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# A Practical Route to Fluoroalkyl- and Fluoroarylamines by Base-Catalyzed [1,3]-Proton Shift Reaction

**Vadim A. Soloshonok*[1]**

*Catalysis Research Center and Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan*

**Alexander G. Kirilenko and Valery P. Kukhar**

*Institute of Bioorganic Chemistry and Petrochemistry, Ukrainian Academy of Sciences, Kiev 253160, Ukraine*

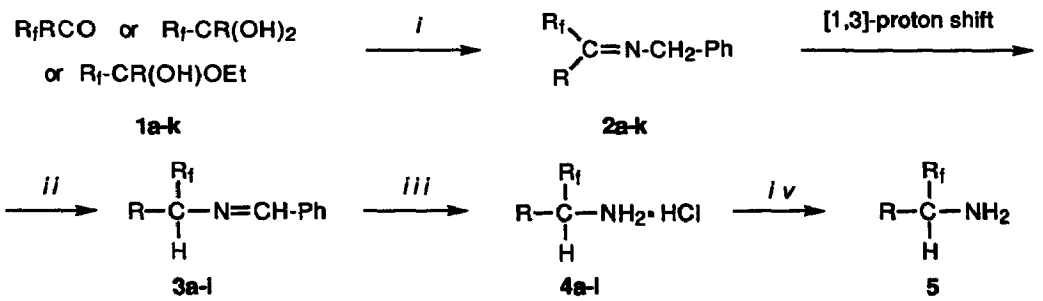
**Guiseppe Resnati**

*Dipartimento di Chimica, Politecnico di Milano, Via Mancinelli, 7, Milano 20131, Italy*

***Abstract:*** *The base-catalyzed [1,3]-proton shift reaction is shown to be an efficient general approach to fluoroalkyl and fluoroaryl amines starting from appropriate carbonyl compounds and benzylamine.*

Fluorine-containing analogs of natural products have attained a position of prominence in the area of new chemotherapeutic drug design due to the unique physical and biological properties imparted by fluorine.[2] Since a huge number of naturally occurring biologically active molecules contain an amino function, the synthesis of fluorinated amino compounds has gained in recent years a great deal of attention.[2, 3] The most direct synthetic approach to creation of an amino function is the reductive amination of an appropriate carbonyl compound.[4] The established concept of this transformation invariably necessitates the application of reducing reagents, amongst which sodium cyanoborohydride (Borch reduction)[5] and sodium triacetoxyborohydride (Gribble reduction)[6] are the most popular and general to carry out the reduction of C=N double bond. The extension of

**Scheme 1**




| | a | b | c | d | e | f | g | h | i | j |
|---|---|---|---|---|---|---|---|---|---|---|
| $R_f$ | $CF_3$ | $C_4F_9$ | $H(CF_2)_4$ | $H(CF_2)_6$ | $C_6F_5$ | $C_6HF_4$ | $CF_3$ | $CF_3$ | $C_2F_5$ | $CF_3$ |
| R | H | H | H | H | H | H | Ph | 4-$CF_3$-Ph | Ph | $PhCH_2$ |

Reaction conditions: *i*, benzylamine/ bezene or toluene, Dowex-50 ($H^+$-form), reflux, 2 - 7h; *ii*, base, see Table 1; *iii*, 2*N* HCl/$Et_2O$, room temperature, 4 h; *iv*, triethylamine/$Et_2O$, room temperature, 3 h.

this aproach to fluorocarbons was recently demonstrated by J.R.McCarty.[7] It was shown that Borch reduction provides a convenient access to α-trifluoromethylamines from corresponding ketones.

Some years ago we discovered that *N*-benzylimines of perfluoroalkyl-containing aldehydes in the presence of organic bases undergo [1,3]-proton shift to give corresponding *N*-benzylideneamines in excellent chemical yield.[8] This base-catalyzed isomerization is expected to be a conceptually new approach to reductive amination of fluorocarbonyl compounds, in which biomimetic [1,3]-proton shift excludes the necessity to use a reductive agent. Recently we have proved this with the elaboration of general method for synthesis of β-fluoroalkyl-β-aminocarboxylic acids *via* biomimetic transamination of β-fluoroalkyl-β-ketocarboxylic esters with benzylamine.[9] For this base-catalyzed [1,3]-proton shift reaction to be generally useful for synthetic chemistry, its application to other fluorinated carbonyl compounds need to be explored. We now report the efficient high yield method for preparation of various fluoroalkyl- and fluoroarylamines starting from corresponding carbonyl compounds and benzylamine using our biomimetic approach.

