ORGANIC LETTERS

2010
Vol. 12, No. 13
2932−2935

Nucleophilic Perfluoroalkylation of Imines and Carbonyls: Perfluoroalkyl Sulfones as Efficient Perfluoroalkyl-Transfer Motifs

G. K. Surya Prakash,* Ying Wang, Ryo Mogi, Jinbo Hu,† Thomas Mathew, and George A. Olah

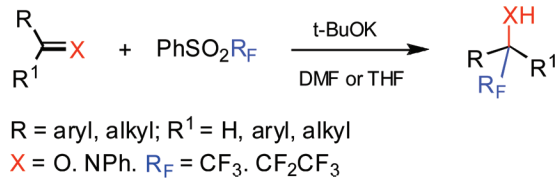
Donald P. and Katherine B. Loker hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661

gprakash@usc.edu

Received April 21, 2010

Downloaded via SHANGHAI INST OF ORGANIC CHEMISTRY on December 17, 2020 at 08:43:50 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

ABSTRACT



Alkoxide-induced nucleophilic pentafluoroethylation and trifluoromethylation of aldehydes, ketones, and imines using pentafluoroethyl phenyl sulfone ($PhSO_2CF_2CF_3$, 1) and trifluoromethyl phenyl sulfone ($PhSO_2CF_3$, 2), respectively, have been successfully achieved. High diastereoselectivity was observed during the perfluoroalkylation of homochiral sulfinimines to give the corresponding perfluoroalkyl sulfinamides.

Fluorine-containing compounds are widely used in pharmaceutical, agrochemical and material fields.[1] Due to the small size and high electronegativity, fluorine can impart unique chemical and biological properties to an organic molecule, including stability, high lipophilicity, and bioavailability that can favorably change in vivo drug transport and absorption rates.[2] In the past two decades, introducing fluorine into organic compounds has attracted much attention. There are many reports on the development of trifluoromethylation methods, including nucleophilic,[3] electrophilic,[4] radical,[5] and organometallic[6] trifluoromethylation protocols. The most common trifluoromethylation reagent, (trifluoromethyl)trimethylsilane ($TMSCF_3$, Ruppert−Prakash reagent), has been widely used under mild reaction conditions.[3b,d,7] Methods to add the pentafluoroethyl group into organic compounds are limited. We previously reported the use of (pentafluoroethyl)trimethylsilane as a pentafluoroethide equivalent.[3e]

† Current Addresss: Head, CAS Key Laboratory for Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Ling Ling Road 345, Shanghai 200032, China.

(1) (a) Hiyama, T., Eds. *Organofluorine compounds. Chemistry and Applications*, Springer: New York, 2000. (b) McCarthy, J. R. *Utility of Fluorine in Biologically Active Molecules, ACS Fluorine Division Tutorial*; 219th National ACS Meeting, San Francisco, March 26, 2000. (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.

(2) (a) McCarthy, J. R. *Fluorine in Drug Design: A Tutorial Review*; 17th Winter Fluorine Conference, St. Pete Beach, FL, 2005. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2007.

(3) (a) Motherwell, W. B.; Storey, L. J. *J. Fluorine Chem.* **2005**, *126*, 491. (b) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123. (c) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771. (d) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (e) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984. (f) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

(4) (a) Shreeve, J. M.; Yang, J.-J.; Kirchmeier, R. L. U. S. Patent 6215021, 2001. (b) Barhdadi, R.; Troupel, M.; Périchon, J. *Chem. Commun.* **1998**, 1251. (c) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (d) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (e) Umemoto, T.; Gotoh, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3307.

(5) (a) Dolbier, W. R., Jr. *Top. Curr. Chem.* **1997**, *192*, 97. (b) Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557.

(6) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.

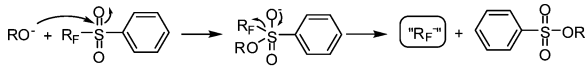
(7) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847. (c) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, *1*, 77.

