

# Synthesis of highly 1,3-proton shift transferable *N*-benzyl imines of trifluoroacetophenone under the “low-basicity” reaction conditions

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## Abstract

The standard reaction conditions commonly used for the condensation of carbonyl compounds with amines were found to be synthetically inefficient for preparation of the imines derived from trifluoroacetophenone and benzylamines owing to the susceptibility of these imines to 1,3-proton shift. Application of a “low-basicity” method, using instead of free benzylamines their salts formed from acetic acid (AA), allowed synthesis of the target compounds in chemically pure form and excellent chemical yields.

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## 1. Introduction

$\alpha$ -Trifluoromethyl containing amines **A** (Fig. 1) represent one of the most synthetically powerful fluorine-containing building block-synthons in modern organic chemistry. For instance, the SciFinder search for the fixed structure **B** (Fig. 1) yielded more than 11,466 compounds and 2204 references, which is truly remarkable considering that all of these derivatives are purely synthetic. This unique interest in chemistry of  $\alpha$ -trifluoromethyl containing amino-compounds is driven mostly by agricultural and pharmaceutical industries<sup>1</sup> using the structural motif **B** as a pharmacophore unit in the design of new generations of fungicides, pesticides, herbicides, desiccants, defoliants, insecticides, arthropodocides, microbicides, selective antibacterial agents, therapeutic agents/probes, enzyme inhibitors, enzyme receptor antagonists/agonists [1–4]. There is also significant continued interest in fluorinated amino-compounds in the area of material science, in particular, in the development of new electroluminescent devices and liquid crystals [1–4]. An emerging and quite exciting area, so far stemming from a purely academic interest in fluorinated amino-compounds, is the application of their chiral and enantiomerically pure derivatives as chiral internal/external ligands, auxiliaries, and

catalysts for general asymmetric synthesis [2b,3,4e,4f,4h]. For instance, taking into account a uniquely wide range of various synthetic applications of  $\alpha$ -phenylethylamine (Fig. 2) and its derivatives in the modern asymmetric synthesis [5], the synthetic potential offered by its enantiomerically pure trifluoro-analog **1**, wherein the trifluoromethyl might play the role of a stereodirecting group, is enormous [2b,4,6].

Taking into account the importance of  $\alpha$ -trifluoromethyl (and more generally, perfluoroalkyl/aryl) containing amines, as discussed above, it is not surprising that the development of synthetic methods for preparing these compounds has been the focus of numerous research groups [4,7–14,16,17] (see also footnote 2). The vast variety of the approaches available in the literature can be divided into the following methods: (a) a conventional (with application of external reducing reagents) reductive amination of the corresponding trifluoromethyl ketones [7]; (b) a nucleophilic addition of alkyl groups (Grignard reagents, sulfoxide-stabilized carbanions) to  $\alpha$ -trifluoromethyl-imines [8] or hydrazones [9]; (c) reactions of the trifluoromethyl-imines [10]; (d) a nucleophilic addition of trimethyl(trifluoromethyl)silane to nitrones [11] or imines [12]; (e) a reduction or nucleophilic opening of fluoral-derived 1,3-oxazolidines [13]; (f) elaboration of trifluoroacetimidoyl halides [14].

For quite some time, we have been developing a new method conceptually different from the methods listed above. This method avoids the use of conventional reducing reagents but results in a product corresponding to a reductive

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<sup>1</sup> More than 90% of the references retrieved by SciFinder are patents, a fact manifesting the remarkable industrial interest in this class of compounds.

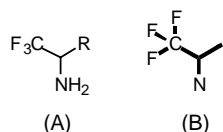


Fig. 1. General structure  $\alpha$ -trifluoromethyl containing amino compounds (A), and fixed structure (B) used for the SciFinder search.

