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Direct Electrophilic α-Fluorination of Imines: Efficient Synthesis of Mono- and Difluoroimines

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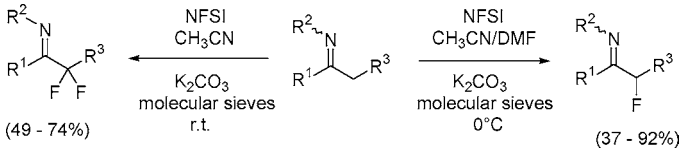
ABSTRACT



A mild and efficient procedure to synthesize α-fluoro- and α,α-difluoroimines was developed. Various *N*-alkylimines derived from acetophenones were successfully monofluorinated using NFSI (*N*-fluorobenzenesulfonimide) in a mixture of CH_3CN and DMF at 0 °C. Alternatively, the same procedure without DMF gave rise to difluorinated imines when performed at room temperature. The obtained α- and α,α-difluorinated imines were subsequently reduced to give the corresponding *β*-fluoro- and *β*,*β*-difluoroamines in good yield.

The growing interest in site-specific fluorinated compounds in medicinal and agricultural chemistry is a result of the undisputed biological importance of a fluorine substituent at relevant positions in bioactive compounds.[1,2] The presence of a fluorine atom alters the electronic distribution of the molecule drastically without major changes concerning the steric properties of the compound and, as a consequence, can lead to improved bioactivities.[3,4] In this regard, there exists an increasing demand for generally applicable fluorination methods, especially concerning the fluorination of ketones and imines as these building blocks play an important role in heterocyclic chemistry. In contrast to the significant number of methodologies to introduce fluorine next to ketones and aldehydes,[1,2,5−7] no fluorinated imines have been prepared via electrophilic fluorination of imines. Imines bearing one or two fluorine atoms at the α-position not only can be used directly in the synthesis of fluorinated azaheterocyclic compounds but also permit a mild and efficient synthesis of *β*-fluorinated amines, which are of interest in medicinal and agricultural chemistry.[1] Although enamines and enamides proved useful as intermediates in the synthesis

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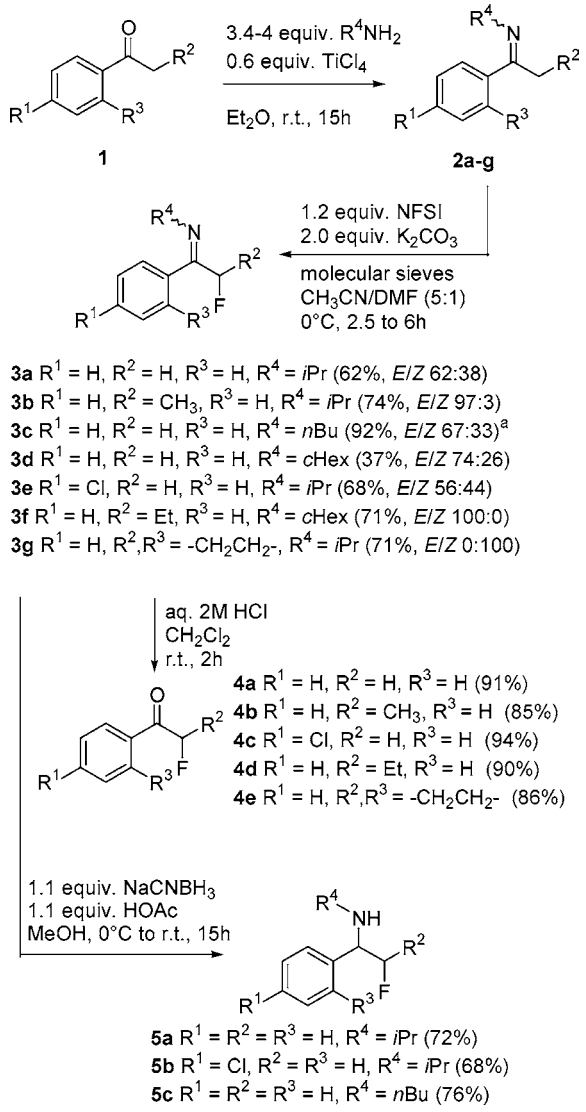
of α-fluorinated ketones,[8] only two publications report the electrophilic fluorination of imines, where it seemed impossible to prevent the formed imines from hydrolysis or to synthesize the corresponding monofluorinated ketones without simultaneous difluorination reactions.[9,10]