10.1021/ol100918d © 2010 American Chemical Society
Published on Web 06/02/2010

Röschenthaler has carried out perfluoroalkylation of various substrates using (perfluoroalkyl)trimethylsilanes and perfluorinated phosphonate reagents by following different synthetic strategies.[8] Recently, Dolbier and co-workers[9] reported the use of C_2F_5I with tetrakis(dimethylamino)ethylene (TDAE) in the nucleophilic perfluoroalkylation reactions of aldehydes, ketones, imines, disulfides, and diselenides. In addition, the C_2F_5I/CH_3Li system originally developed by Gassman et al.[10] and ultrasound-promoted C_2F_5X (X = Br, I)/Zn system by Kitazume et al.[11] were also documented for the introduction of pentafluoroethyl group to carbonyl compounds. However, alkoxide-induced nucleophilic pentafluoroethylation using pentafluoroethyl sulfone **1** has not been investigated.

Our previous studies[12] showed that trifluoromethyl phenyl sulfone **2** can be used as a "CF_3^-" synthon in the presence of potassium *tert*-butoxide (*t*-BuOK) for efficient trifluoromethylation of nonenolizable carbonyl compounds and disulfides. However, the trifluoromethylation and pentafluoroethylation of imines by the corresponding perfluoroalkyl sulfones have not been investigated. Herein, we wish to report the successful alkoxide-induced nucleophilic pentafluoroethylation and trifluoromethylation of aldehydes, ketones, and imines by using pentafluoroethyl phenyl sulfone (**1**) and trifluoromethyl phenyl sulfone (**2**), respectively. The chemistry behind this simple and highly feasible transformation is based on the nucleophilic attack of the alkoxide ion on the thio center of **1** or **2** resulting in the generation of pentafluoroethyl anion ("$CF_3CF_2^-$") or trifluoromethyl anion ("CF_3^-") in situ (Scheme 1).

Scheme 1. Alkoxide Induced "R_F^-" Generation from Perfluorosulfones



1: $R_F = CF_2CF_3$
2: $R_F = CF_3$

The fluorine reagent, trifluoromethyl phenyl sulfone (**2**), is commercially available. Pentafluoroethyl phenyl sulfone was prepared in good yields from the reaction[13] between potassium pentafluoropropionate (CF_3CF_2COOK) and diphenyl disulfide followed by oxidation.

(8) (a) Cherneka, A. N.; Kolomeitsev, A. A.; Yagupolskij, Y. L.; Gentzsch, A.; Röshenthaler, G.-V. *J. Fluorine Chem.* **1994**, *70*, 271. (b) Sosnovskikh, V. Ya.; Sevenard, D. V.; Usachev, B. I.; Röshenthaler, G.-V. *Tetrahedron Lett.* **2003**, 2097. (c) Sonovskikh, V. Y.; Usachev, B. I.; Sevenard, D. V.; Röshenthaler, G.-V. *J. Org. Chem.* **2003**, *68*, 7747. (d) Tverdomed, S. N.; Röshenthaler, G.-V.; Kalinovich, E. L.; Dogadina, A. V.; Ionin, B. I. *J. Fluorine Chem.* **2008**, *129*, 478.

(9) Pooput, C.; Dolbier, W. R., Jr.; Médebielle, M. *J. Org. Chem.* **2006**, *71*, 3564.

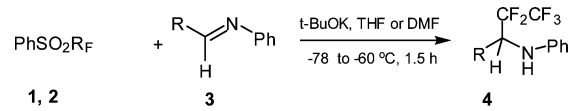
(10) (a) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481. (b) Gassman, P. G.; O'Reilly, N. J. *Tetrahedron Lett.* **1985**, *26*, 5243.

(11) (a) Kitazume, T.; Ikeya, T. *J. Org. Chem.* **1988**, *53*, 2349. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186.

(12) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253. (b) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216. (c) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930. (d) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793.

(13) Roques, N. *J. Fluorine. Chem.* **2001**, *107*, 311.

Scheme 2. Perfluoroalkylation of Imines Using $PhSO_2R_F$



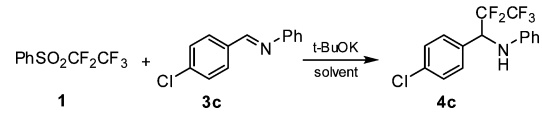
1, 2 **3** **4**

1: $R_F = CF_2CF_3$
2: $R_F = CF_3$

R = aryl, alkyl

Nucleophilic addition reactions between $PhSO_2CF_2CF_3$ (**1**) and imines (**3**) were performed under argon atmosphere by slowly adding a base into the mixture of **1** and **3** in DMF (Scheme 2). Optimization of reaction conditions for base (alkoxide) induced perfluoroalkyl transfer to imines was smooth, and the results are shown in Table 1.

