Synthesis of C₆F₅-Substituted Aminoethanols via Acetate Ion Mediated C₆F₅-Group Transfer Reaction

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Abstract: A new approach for the synthesis of N-(pentafluorophenylmethyl)aminoethanols is developed. The method includes alklylation of imines with 2-tris(pentafluorophenyl)silyloxyethyl triflate, prepared from ethylene oxide and (C₆F₅)₃SiOTf, to give 2-silyloxyethyliminium ions. Their treatment with sodium acetate induces C–C bond formation proceeding as transfer of the C₆F₅ group from the five-coordinate silicate intermediate to the iminium center.

Key words: silicon, hypercoordination, amino alcohols, imines, tris(pentafluorophenyl)silyl derivatives

β-Aminoalcohols constitute an important class of organic compounds. They have found wide utilization in asymmetric synthesis as chiral auxiliaries and ligands. Another significant area of applications of β-aminoalcohols is associated with their diverse biological activity. At the same time it is known that the presence of a fluorinated substituent at the α-position of the nitrogen atom of amines, i.e. as in the fragment R¹–CR₂–NR₃, also may provide derivatives displaying interesting pharmacological properties and the latter phenomenon has stimulated the intense investigations directed towards synthesis of fluorinated amines. As a consequence, fluorinated β-aminoalcohols, containing two adjacent pharmacophore fragments, have become attractive targets. Herein we present our studies towards a sub-class of fluorinated β-aminoalcohols, namely N-(pentafluorophenylmethyl)aminoethanols 1.

We have recently reported a method for the synthesis of (pentafluorophenylmethyl)amines via a three-component silicon Mannich reaction [Scheme 1, (a)]. However, application of this protocol to the coupling of benzaldehyde and N-methylethanalamine afforded the desired product in only 28% yield after a reaction time of 67 hours. In this paper we describe a more efficient approach to aminoalcohols 1 based on the coupling of imines, ethylene oxide, and tris(pentafluorophenyl)silyl triflate as a source of C₆F₅ group [Scheme 1, (b)]. The key steps of the process involve the formation of silyloxyethyliminium salts and Lewis base mediated transfer of the pentafluorophenyl group from the silicon to the iminium carbon atom.

Addition of ethylene oxide to the mixture of N-methyl-C-phenylimine (2a) and (C₆F₅)₃SiOTf in dichloromethane at room temperature cleanly gave iminium salt 3a (Scheme 2). However this procedure cannot be applied to enolizable imines, since the latter are incompatible with silyl triflate. Thus, when N-methyl-C-isopropylimine (2b) was mixed with (C₆F₅)₃SiOTf in CDCl₃, the N-silylamine and protonated imine were immediately observed by NMR spectroscopy, suggesting that the silyl group is first transferred from (C₆F₅)₃SiOTf onto 2b followed by deprotonation of silyliminium cation by another molecule of 2b (Scheme 2).

To overcome the problem of imine silylation we decided to introduce the silyloxyethyl group by means of direct alkylation of the imine. For this purpose we synthesized 2-
tris(pentafluorophenyl)silyloxyethyl triflate 4 by the interaction of (C$_{6}$F$_{5}$)$_{3}$SiOTf with ethylene oxide in the presence of 5 mol% of pyridine\(^{9}\) (Equation 1). Surprisingly, triflate 4 turned out to be a quite stable solid (mp 63–66 °C), which can be recrystallized from hexane. This compound can be conveniently handled under an argon atmosphere at room temperature, whereas cooling to –25 °C is preferable for long-term storage to prevent decomposition.

The crystal and molecular structure of 4 was studied by X-ray diffraction analysis (Figure 1). Analysis of Cambridge database reveals that compound 4 is the first example where the OTf group is bound to an acyclic chain,\(^{10}\) while published data include structures of aryl, vinyl, and carbohydrate triflates.\(^{11}\) The O(2)–C(2) bond of 1.481 Å is close to that in carbohydrate derivatives (1.46–1.49 Å), but longer than in \(sp^{2}\) bound triflates (1.41–1.45 Å). Of special note is the gauche arrangement of OTf and OSi(C$_{6}$F$_{5}$)$_{3}$ substituents (torsion angle OCCO is equal to 74.6°, see projection), which is characteristic for stereoelectronic interactions between \(\sigma_{C-H}\) and \(\sigma^{*}_{C-X}\) orbitals.\(^{12}\) It should be also noted that in 4 the interatomic distance between O(2) of triflate group and C(16) of phenyl ring is equal to 2.956 Å, that is noticeably shorter than the sum of van der Waals radii (3.33 Å). Possibly the high steric overcrowding in molecule leads to weak nonbonding interactions between alkyl triflate and pentafluorophenyl moieties.

