Very Important Publication

The Reactivity of Difluorocarbene with Hydroxylamines: Synthesis of Carbamoyl Fluorides

Hannah Baars,[a] Julien Engel,[a] Lucas Mertens,[a] Daniela Meister,[a] and Carsten Bolm[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2391; e-mail: Carsten.Bolm@oc.rwth-aachen.de

Received: March 21, 2016; Revised: May 23, 2016; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600308.

Abstract: Carbamoyl fluorides are formed in reactions of hydroxylamines with difluorocarbene generated from sodium bromodifluoroacetate as readily available and non-toxic carbene precursor. The process shows a high functional group tolerance, and the reaction path has been rationalized by computational calculations.

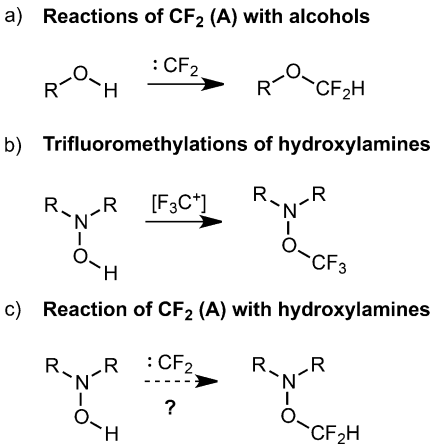
Keywords: carbenes; fluorine; reaction mechanism; synthetic methods

The unique stability, reactivity and biological properties of organofluorine compounds has led to their widespread use in materials, pharmaceuticals and agrochemicals.[1] Thus, mild, selective and cost-effective fluorination strategies are of high interest. Difluorocarbene (CF_2, **A**), as a versatile and reactive intermediate, offers excellent opportunities for introducing fluorine moieties into organic molecules.[2] Traditionally, difluorocarbene is formed from ozone-depleting substances such as HCF_2Cl and HCF_2Br or from hazardous reagents such as Me_3SnCF_3 and CF_3HgI.[2] During the last decades, many new and efficient difluorocarbene sources have been developed. They were utilized in a variety of transformations including trifluoromethylations,[3] difluoromethylations of alkynes[4] and X–H bonds (X = N, O, S),[5] *gem*-difluorocyclizations,[5d,f,6] *gem*-difluoroolefinations,[7] and transition metal coordinations.[8] With these reactions, a range of privileged functional motifs could be constructed including the difluoromethyl group which proved to be bioisosteric to amines, hydroxides and thiols with the ability to form lipophilic hydrogen bonds.[9]

Intrigued by these reports [Scheme 1, a)] we wondered about other substrates to be difluoromethylated. In this context, the recently published electrophilic trifluoromethylation of hydroxylamines by Togni [Scheme 1, b)][10] attracted our attention, and we decided to study the formation of analogous difluoromethylated products [Scheme 1, c)].

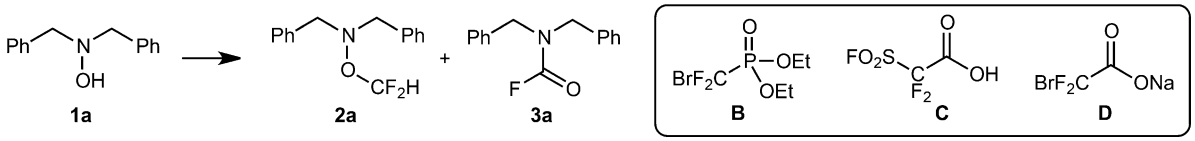
N,N-Dibenzylhydroxylamine (**1a**) was chosen as representative substrate and subjected to typical difluoromethyl etherification procedures (Table 1). First, the conditions described by Segall[5a] were tested, using diethyl bromodifluoromethanephosphonate (**B**) as the carbene precursor and potassium hydroxide as the base in a mixture of acetonitrile and water. Indeed, after one hour of reaction time while warming from −78 °C to room temperature the desired product **2a** was formed in 26% yield, as determined by ^{19}F NMR (Table 1, entry 1). Unfortunately however, isolation by column chromatography failed due to formation of a second, unexpected product which could not be separated. This by-product was identified as carbamic fluoride **3a**.

Carbamoyl fluorides are interesting compounds in their own right. As such they have been applied as insecticides[11] and inhibitors of esterases.[12] Furthermore, they were used in syntheses of isocyanates[13]



Scheme 1. Background and initial aim of this study.