We developed here a mild and efficient procedure to synthesize and isolate either α-fluoroimines or α,α-difluoroimines via direct electrophilic fluorination of ketimines using *N*-fluorobenzenesulfonimide (NFSI), which is a commercially available, easy to use, and stable fluorinating reagent.

In contrast to the chlorination or bromination of ketones and imines, a direct fluorination seems not to be as straightforward, which makes the study of fluorination reactions still worthwhile. To develop a mild, efficient, and fast method to access α-fluorinated imines, efforts were performed using various starting ketimines, which were prepared from the parent ketones via known Dean Stark protocols or by the use of titanium(IV) chloride as an activating and dehydrating agent in the imination reactions.[11] To avoid problems of volatility and stability of the fluorinated imines, exploring reactions were performed using the *N*-isopropylimine of acetophenone **2a** (Scheme 1, $R^1 = R^2 = R^3 = H$; $R^4 = i$Pr). Initial attempts to fluorinate imine **2a** using *N*-fluoro-2,4,6-trimethylpyridinium triflate or 4-iodotoluene difluoride did not afford α-fluoro or α,α-difluoroimines. In contrast, when NFSI (*N*-fluorobenzenesulfonimide) or Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate) was used in reactions with *N*-(1-phenylethylidene)isopropylamine **2a** in acetonitrile, α-fluorination occurred albeit as mixtures of both monofluorinated and difluorinated imines **3a** and **9a** in varying ratios together with the corresponding ketones (due to hydrolysis). Because it was observed that NFSI reacted faster with imine **2a** as compared to Selectfluor, further reaction optimization was performed using NFSI as the reagent of choice. To avoid hydrolysis of the formed fluorinated imines, acetonitrile was dried over CaH_2 prior to use and potassium carbonate was added to the reaction mixture to exclude protonation of formed imines by in situ generated dibenzenesulfonimide. In addition, molecular sieves were added to the solvent containing 2 equiv of K_2CO_3 and 1.2 equiv of NFSI, and this mixture was stirred at 0 °C for 15 min, prior to the addition of the imine **2a**. It was found that when this reaction was performed at 0 °C almost no α,α-difluorination of imines **2** occurred. In addition, the use of DMF as a cosolvent to acetonitrile (ratio CH_3CN/DMF 5:1) apparently slowed the reaction, enabling a clean α-monofluorination of imines **2a**−**g** (Scheme 1).

Because of the fact that the best results were obtained with the use of 1.2 equiv of NFSI and 2 equivalents of K_2CO_3 in CH_3CN−DMF (ratio 5:1) in the presence of molecular sieves, the excess NFSI had to be removed after completion of the reaction. The NFSI removal was accomplished by reduction with potassium iodide (fast reaction) followed by an aqueous workup using sodium bisulfite. A direct reduction of NFSI with sodium bisulfite appeared to be too slow giving rise to hydrolysis products, i.e., monofluorinated ketones **4**. In an alternative workup procedure, an excess of triethylamine was added to the reaction mixture at 0 °C prior to standard aqueous workup using saturated brine. NFSI reacts very fast with Et_3N to yield compounds that are readily washed out and that do not interfere with the reaction products. Using the optimized reaction conditions, various aryl-substituted ketimines **2** were monofluorinated in high yields (Scheme 1). The obtained imines **3a**−**g** occurred as *E*- and *Z*-isomers in a ratio which varies depending on the steric properties of the substituents at nitrogen and at the 2-position (Scheme 1). Whereas the 2-unsubstituted *N*-isopropylimine of acetophenone occurs in an *E*/*Z* ratio of 91:9, the ratio of the 2-fluorinated derivative changes to 62:38

Scheme 1



[a] Not purified (purity 82%).