Triflate 4 smoothly reacted with imines 2 generating iminium salts 3 (Equation 2). The alkylation of C-arylimines was usually performed in refluxing dichloroethane and proceeded quite cleanly. The reaction of N-butyl-C-isopropylimine (2b) was carried out at room temperature for 16 hours furnishing salt 3b along with significant amounts of by-products. Although isolation of pure 3b was problematic, it was successfully employed in further transformation to give the final aminoethanol in a reasonable yield (vide infra). Imines derived from linear aldehydes, e.g. N-butyl-C-ethylimine, gave complex mixtures that may be tentatively rationalized by facile loss of a proton from silyloxyethyliminium cation at the rate comparable to the rate of alkylation. Iminium salts derived from C-arylimines 3 can be isolated in individual state and characterized by \(^{1}H,\ ^{13}C,\ ^{19}F\) NMR spectroscopy, as exemplified for 3a, 3c. For 3c the structure was established by X-ray diffraction analysis (Figure 2) that demonstrated the gauche conformation of silyloxy and iminium functionalities similar to that in 4. The configuration of C–N double bond was established either by NOE experiments (for 3a, E:Z = 8:1) or from X-ray data (for 3c, E). It is interesting to note that substituents \(R^{1}\) and \(R^{2}\), being in \(trans\) orientation in starting imines 2a,c, are in \(cis\) arrangement in iminium salts 3a,c. This phenomenon may be explained by the C–N double bond isomerization, which takes place either in starting imine prior to alkylation or in iminium cation.

Equation 1

\[
\text{2a} \quad \text{3a} \quad \text{3b} \quad \text{3c}
\]

Equation 2

The transformation of salts 3 into ethanolamines 1 relies on the activation of silicon atom by a Lewis base to generate pentacoordinate silicate intermediate with subsequent intra- or intermolecular transfer of C$_{6}$F$_{5}$ group onto 4.
iminium electrophile (Scheme 3). Using isolated salt 3a as model substrate we performed the optimization of reaction conditions for the synthesis of 1a (R1 = Ph, R2 = Me) by varying the nucleophilic mediator (Table 1).

**Scheme 3**

Pyridine-N-oxide and hexamethylphosphoric acid triamide, which are known to be one of the strongest neutral silicon specific Lewis bases, proved to be completely unreactive coexisting with 3a with no signs of interaction (Table 1, entries 1 and 2). In recent reports Mukaiyama and co-workers demonstrated that lithium or tetrabutylammonium acetate in DMF effected trifluoromethylation of carbonyl compounds and activated imines by Me₃SiCF₃. We tested the Mukaiyama conditions for our system and observed that acetate ion taken in any form and in different solvents worked well for the transfer of C₆F₅ group in salt 3a. Indeed, acetate ion either generated in situ from acetic acid and triethylamine or added in the form of lithium or sodium salt instantaneously initiated the reaction, furnishing after desilylative workup fluorinated aminoalcohol 1a in high yield (Table 1, entries 3–7). Employment of sodium acetate in tetrahydrofuran seems to be the most practical, and this procedure was selected for further investigations.

Under the optimized conditions a series of imines was employed in acetate ion mediated synthesis of N-(pentafluorophenylmethyl)aminoethanols 1. Table 2 lists the conditions for the generation of silyloxyethyliminium ions 3, which were used without isolation. Their treatment with sodium acetate uniformly required 20 minutes at room temperature. Imines containing at the carbon atom electron-donating and electron-withdrawing substituents, tert-butyl and α-branched alkyl groups, gave good yields of products.