Table 1. Initial screening of typical difluoromethyl etherification procedures.[a]



Entry	Reagent (equiv.)	t [h]	T [°C]	Solvent	Base (equiv.)	Yield of **2a** [%]	Yield of **3a** [%]
1	**B** (2)	1	−78 to r.t.	MeCN:H_2O = 1:1	KOH (20)	26[b]	25[b]
2	**C** (1)	3	60	MeCN	NaH (7.5)	0	21
3	**C** (0.33)	1	45	MeCN	Na_2SO_4 (2)	0	32
4	**D** (2)	1.5	95	DMF	K_2CO_3 (2)	0	46

[a] Performed on a 0.25 mmol scale with respect to *N,N*-dibenzylhydroxylamine (**1a**).
[b] Determined by ^{19}F NMR after column chromatography.

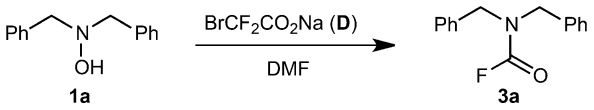
and *N,N*-dialkylaminosulfenyl carbamate-based insecticides.[14] Usually, carbamoyl fluorides are prepared from amines with fluorophosgene[11,13,15] or carbonic fluoride chloride.[15,16] Another possibility is the reaction of a fluoride source with carbamoyl chlorides,[17] which are accessed from phosgene or triphosgene. All these transformations involve highly toxic (gaseous) reagents which makes their handling difficult. Hence, the synthesis of carbamoyl fluorides *via* difluorocarbenes offers an attractive alternative.

To our delight, when applying difluoro(fluorosulfonyl)acetic acid (**C**) under the conditions reported by Marcor,[18] carbamic fluoride **3a** was selectively formed, albeit only in 21% yield (Table 1, entry 2). Applying the same reagent (**C**) under Wu's conditions,[5b] which involved performing the reaction at 45 °C instead of 60 °C and adding sodium sulfate instead of sodium hydride (entry 3), raised the yield of **3a** to 32%.[5b] With a combination of sodium bromodifluoroacetate (**D**) and potassium carbonate in dimethylformamide at 95 °C[5c] **3a** was obtained in 46% yield (entry 4).

Considering the difficulties in the purification of **2a** and having achieved an interesting result by obtaining **3a** from sodium bromodifluoroacetate (**D**), we decided to change direction and to focus our attention on the synthesis of the latter product type. The respective experiments are discussed herein. Moreover, computational studies were performed with the goal to shine light on the underlying mechanistic principles of the unprecedented formation of carbamic fluoride **3a** *via* difluorocarbene.

Initial optimization attempts to increase the yield by extending the reaction time (Table 2, entry 2) or by switching to another solvent (see the Supporting Information, Table S1) remained unsuccessful. Advantageously, the base was not necessary for the formation of the product (entry 3). Furthermore, the reagent concentration played a crucial role (entries 4–6). While the use of less solvent led to a decrease in the yield of **3a** (34%; entry 4), the product amount increased to 67% in a more diluted system (entry 6). Although no defined side products were identified at this stage, the observed concentration effects were attributed to follow-up reactions between product and starting material, which were less productive in dilute solution. Also the temperature affected the reaction outcome (entries 7–9). Both higher and lower temperatures led to a decrease in yield of **3a**. To our surprise, however, the product could be isolated at room temperature, albeit in only moderate yield (43%, entry 9). Apparently, the decarboxylation of sodium bromodifluoroacetate to give difluorocarbene occurred even at ambient temperature,[5c,19] but then the subsequent trapping of the carbene with **1a** was insufficient under these conditions.

