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Difluoro-λ^3-bromane-Induced Hofmann Rearrangement of Sulfonamides: Synthesis of Sulfamoyl Fluorides

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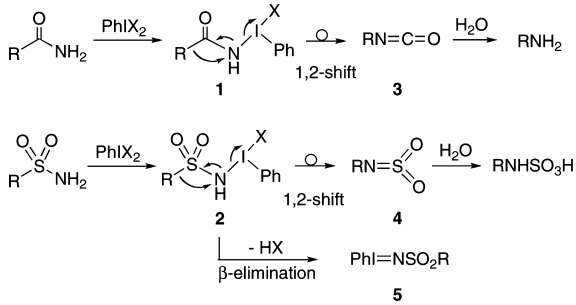
The Hofmann rearrangement with sodium hypobromite effects conversion of primary carboxamides to amines possessing one less carbon atom through the intermediacy of *N*-bromo amides;[1] however, the Hofmann rearrangement of sulfonamides has never been reported and remains to be established experimentally. Phenyl-λ^3-iodanes such as $PhIX_2$ (X = $OCOCF_3$ and OAc) are the reagents of choice in recent versions of Hofmann rearrangement under mildly acidic or neutral conditions (Scheme 1).[2] The reaction involves intermediacy of *N*-λ^3-iodanyl amides **1** and their rate-limiting concerted migration of alkyl groups from a carbon to an electron-deficient nitrogen center, yielding isocyanates **3** as an initial product. On the other hand, it has been well established that reaction of phenyl-λ^3-iodanes with primary sulfonamides does not undergo Hofmann rearrangement at all but instead affords sulfonylimino-λ^3-iodanes **5** selectively,[3] being excellent progenitors for generation of metal−nitrenoid species either in the aziridination of alkenes or in the amidation of alkanes via C−H insertion.[4] Formation of imino-λ^3-iodanes **5** involves an initial ligand exchange on iodane(III) with generation of amido-λ^3-iodanes **2**, followed by the β-elimination of HX. The differences in pK_a values between carboxamides and sulfonamides, the latter being more acidic,[5] will probably control these two reaction pathways, 1,2-migration and β-elimination. In fact, relatively acidic trifluoroacetamide selectively undergoes β-elimination, instead of the Hofmann rearrangement, yielding imino-λ^3-iodane $CF_3CON{=}IPh$.[5−7]

Scheme 1



It occurred to us that increasing the nucleofugality of the leaving groups on the nitrogen atom of **2** by replacing with aryl-λ^3-bromanyl groups[8] would enhance the tendency toward 1,2-migration of R groups rather than β-elimination. We report herein, for the first time, the Hofmann rearrangement of primary arenesulfonamides, which relies on the use of *p*-trifluoromethylphenyl(difluoro)-λ^3-bromane (**6**)[9] instead of an aryl-λ^3-iodane and affords *N*-arylsulfamoyl fluorides selectively at room temperature.

Scheme 2

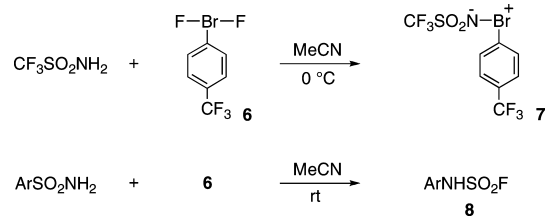


Table 1. Synthesis of Sulfamoyl Fluoride **8a** Using Bromane **6**[a]

entry	bromane **6** (equiv)	solvent	conv. (%)[b]	yield (%)[b]
1	1.1	MeCN	62	37
2	1.1	CH_2Cl_2	55	48
3	1.1	$CHCl_3$	59	33
4	1.1	CCl_4	55	17
5	1.1	$(ClCH_2)_2$	78	45
6	1.1	THF	59	27
7	1.1	acetone	50	10
8	1.1	PhH	71	71[c]
9	1.5[d]	PhH	88	88 (81)[c]
10	1.1	PhF	61	61
11	1.1	$PhCF_3$	51	17
12	1.5[d,e]	PhH	0	0

[a] Conditions: *p*-toluenesulfonamide (0.05 M)/bromane **6**/room temperature/1 h/Ar. [b] ^{1}H NMR yields. Numbers in parentheses are isolated yields. [c] Diaryl-λ^3-bromane *p*-$CF_3C_6H_4$(Ph)BrF was produced in 10−11% yields. [d] Reaction time: 2 h. [e] Difluoro-λ^3-iodane (*p*-$CF_3C_6H_4IF_2$), instead of **6**, was used.

Recently, we reported that reaction of considerably acidic trifluoromethanesulfonamide[5] with difluoro-λ^3-bromane **6** in acetonitrile produced triflylimino-λ^3-bromane **7** selectively in a high yield.[10] The iminobromane**7** serves as an efficient imido group donor and directly undergoes aziridination of olefins stereospecifically with retention of stereochemistry under metal-free conditions. In marked contrast, exposure of less acidic *p*-toluenesulfonamide[5] to difluorobromane **6** (1.1 equiv) showed no evidence for formation of the corresponding iminobromane at all but instead afforded unique *N*-*p*-tolylsulfamoyl fluoride (**8a**) (Ar = *p*-MeC_6H_4) in acetonitrile at room temperature in 37% yield (^{1}H NMR), probably through novel Hofmann rearrangement of sulfonamides (Table 1, entry 1). Sulfamoyl fluoride **8a** is labile toward hydrolysis but can be purified by silica gel column chromatography deactivated by adding 5% of H_2O.