As obvious from these results, the transfer of C₆F₅ group leading to C–C bond formation was cleanly performed under standard conditions, and is expected to pose no problems when applied to different silyloxyiminium salts 3. On the other hand, the synthesis of salts 3 involving C–N bond formation is more sensitive and substrate-dependent process, and, in fact, availability of salts 3 defines the scope of the present methodology.

In summary, a convenient approach for the preparation of N-(pentafluorophenylmethyl)aminoethanols based on coupling of imines with silyloxyethyl triflate derived from ethylene oxide and (C₆F₅)₃SiOTf, has been developed.

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**Table 1** Variation of Lewis Basic Mediator and Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis base</th>
<th>Solvent</th>
<th>Yield of 1a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Py-N-oxide</td>
<td>CDCl₃–CD₃CN</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>(Me₂N)₃PO</td>
<td>CDCl₃–CD₃CN</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>AcOH–Et₂N</td>
<td>CH₂Cl₂</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>LiOAc</td>
<td>DMF</td>
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<tr>
<td>5</td>
<td>NaOAc</td>
<td>DMF</td>
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<tr>
<td>6</td>
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<td>7</td>
<td>NaOAc</td>
<td>THF</td>
<td>94</td>
</tr>
</tbody>
</table>

*Conditions: r.t., 20 min; the ratio of reagents: 3a/Lewis base = 1:1.2. Isolated yield. Reaction performed in a mixed solvent and monitored by ¹H NMR.*

The C–N bond formation occurs via alkylation of imines, whereas the key step for the C–C bond formation includes the activation of silicon with acetate ion, allowing for the transfer of pentafluorophenyl group from pentacoordinate silicate species onto iminium carbocation.
All reactions were performed under an argon atmosphere. Dichloromethane and dichloroethane were distilled from CaH₂ prior to use. Acetonitrile was distilled from CaH₂ and stored over MS 4 Å. All reactions were performed under an argon atmosphere. Dichloromethane and dichloroethane were distilled from CaH₂ prior to use.

Acetonitrile was distilled from CaH₂ and stored over MS 4 Å.

1H NMR (200 MHz, CDCl₃): δ = 62.9, 75.6, 104.1 (tm, J = 27 Hz), 118.6 (q, J = 319.4 Hz), 137.6 (dm, J = 255.5 Hz), 144.2 (dm, J = 259.8 Hz), 149.3 (dm, J = 247.0 Hz).

19F NMR (188 MHz, CDCl₃): δ = –160.34 (m, meta), –146.71 (tt, J = 5.1, 19.4 Hz, para), –128.81 (m, ortho), –76.10 (s, CF₃).

Impurities
1H NMR (200 MHz, CDCl₃): δ = 3.57 (t, J = 4 Hz), 3.77 (t, J = 4.3 Hz), 4.06 (t, J = 4.1 Hz), 4.53 (t, J = 4.5 Hz).

2-Tris(pentafluorophenyl)silyloxyethyl Triflate (4)
Pyridine (31 mL, 0.38 mmol) and ethylene oxide (0.47 mL, 9.41 mmol) were successively added to a suspension of silyltriflate (5.11 g, 7.53 mmol) in CH₂Cl₂ (10 mL) at 0 °C. After 10 min at 0 °C the cold solvent was decanted, the solid was washed with hexane (2 × 5 mL) at rt. The combined hexane phase was warmed to obtain a clear solution and left in the freezer (–23 °C) overnight. The cold solvent was decanted, the solid was washed with hexane (5 mL), and dried under vacuum to afford 4 (4.51 g) that corresponds to 83% yield. However, according to 1H NMR the product contains ca. 10 mol% of unidentified impurities. Further purification of this material failed. The single crystals for X-ray analysis were grown by recrystallization from large amount of hexane at 5 °C; mp 63–66 °C.

1H NMR (200 MHz, CDCl₃): δ = 4.26 (t, J = 4.1 Hz, 2 H), 4.64 (t, J = 4.1 Hz, 2 H).