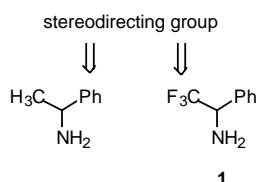
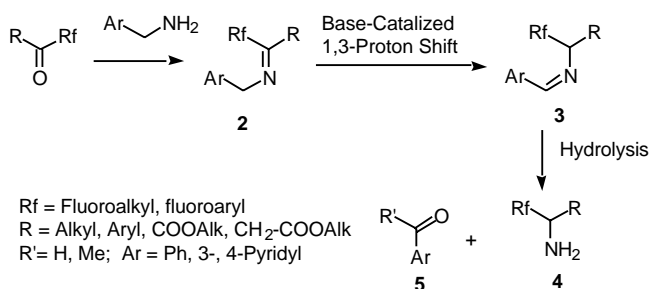


Fig. 2.  $\alpha$ -Phenylethylamine its trifluoro-analog **1**.



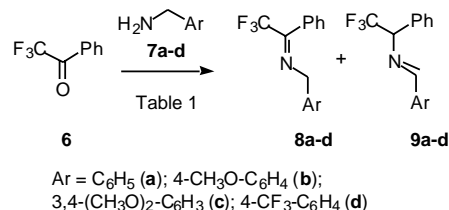
Scheme 1. Biomimetic, conventional reducing reagent-free reductive amination of carbonyl compounds.

amination of fluorocarbonyl compounds to the corresponding fluorine-containing amines and amino acids (Scheme 1). This approach, mimicking biological transamination [15], represents the most ideal solution to the reductive amination of carbonyl compounds (Scheme 1) making use of the intramolecular reduction–oxidation process via a base-catalyzed 1,3-proton shift in the azaallylic system of azomethines (imines) **2**. We were the first to demonstrate that the presence of electron-withdrawing perfluoroalkyl or perfluoroaryl groups in  $\alpha$ -position to the imine function in derivatives **2** makes their base-catalyzed isomerization to Schiff bases **3** virtually irreversible and thus synthetically useful. Products **3** can be easily hydrolyzed under mild acidic conditions giving rise to a readily separable mixture of the target fluorinated amino **4** and carbonyl **5** compounds. The synthetic advantage of this biomimetic approach over the literature methods is its generality and operational convenience.<sup>2</sup> Previously we reported an efficient applica-

tion of this biomimetic approach for preparation of fluorine-containing amines [16],  $\alpha$ - and  $\beta$ -amino acids [17] starting from readily available fluorinated aldehydes and ketones, or  $\alpha$ - and  $\beta$ -keto carboxylic acids, respectively. Our most recent achievement in this area is the development of double-PSR methodology for a direct, one-pot conventional reducing reagent-free transformation of perfluoroalkyl-carboxylic acids to the corresponding  $\alpha,\alpha$ -dihydroperfluoroalkylamines [18]. Of particular interest are the results reported by other research groups on application of the PSR methodology for transamination of fluorine-free carbonyl compounds to the corresponding amino-derivatives [19] as well as the preparation of fluorine-containing phosphorus analogs of  $\alpha$ - and  $\beta$ -amino acids [20].

## 2. Results and discussion

As a part of our current project on the development of catalytic version of the asymmetric PSR method, we needed a series of non-enaminolizable *N*-benzyl imines of trifluoroacetophenone **8a–d** (Scheme 2). The method previously reported by us [16b] for preparation of imine **7a** involves the standard condensation reaction conditions between trifluoroacetophenone (**6**) and benzylamine (**7a**) using *p*-tolylsulphonic acid (*p*-TSA) as a catalyst, toluene as a solvent and a Dean–Stark trap to remove the produced water. While this method is operationally simple it is, unfortunately, not synthetically efficient, allowing preparation of the target imine **8a** in only moderate chemical yield (up to 68%) and involving tedious purification by flash-chromatography. The major drawback of this reaction conditions is that, during the reaction, the imine **8a** easily undergoes 1,3-proton shift isomerization to give Schiff base **9a** (Table 1, entry 1). Due to the similarity between structures **8a** and **9a** their separation is difficult. Moreover, some 10% of other byproducts were observed in the crude mixture by <sup>19</sup>F NMR. Similar results were obtained in the reactions of ketone **6** with benzylamines **7b–d**, having electron releasing (entries 2 and 3) and electron-withdrawing (entry 4) substituents on the phenyl ring. As expected, [16c,16d] the largest amount of the isomerized product **9d** was observed in the reaction of the trifluoromethyl derivative **7d**, giving rise to an almost 1:1 mixture of imines **8d** and **9d**. The isomerization of **8a–d** to **9a–d** could be catalyzed by the benzylamine remaining in the reaction mixture acting as a base, or, taking into account the reaction high temperature, the transformation may be a



Scheme 2.

