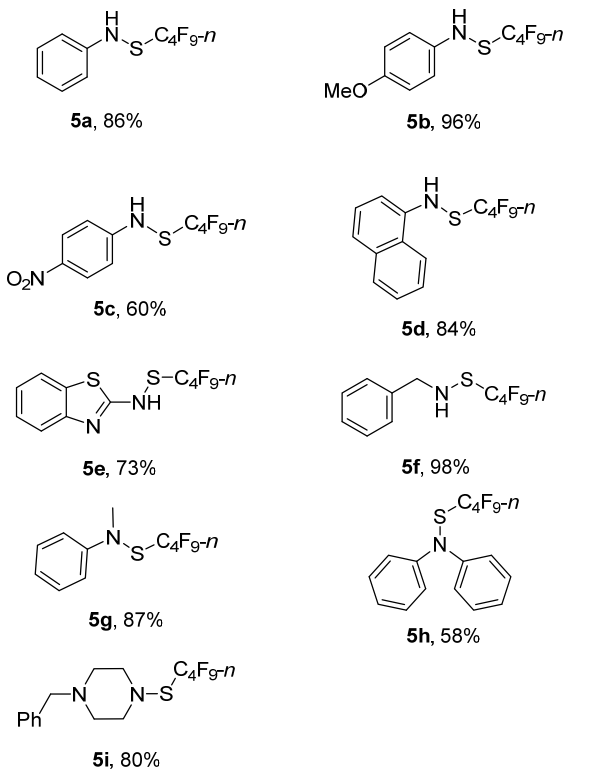
forded sulfenamides **5b** and **5c** in 96% and 60% yield, respectively. 1-Naphthylamine, 2-benzothiazolamine and benzylamine also reacted well to give sulfenamides **5d**－**5f** in good yields. Similarly, secondary amines such as *N*-methylaniline, diphenylamine and 1-benzylpiperazine reacted readily with **2b** to afford the desired sulfenamides in moderate to good yields.

Table 2 The reactions of sulfenyl chloride **2b** with amines

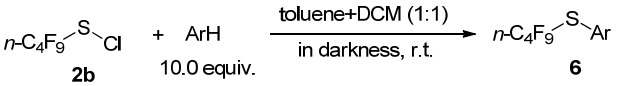


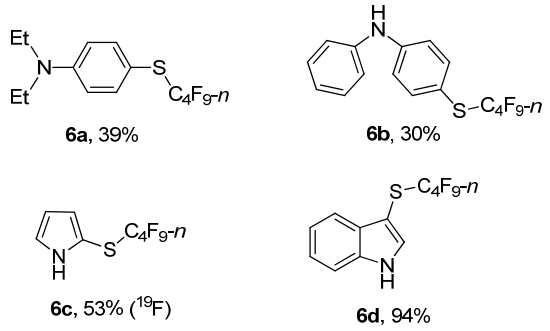


Reaction conditions: **2b** (0.4 mmol), amine (4.0 mmol), toluene (5 mL), DCM (5 mL), 0－5 ℃, in darkness, isolated yield.

Having achieved the reaction of **2** with amines, We continued to test the reactions of **2b** with (hetero)arenes (Table 3). It was found that only some electron-rich arenes could react with **2b**. For example, the reaction of *N,N*-diethylaniline with **2b** occurred at room temperature to give sulfide **6a** in 39% yield, and a large amount of disulfide *n*-C_4F_9-S-S-C_4F_9-*n* was formed as major product. In the case of *N*-phenylaniline, the corresponding sulfide **6b** was obtained in 30% yield and sulfenamide **5f** was the major product. Pyrrole performed better and sulfide **6c** was formed in 53% yield as indicated by ^{19}F NMR. Unfortunately, **6c** was not stable enough to isolate. Among all arenes tested, indol is the most efficient substrate, giving 3-indolyl sulfide **6d** in 94% yield. Some other activated aromatic derivates were also tried, such as furane, 1,3-dimethoxybenzene and toluene, but no desired substitution product was obtained, and disulfide *n*-C_4F_9-S-S-C_4F_9-*n* was the only product. It was reported that trifluoromethylsulfenyl chloride could react with these substrates easily.[9] The above results demonstrated that the reactivity of perfluoroalkanesulfenyl chlorides with longer chain has lower reactivity compared with CF_3SCl.