Table 1. Optimization of Reaction Conditions for the Introduction of $CF_3CF_2^-$ into Imines



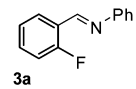
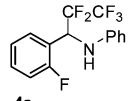
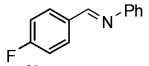
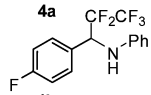
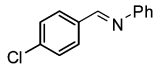
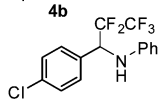
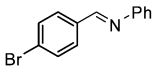
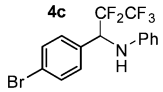
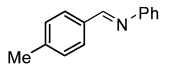
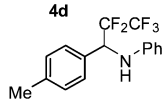
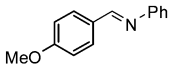
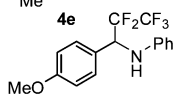
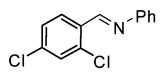
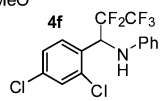
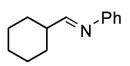
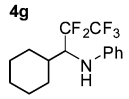
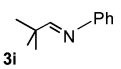
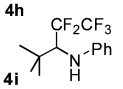
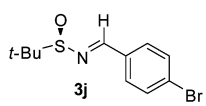
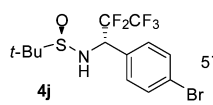
1 **3c** **4c**

entry	sulfone **1** (equiv)	imine **3** (equiv)	*t*-BuOK (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	1.0	2.0	2.0	DMF	−30 to rt	1.5	34[a]
2	1.5	1.0	6.0	DMF	−65	1.5	69[b]
3	1.5	1.0	6.0	DMF	−55	1.5	mixture[c]
4	1.5	1.0	4.5	THF	−78	1.5	99[b]

[a] Yield was estimated by ^{19}F NMR. [b] Isolated yields. [c] Yield was not determined.

In order to find the most effective reaction conditions and enhance the yields, the reaction has been conducted by changing reaction parameters such as solvents, reaction temperatures, and reactant ratios. A previous study[12] demonstrated that DMF as a solvent and *t*-BuOK as a base were the apt choice for trifluoromethylation reaction using $PhSO_2CF_3$ (**2**). Therefore, we initially applied the similar reaction conditions for the pentafluoroethylation reaction using $PhSO_2CF_2CF_3$ (**1**). However, the yield was low and the reaction was not complete. By modifying the reaction conditions as before,[12a,b] we found that low temperatures and slight excess of sulfone **1** and large excess of *t*-BuOK favored the reaction. When the temperature was lowered to −78 °C with THF as solvent instead of DMF, the yield was found to be almost quantitative (99%, Table 1, entry 4). After carefully modifying the reaction conditions, we ascertained that good yield (60−99%) can be obtained by the dropwise addition of 4.5 equiv of *t*-BuOK in THF to the mixture of 1.5 equiv of the perfluoroalkyl sulfone **1** and 1 equiv of imine **3** in THF at −75 to −70 °C followed by stirring the mixture for 1.5 h under argon atmosphere. The results are summarized in Table 2.

Table 2. Pentafluoroethylation of Imines Using $PhSO_2CF_2CF_3$

entry	imine (**3**)	product (**4**)	yield [%][a]
1	 **3a**	 **4a**	88
2	 **3b**	 **4b**	96
3	 **3c**	 **4c**	99
4	 **3d**	 **4d**	99
5	 **3e**	 **4e**	88
6	 **3f**	 **4f**	82
7	 **3g**	 **4g**	96
8	 **3h**	 **4h**	57
9	 **3i**	 **4i**	50
10	 **3j**	 **4j**	57

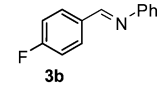
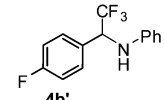
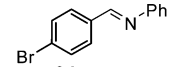
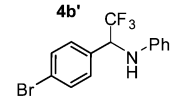
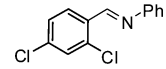
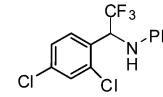
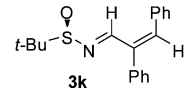
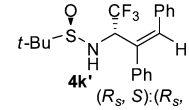
$(R_S, S):(R_S, R)^b = 97:3^b$

[a] Isolated yields. [b] Diastereomeric ratio was determined by ^{19}F NMR spectroscopy of the reaction mixture.