<sup>2</sup> A concept of the “Atom Economy” introduced by Professor Barry M. Trost has found quick and unanimous understanding, support and appreciation in the chemistry community as a philosophical guideline for the development of organic synthesis in 21st century. On the other hand, in the current literature one can notice another trend shaping a paradigm of the synthetic methodology of the future, which is simplicity of experimental conditions, or as we prefer to call it, operationally convenient reaction conditions.

Table 1  
Reactions of trifluoroacetophenone **6** with amines **7a–d**. Synthesis of imines **8a–d** (Scheme 2)<sup>a</sup>

Entry	<b>7a–d</b>	Solvent	Method <sup>b</sup>	<i>T</i> (h)	Yield %	Ratio <sup>c</sup> <b>8/9</b>
1	<b>a</b>	Toluene	A	9	87	71/29
2	<b>b</b>	Toluene	A	9	85	67/33
3	<b>c</b>	Toluene	A	9	86	66/34
4	<b>d</b>	Toluene	A	9	41	56/44
5	<b>a</b>	Benzene	A	16	90	61/39
6	<b>a</b>	Chloroform	A	22	96	74/26
7	<b>a</b>	Toluene	B	1	96	85/15
8	<b>c</b>	Toluene	B	1	97	97/3
9	<b>a</b>	Benzene	B	3	94	>98/2
10	<b>b</b>	Benzene	B	3	95	>98/2
11	<b>c</b>	Benzene	B	3	96	>98/2
12	<b>d</b>	Benzene	B	3	92	90/10
13	<b>a</b>	Chloroform	B	20	97	>99/1
14	<b>b</b>	Chloroform	B	20	94	>99/1
15	<b>c</b>	Chloroform	B	20	97	>99/1
16	<b>d</b>	Chloroform	B	20	96	>99/1

<sup>a</sup> All reactions were conducted at reflux in the indicated solvent.

<sup>b</sup> Method A: ketone **6** (1 equivalent), amine **7** (1.1 equivalent), *p*-TSA (0.1 equivalent). Method B: ketone **6** (1 equivalent), amine **7** (1.1 equivalent), acetic acid (1.1 equivalent).

<sup>c</sup> Determined by <sup>19</sup>F NMR (300 MHz) analysis of the crude reaction mixtures.

thermally induced process. To determine the cause of the 1,3-proton shift under these reaction conditions we conducted two experiments. Thus, after refluxing of pure imine **8a** in toluene for several hours it was isolated intact, while addition of benzylamine (catalytic amounts: 10 mol%) to a solution of **8a** in toluene, even at room temperature, resulted in fast isomerization of imine **8a** to Schiff base **9a**. Furthermore, even though we found that the reaction temperature had a noticeable effect on the rate of imine **8a** formation, its influence on the isomerization and ratio of products **8a** and **9a** was rather insignificant. Thus, the reactions between ketone **6** and benzylamine **7a**, conducted in benzene (entry 5) and chloroform (entry 6) were much slower giving rise to a mixture of **8a** and **9a** in a ratio comparable with that observed in reaction conducted in toluene (entry 1).

Having analyzed the data obtained, we concluded that the *p*-TSA-catalyzed condensation conditions are incompatible with the high susceptibility of the target imines **8** to 1,3-proton-shift. Therefore, we decided to try the “low-basicity” reaction conditions recently reported by us [21]. These conditions, consisting in the reaction of a carbonyl compound with a salt of amine and acetic or trifluoroacetic acid, were originally developed for the preparation of imines derived from highly electrophilic and polyfunctional fluorinated carbonyl compounds. For example, application of the corresponding salts of benzylamine, instead of benzylamine and catalytic amounts of *p*-TSA, allowed us to exclude the haloform-type decomposition of polyfluorinated carbonyl compounds as well as to dramatically improve the chemo- and regio-selectivity in the reactions of fluorinated  $\alpha$ - and  $\beta$ -keto esters.