Table 2. Reaction optimization.[a]

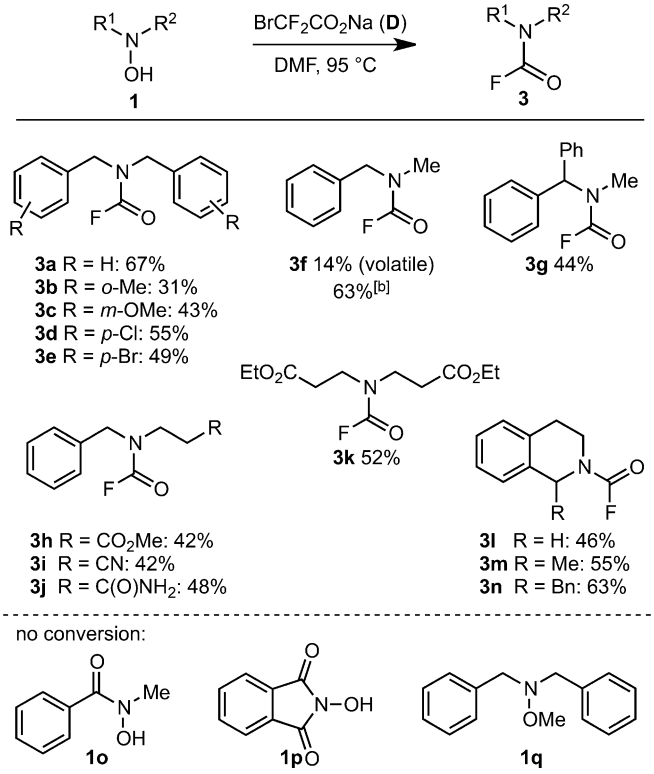


Entry	V_{DMF} [mL]	T [°C]	t [h]	Yield [%]
1[b]	2	95	1.5	46
2[b]	2	95	3	44
3	2	95	1.5	44
4	1	95	1.5	34
5	4	95	1.5	56
6	**8**	**95**	**1.5**	**67**
7	8	150	1.5	51
8	8	60	1.5	57
9	8	r.t.	1.5	43

[a] *Reaction conditions:* *N,N*-dibenzylhydroxylamine (**1a**, 0.25 mmol) and $BrCF_2CO_2Na$ (**D**, 0.50 mmol) in DMF.
[b] Addition of K_2CO_3 (2 equiv.).

With the optimized conditions in hand, the substrate scope was investigated (Table 3). First, other symmetrical *N,N*-dibenzylhydroxylamines were tested. *ortho*-Methyl- and *meta*-methoxy-substituted derivatives **1b** and **1c** provided the corresponding

Table 3. Synthesis of carbamoyl fluorides **3** from hydroxylamines **1** and sodium bromdifluoroacetate (**D**).[a]

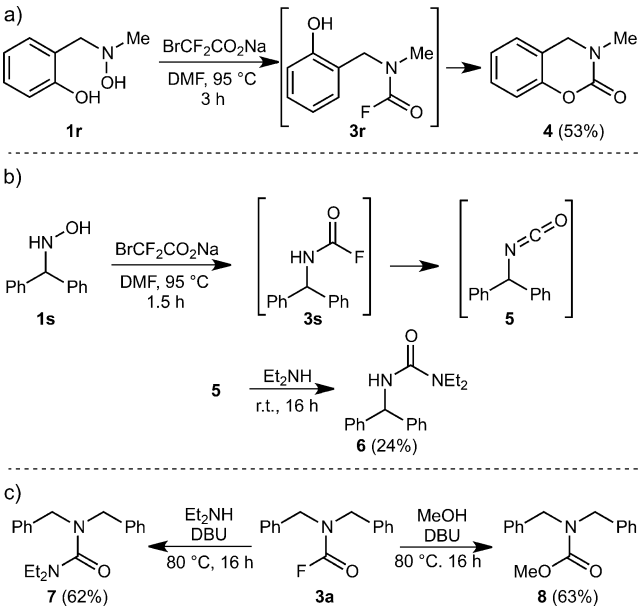


[a] *Reaction conditions:* hydroxylamine (**1**, 0.25 mmol), $BrCF_2CO_2Na$ (**D**, 0.50 mmol) in DMF (8 mL).
[b] Determined by ^{19}F NMR using trifluoroethanol as standard.

products in yields of 31% (for **3b**) and 43% (for **3c**), respectively. Substrates **1d** and **1e** with halo substituents in *para* positions reacted better leading to yields of 55% for **3d** and 49% for **3e**. Unsymmetrical benzylmethylcarbamic fluoride (**3f**) was isolated in only 14% yield, which we attributed to the high volatility of **3f** resulting in product loss during work-up. This hypothesis was confirmed by ^{19}F NMR spectroscopy of the crude reaction mixture, which indicated the formation of **3f** in *ca.* 63% yield. Increasing the size of the benzyl substituent of the hydroxylamine affected the reaction efficiency, and benzhydryl-substituted product **3g** was obtained in 44% yield. Various functional groups were tolerated as reflected by the good results (up to 52% yield) achieved with carbonylic hydroxylamine derivatives leading to carbamic fluorides **3h–k** as products. Finally, cyclic *N*-hydroxytetrahydroisoquinolines were applied. These substrates, which are of interest as they resemble natural alkaloid motifs, provided the corresponding products (**3l–n**) in yields ranging from 46% to 63%.

