

# Synthesis of *N*-Protected 3,3-Difluoroazetidin-2-ones

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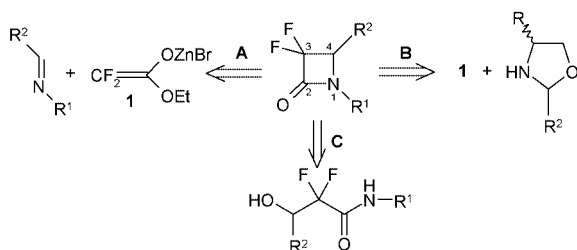
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**Abstract:** Representative *N*-protected 3,3-difluoroazetidin-2-ones **3** were obtained, either in one step by cycloaddition of zinc enolate **1** derived from ethyl bromodifluoroacetate onto *N,N,N'*-trisubstituted hexahydro-1,3,5-triazines **2** (Schiff base trimer) in the case of **3a** [*N*-(*p*-methoxybenzyl) derivative], or in two steps consisting of a Reformatsky-type reaction for the preparation of *N*-substituted 3-amino-2,2-difluoropropanones **8** followed by N1–C2 cyclization under basic conditions in the cases of **3b** (*N*-anisyl derivative) and **3c** (*N*-benzhydryl derivative).

**Key words:** fluoroazetidinone, Reformatsky-type reaction, cycloaddition, cyclization

3,3-Difluoroazetidin-2-one derivatives (Scheme 1) have been prepared either as enzyme inhibitors, or as synthetic intermediates for modified peptides.<sup>1–3</sup> Generally, the compounds were equipped with substituents in positions N1 and C4, and resulted from the cycloaddition of difluoroenolate **1** with Schiff bases (Method A),<sup>4–6</sup> or oxazolidines (Method B).<sup>7</sup> The N1–C4 cyclization of 3-hydroxy-2,2-difluoropropionamide derivatives under Mitsunobu conditions (Method C) was also described.<sup>8–11</sup>

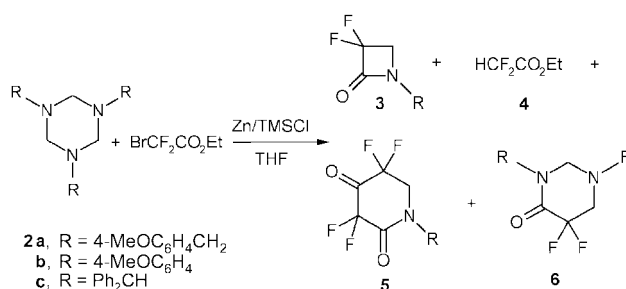


Scheme 1

The related C4 unsubstituted azetidinones (Scheme 1,  $R^2 = H$ ) are scarcely described in the previous literature;<sup>12–14</sup> only one method of synthesis of 3,3-difluoroazetidin-2-one derivatives has been reported by Wakselman et al., based on the N1–C4 cyclization of *N*-aryl-3-bromo-2,2-difluoropropionamides under strongly basic conditions. The precursor of the required anilides was ethyl 3-bromo-2,2-difluoropropanoate obtained by fluorination of ethyl bromopyruvate with sulfur tetrafluoride in an autoclave.<sup>12</sup>

In the course of a medicinal chemistry program aimed at the discovery of new serine protease inhibitors, we needed an easy and secure access towards *N*-protected 3,3-difluoroazetidin-2-ones (Scheme 1,  $R^2 = H$ ). Thus, we investigated first the usual cycloaddition method of enolate **1** onto appropriate Schiff bases. Since disappointing results were collected, we turned to a two-step approach based on the Reformatsky reaction of ethyl bromodifluoroacetate with *N*-substituted 1*H*-benzotriazolyl-1-methylamine,<sup>15</sup> followed by N1–C2 cyclization in the presence of an organomagnesium reagent. In this paper, we describe a practical synthesis of 3,3-difluoroazetidin-2-one bearing representative *N*-protecting groups.<sup>16,17</sup>

Schiff bases derived from formaldehyde cannot be isolated as such, but as cyclic trimers, i.e. *N,N,N'*-trisubstituted hexahydro-1,3,5-triazines, which are in equilibrium with the corresponding monomers in solution. Compounds **2a**,<sup>18</sup> **2b**,<sup>19</sup> and **2c**<sup>20</sup> were thus prepared and engaged in cycloaddition reactions with enolate **1** formed by treatment of ethyl bromodifluoroacetate with zinc dust. NMR analysis of the crude reaction mixtures revealed the presence of at least four products: the expected azetidinones **3**, ethyl difluoroacetate (**4**), and two 6-membered heterocycles resulting from 2:1 (**5**) and 1:2 (**6**) condensations, respectively (Scheme 2).



