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Synthesis of 3-Substituted 2-Fluoro- and 2,2-Difluoroaziridines

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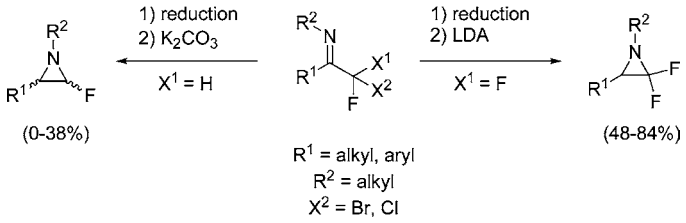
ABSTRACT



A new route for the synthesis of stable 3-alkyl- and 3-aryl-2(,2)-(di)fluoroaziridines was developed by hydride reduction of novel α-bromo- and α-chloro-α(,α)-(di)fluoroketimines and subsequent ring closure of *β*-fluorinated *β*-chloro- and *β*-bromoamines. This is the first report on the synthesis of 2,2-difluoroaziridines sensu stricto.

Fluorinated heterocyclic compounds have become increasingly important in pharmaceutical chemistry, and hence numerous synthetic methods are being developed to incorporate the smallest and most electronegative halogen in organic compounds.[1] In addition, the effects of fluorine as a substituent in organic compounds on chemical reactivity and stability are worth exploring to gain a more profound insight into fluorine chemistry. Our interest was drawn to α-fluorinated imines, which constitute a promising class of building blocks for the synthesis of fluorinated heterocycles.[2] In that respect, efforts were made to use α-fluoroimines to synthesize fluorinated aziridines. Although these peculiar compounds could serve as useful starting materials for further organic transformations, fluorinated aziridines have received only very limited attention in the literature. 2,2-Difluoroaziridines have previously not been synthesized at all, apart from some perfluorinated and trifluoromethylated aziridines, which are prepared via carbene or nitrene cycloaddition reactions to specific imines or olefins.[3] There are only a few reports in the literature on the synthesis of monofluorinated aziridines, most of which deal with fluorocarbene cycloadditions to imines.[4] In the present report, a new approach to synthesize fluorinated aziridines was developed, based on reduction of the appropriate novel α-fluorinated α-bromo- and α-chloroketimines and cyclization via intramolecular substitution of the resulting *β*-bromo- and *β*-chloroamines.

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(1) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (b) Baasner, B.; Hageman, H.; Tatlow, J. C. Organo-Fluorine Compounds. In *Houben-Weyl Methods of Organic Chemistry*, E10a-c, additional and supplementary vol. to the 4th ed.; Georg Thieme-Verlag, Stuttgart: New York, 1999; Vol. E10a-c. (c) Olah, G. A.; Chambers, R. D.; Prakash, G. K. Surya. *Synthetic Fluorine Chemistry*; John Wiley & Sons: New York, 1992. (d) Curran, D. P.; Mikami, K.; Soloshonok, V. A. (Guest Eds.) *J. Fluorine. Chem.* **2006**, *127*, 456.

(2) Verniest, G.; Van Hende, E.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 4767.

(3) (a) Zeifman, Y. V.; Ter-Gabrielyan, E. G.; Gambaryan, N. P.; Knunyants, I. L. *Russ. Chem. Rev.* **1984**, *53*, 256. (b) Lork, A.; Gard, G.; Hare, M.; Mews, R.; Stohrer, W. D.; Winter, R. *J. Chem. Soc., Chem. Commun.* **1992**, *12*, 898. (c) Krespan, C. G. *J. Org. Chem.* **1986**, *51*, 332. (d) Petrov, V. A. *J. Fluorine Chem.* **2000**, *106*, 25. (e) Logothetis, A. L. *J. Org. Chem.* **1964**, *29*, 3049. (f) Carpenter, W. R.; Haymaker, A.; Moore, D. W. *J. Org. Chem.* **1966**, *31*, 789.