Changing the solvent to dichloromethane and dichloroethane slightly increased the yields of the fluoride **8a** (entries 2, 5). Benzene was found to be a solvent of choice, and 1.5 equiv of the bromane **6** afforded a high yield (88%) of **8a** (entry 9); however, this reaction competes with an electrophilic aryl-λ^3-bromanation of benzene to some extent and yields a small amount (11%) of diaryl-λ^3-bromane

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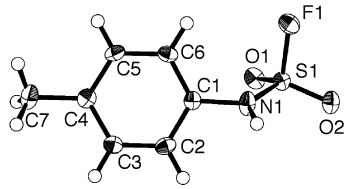


Figure 1. ORTEP drawing of sulfamoyl fluoride **8aa** with thermal ellipsoids at 50% probability. Selected bond lengths (Å) and angles (deg): C1−N1 1.456(4), N1−S1 1.587(3), S1−F1 1.5614(19), C1−N1−S1 120.3(2).

Table 2. Synthesis of Sulfamoyl Fluorides **8** Using Bromane **6**[a]

entry	$ArSO_2NH_2$	**8**	conv. (%)[b]	yield (%)[b,c]
1	*p*-$MeOC_6H_4SO_2NH_2$	**8b**	81	81 (64)
2	*o*-$MeC_6H_4SO_2NH_2$	**8c**	92	92 (82)
3	$PhSO_2NH_2$	**8d**	88	82 (52)
4	*p*-$FC_6H_4SO_2NH_2$	**8e**	90	86 (62)
5	*p*-$ClC_6H_4SO_2NH_2$	**8f**	81	(71)
6	*p*-$CF_3C_6H_4SO_2NH_2$	**8g**	82	82 (60)
7	3,5-$(CF_3)_2C_6H_3SO_2NH_2$	**8h**	17	−
8	*p*-$NO_2C_6H_4SO_2NH_2$	**8i**	5	−

[a] Conditions: arenesulfonamide (0.05 M)/bromane **6** (1.5 equiv)/benzene/room temperature/2 h/Ar. [b] ^1H NMR yields. Numbers in parentheses are isolated yields. [c] Diaryl-λ^3-bromane *p*-$CF_3C_6H_4(Ph)BrF$ was also produced in 10−25% yields.

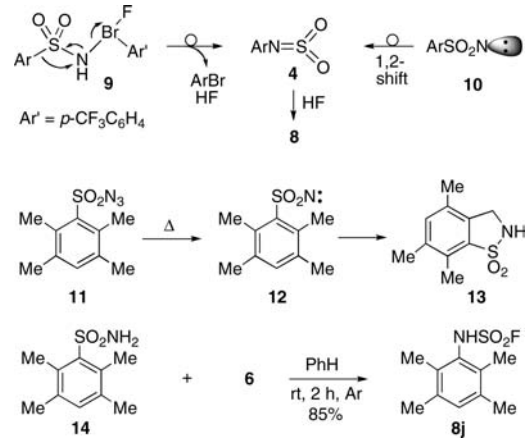
p-$CF_3C_6H_4(Ph)BrF$ as a byproduct. Use of electron-deficient benzenes such as PhF and $PhCF_3$ suppressed the byproduct formation but also decreased the yields of **8a** (entries 10, 11). Note that no formation of sulfamoyl fluoride **8a** was detected, when difluoro-λ^3-iodane *p*-$CF_3C_6H_4IF_2$ was used instead of the bromane **6**, and *p*-toluenesulfonamide was recovered unchanged (entry 12). These results indicate higher reactivity of the bromane **6**.

Three intense bands in the IR spectrum of **8a** at 1446, 1203, and 769 cm^{-1} are indicative of the presence of the NSO_2F group and are attributed to the SO_2 asymmetric and symmetric stretching and S−F stretching modes, respectively.[11,12] The molecular structure was firmly established by a single-crystal X-ray analysis (Figure 1), which showed the existence of four independent but closely related molecules **8aa**−**8ad** with mean N−S (1.582 Å) and S−F (1.565 Å) distances (see Figure S1). Arrangement of atoms around the nitrogen of **8ab** and **8ac** is almost planar, but **8aa** and **8ad** tend to exhibit some pyramidalization with the sums of N-centered bond angles being 348.3° and 351.8°, respectively.[13] In all of these molecules, the nitrogen lone pairs are oriented almost parallel to the S−F bonds, probably because of the stabilizing $n_N-\sigma_{S-F}^*$ negative hyperconjugation.[14]

Arenesulfonamides with electron-donating (*p*-MeO and *o*-Me) and -withdrawing substituents (*p*-F, *p*-Cl, and *p*-CF_3) efficiently undergo λ^3-bromane-induced Hofmann rearrangement under our conditions and afforded *N*-arylsulfamoyl fluorides **8** in good to excellent yields (Table 2). The sterically demanding *o*-Me group enhances the rates of Hofmann rearrangement of *N*-bromobenzamides, because of the decrease in the entropy of the initial state compared to the *p*-isomer,[15] whereas the highly electron-withdrawing *p*-NO_2 group retards the rearrangement.[1] Thus, sulfonamide with the *o*-Me group gave the fluoride **8c** in a high yield, but those with NO_2 and bis(trifluoromethyl) groups showed no evidence of Hofmann rearrangement (entries 2, 7, 8).