Table 2 Synthesis of Aminoalcohols 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
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<th>R²</th>
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<th>Time (h)b</th>
<th>Yield of 1 (%)c</th>
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<tr>
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<td>2a</td>
<td>Ph</td>
<td>Me</td>
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<td>i-Pr</td>
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<td>3e</td>
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<td>1c</td>
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<td>86</td>
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<tr>
<td>4</td>
<td>2d</td>
<td>p-MeOCH₂H₄</td>
<td>Bn</td>
<td>1d</td>
<td>1</td>
<td>85</td>
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<td>t-Bu</td>
<td>Bn</td>
<td>1e</td>
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<td>66</td>
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<tr>
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<td>Ph</td>
<td>Ph</td>
<td>1h</td>
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<tr>
<td>9</td>
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<td>a-thienyl</td>
<td>p-MeOCH₂H₄</td>
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<td>80</td>
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<tr>
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<td>a-furyl</td>
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<td>1j</td>
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<tr>
<td>11</td>
<td>2k</td>
<td>E-PhCH=CH</td>
<td>Ph</td>
<td>1k</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>2l</td>
<td>c-C₅H₉</td>
<td>Bn</td>
<td>1l</td>
<td>1</td>
<td>67</td>
</tr>
</tbody>
</table>

a The ratio of reagents: 2/4/NaOAc = 1:1.05:1.2.
b Time for the interaction of 2 with 4 to give iminium salt 3.
c Isolated yield.
d Interaction of 2 with 4 was performed in CH₂Cl₂ at r.t.

**Z Isomer**

\[ ^{13}C\text{ NMR (50 MHz, CDCl}_{3}–\text{CD}_{3}\text{CN, 4:1): } \delta = 47.8, 55.2, 60.3, 174.5. \]

**Yield:** 245 mg (78%); oil;

Found: C, 41.28; H, 1.54; N, 1.64.

**N-Methyl-N-(2-tris(pentafluorophenyl)silyloxyethyl)-C-furfuryliminium Triflate (3c)**

Imine 2c (68 mg, 0.571 mmol) was added to a suspension of triflate (0.95 mmol) was added to a suspension of triflate. A white precipitate was formed. The solvent was decanted, the resulting powder was washed with DCE (2 × 0.5 mL), and dried under vacuum to give crude 3c. The solvent was decanted, the resulting powder was washed with DCE (2 × 0.5 mL), and dried under vacuum to give crude 3c. Recrystallization from DCE–MeCN; mp 173–175 °C (decomp).

**Yield:** 353 mg (85%); oil;

Found: C, 52.41; H, 4.79; N, 4.31.

**Synthesis of Ethanolamines 1; General Procedure**

Imine 2a,d-l (0.95 mmol) was added to a suspension of triflate 4 (722 mg, 1 mmol) in DCE (1.8 mL) at r.t. The resulting mixture was refluxed for a time indicated in Table 2 and evaporated under vacuum to give crude 3a-l. To the residue THF (2 mL) and powdered NaOAc (93 mg, 1.14 mmol) were successively added, the mixture was stirred for 20 min, cooled with ice/water bath, and quenched with sat. aq Na2CO3 (0.2 mL). After stirring for several minutes at r.t. the mixture was diluted with hexane–EtOAc (10 mL; 3:l), filtered through Na2SO4, concentrated and chromatographed on silica gel.

The interaction of imine 2b with 4 was performed in CH2Cl2 at r.t. for 16 h following by concentration in vacuum. Subsequent treatment of 3b was carried out in THF according to the general procedure.

The interaction of 2c with 4 was performed in THF at r.t. for 30 min followed by the addition of NaOAc. Subsequent workup was carried out according to the general procedure.

(±)-N-Methyl-N-(pentafluorophenylmethyl)-2-aminoethanol (1a)*

Yield: 243 mg (66%); oil; \( R_{f} \) 0.42 (hexanes–EtOAc, 3:1).

(±)-N-Methyl-N-(2-methyl-1-pentafluorophenylpropyl)-2-amo

Synthesis of C6F5-Substituted Aminoethanols

**Yield:** 245 mg (78%); oil; \( R_{f} \) 0.36 (hexanes–EtOAc, 3:1).

(±)-N-Methyl-N-(2-methyl-1-pentafluorophenylpropyl)-2-amo

Yield: 158 mg (56%); oil; \( R_{f} \) 0.22 (hexanes–EtOAc, 4:1).
Yield: 283 mg (73%); oil; \( R_f 0.26 \) (hexanes–EtOAc, 3:2).