Initial imines **2a-k**[10] were easily prepared in 85-98% yields[11] by heating benzene or toluene solution of carbonyl compound with a stoichiometric amount of benzylamine in the presence of cation-exchange resin Dowex-50 ($H^+$-form) as an acidic catalyst. It is important to note that imine formation also readily proceeds starting from corresponding hydrates and hemiacetals since these compounds are more available and stable than free fluoroalkylaldehydes (Scheme 1).

In aliphatic aldehyde series trifluoromethyl-containing imine **2a** was the least reactive compound, and complete transformation of **2a** to **3a** with 93% isolated yield was achieved only in boiling triethylamine (Table 1, entry 1). In contrast to imine **2a** per(poly)fluoroalkyl derivatives **2b-d** were successfully isomerized with triethylamine at ambient temperature to give *N*-benzylidene derivatives **3b-d** in excellent isolated yields (entries 3, 4, 7). Heating of triethylamine solutions of imines **2b-d** greatly accelerates [1,3]-proton shift reaction giving arise products **3b-d** in nearly the same isolated yields but in more convenient time span (entries 2, 5, 9). We reasoned that one-pot transformation of imines **2** directly to hydrochloride salts **4** or free amines **5** is very important from a preparative point of view. We have shown such possibility with preparative (0.1 mol scale) synthesis of α,α,ω-trihydroperfluoropentylamine (**5c**) (entry 6) and α,α,ω-trihydroperfluorohexylamine hydrochloride (**4d**) (entry 8) which were obtained in 87% and 90% yield, respectively, directly from *N*-benzylimines **2c,d** without isolation of *N*-benzylidene derivatives **3c,d**.

The application of [1,3]-proton shift reaction in fluoroaromatic aldehyde series is demonstrated with preparation of pentafluorobenzylamine **4e** and tetrafluorobenzylamine **4f** as the hydrochloride salts (entries 10, 11). Quite unexpectedly, [1,3]-proton shift in transformation **2e** to **3e** was found to proceed more easily than isomerization of imine **2a** which possesses more electron-withdrawing trifluoromethyl group (entry 1). Thus, isomerization of **2e** to **3e** smoothly occurred in the triethylamine solution at room temperature giving arise desired products **3e** in nearly quantitative yield (entry 10). The same reactivity was observed for 2,3,5,6-tetrafluorophenyl derivative **2f** to give **3f** in 96% yield (entry 11). Alike aliphatic series, heating of triethylamine solutions of aromatic imines **2e,f** accelerated their isomerization to **3e,f** but decreased isolated yield of final products **3e,f**.

In ketone series, triethylamine was incapable to catalyze isomerization ofketimine **2g** to aldimine **3g** at room temperature. However, in boiling triethylamine trifluoroacetophenone derivative **2g** was completely