Attempts to convert hydroxylamines **1o** or **1p** bearing a carbonyl function in the α-position afforded only traces of products. These negative results were relevant for the mechanistic interpretation of the data because they revealed the requirement of a substrate nitrogen with a good nucleophilicity, which was reduced in compounds **1o** and **1p** by electron lone pair delocalization. Also methyl ether **1q** did not react, confirming the importance of the free OH group of the hydroxylamines for the success of the product formation.

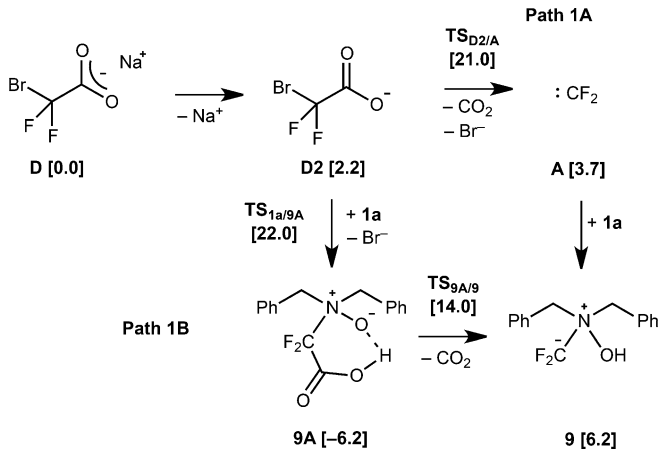
Additional experiments demonstrated the synthetic utility of the reaction products. An *in situ* functionalization occurred in the reaction of *ortho*-hydroxy-substituted substrate **1r** and dihydro-1,3-benzoxazin-2-one **4** was obtained in 53% yield [Scheme 2, a)]. Primary hydroxylamine **1s** underwent two sequential hydrogen fluoride eliminations giving *in situ* isocyanate **5**, which could be trapped with diethylamine to give urea **6** [Scheme 2, b)]. Finally, carbamoyl fluoride **3a** reacted with diethylamine and methanol in the presence of DBU providing urea **7** and carbamate **8**, respectively [Scheme 2, c)].



Scheme 2. *In situ* functionalization and product derivatization experiments.

To gain a better understanding of the reaction principle, the mechanism was investigated with computational methods. *N,N*-Dibenzylhydroxylamine (**1a**) was chosen as the model substrate for our study.

First, the generation of difluorocarbene (**A**) from sodium bromodifluoroacetate (**D**) under formation of carbon dioxide and sodium bromide was studied.[19] Results of Hine suggested that the decomposition of the related sodium chlorodifluoroacetate occurred in a single step from the corresponding anion.[20] Our DFT calculations on the decarboxylation process revealed a concerted reaction of bromodifluoroacetate



Scheme 3. Formation of **9** from sodium bromodifluoroacetate (**D**) and *N,N*-dibenzylhydroxylamine (**1a**) (relative free energies to **D** and **1a** in kcal mol^{-1}).