(4) (a) Khlebnikov, A. F.; Novikov, M. S.; Shinkevich, E. Y.; Vidovic, D. *Org. Biomol. Chem.* **2005**, *3*, 4040. (b) Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Tetrahedron Lett.* **2005**, *46*, 8337. (c) Usuki, Y.; Fukuda, Y.; Ilo, H. *ITE Lett. Batteries, New Technol. Med.* **2001**, *2*, 237. (d) Seyferth, D.; Woodruff, R. A. *J. Org. Chem.* **1973**, *38*, 4031. (e) Yamanaka, H.; Kikui, J.; Teramura, K.; Ando, T. *J. Org. Chem.* **1976**, *41*, 3794. (f) Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F. *Russ. J. Org. Chem.* **2007**, *43*, 286.

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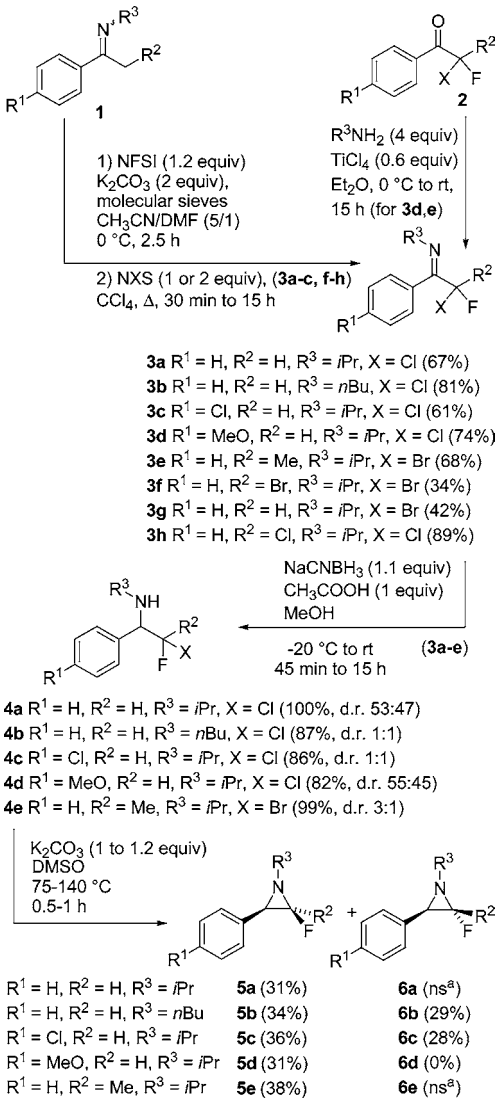
Having in hand a new method to synthesize α-fluorinated imines via electrophilic fluorination of imines using NFSI,[2] efforts were made to use these compounds for further α-functionalization. Therefore, *N*-(2-fluoro-1-phenylethylidene)-isopropylamine was treated with NCS in refluxing CCl_4 yielding (*E*)-*N*-(2-chloro-2-fluoro-1-phenylethylidene)isopropylamine **3a** or (*E*)-*N*-(2,2-dichloro-2-fluoro-1-phenylethylidene)isopropylamine **3h**, depending on whether one or two equivalents of halogenating agent were used (Scheme 1). The same strategy led to the formation of α-brominated imines **3g** and **3f** by the use of NBS in CCl_4. Because the α-chlorination proceeded in higher yield as compared to the α-bromination, further elaboration of the reactivity was predominantly performed using α-chloro-α-fluoroimines. The ease of α-chlorination of α-fluoroimines is in sharp contrast with the difficulties which were observed to chlorinate α-fluoroacetophenone. α-Chlorination only occurred when α-fluoroacetophenone was treated with a large excess of chlorine gas in acetic acid at 80 °C for 20 h yielding 95% α-chloro-α-fluoroacetophenone. Bromination of α-fluoroacetophenone using bromine and aluminum(III) chloride yielded α-bromo-α-fluoroacetophenone, as reported in the literature,[5] but in this case, subsequent imine formation with isopropylamine in the presence of titanium(IV) chloride to obtain the corresponding α-bromo-α-fluoroimine failed. However, the latter imine condensation protocol with titanium(IV) chloride proved successful in the synthesis of (*E*)-*N*-(2-bromo-2-fluoro-1-phenylpropylidene)isopropylamine **3e**[6] and (*E*)-*N*-(2-chloro-2-fluoro-1-(4-methoxyphenyl)ethylidene)isopropylamine **3d**, starting from the corresponding ketones **2** (R^1 = MeO, H; R^2 = H, Me; X = Cl, Br).