Table 3 The reactions of perfluorobutanesulfenyl chloride **2b** with arenes



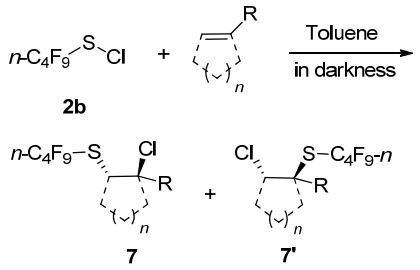


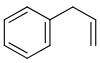
Reaction conditions: **2b** (0.4 mmol), arene (4.0 mmol), toluene (5 mL), DCM (5 mL), r.t., in darkness, isolated yield.

The addition to carbon-carbon double bond is a typical property of sulfenyl chloride, differing from other chlorides such as acyl chloride, sulfonyl chloride and sulfinyl chloride, which rarely undergo this kind of addition reaction.[10] There have been several reports on the addition reactions of nonfluorine-containing sulfenyl chlorides.[10] Therefore, taking **2b** as a model substrate, we further studied the addition reactions of **2** and alkenes. Condition screening showed that the addition reaction of **2b** and 1-octene occurred at a higher temperature (55 ℃) and the amount of alkene had an important influence on the reaction. When 2.0 equivalent of 1-octene was used, perfluorobutyl disulfide (*n*-C_4F_9-S-S-C_4F_9-*n*) was formed as the major product. Full conversion and high selectivity for the desired addition products were reached using 10 equiv. of 1-octene (88% isolated yield). As shown in Table 4, the addition reaction was very sensitive to the structure of alkenes. While acyclic alkenes such as 1-octene, 1, 7-octa-diene and allylbenzene reacted with **2b** at 55 ℃ (Table 4, Entries 1－3), the reaction of cyclohexene took place at room temperature to give the corresponding adducts in good yield (Entry 4), and even lower temperature was needed for the reaction of cyclopentene (0－5 ℃, Entry 5). In the case of acyclic alkenes, both Markovnikov adducts (**7**) and *anti*-Markovnikov adducts (**7′**) were obtained with a ratio ranging from 1∶0.1 to 1∶0.4. It is worth mentioning that only one double bond participated the addition when non-conjugated

diene was used. Contrary to common nonfluorinated sulfenyl chlorides which easily reacted with conjugated dienes and electron-deficient alkenes,[10] **2b** could not react with those alkenes such as dimethylbutadiene and 2-cyclopentenone even at 70 ℃ for prolonged reaction time.

Table 4 The reactions of **2b** with alkenes



Entry[a]	Alkene	Temp./℃	*t*/h	Yield[b]/%
1		55	7.5	88 (1∶0.3)
2		55	7.5	87 (1∶0.4)
3		55	6.5	81 (1∶0.1)
4		r.t.	12	84
5		0—5	5	85

[a] Reaction conditions: **2b** (0.4 mmol), alkene (4.0 mmol), toluene (5 mL), DCM (5 mL), in darkness. [b] Total isolated yield of **7** and **7'**; the ratio of **7** and **7'** in parenthesis was determined by ^{19}F NMR spectroscopy.

Conclusions

In summary, perfluoroalkanesulfenyl chlorides could be easily prepared from the corresponding sulfenyl acids. Compared with nonfluorine-containing sulfenyl chlorides and trifluoromethanesulfenyl chloride, these perfluoroalkylated sulfenyl chlorides showed similar properties in some substitution and addition reactions, but their reactivity was relatively lower in certain reactions. Under mild conditions, they could react readily with many sulfur and nitrogen nucleophiles, aniline and pyrrole derivatives, and common alkenes, providing useful methods for the preparation of a series of perfluoroalkyl-containing disulfides, sulfenamides, aryl sulfides and α-chlorosulfides.