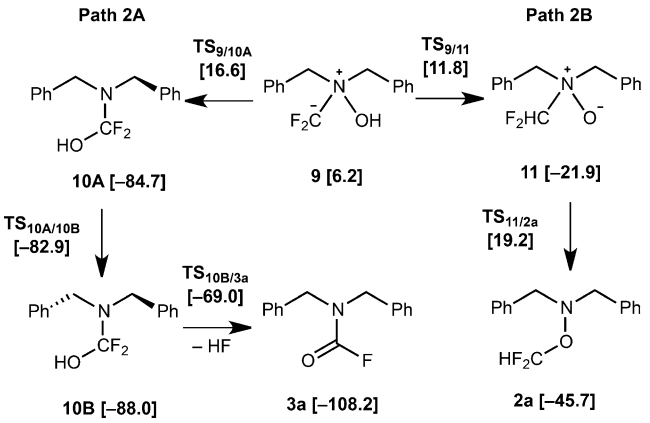
(**D**) to difluorocarbene (**A**) (Scheme 3, Path 1A). The barrier for this reaction (**TS$_{D2/A}$**) was 21.0 kcal mol^{-1}. The generation of **A** was slightly endergonic with a free energy difference of 3.7 kcal mol^{-1}.[21] Other trihaloacetates have been reported to decarboxylate to give trihalomethyl anions (CX_3^-).[22] These anions could then either be protonated to the corresponding haloform CX_3H,[23] or they eliminated halide to form the corresponding dihalocarbene. In this respect, our results remained inconclusive and we could not unequivocally determine whether the process involved difluorocarbene (**A**) and bromide or a bromodifluoromethyl anion ($BrCF_2^-$, **A2**). We performed an IRC calculation of the corresponding transition state **TS$_{D2/A}$**. The last calculated point on the reaction coordinate showed a bromide carbon distance of 2.55 Å. This was shorter than the corresponding distance in the optimized structure of **A2** (2.64 Å). However, the dissociation of **A2** to **A** and bromide is driven by entropy. Increasing the distance in **A2** monotonically raised the electronic energy of the structure until the energy of the separated fragments was reached (see the Supporting Information for details). Nevertheless, the Gibbs free energy of the dissociated difluorocarbene was 7.1 kcal mol^{-1} lower. Therefore, we concluded that the elimination of bromide occurred at a certain bromide–carbon distance. Moreover, **A2** could even be unstable at any bromide–carbon distance. Within the approximations of the computational method it was not possible to finally clarify this issue. Regardless of the primary product of the decomposition of reagent **D**, our results indicated that difluorocarbene (**A**) could be formed, then becoming an active species in the reaction with the hydroxylamines.

We also considered the decarboxylation from sodium bromodifluoroacetate (**D**) with concerted formation of sodium bromide. However, this pathway was found to be disfavored (see the Supporting Information for details).

The barrier of 21.0 kcal mol^{-1} for the decarboxylation of **D** was rather high considering the fact that the reaction also took place at room temperature (Table 2, entry 9). Xiao and co-workers reported that, contrary to prior postulations, difluorocarbene was not the active species in the generation of difluoromethylphosphorane Wittig reagents from bromodifluoroacetate (**D**) with phosphines.[7b] Instead, they described a substrate-assisted decomposition of the reagent which decarboxylated only after addition to the phosphine. Thus, we also questioned the involvement of difluorocarbene (CF_2, **A**) in our reaction, and investigated the nucleophilic attack of the substrate at the reagent in analogy to the substrate-assisted pathway of Xiao (Scheme 3, Path 1B). The attack of **1a** at **D2** resulted in elimination of bromide and the formation of **9A** (**TS$_{1a/9A}$**). As indicated by IRC calculations, the reaction proceeded with a concerted proton transfer from the hydroxylamine to the carboxyl group of the reagent. The relative free energy of **TS$_{1a/9A}$** of this substrate-assisted decomposition pathway was 22.0 kcal mol^{-1} relative to **D**. Although this indicated that the formation of difluorocarbene was favored, it has to be noted that the energy difference between the transition states for both decomposition pathways (**TS$_{D2/A}$** and **TS$_{1a/9A}$**) was rather small (1.0 kcal mol^{-1}). In any case, both pathways gave then rise to the same zwitterionic structure **9**. The transition state for the decarboxylation of **9A** to **9** (**TS$_{9A/9}$**) had a relative energy of 14.0 kcal mol^{-1}. In this step, the hydroxy group was regenerated through a proton transfer from the carboxyl group as shown by IRC calculations. Alternatively, the addition of difluorocarbene (**A**) to **1a**, forming **9**, was endergonic with a free energy difference of 2.5 kcal mol^{-1} to the separated molecules **1a** and **A**. A transition state for the reaction of **1a** with **A** could not be obtained since the electronic energy is strictly decreasing from the separated molecules to **9**.