Scheme 2

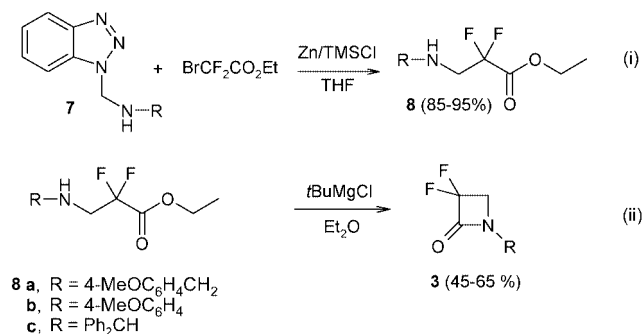
The H,F coupling constant values in <sup>1</sup>H and <sup>19</sup>F NMR spectra are typical features that allow to differentiate the cycloadducts: <sup>3</sup>J<sub>H-F</sub> was 6 Hz for the four-membered heterocycle **3** and 12 Hz for the six-membered heterocycles **5** and **6**. The reduction product **4** was characterized by a <sup>2</sup>J<sub>H-F</sub> value of 53 Hz.

In all cases, azetidinones **3** were the minor products, and the chromatographic purifications were arduous. Pure *N*-*p*-methoxybenzyl-3,3-difluoroazetidin-2-one (**3a**) could be recovered in 25% yield, but *N*-anisyl (**3b**) and *N*-ben-

hydrazide (**3c**) derivatives could not be satisfactorily purified. Changing the experimental conditions (ratio of reagents, temperature, zinc activation) did not allow an improvement in the yield of azetidinones **3**.

Since we recently developed a practical synthesis of  $\alpha,\alpha$ -difluoro- $\beta$ -alanine,<sup>15</sup> we tried to apply the cyclization methods described in the literature to this precursor for the preparation of azetidin-2-one from  $\beta$ -alanine.<sup>21</sup> Formation of the lactam bond by treatment with triphenylphosphine and 2,2'-dithiopyridine<sup>21</sup> (Mukaiyama's reagent) failed. Similarly, no cyclization product could be identified in the crude reaction mixtures following treatment of  $\alpha,\alpha$ -difluoro- $\beta$ -alanine with 2-chloro-*N*-methylpyridinium iodide<sup>22</sup> or with *N*-*tert*-butyl-2-benzothiazolysulfenamide.<sup>23</sup> Furthermore, attempts to cyclize ethyl  $\alpha,\alpha$ -difluoro- $\beta$ -alaninate<sup>15</sup> via *N*-silylation followed by treatment with an organomagnesium reagent<sup>24</sup> were unsuccessful.

Clearly, *N*-substituted  $\alpha,\alpha$ -difluoro- $\beta$ -alanine precursors should be better candidates for N1–C2 cyclization. Therefore, we prepared *N*-protected ethyl  $\alpha,\alpha$ -difluoro- $\beta$ -alaninates **8** according to the Reformatsky-type strategy outlined in Scheme 3 (i).



Scheme 3

The required *N*-protected 1*H*-benzotriazolyl-1-methylamine reagents **7** were prepared following a known procedure<sup>15,25</sup> from benzotriazole, formaldehyde and the corresponding amines, namely *p*-methoxybenzylamine (for **7a**), *p*-anisyl (for **7b**) and benzhydrylamine (for **7c**). The crude compounds **7** were recovered in nearly quantitative yields. However, under recrystallization conditions (hot methanol), **7a** was unstable and slowly transformed into benzotriazole and **2a**. On the other hand, **7b** (now commercially available reagent) and **7c** were stable and could be stored in the solid state. Reagents **7** behave as masked iminium salts, susceptible to be quenched by organometallic compounds.<sup>26</sup> Thus, reaction of **7** with zinc enolate **1** derived from ethyl bromodifluoroacetate furnished *N*-substituted ethyl 3-amino-2,2-difluoropropanoates **8**. Several reaction parameters have been changed in view to improve the yields of product **8**; in our hands, the best conditions of this Reformatsky-type coupling were as follows: two equivalents of zinc activated with one equivalent of trimethylsilyl chloride, three hours