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References

[1] (a) Patai, S. *The Chemistry of Sulphenic Acids and Their Derivatives*, Wiley, Chichester, **1990**; (b) Khle, E. *The Chemistry of the Sefenic Acids*, Georg Thieme, Stuttgart, **1973**; (c) Chachignon, H.; Cahard, D. *Chin. J. Chem.* **2016**, *34*, 445; (d) Glenadel, Q.; Billard, T. *Chin. J. Chem.* **2016**, *34*, 455.

[2] (a) Block, E.; Penn, R. E.; Revelle, L. *J. Am. Chem. Soc.* **1978**, *100*, 3622; (b) Heinecke, J.; Ford, P. C. *J. Am. Chem. Soc.* **2010**, *132*, 9240.

[3] (a) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016; (b) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929; (c) Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 8000; (d) Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 3150; (e) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929; (f) Shelton, J. R.; Davis, K. E. *J. Am. Chem. Soc.* **1967**, *89*, 718; (g) Davis, F. A.; Jenkins, R. H.; Rizvi, S. Q. A.; Yocklovich, S. G. *J. Org. Chem.* **1981**, *46*, 3467; (h) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016; (i) Davis, F. A.; Awad, S. B.; Jenkins, R. H.; Billmers, R. L.; Jenkins, L. A. *J. Org. Chem.* **1983**, *48*, 3071; (j) Davis, F. A.; Billmers, R. L. *J. Org. Chem.* **1985**, *50*, 2593; (k) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033; (l) Turecek, F.; Drinkwater, D. E.; Mc Lafferty, F. W. *J. Am. Chem. Soc.* **1989**, *111*, 7696; (m) Davis, F. A.; Billmers, R. L. *J. Org. Chem.* **1985**, *50*, 2593; (n) Lacombe, S.; Loudet, M.; Banchereau, E.; Simon, M.; Pfister-Guillouzo, G. *J. Am. Chem. Soc.* **1996**, *118*, 1131; (o) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921; (p) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033; (q) Davis, F. A.; Rizvi, S. Q. A.; Ardecky, R.; Gosciniak, D. J.; Friedman, A. J.; Yocklovich, S. G. *J. Org. Chem.* **1980**, *45*, 1650; (r) Davis, F. A.; Jenkins, R. H. Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7967.

[4] (a) Bachi, M. D.; Gross, A. *J. Org. Chem.* **1982**, *47*, 897; (b) Chou, T. S.; Burgtorf, J. R.; Ellis, A. L.; Lammert, S. R.; Kukolja, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 1609; (c) Yoshimura, T.; Tsukurimichi, E.; Yamazaki, S.; Soga, S.; Shimasaki, C.; Hasegawa, K. *J. Chem. Soc., Chem. Commun.* **1992**, *18*, 1337; (d) Nakamura, N. *J. Am. Chem. Soc.* **1983**, *105*, 7172; (e) Goto, K.; Tokitoh, N.; Okazaki, R. *Angew. Chem.* **1995**, *107*, 1202; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1124; (f) Goto, K.; Holler, M.; Okazaki, R. *Phosphorous Sulfur Silicon Relat. Elem.* **1997**, *120*, 325; (g) Ishii, A.; Komiya, K.; Nakayama, J. *J. Am. Chem. Soc.* **1996**, *118*, 12836; (h) Fries, K. *Chem. Ber.* **1912**, *45*, 2965; (i) Bruice, T. C.; Markiv, R. T. *J. Am. Chem. Soc.* **1957**, *79*, 3150; (j) Bimal, C. P.; Mayo, U.; David, G. D.; Waldo, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 3634; (k) Walter, W.; Bode, K. D. *Ann. Chem.* **1966**, *698*, 122.