Next, the formation of the carbamoyl fluorides (Scheme 4, Path 2A) was investigated. Migration of the hydroxy group to the difluoromethylide moiety gave alcohol **10** (**TS$_{9/10A}$**, Figure 1). This rearrangement step had a barrier of 16.6 kcal mol^{-1} to **1a** and was strongly exergonic with a free energy difference of −84.7 kcal mol^{-1} for **10** to **1a**. After a conformational rearrangement (**TS$_{10A/10B}$**) with a low barrier, the elimination of hydrogen fluoride resulted in the experimentally observed carbamoyl fluoride **3a**. The transition state **TS$_{10B/3a}$** had a free energy difference of −69.0 kcal mol^{-1} to **1a** and 19.0 kcal mol^{-1} to the intermediate **10**.

Experimentally, the formation of the carbamoyl fluorides was found to be favored over the etherification when reagents **C** or **D** were used. Hence, the calculat-



Scheme 4. Reaction pathway from *N,N*-dibenzylhydroxylamine (**1a**) to carbamoyl fluoride **3a** (Path 2A) and difluoromethyl ether **2a** (Path 2B) (free energies to **D** and **1a** in kcal mol^{-1}).

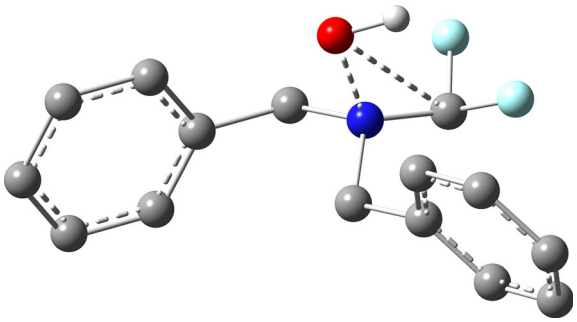


Figure 1. Transition state for the migration of the hydroxy group ($\mathbf{TS_{9/10A}}$); hydrogen atoms are omitted for clarity.

ed pathway to give the former products should be lower in energy than the one leading to difluoromethyl ether **2a**. In the calculated reaction pathway towards **2a** (Scheme 4, Path 2B) the zwitterionic intermediate **9** could isomerize through a proton transfer step to give **11**. In this structure the difluoromethyl group of the product **2a** was already shaped. The proton transfer step ($\mathbf{TS_{9/11}}$) had a barrier of only 11.8 kcal mol^{-1} relative to **1a**, which was lower than the rearrangement from **9** to **10A**. Furthermore, **11** was thermodynamically favored over **9**, since the negative charge at the oxygen atom was more stable. Nevertheless, the migration of the difluoromethyl group to the oxygen ($\mathbf{TS_{11/2a}}$, Figure 2) had a barrier of 19.2 kcal mol^{-1} compared to **1a**. Hence, this step was disfavored over the rearrangement of **9** to **10A**. Furthermore, the conversion of **9** to **11** should be reversible. In contrast, the reaction to **10A** was irreversible, since the back-reaction from **10A** had a barrier of 101.3 kcal mol^{-1}.

The intramolecular attack of the oxygen to the difluoromethyl group in **11** and step-wise elimination of hydrogen fluoride was found to be non-competitive to Path 2A (see the Supporting Information for details).

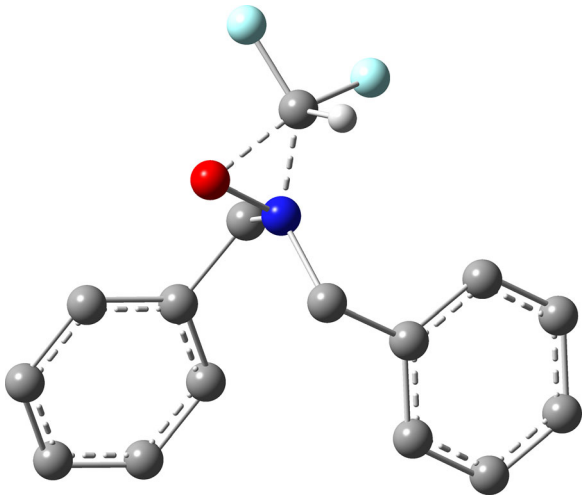


Figure 2. Transition state for the migration of the difluoromethyl group ($\mathbf{TS_{11/2a}}$); hydrogen atoms are omitted for clarity.

Segall and co-workers proposed that the formation of difluoromethyl ethers with **B** occurred through addition of difluorocarbene to the deprotonated hydroxy group.[5a] This pathway was not relevant for our system since no strong base for the deprotonation was present.