A variety of structurally diverse imines **3** were used to react with **1** in the presence of *t*-BuOK to give the corresponding pentafluoroethyl amines with excellent yields. Imines bearing an α-hydrogen atom were also found to be reactive to **1** in the basic environment. Noticeably, when a homochiral sulfinimine **3j** was used as a substrate in the perfluoroethylation reaction using sulfone **1**, the corresponding product **4j** was obtained with high diastereoselectivity (Table 2, entry 10, dr = 97:3). Similarly, the reaction of imine **3k** with the trifluoromethyl sulfone **2** was also found to be highly diastereoselective forming the corresponding trifluoromethyl sulfinamide **4k′** in good yield (Table 3, entry 4).[7b] The chiral sulfinamides can be further converted into fluorinated amines in enantiomerically pure form,[7] which provides an effective and highly stereoselective method for the preparation of perfluoroalkylated amines.

Extensive studies on the application of fluoromethyl phenyl sulfones as fluoromethyl pronucleophile have been conducted in our laboratories.[14] As reported before,[12] trifluoromethylation of carbonyl compounds using $PhSO_2CF_3$/*t*-BuOK system was very convenient and efficient. We found that *t*-BuO^- induced trifluoromethylation of imines using $PhSO_2CF_3$ also worked very well. In this case, higher yields and cleaner products were observed when DMF was used as the solvent instead of THF, which indicated that "CF_3^-" is more stable in DMF than in THF. The optimized reaction conditions involve a mixture with 1.5:1:4.5 equiv ratio of $PhSO_2CF_3$/imine/*t*-BuOK, at −70 to −60 °C, for a period of 1.5 h in DMF as solvent. The results are shown in Table 3.

Table 3. Trifluoromethylation of Imines Using $PhSO_2CF_3$

entry	imine (**3**)	product (**4**)	yield (%)[a]
1	 **3b**	 **4b'**	59
2	 **3d**	 **4d'**	72
3	 **3g**	 **4g'**	91
4	 **3k**	 **4k'**	68

$(R_S, S):(R_S, R)^b = 98:2^b$

[a] Isolated yields. [b] Diastereomeric ratio was determined by ^{19}F NMR spectroscopy of the reaction mixture.

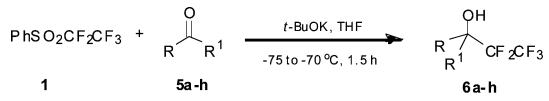
α-Trifluoromethylamines and amino acids are of great interest as potent inhibitor candidates for amino acid-processing enzymes which include amine oxidases and amino acid decarboxylases.[15] For the synthesis of this family of compounds, the present method will serve as an additional convenient and feasible method along with the previously reported ones. More importantly, ^{19}F NMR can act as an effective tool to garner valuable mechanistic information in the biological activity of amino acid-processing enzymes by using fluorinated enzyme inhibitors.[16] Pentafluoroethylation of aldehydes and ketones using $PhSO_2CF_2CF_3$ was also very successful (Table 4). In this case, we applied the same reaction conditions as in the case of pentafluoroethylation of imines, and good yields of pentafluoroethyl carbinols were obtained.