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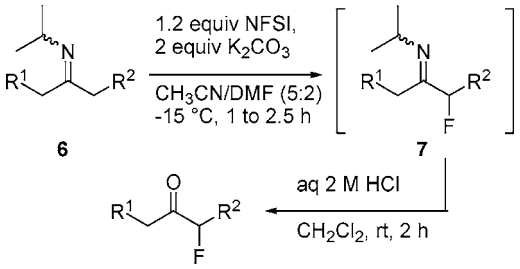
(comparable with the *E*/*Z* ratio of 56:44 of the 2-methyl substituted imine **2b**). When more sterically demanding substituents are present, e.g., in the case of imine **3b**[12] and **3f**, the *E*/*Z* ratio shifts toward 93:7 and 100:0, respectively. It is noteworthy that the *N*-isopropylimine of 2-fluoro-α-tetralone **3f** exclusively occurs in a *Z*-configuration, which was proven by ^{1}H NMR spectroscopy and NOE analysis. To determine the chemical shifts in ^{1}H NMR of both *E*- and *Z*-isomers of fluorinated imines **3**, an aromatic solvent induced shift (ASIS) experiment was performed on imine **3a** using deuterated benzene. An upfield shift of 0.56 ppm was observed for the CHF proton of the *Z*-isomer as compared to data obtained in $CDCl_3$ (whereas the same proton of the *E*-isomer shifted only 0.16 ppm). In addition, it was observed that the NCH proton of the *Z*-isomers of imines **3** showed a small J_{HF} coupling of 1.3−2.7 Hz, which can be explained by a through-space F,H-coupling (no such coupling was observed in the *E*-isomers). Through-space F,H-couplings can occur when a fluorine and a hydrogen substituent are close together spatially.[13]

The obtained α-fluorinated imines are obvious precursors for *β*-fluorinated amines, which are of importance in medicinal chemistry as building blocks for physiologically active compounds.[1] The reduction of imines **3** with sodium cyanoborohydride in methanol in the presence of acetic acid (1.1 equiv) yielded the corresponding new *β*-fluoroamines **5a**−**c** in excellent yield, although some loss of material was observed during flash chromatography on silica gel. In addition, a hydrolysis of the imino functionality of **3a**−**g** resulted in monofluoroketones **4a**−**e**[6i,8,14,15] in good yields. The same methodology for the fluorination of imines **2** was applied to aliphatic ketimines **6**, where a double fluorination at both the α- and the α′-position is plausible. Fortunately, when the reaction temperature was lowered to −15 °C, only one fluorine substituent was introduced adjacent to the imine moiety (Scheme 2). However, because of the instability of the obtained α-fluoroimines **7** toward hydrolysis, no purification was possible. Instead, the corresponding monofluorinated ketones **8a**−**c** were obtained after treatment of the reaction mixture with aqueous HCl. The minor amount of difluorinated ketones (4−10%) that was formed during the reaction was easily separated from the monofluoroketones **8**[6n,16,17] using flash chromatography.