[5] (a) Sosnovsky, G. *Austral 206652*, **1957** [*Chem. Abstr.* **1959**, *53*, 17904]; (b) Lecher, H. *Chem. Ber.* **1925**, *58*, 409; (c) Fuson, R. C.; Price, C. C.; Bauman, R. A.; Bullitt, O. H.; Hatchard, W. R.; Maynert, E. W. *J. Org. Chem.* **1946**, *11*, 469; (d) Mayer, R.; Frey, H. J. *Angew. Chem., Int. Ed.* **1964**, *3*, 705; (e) Grigat, G. *Angew. Chem, Int. Ed.* **1969**, *8*, 607; (f) Havlik, A.; Wald, M. M. *J. Am. Chem. Soc.* **1955**, *77*, 5171; (g) Thaler, W. A. *Chem. Commun.* **1968**, 527.

[6] (a) Li, X.-B.; Xu, Z.-F.; Liu, L.-J.; Liu, J.-T. *Eur. J. Org. Chem.* **2014**, 1182; (b) Li, X.-B.; Zhao, J.; Jiang, M.; Liu, J.-T. *J. Fluorine Chem.* **2016**, *185*, 24.

[7] (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqu, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551; (b) Yagupol'skii, L. M.; Bezdudnyi, A. V.; Yagupol'skii, Y. L. *Russ. J. Org. Chem.* **2006**, *42*, 1275; (c) Scribner, R. M. *J. Org. Chem.* **1966**, *31*, 3671; (d) Hartzler, W. Q. *J. Org. Chem.* **1964**, *29*, 1194; (e) Borowski, H. E.; Haas, A. *Chem. Ber.* **1982**, *115*, 523; (f) Ceacareanu, D. M.; Gerstenberger, M. R. C.; Haas, A. *Chem. Ber.* **1983**, *116*, 3325; (g) Gerstenberger, M. R. C.; Haas, A.; Wille, R.; Yazdanbakhsch, M. *Rev. Chim. Miner.* **1986**, *23*, 485; (h) Geisel, M.; Mews, R. *Chem. Ber.* **1987**, *120*, 1675; (i) Kolasa, A.; Lieb, M. *J. Fluorine Chem.* **1995**, *70*, 45; (j) Munavalli, S.;

Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth*. *Commun*. **2000**, *30*, 2847; (k) Wagner, W. G.; Durst, H. D. *Phosphorus*, *Sulfur Silicon Relat*. *Elem*. **2003**, *178*, 107.

[8] (a) Sahu, K. K.; Ravichandran, V.; Mourya, V. K.; Agrawal, R. K. *Med*. *Chem*. *Res*. **2007**, *15*, 418; (b) Schallner, O.; Schwarz, H.-G.; Hoischen, D.; Linker, K.-H.; Drewes, M. W.; Dahmen, P.; Feucht, D.; Pontzen, R. *Preparation of Benzoxazinones and Related Compounds as Herbicides*, *WO 2002006277A1*, **2002**; (c) Tabuchi, T.; Yamamoto, T.; Nakayama, M. *Preparation of Aryl- or Heterocyclylsulfonamide Derivatives as Agricultural and Horticultural Microbicides*, *WO 200006591 3A1*, **2000**.

[9] (a) Haas, A.; Lieb, M.; Zhang, Y. *J*. *Fluorine Chem*. **1985**, *30*, 203; (b) Gerstenberger, M. R. C.; Haas, A. *J*. *Fluorine Chem*. **1983**, *23*, 525; (c) Andreades, S.; Harris, J. F.; Sheppard, W. A. *J*. *Org*. *Chem*. **1964**, *29*, 898.

[10] (a) Mueller, W. H.; Butler, P. E. *J*. *Am*. *Chem*. *Soc*. **1968**, *90*, 2075; (b) Jalobs, T. L.; Mocomber, R. S. *Quart*. *Rep*. *Sulfur Chem*. **1967**, *2*, 307; (c) Melloni, G.; Modena, G.; Scorrano, G. *Quart*. *Rep*. *Sulfur Chem*. **1967**, *2*, 365; (d) Calo, V.; Scorrano, G.; Modena, G. *J*. *Chem*. *Soc*. *C* **1968**, 1339.

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