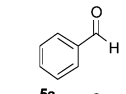
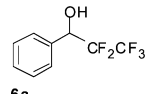
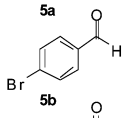
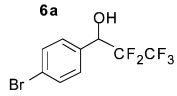
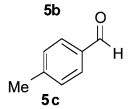
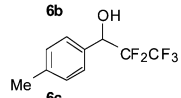
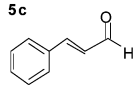
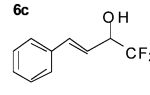
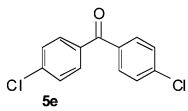
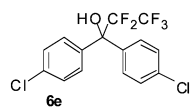
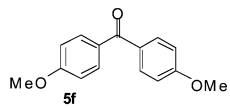
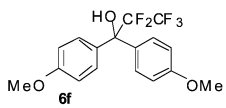
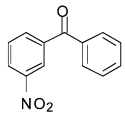
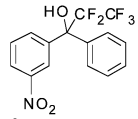
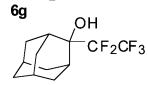
(14) (a) Prakash, G. K. S.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4933. (b) Prakash, G. K. S.; Xiaoming, Z.; Chacko, S.; Wang, F.; Vaghoo, H.; Olah, G. A. *Beilstein J. Org. Chem.* **2008**, *4*, 17. (c) Prakash, G. K. S.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4090.

(15) Moroni, M.; Koksch, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130. (b) Burger, K.; Gaa, K.; Höss, E. *J. Fluorine Chem.* **1990**, *47*, 89.

(16) Berkowitz, D. B.; Karukurichi, K. R.; de la Salud-Bea, R.; Nelson, D. L.; McCune, C. D. *J. Fluorine Chem.* **2008**, *129*, 731.

Table 4. Pentafluoroethylation of Carbonyl Compounds Using $PhSO_2CF_2CF_3$



entry	aldehyde/ketone (**5**)	perfluoroethylcarbinol (**6**)	yield (%)[a]
1	 **5a**	 **6a**	91
2	 **5b**	 **6b**	85
3	 **5c**	 **6c**	84
4	 **5d**	 **6d**	89
5	 **5e**	 **6e**	93
6	 **5f**	 **6f**	99
7	 **5g**	 **6g**	67
8	 **5h**	 **6h**	99

[a] Isolated yields.

Our studies showed that both nonenolizable and enolizable aldehydes worked in this reaction, but enolizable aldehydes gave lower yields due to the competing enolization occurring in the presence of the base. The workup procedure of this reaction is quite simple. After ether extraction and aqueous washing, byproducts *tert*-butyl alcohol and benzensulfonic acid were removed and pure pentafluoroethyl alcohols were obtained by recrystallization. Among most recent perfluoroalkylation studies, trifluoromethylation at the α-position to carbonyl function reported by MacMillan et al. is quite useful and practical.[17]

To establish the versatility of the protocol, pentafluoroethylation of alkyl halides were also attempted. Kobayashi reported the trifluoromethylation of *n*-decyl iodides with preprepared CF_3Cu/HMPA in 48% yield.[18] Chambers et al. found that sodium perfluoroalkane carboxylates are potential sources for perfluoroalkylation of aromatic halides and alkyl iodides[19] Chen et al. reported the trifluoromethylation of aliphatic halides using methyl chlorodifluoroacetate in the presence of potassium fluoride, copper iodide, and cadmium iodide at 120 °C in HMPA.[20] Our preliminary studies on pentafluoroethylation of alkyl halides using 4-phenyl-*n*-butyl/3-phenoxy-*n*-propyl iodide with pentafluoroethyl sulfone **1** indicated the formation of the corresponding perfluoroethylalkanes, 1,1,1,2,2-pentafluoro-6-phenylhexane, and 1,1,1,2,2-pentafluoro-5-phenoxypentane in significant amounts (by ^{19}F NMR analysis). (Not isolated. Further studies are underway.)

In summary, a new and efficient method was developed for the preparation of pentafluoroethyl substituted amines, alcohols, alkanes, and trifluoromethyl substituted amines using $PhSO_2CF_2CF_3$ or $PhSO_2CF_3$ as the pentafluoroethyl or trifluoromethyl anion sources. It has been found that trifluoromethyl and pentafluoroethyl sulfinamides can also be obtained with high diastereoselctivity from their corresponding sulfinimine precursors through the developed nucleophilic perfluoroalkylation reactions.

Acknowledgment. Support of our work in part by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: Experimental procedures for the preparation of **4** and **6** and spectral data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100918D

(17) (a) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

(18) Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 4071.

(19) Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Chem. Soc., Perkin Trans. I* **1988**, 921.

(20) Chen, Q.; Duan, J. *Tetrahedron Lett.* **1993**, *34*, 4241.