Other than the Hofmann rearrangement pathway involving the 1,2-shift of aryl groups from sulfur to the electron-deficient nitrogen atom in putative sulfonamido-λ^3-bromane intermediates **9** yielding sulfonylamines **4**, generation of free nitrenes **10** from **9** could also explain the formation of sulfamoyl fluorides **8** (Scheme 3). Thermally generated nitrene **12** from sulfonyl azide **11** affords sultam **13** via intramolecular C−H insertion, because of the buttressing effects of *meta* methyl groups.[16] Reaction of sulfonamide **14** with bromane **6**, however, produced a high yield of sulfamoyl fluoride **8j** selectively, and no formation of **13** was detected. These results probably indicate that generation of nitrene **10** will not be involved in our rearrangement reaction.

Scheme 3



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Supporting Information Available: Text giving experimental details, Figures S1, and X-ray crystallographic data in CIF format for **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Wallis, E. S.; Lane, J. F. *Org. React.* **1946**, *3*, 267. (b) Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 795.
(2) (a) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272. (b) Lazbin, I. M.; Koser, G. F. *J. Org. Chem.* **1987**, *52*, 476. (c) Moriarty, R. M.; Chany, C. J., II.; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.
(3) (a) Abramovitch, R. A.; Bailey, T. D.; Takaya, T.; Uma, V. *J. Org. Chem.* **1974**, *39*, 340. (b) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361. (c) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (d) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
(4) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (c) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (d) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (e) Fructos, M. R.; Trofimenko, S.; Diaz-Requejo, M. M.; Perez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784. (f) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184.
(5) pK_a values in DMSO: $MeCONH_2$, 25.5; $PhCONH_2$, 23.35; CF_3CONH_2, 17.2; $MeSO_2NH_2$, 17.5; $PhSO_2NH_2$, 16.1; *p*-$MeC_6H_4SO_2NH_2$, 16.3; $CF_3SO_2NH_2$, 9.7 (6.3 in H_2O). See: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Koppel, I. A.; Koppel, J.; Leito, I.; Koppel, I.; Mishima, M.; Yagupolskii, L. M. *J. Chem. Soc., Perkin Trans. 2* **2001**, 229.
(6) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161.
(7) Expected low migratory aptitude of highly electron-withdrawing trifluoromethyl group will also be responsible for the low tendency of CF_3CONH_2 toward Hofmann rearrangement.
(8) Nucleofugality of ary-λ^3-bromanyl groups is greater than that of ary-λ^3-iodanyl groups. See: (a) Ochiai, M.; Tada, N.; Okada, T.; Sota, A.; Miyamoto, K. *J. Am. Chem. Soc.* **2008**, *130*, 2118.
(9) (a) Frohn, H. J.; Giesen, M. *J. Fluorine Chem.* **1998**, *89*, 59. (b) Ochiai, M.; Nishi, Y.; Goto, S.; Shiro, M.; Frohn, H. J. *J. Am. Chem. Soc.* **2003**, *125*, 15304. (c) Ochiai, M.; Yoshimura, A.; Mori, T.; Nishi, Y.; Hirobe, M. *J. Am. Chem. Soc.* **2008**, *130*, 3742.
(10) Ochiai, M.; Kaneaki, T.; Tada, N.; Miyamoto, K.; Chuman, H.; Shiro, M.; Hayashi, S.; Nakanishi, W. *J. Am. Chem. Soc.* **2007**, *129*, 12938.
(11) Alvarez, R. M. S.; Valdez, M. I. M.; Cutin, E. H.; Della Vedova, C. O. *J. Mol. Struct.* **2003**, *657*, 291.
(12) The relationship ν SO_2 asymmetric/ν SO_2 symmetric = 1.20 supports these assignments. See: (a) Alvarez, R. M. S.; Cutin, E. H.; Della Vedova, C. O. *Spectrochim. Acta* **2002**, *58A*, 149.
(13) Ohwada, T.; Okamoto, I.; Shudo, K.; Yamaguchi, K. *Tetrahedron Lett.* **1998**, *39*, 7877.
(14) Bharatam, P. V.; Gupta, A.; Kaur, D. *Tetrahedron* **2002**, *58*, 1759.
(15) Imamoto, T.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1632.
(16) Abramovitch, R. A.; Chellathurai, T.; Holcomb, W. D.; McMaster, I. T.; Vanderpool, D. P. *J. Org. Chem.* **1977**, *42*, 2920.

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