The described pathways rationalized the formation of the carbamoyl fluorides instead of the expected difluoromethyl ethers from hydroxylamines with sodium bromodifluoroacetate (**D**). Nonetheless, they could not account for the mixture of carbamoyl fluorides and difluoromethyl ethers obtained with diethyl bromodifluoromethanephosponate (**B**). The selectivity of this reaction might have been shifted due to the strong base or the complex solvent mixture.

In summary, we have investigated and rationalized an unprecedented reactivity of difluorocarbenes with hydroxylamines towards carbamoyl fluorides both experimentally and computationally. Preparatively, the new method is interesting because it involves the use of readily accessible starting materials and the nontoxic and cheap reagent **D**, which react rapidly under experimentally straightforward conditions. Various hydroxylamines were applicable forming the products in moderate to good yields. Subsequent (*in situ*) product derivatizations provide heterocycles, carbamates, and ureas.

Experimental Section

Computational Details

All quantum chemical calculations were performed with the *Gaussian 09* suite[24] at the HPC facilities of the IT Center of RWTH Aachen University. Geometry optimizations were

performed with the ωB97XD long range corrected hybrid density functional of Head–Gordon.[25] with Dunning's correlation consistent double-ζ basis set cc-pVDZ.[26] The convergence criteria were increased using the keyword "tight". Numerical integrations were performed with the "ultrafine" grid option of *Gaussian 09*. Single-point calculations were done with the correlation consistent cc-pVTZ triple-ζ basis set of Dunning and a polarizable continuum solvation model (PCM) for *N*,*N*-dimethylformamide (DMF) as implemented in *Gaussian 09*. Gibbs free energies were calculated at a temperature of 298.15 K. A standard state correction for a 1 M ideal solution was added to the energy of each structure. Minima and transition states were confirmed with normal mode analysis. The transition states were connected to the corresponding intermediates with IRC calculations (see the Supporting Information for details on the IRC calculations).

General Procedure for the Synthesis of Carbamoyl fluorides from Hydroxylamines

A solution of hydroxylamine **1** (0.25 mmol) and sodium bromodifluoroacetate (**D**, 98 mg, 0.50 mmol) in DMF (8 mL) was stirred under argon at 95 °C for 90 min. Then, water (10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. The product was purified by column chromatography.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft through the International Research Training Group Seleca (IGRK 1628). We thank Prof. Dr. P. Kirsch (Merck KGaA) for encouragement and helpful discussions.

References

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd edn., Wiley-VCH, Weinheim, **2013**; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; e) I. Ojima, *J. Org. Chem.* **2013**, *78*, 6358–6383; f) S. Altomonte, M. Zanda, *J. Fluorine Chem.* **2012**, *143*, 57–93; g) *Fluorine in Medicinal Chemistry and Chemical Biology*; (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**; h) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; i) S. Pursur, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; j) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; k) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29; l) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

[2] For reviews, see: a) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842–863; b) W. R. Dolbier, M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071–1098; c) M. Fedorynski, *Chem. Rev.* **2003**, *103*, 1099–1132; d) D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585–1632.

[3] For selected recent examples, see: a) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier, *Nat. Chem.* **2013**, *5*, 941–944; b) J. Zheng, J.-H. Lin, X. Y. Deng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 532–535.

[4] For selected examples, see a) S. Okusu, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 3802–3805; b) W. Zhang, F. Wang, J. Hu, *Org. Lett.* **2009**, *11*, 2109–2112; corrigendum: *Org. Lett.* **2013**, *15*, 5613.

[5] For selected examples, see a) Y. Zafrani, G. Sod-Moriah, Y. Segall, *Tetrahedron* **2009**, *65*, 5278–5283; b) Q.-Y. Chen, S.-W. Wu, *J. Fluorine Chem.* **1989**, *44*, 433–440; c) V. P. Mehta, M. F. Greaney, *Org. Lett.* **2013**, *15*, 5036–5039; d) L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem.* **2013**, *125*, 12616–12620; *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394; e) G. K. S. Prakash, S. Krishnamoorthy, S. K. Ganesh, A. Kulkarni, R. Haiges, G. A. Olah, *Org. Lett.* **2014**, *16*, 54–57; f) X.-Y. Deng, J.-H. Lin, J. Zheng, J.-C. Xiao, *Chem. Commun.* **2015**, *51*, 8805–8808.