of reaction in THF of spectroscopic grade and a temperature comprised between 25 °C and 50 °C. By this way, adducts **8b** and **8c** were obtained in about 90% yield but not compound **8a** because reagent **7a** decomposed under heating and no clean reaction occurred at lower temperatures. In <sup>1</sup>H NMR, the NCH<sub>2</sub>CF<sub>2</sub> methylene of **8** gave a triplet with a <sup>3</sup>J<sub>H-F</sub> coupling constant value of 13 Hz.

Intermediates **8b,c** were further cyclized by treatment with *tert*-butylmagnesium chloride in anhydrous ether at 0 °C (Scheme 3, equation 2). A total amount of two equivalents of base was used, added in two fractions. Pure azetidinones **3b,c** were recovered in moderate yields after column chromatography on silica gel. Compounds **3b,c** were characterized by a <sup>3</sup>J<sub>H-F</sub> coupling constant value of 6.3 Hz; a similar value was previously observed for azetidinone **3a** synthesized according to Scheme 2.

Thus representative *N*-protected 3,3-difluoroazetidin-2-ones **3** were obtained in one step by cycloaddition of zinc enolate **1** onto Schiff base trimer **2** for *N*-(*p*-methoxybenzyl) derivative **3a**, and in two steps by N1–C2 cyclization of a  $\beta$ -amino acid precursor **8** resulting from addition of enolate **1** onto 1*H*-benzotriazolyl-1-methylamine derivative **7**, in the cases of *N*-anisyl (**3b**) and *N*-benzhydryl (**3c**) derivatives. This method could be readily applied for the synthesis of *N*-aryl-3,3-difluoroazetidin-2-ones which is of interest as suicide inhibitors of serine proteases.<sup>14</sup> Compounds **3a–c** tested against porcine pancreatic elastase (PPE)<sup>27</sup> were found to be inactive.

Melting points were determined with an electrothermal microscope and are uncorrected. IR spectra were taken with a Bio-Rad FTS 135 instrument and calibrated with polystyrene. The <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded on Varian Gemini 300 (300 MHz for <sup>1</sup>H, 50 MHz for <sup>13</sup>C, and 282 MHz for <sup>19</sup>F). References for the NMR spectra were TMS for <sup>1</sup>H NMR, CDCl<sub>3</sub> for <sup>13</sup>C NMR and CFCl<sub>3</sub> for <sup>19</sup>F NMR. Mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70 eV (chemical ionization mode). Microanalyses were performed at the Christopher Ingold Laboratories, University College, London, UK. HRMS were recorded at the University of Mons, Belgium (Prof. R. Flammang).

TLC was carried out on silica gel 60 plates F254 (Merck, 0.1 mm thickness); visualization was effected with UV light. Column chromatography (under medium pressure) was carried out with Merck silica gel 60 of 230–240 mesh ASTM.

#### Reformatsky-Type Reaction for the Preparation of **3** and **8**; General Procedure

Trimethylsilyl chloride (1 equiv) was added under stirring to a suspension of zinc powder (2 equiv) in THF (1 mL/100 mg Zn). After 10 min, ethyl bromodifluoroacetate (1 equiv) was added dropwise under cooling with an ice bath. After 25 min, a solution of compound **2** or **7** (1 equiv) in THF (3 mL/mmol) was added at r.t. The mixture was then stirred during 3 h (at r.t. or at 50 °C, see particular cases below). The mixture was quenched by addition of aq NaHCO<sub>3</sub>. After filtration on Celite, the aqueous phase was extracted with EtOAc (2 ×). The organic phases were combined, washed with brine, dried (MgSO<sub>4</sub>) and evaporated under vacuum. The residue was dissolved in Et<sub>2</sub>O and the eventual precipitate was filtered off. The crude adduct could be purified by column chromatography on silica gel.

**1-(4'-Methoxybenzyl)-3,3-difluoroazetidin-2-one (3a)**

Azetidinone **3a** was obtained from the trimer of *N*-(4'-methoxybenzyl)imine (**2a**; 500 mg, 3.4 mmol, 1 equiv) and zinc enolate **1** prepared according to the general procedure. The mixture was stirred for 3 h at 25 °C. Pure **3a** (193 mg, 25%) was recovered by column chromatography (silica gel; hexane–CH<sub>2</sub>Cl<sub>2</sub>, 7:3; R<sub>f</sub> 0.26) as a pale orange oil.