Scheme 1



[a] ns = not separable from the *cis*-isomer via flash chromatography.

The obtained novel α-bromo- and α-chloro-α-fluoroimines **3a**−**e** were reduced using sodium cyanoborohydride in methanol resulting in stable *β*,*β*-dihalogenated amines **4a**−**e**, although as a mixture of both diastereomers. Attempts to increase the diastereomeric excess by adding Lewis acids, such as LiCl, $TiCl_4$, or $ZnCl_2$ instead of acetic acid to induce a complexation between the metal and the halogen (Cl or F), gave no significant improvement of the diastereomeric excess, even when the reaction was performed at −78 °C.

Using α-bromoimine **3e**, the reduction had to be carefully controlled at −20 °C for 45 min to obtain a 3:1 mixture of diastereomers **4e**. Treatment of *β*-chloro- and *β*-bromo-*β*-fluoroamines **4a**−**e** with K_2CO_3 in DMSO at 75−140 °C gave rise to new 2-fluoroaziridines **5a**−**e** and **6a**−**e**.

In some cases, the *cis*- and *trans*-isomers could be separated via flash chromatography on silica gel. It was observed that *trans*-aziridines **6** were not as stable on silica gel as the *cis*-analogues **5**, giving rise to purification problems during chromatography. This observation is analogous to non-fluorinated 2-methyl-3-phenylaziridines, where the *cis*-isomer is also the most stable.[6,7]

The stereochemical assignment of the two isomers **5a**−**d** and **6a**−**d** was based on the vicinal H,H- and H,F-coupling constants in ^{1}H NMR. No conclusions could be drawn from NOE analysis results. In the case of *cis*-aziridine **5a**, a vicinal H,H-coupling of 4.4 Hz and a vicinal H,F-coupling of 2.5 Hz were measured, whereas the *trans*-isomer **6a** gave coupling constants of 0 and 6.1 Hz, respectively. The same difference in H,F-coupling (3.3 and 9.1 Hz) was found in the ^{1}H NMR spectrum of aziridines **5e** and **6e**, which provided a clear discrimination of both isomers and is in accordance with literature data of other *cis*- and *trans*-substituted fluoroaziridines.[4c]

Encouraged by the results described above, α-chloro-α,α-difluoroimines **9a**−**d** were used as substrates for the synthesis of 3-substituted 2,2-difluoroaziridines **12**, a virtually new class of compounds. Because α,α-difluoroacetophenone

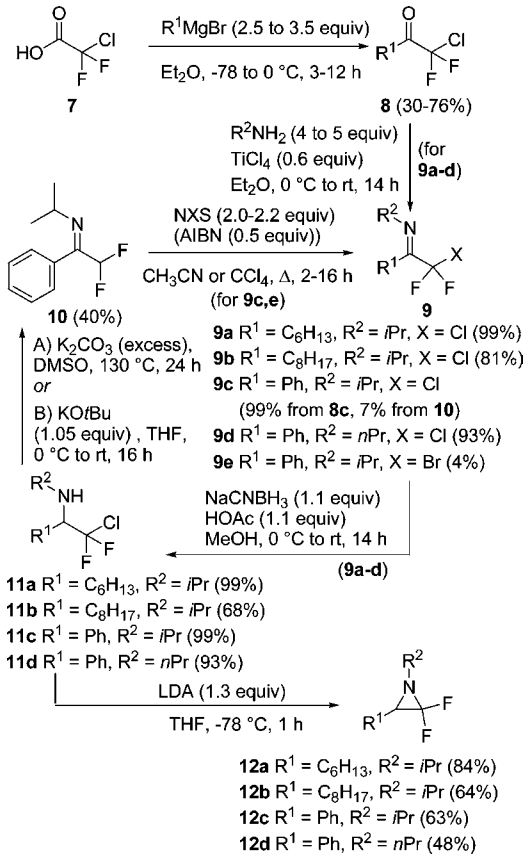
(5) Bergmann, F.; Kalmus, A.; Vromen, S. *J. Am. Chem. Soc.* **1955**, *77*, 2494.

(6) Synthesis of ketone **2e**: De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Tetrahedron Lett.* **1980**, *21*, 2257.