**Table I. Base-Catalyzed [1,3]-Proton Shift**

| Entry | Imine | | Conditions[a] | | | Yield[b], % | | |
|---|---|---|---|---|---|---|---|---|
| | $R_f$ | R | base | temp. | time (h) | **3a-k** | **4a-k** | **5** |
| 1 | (a) $CF_3$ | H | $NEt_3$[c] | reflux | 50 | 93 | 87 | - |
| 2 | (b) $C_4F_9$ | H | $NEt_3$[c] | reflux | 4 | 89 | 91 | - |
| 3 | (b) $C_4F_9$ | H | $NEt_3$[c] | 23 °C | 100 | 92 | - | - |
| 4 | (c) $H(CF_2)_4$ | H | $NEt_3$[c] | 25 °C | 90 | 98 | - | - |
| 5 | (c) $H(CF_2)_4$ | H | $NEt_3$[c] | 70 °C | 5 | 95 | 95 | 87 |
| 6 | (c) $H(CF_2)_4$ | H | $NEt_3$[c] | 70 °C | 5 | - | - | 87 |
| 7 | (d) $H(CF_2)_6$ | H | $NEt_3$[c] | 23 °C | 96 | 86 | 92 | 94 |
| 8 | (d) $H(CF_2)_6$ | H | $NEt_3$[c] | 23 °C | 96 | - | 90 | 96 |
| 9 | (d) $H(CF_2)_6$ | H | $NEt_3$[c] | 70 °C | 4 | 96 | - | - |
| 10 | (e) $C_6F_5$ | H | $NEt_3$[c] | 24 °C | 140 | 98 | 95 | - |
| 11 | (f) $C_6HF_4$ | H | $NEt_3$[c] | 24 °C | 150 | 96 | 99 | - |
| 12 | (g) $CF_3$ | Ph | $NEt_3$[c] | reflux | 10 | 80 | 96 | 91 |
| 13 | (g) $CF_3$ | Ph | DBU[d] | 21 °C | 4 | 89 | - | 93 |
| 14 | (h) $CF_3$ | 4-$CF_3$Ph | DBU[d] | 21 °C | 4 | 79 | - | 93 |
| 15 | (i) $C_2F_5$ | Ph | DBU[d] | 21 °C | 4 | 84 | 97 | - |
| 16 | (j) $CF_3$ | $CH_2Ph$ | DBU[d] | 60 °C | 1 | 84 | 97 | 97 |

[a] Conversion of starting imine more than 95%, as controlled by GLC. [b] Isolated yield. All new compounds gave satisfactory C, H analyses. For NMR data see ref 12. [c] Reactions were run in $NEt_3$ solution. [d] Imine/DBU ratio 1/0.05-0.1, neat.

isomerized into aldimine **3g** with 80% isolated yield (entry 12). We have found that lower ability of ketimines **2g-j** to undergo [1,3]-proton shift can be overcome by use of more strong bases than triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is very effective as a catalyst for [1,3]-proton shift in ketimine series. Thus, even in the presence of 5 mol % of DBU, ketimine **2g** can be completely isomerized at room temperature in 4 h to give aldimine **3g** in 89% yield (entry 13). Nearly the same reactivity was observed in transformations of ketimines **2h**, bearing trifluoromethyl group in *p*-position of phenyl ring, and **2i**, possessing pentafluoroethyl group in the alkyl site of starting ketimine (entries 14, 15). As one could expect, substitution of phenyl group with benzyl one, which is unable to stabilize carbanion, decreased an ability of ketimine/enamine[10] **2j** to undergo [1,3]-proton shift reaction. Nevertheless, 2-phenyl-1-(trifluoromethyl)ethylamine derivative **3j** was prepared in high isolated yield (84%) using DBU as a catalyst by the transformation of **2j** (entry 16).

As it is shown in the Scheme 1, hydrochlorides **4** and free amines **5** can be easily prepared in excellent yields from *N*-benzylidene derivatives **3** by using known chemistry. In conclusion, we have reported a short and efficient method for preparation of various fluoroalkyl(aryl)amines *via* biomimetic transamination of corresponding carbonyl compounds with benzylamine. The high yields, the simplicity of experimental procedure, and low cost of all reagents may render this reaction the most practical route to primary fluoroamine compounds developed to date. Mechanism of [1,3]-proton shift and its proceeding in asymmetric sense are presently under study.

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1 Permanent address: Institute of Bioorganic Chemistry and Petrochemistry of the Ukrainian Academy of Sciences, Kiev 253160, Ukraine.

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10 Benzyl trifluoromethyl ketone (**1j**) gave a mixture of imine **2j** and corresponding enamine in approximate 2:1 ratio.