First, we conducted the reaction of ketone **6** with acetic acid (AA) salts of benzylamines **7a,c** (**7a-AA**) using toluene as a solvent. We found that the reactions occurred with remarkably increased rates and chemical yields (entries 7 and 8) giving rise to a mixture of **8a,c** and **9a,c**, however. Even though we did not obtain the desired result, preparation of pure imines **8**, the substantially improved ratio of products **8a,c** and **9a,c** was quite encouraging. Using benzene as a solvent for the reactions of ketone **6** with salts **7a–d-AA** decreased the reaction rates, but further increased the ratio of **8a–d** and **9a–d** (entries 9–12) to an almost satisfactory level of >98/2, except for the reaction of the trifluoromethyl derivative **9d** (entry 12). Finally, we carried out the reactions in chloroform. To our satisfaction in all cases (entries 13–16) we observed clean and complete conversion of ketone **6** giving rise to only the target imines **8a–d**, which could be isolated chemically pure and in excellent yields.

### 3. Conclusion

In summary, we found that the standard reaction conditions commonly used for the condensation of carbonyl compounds with amines are synthetically inefficient for preparation of the target imines derived from trifluoroacetophenone and benzylamines. On the other hand, application of the “low-basicity” method, using instead of free benzylamines their salts with acetic acid, allowed synthesis of the target compounds in chemically pure form suitable for catalytic and kinetic studies.

### 4. Experimental

#### 4.1. General

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out in a regular atmosphere without any special caution to exclude air. Unless indicated, <sup>1</sup>H, <sup>19</sup>F, and <sup>13</sup>C NMR spectra, were taken in CDCl<sub>3</sub> solutions at 299.95, 282.24, and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS and CFCl<sub>3</sub> as the internal standards.

Yields refer to isolated yields of products of greater than 95% purity as estimated by <sup>1</sup>H and <sup>19</sup>F NMR spectrometry. All new compounds were characterized by <sup>1</sup>H, <sup>19</sup>F, <sup>13</sup>C NMR and mass spectrometry.

#### 4.2. Typical procedure for preparing imines **8a–d**

##### 4.2.1. *N*-(1-Phenyl-2,2,2-trifluoroethylidene)benzylamine (**8a**) [16b]

A solution of ketone **6** (5.000 g, 28.88 mmol) in 5 ml of chloroform was added at room temperature to a solution of

benzylamine (3.714 g, 34.66 mmol) and acetic acid (2.080 g, 34.66 mmol) in chloroform (20 ml). The resultant mixture was refluxed until the reaction was completed (20 h, monitored by  $^{19}\text{F}$  NMR).

Yields of imines **8a–d** are listed in Table 1 (entries 13–16).

#### 4.2.2. *N*-(1'-Phenyl-2',2',2'-trifluoroethylidene)-4-methoxybenzylamine (**8b**)

$^1\text{H}$  NMR:  $\delta$  7.47 (m, 3H), 7.28 (m, 2H), 7.16 (d,  $J = 8.1$  Hz, 2H), 6.86 (d,  $J = 8.1$  Hz, 2H), 4.54 (s, 2H), 3.77 (s, 3H).  $^{19}\text{F}$  NMR:  $\delta$  -71.36 (s).  $^{13}\text{C}$  NMR:  $\delta$  158.76, 158.55 (q,  $J = 32.3$  Hz), 131.94, 130.17, 130.03, 128.84, 128.80, 127.63, 119.71 (q,  $J = 278.7$  Hz), 113.95, 56.31, 55.17.

#### 4.2.3. *N*-(1'-Phenyl-2',2',2'-trifluoroethylidene)-3,4-dimethoxybenzylamine (**8c**)

$^1\text{H}$  NMR:  $\delta$  7.51 (dd,  $J = 2.1, 4.8$  Hz, 2H), 7.28 (m, 3H), 6.83 (d,  $J = 3$  Hz, 1H), 6.80 (s, 1H), 6.74 (dd,  $J = 2.1, 7.8$  Hz, 1H), 4.55 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H).  $^{19}\text{F}$  NMR:  $\delta$  -71.40 (s).  $^{13}\text{C}$  NMR:  $\delta$  158.71 (q,  $J = 33.9$  Hz), 149.00, 148.17, 130.50, 130.21, 129.99, 128.86, 127.65, 119.68 (q,  $J = 278.7$  Hz), 119.67, 111.12, 110.94, 56.55, 55.87, 55.79.