\[ ^1H \text{ NMR (250 MHz, CDCl}_3\): \delta = 2.28 (s, 3 H, NCH}_3\), 2.60 (t, J = 5.6 Hz, 2 H, OCH}_2\), 3.71 (t, J = 5.5 Hz, 2 H, OCH}_2\), 5.31 (s, 1 H, CH), 7.63 (d, J = 8.5 Hz, 2 H, CH=CH), 8.15 (d, J = 8.8 Hz, 2 H, CH=CH).

\[ ^13C \text{ NMR (63 MHz, CDCl}_3\): \delta = 38.7, 56.3, 58.7, 63.6, 112.3 (tm, J = 14.7 Hz), 123.8, 127.9, 137.8 (dm, J = 254.0 Hz), 140.8 (dm, J = 255.8 Hz), 144.9 (dm, J = 252.2 Hz), 146.6, 147.2. \]

\[ ^19F \text{ NMR (188 MHz, CDCl}_3\): \delta = –161.42 (m, meta), –154.16 (t, J = 20.8 Hz, para), –138.73 (dm, J = 16.7 Hz, ortho). \]

Anal. Calcd for C\(_{16}\)H\(_{13}\)F\(_5\)N\(_2\)O\(_3\): C, 51.07; H, 3.48; N, 7.44. Found: C, 51.01; H, 3.48; N, 7.44. Anal. Calcd for C\(_{21}\)H\(_{22}\)F\(_5\)NO\(_2\): C, 63.15; H, 5.55; N, 3.51. Found: C, 63.11; H, 5.41; N, 3.51.

\( ^1H \text{ NMR (250 MHz, CDCl}_3\): \delta = 1.78 (m, 6 H, C\(_5\)H\(_9\)), 2.09–2.41 (m, 3 H, C\(_5\)H\(_9\) + OH), 2.81–3.02 (m, 2 H, CH\(_2\)N), 3.10 (dt, J = 3.4, 10.5 Hz, 1 H, OCHA), 3.39–3.53 (m, 4 H, (CH\(_2\))\(_2\)), 5.70 (d, J = 4.0 Hz, 1 H, CHN), 6.60–6.70 (m, 2 H, CH=CH), 6.96–7.49 (m, 10 H, 2 × Ph).

\[ ^13C \text{ NMR (50 MHz, CDCl}_3\): \delta = 25.1, 25.1, 30.8, 32.1, 40.0 (t, J = 2.7 Hz), 51.4, 54.4, 58.7, 62.0, 111.8 (tm, J = 19.0 Hz), 127.3, 128.5, 128.7, 137.5 (dm, J = 252.0 Hz), 139.1, 140.0 (dm, J = 253.4 Hz), 145.5 (dm, J = 242.7 Hz). \]

\[ ^19F \text{ NMR (188 MHz, CDCl}_3\): \delta = –161.25 (m, meta), –155.74 (t, J = 20.8 Hz, para), –141.97 (dd, J = 5.6, 22.2 Hz, ortho). \]

\[ ^1F \text{ NMR (188 MHz, CDCl}_3\): \delta = –162.43 (m, meta), –155.45 (t, J = 20.8 Hz, para), –139.39 (dm, J = 16.7 Hz, ortho). \]

Acknowledgment

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Synthesis of C6F5-Substituted Aminoethanols

References


(8) When N-methyl-C-phenylimine (2a) was combined with (C6F5)3SiOTf in CDCl3, no silyl iminium ion was observed (1H, 19F NMR control). Correspondingly, it is believed that silyl iminium ion from 2b and (C6F5)3SiOTf is formed in small equilibrium concentration.

(9) In the absence of pyridine lower yields of 4 were achieved, presumably owing to oligomerization of ethylene oxide by traces of triflic acid.


(11) (a) Selected structures of sp² bound triflates: BASXEX, HOYWEX, XOHEJE, LOKBAO. (b) Selected structures of carbohydrate triflates: HIFVAT, HUDDUK, UNEVAK.


(15) NaOAc is insoluble in THF. However, it dissolves in reaction mixture as C6F5 group transfer occurs, thereby allowing for convenient monitoring of reaction progress.

(16) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC 275041 (for 4) and 275042 (for 3e) and are available free of charge at CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].