11 Excepting phenyl trifluoromethyl ketone (**1g**) which gave imine **2g** in 43% yield.

12 Some characteristic NMR data ($CDCl_3$ or $CD_3COCD_3$) of compounds **2-5**: **2a**, ($^1H$), 4.86 (br s, 2H), 7.25-7.50 (m, 5H), 8.02 (m, 1H). ($^{19}F$), 70.66 (m). **3a**, 4.38 (q, $^3J_{HF}$ = 9.9 Hz, 2H), 7.20-7.75 (m, 5H), 8.53 (br s, 1H). ($^{19}F$), 72.1 (t, $^3J_{HF}$ = 9.9 Hz). **2b**, 4.60 (br s, 2H), 7.15 (m, 5H), 7.50 (t, $^3J_{HF}$ = 6 Hz, 1H). **3b**, 3.93 (t, $^3J_{HF}$ = 16 Hz, 2H), 7.33 (m, 5H), 8.05 (s, 1H). **2c**, 4.89 (br s, 2H), 6.09 (t t, $^2J_{HF}$ = 52.0 Hz, $^3J_{HF}$ = 5.4 Hz, 1H), 7.20 (m, 5H), 7.74 (t, $^3J_{HF}$ = 6 Hz, 1H). **3c**, 4.23 (t, $^3J_{HF}$ = 15.6 Hz, 2H), 6.13 (t t, $^2J_{HF}$ = 52.0 Hz, $^3J_{HF}$ = 5.4 Hz, 1H), 7.5 (m, 5H), 8.35 (s, 1H). **2e**, ($^1H$), 4.90 (s, 2H), 7.35 (m, 5H), 8.63 (br s, 1H); ($^{19}F$), 142.88 (m, 2F), 152.75 (m, 1F), 163.09 (m, 2F). **3e**, ($^1H$), 4.84 (s, 2H), 7.51 (m, 5H), 8.44 (s, 1H); ($^{19}F$), 144.43 (m, 2F), 156.71 (m, 1F), 163.62 (m, 2F). **4e**, ($^1H$) , 4.30 (br s, 2H). ($^{19}F$), 140.68 (m, 2F), 152.21 (m, 1F), 161.69 (m, 2F). **2f**, 4.87 (s, 2H), 7.11 (m, 1H), 7.39 (m, 5H), 8.56 (s, 1H). **3f**, 4.81 (s, 2H), 7.11 (m, 1H), 7.55 (m, 5H), 8.39 (s, 1H). **2g**, 4.42 (br s, 2H), 7.33-7.51 (m, 10H). **3g**, 4.60 (q, $^3J_{HF}$ = 7.5 Hz, 1H), 7.13-7.37 (m, 10H), 8.15 (s, 1H). **4g**, 5.46 (q, $^3J_{HF}$ = 7.4 Hz, 1H), 7.58-7.62 (m, 3H), 7.68-7.76 (m, 2H). **5g**, 4.15 (q, $^3J_{HF}$ = 7.5 Hz, 1H), 7.57 (m, 5H). **2h**, 4.65 (br s, 2H), 7.37-7.65 (m, 9H). **3h**, 4.55 (q, $^3J_{HF}$ = 7.4 Hz, 1H), 7.15-7.63 (m, 9H), 8.17 (s, 1H). **4h**, 5.50 (q, $^3J_{HF}$ = 7.4 Hz, 1H), 7.61-7.63 (m, 4H). **2i**, 4.66 (br s, 2H), 7.32-7.50 (m, 10H). **3i**, 4.53 (q, $^3J_{HF}$ = 7.5 Hz, 1H), 7.12-7.42 (m, 10H), 8.19 (s, 1H). **2j**, *for enamine*, 4.13 (s, 2H), 6.08 (br s, 1H), 7.07-7.48 (m, 5H), *for ketimine*, 4.06 (s, 2H), 4.86 (d, $^4J_{HF}$ = 1.9 Hz, 2H), 7.07-7.48 (m, 5H). **3j**, ($^1H$), 3.17 (ABX, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 3.2 Hz, 2H), 4.08 (d q d, $^3J_{HF}$ = 7.3 Hz, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 7.12-7.73 (m, 10H), 8.83 (s, 1H). ($^{19}F$), 69.88 (d, $^3J_{HF}$ = 7.3 Hz).


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