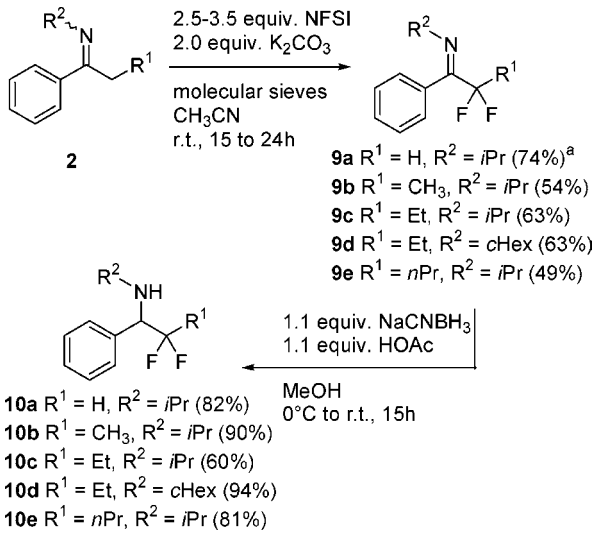
The developed methodology for the synthesis of α-fluoroimines **3** was also used to achieve the synthesis of α,α-difluoroimines. Therefore, imine **2b** (Scheme 3, $R^1 = CH_3$, $R^2 = i$Pr) was treated with 2.5 equiv of NFSI in acetonitrile (without DMF as a cosolvent because of its restraining effect on the fluorination reaction; see above) in the presence of 2 equiv of K_2CO_3 and 4 Å molecular sieves. It was found that when the reaction was performed at room temperature a clean difluorination of imine **2b** could be obtained toward **9b**. During the evaluation of other imines as precursors for difluorinated imines **9a** and **9c**−**d**, it was observed that in the case of the *N*-cyclohexyl- and *N*-isopropylimine derived from butyrophenone and valerophenone, respectively, the difluorination reaction did not go to completion when the above-mentioned procedure was used. Instead, the corresponding monofluorinated imines (60−70%) together with difluoroimines **9d** and **9e** were isolated after reaction for 15 h. However, when one more equivalent of NFSI was added to the reaction mixture after 15 h and stirring was continued for 9 h, a complete conversion to difluoroimines **9d** and **9e** could be established. Analogously, imine **9c** was synthesized using 3.0 equiv of NFSI after stirring for 24 h. The *N*-isopropylimine **9a** derived from α,α-difluoroacetophenone could not be obtained without the formation of a minor amount (18%) of α-fluoroacetophenone **4a** due to hydrolysis of the intermediate α-fluoroimine.

In addition, it was observed that the use of commercial NFSI from different production batches could influence the

Scheme 2



Scheme 3



[a] Not purified (purity 84%).

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required reaction time even after recrystallization of the reagent (CH_2Cl_2). When attempts were performed to synthesize difluoroimines **9c**−**e**, it was observed that in some experiments the reaction could not be forced to completion, even after prolonged reaction times (48 h). To overcome these problems and because it is known that the addition of acids to imines enhances enamine formation, experiments were performed where a catalytic amount of acid was added to the reaction mixture to speed up the difluorination reaction. Imine **2b** was treated with 2 equiv of NFSI in the presence of a catalytic amount of CF_3COOH. Unfortunately, no clean difluorination was obtained (due to hydrolysis). After evaluation of numerous reaction conditions, it could be concluded that K_2CO_3 is needed for the α-monofluorination, which excludes the use of acids at this point. This hypothesis was verified by performing the difluorination in two steps, where first the α-fluoroimine **3b** was synthesized using NFSI and K_2CO_3 followed by a standard workup. Subsequently, imine **3b** was reacted with 1.2 equiv of NFSI in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ as a Lewis acid. The latter reaction conditions enabled the difluorination toward imine **9b** in 6 h (vs 24 h when the reaction was performed in one pot). Although in some cases this procedure reduced the reaction time, the ease of a one-pot procedure (Scheme 3) is not to be ignored. The obtained difluoroimines **9a**−**e**, which all occurred as *E*-isomers with respect to the C═N bond, could be purified by flash chromatography using dry solvents ($MgSO_4$) and dried silica gel (100 °C, 0.1 mmHg) and are stable for several weeks at low temperatures (−20 °C). Because of the interest in *β*-fluorinated amines, as described above, the obtained imines **9** were reduced using sodium cyanoborohydride in the presence of acetic acid in methanol, yielding various new *β*,*β*-difluoroamines **10** in good yield (Scheme 3).

In conclusion, it can be stated that for the first time both α- and α,α-difluorinated imines were prepared via a direct electrophilic fluorination of the parent imines. Depending on the solvent system used and the reaction temperature, either mono- or difluoroimines were obtained using NFSI as the fluorinating agent. In addition, the isolated imines were transformed to fluorinated ketones and *β*-fluoroamines via hydrolysis and reduction of the α-fluorinated imines, respectively.

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Note Added after ASAP Publication. There were errors in the corresponding author's phone and fax numbers and Scheme 2 in the version published ASAP September 15, 2006; the corrected version was published ASAP September 20, 2006.

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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