(7) (a) Taguchi, T.; Kojima, M. *Chem. Pharm. Bull.* **1959**, *7*, 103. (b) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185. (c) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1980**, *45*, 5319.

could not be α-chlorinated nor α-brominated and the α-halogenation of its *N*-isopropylimine **10** turned out to be extremely difficult (yield 4−7%), the corresponding α-chloro-α,α-difluoroketones **8**[8] were synthesized from α-chloro-α,α-difluoroacetic acid **7**.[9] These α-chloro-α,α-difluoroketones **8** were subsequently treated with primary amines in the presence of titanium(IV) chloride (Scheme 2) yielding imines

Scheme 2



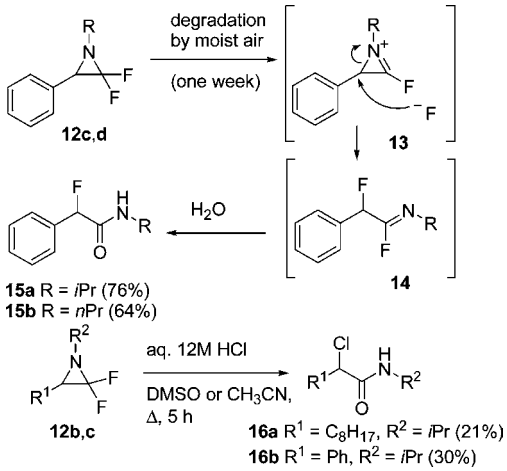
9a−**d**. The compounds were reduced with sodium cyanoborohydride in methanol in the presence of acetic acid toward the corresponding *β*,*β*,*β*-trihalogenated amines **11** in high yield. Subsequently, amine **11c** was treated with K_2CO_3 in DMSO, analogous to the synthetic procedure for monofluoroaziridines **5** and **6**. These reactions did not yield any difluoroaziridine **12c** but instead gave rise to difluoroimine **10** via a 1,2-dehydrochlorination and subsequent enamine−imine tautomerization. The same result was obtained when using KO*t*Bu in THF. Treatment of amines **11** with the more sterically hindered and stronger base LDA did not result in a 1,2-dehydrochlorination but gave 2,2-difluoroaziridines **12** in good yield. This is the first efficient synthesis of 2,2-difluoroaziridines described in the literature.

(8) (a) Simons, J. H.; Herman, D. F. *J. Am. Chem. Soc*. **1943**, *65*, 2064. (b) Kitazume, T.; Asai, M.; Tsukamoto, T.; Yamazaki, T. *J. Fluorine Chem.* **1992**, *56*, 271. (c) Yamana, M.; Ishihara, T.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 507.

(9) (a) Qiu, Z.-M.; Burton, D. J. *J. Org. Chem.* **1995**, *60*, 5570. (b) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 428.

It was observed that 3-alkyl-2,2-difluoroaziridines **12a**,**b** were significantly more stable on silica gel as compared to 2,2-difluoro-3-phenylaziridines **12c**,**d**, which tended to decompose upon purification by flash chromatography. Indeed, although both 3-alkyl- and 3-aryl-2,2-difluoroaziridines were stable for several days at room temperature, the degradation of 2,2-difluoroaziridines **12c**,**d** was observed even at low temperature (−20 °C). In the presence of moist air, a complete conversion toward α-fluoroamides **15** took place via expulsion of a fluoride anion by nitrogen, subsequent ring opening of the azirinium fluoride **13** by fluoride, and nucleophilic addition of water across the imidoyl fluoride **14**. 3-Alkyl-2,2-difluoroaziridines **12a**,**b** did not show this degradation but could be forced to undergo the same reaction pathway toward **16a** by treatment with aqueous HCl in DMSO. Analogous reaction conditions (aqueous HCl in CH_3CN) also converted 2,2-difluoro-3-phenylaziridine **12c** toward the corresponding α-chloroamide **16b** (Scheme 3).

Scheme 3



In conclusion, it can be stated that useful synthetic pathways were developed to access new 2-fluoro- and 2,2-difluoroaziridines starting from halogenated mono- and difluoroimines. It should be noted that, previously, no general method to synthesize difluoroaziridines was available. The obtained fluorinated aziridines were stable enough to isolate, characterize, and store for several days, which is promising for the further elaboration of these novel compounds.

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Supporting Information Available: General experimental conditions and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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