#### 4.2.4. *N*-(1'-Phenyl-2',2',2'-trifluoroethylidene)-4-(trifluoromethyl)benzylamine (**8d**)

$^1\text{H}$  NMR:  $\delta$  7.59 (d,  $J = 8.1$  Hz, 2H), 7.52 (m, 3H), 7.39 (d,  $J = 8.1$  Hz, 2H), 7.27 (m, 2H), 4.65 (s, 2H).  $^{19}\text{F}$  NMR:  $\delta$  -63.00 (s), -71.47 (s).  $^{13}\text{C}$  NMR:  $\delta$  164.37, 159.80 (q,  $J = 34.3$  Hz), 142.03, 130.46, 129.99, 129.04, 127.78, 127.49, 125.52 (q,  $J = 3.7$  Hz), 125.51 (q,  $J = 272.1$  Hz), 119.58 (q,  $J = 278.6$  Hz), 56.20.

Schiff bases **9a–d**, isolated as by-products, can be easily prepared from **8a–d** under the general conditions described previously for synthesis **9a** [16b]. Spectral characteristics of **9b–d** are listed below.

#### 4.2.5. *N*-4'-Methoxybenzylidene-1-phenyl-2,2,2-trifluoroethylamine (**9b**)

$^1\text{H}$  NMR:  $\delta$  8.25 (s, 1H), 7.74 (d,  $J = 9.0$  Hz, 2H), 7.55 (d,  $J = 6.3$  Hz, 2H), 7.33 (m, 3H), 6.88 (d,  $J = 9.0$  Hz, 2H), 4.73 (q,  $J = 7.5$  Hz, 1H), 3.75 (s, 3H).  $^{19}\text{F}$  NMR:  $\delta$  -74.28 (d,  $J = 7.9$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  164.99, 162.37, 135.24, 130.44, 128.78, 128.74, 128.50, 128.27, 124.81 (q,  $J = 280.7$  Hz), 113.98, 74.96 (q,  $J = 28.2$  Hz), 55.23.

#### 4.2.6. *N*-3',4'-Dimethoxybenzylidene-1-phenyl-2,2,2-trifluoroethylamine (**9c**)

$^1\text{H}$  NMR:  $\delta$  8.25 (s, 1H), 7.55 (m, 3H), 7.37 (m, 3H), 7.19 (dd,  $J = 1.8, 8.4$  Hz, 1H), 6.82 (d,  $J = 11.1$  Hz, 1H), 4.76 (q,  $J = 8.1$  Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H).  $^{19}\text{F}$  NMR:  $\delta$  -74.17 (d,  $J = 5.9$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  165.14, 152.04, 149.21, 135.09, 131.52, 128.65, 128.51, 128.43, 124.21 (q,  $J = 281.0$  Hz), 123.96, 110.20, 109.02, 74.81 (q,  $J = 28.2$  Hz), 55.74.

#### 4.2.7. *N*-4'-Trifluoromethylbenzylidene-1-phenyl-2,2,2-trifluoroethylamine (**9d**)

$^1\text{H}$  NMR:  $\delta$  8.43 (s, 1H), 7.95 (d,  $J = 7.8$  Hz, 2H), 7.69 (d,  $J = 7.5$  Hz, 2H), 7.54 (d,  $J = 5.1$  Hz, 2H), 7.40 (m, 3H), 4.84 (q,  $J = 6$  Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  -63.43 (s), -74.36 (d,  $J = 7.9$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  164.38, 138.29, 134.51, 129.41, 129.12, 129.00, 128.83, 128.74, 128.69, 128.62 (q,  $J = 272.0$  Hz), 125.65, (q,  $J = 3.7$  Hz), 75.05 (q,  $J = 28.7$  Hz).

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