[6] For a selected example, see: a) K. Oshiro, Y. Morimoto, H. Amii, *Synthesis* **2010**, 2080–2084; b) Y. Kageshima, C. Suzuki, K. Oshiro, H. Amii, *Synlett* **2015**, *26*, 63–66.

[7] For selected recent examples, see: a) J. Zheng, J.-H. Lin, L.-Y. Yu, Y. Wei, X. Zheng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 6150–6153; b) J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, *Chem. Commun.* **2013**, *49*, 7513–7515; c) M. Hu, Z. He, B. Gao, L. Li, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 17302–17305.

[8] a) D. J. Harrison, G. M. Lee, M. C. Leclerc, I. Korobkov, R. T. Baker, *J. Am. Chem. Soc.* **2013**, *135*, 18296–18299; b) G. M. Lee, D. J. Harrison, I. Korobkov, R. T. Baker, *Chem. Commun.* **2014**, *50*, 1128.

[9] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 742–767; b) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

[10] V. Matousek, E. Pietrasiak, L. Sigrist, B. Czarniecki, A. Togni, *Eur. J. Org. Chem.* **2014**, 3087–3092.

[11] J. Ehrenfreund, Eur. Pat. Appl. EP 238445, **1987**.

[12] a) J. Bieth, S. M. Vratsanos, N. H. Wassermann, A. G. Cooper, B. F. Erlanger, *Biochemistry* **1973**, *12*, 3023–3027; b) I. B. Wilson, M. A. Hatch, S. Ginsburg, *J. Biol. Chem.* **1960**, *235*, 2312–2315; c) D. K. Myers, *Biol. Chem. J.* **1956**, *62*, 556–563.

[13] H. Quan, N. Zhang, X. Zhou, H. Qian, A. Sekiya, *J. Fluorine Chem.* **2015**, *176*, 26–30.

[14] C. E. Hatch, *J. Org. Chem.* **1978**, *43*, 3953–3957.

[15] a) H. J. Emeleus, J. F. Wood, *J. Chem. Soc.* **1948**, 2183–2188; b) F. S. Fawcett, C. W. Tullock, D. D. Coffman, *J. Am. Chem. Soc.* **1962**, *84*, 4275–4285.

[16] A. Haas, T. Maciej, *Z. anorg. allg. Chem.* **1985**, *524*, 33–39.

[17] a) B. Baasner, H. Hagemann, E. Klauke *Eur. Pat. Appl.* EP 052842, **1981**; b) C. K. Rao, S. K. Arora, R. Grover, J. A. Durden, T. D. J. D'Silva, Eur. Pat. Appl. EP 136147, **1984**; c) P. Svec, A. Eisner, L. Kolárová, T. Weidlich, V. Pejchal, A. Ruzicka, *Tetrahedron Lett.* **2008**, *49*, 6320–6323.

[18] R. A. Hartz, V. T. Ahuja, W. D. Schmitz, T. F. Molski, G. K. Mattson, N. J. Lodge, J. J. Bronson, J. E. Macor, *Biorg Med. Lett.* **2010**, *20*, 1890–1894.
[19] For a comparison of $BrCF_2CO_2Na$ and $ClCF_2CO_2Na$, see: K. Oshiro, Y. Morimoto, H. Amii, *Synthesis* **2010**, 2080–2084.
[20] J. Hine, D. C. Duffey, *J. Am. Chem. Soc.* **1959**, *81*, 1131–1136.
[21] Carbene **A** was treated in the singlet state, since calculations on the uωB97XD/cc-pVDZ) level showed an energy difference of $\Delta E = 35.4\ kcal\,mol^{-1}$ to the triplet state.
[22] a) F. H. Verhoek, *J. Am. Chem. Soc.* **1934**, *56*, 571–577; b) R. A. Fairclough, *J. Chem. Soc.* **1938**, 1186–1190; c) L. H. Sutherland, J. G. Aston, *J. Am. Chem. Soc.* **1939**, *61*, 241–244; d) I. Auerbach, F. H. Verhoek, A. L. Henne, *J. Am. Chem. Soc.* **1950**, *72*, 299–300.
[23] J. Hine, N. W. Burske, M. Hine, P. B. Langford, *J. Am. Chem. Soc.* **1957**, *79*, 1406–1412.
[24] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford, CT, **2009**.
[25] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[26] T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007–1023.