IR (film): 1776 cm<sup>-1</sup> (C=O).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.17 (d, 2 H<sub>arom</sub>, *J* = 8.8 Hz), 6.90 (d, 2 H<sub>arom</sub>, *J* = 8.8 Hz), 4.45 (s, 2 H, NCH<sub>2</sub>PhOMe), 3.81 (s, 3 H, PhOCH<sub>3</sub>), 3.55 (t, 2 H, <sup>3</sup>J<sub>H-F</sub> = 5.9 Hz, CH<sub>2</sub>CF<sub>2</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 160.3 (t, <sup>2</sup>J<sub>C-F</sub> = 30.5 Hz, CF<sub>2</sub>C=O), 159.7, 129.5, 125.4 (t, <sup>1</sup>J<sub>C-F</sub> = 245 Hz, CF<sub>2</sub>), 114.5, 113.8, 55.1 (s, PhOCH<sub>3</sub>), 53.8 (t, <sup>2</sup>J<sub>C-F</sub> = 26.1 Hz, CH<sub>2</sub>CF<sub>2</sub>), 45.2 (s, NCH<sub>2</sub>PhOMe).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ = -116.3 (t, <sup>3</sup>J<sub>H-F</sub> = 6.3 Hz).

MS (CI/CH<sub>4</sub>-N<sub>2</sub>O): *m/z* (%) = 228 ([M + H]<sup>+</sup>, 24), 121 ([CH<sub>2</sub>PhOMe]<sup>+</sup>, 100).

HRMS: *m/z* calcd for C<sub>11</sub>H<sub>11</sub>F<sub>2</sub>O<sub>2</sub>N: 228.0836; found: 228.0483.

**Ethyl 2,2-Difluoro-3-[(4'-methoxyphenyl)amino]propanoate (8b)**

Ester **8b** was obtained from **7b** (5 g, 20 mmol, 1 equiv) and zinc enolate **1** prepared according to the general procedure. The mixture was stirred for 3 h at 50 °C. Work-up furnished **8b** (4.58 g, 89%) as a colorless oil which can be further used without purification. An analytical sample was obtained by column chromatography (silica gel, hexane–EtOAc, 8:2; R<sub>f</sub> 0.44).

IR (film): 1784 cm<sup>-1</sup> (C=O).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 6.75 (d, 2 H<sub>arom</sub>, *J* = 8.7 Hz), 6.63 (d, 2 H<sub>arom</sub>, *J* = 8.7 Hz), 4.23 (q, <sup>3</sup>J = 7.2 Hz, 2 H, OCH<sub>2</sub>), 3.73 (t, <sup>3</sup>J<sub>H-F</sub> = 12.6 Hz, 2 H, CH<sub>2</sub>CF<sub>2</sub>), 3.72 (s, 3 H, PhOCH<sub>3</sub>), 1.26 (t, <sup>3</sup>J = 7.2 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 163.5 (t, <sup>2</sup>J<sub>C-F</sub> = 31.8 Hz, CF<sub>2</sub>C=O), 153.1, 140.6, 115.0, 114.8, 114.5 (t, <sup>1</sup>J<sub>C-F</sub> = 251 Hz, CF<sub>2</sub>), 62.9 (s, OCH<sub>2</sub>), 55.7 (s, PhOCH<sub>3</sub>), 48.5 (t, <sup>2</sup>J<sub>C-F</sub> = 27.4 Hz, CH<sub>2</sub>CF<sub>2</sub>), 15.2 (s, CH<sub>2</sub>CH<sub>3</sub>).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ = -110.9 (t, <sup>3</sup>J<sub>H-F</sub> = 12.6 Hz).

MS (CI/CH<sub>4</sub>-N<sub>2</sub>O): *m/z* (%) = 260 ([M + H]<sup>+</sup>, 100), 259 ([M]<sup>+</sup>, 51).

HRMS: *m/z* calcd for C<sub>12</sub>H<sub>15</sub>F<sub>2</sub>O<sub>3</sub>N: 259.1016; found: 259.1020.

**Ethyl 3-(Benzhydrylamino)-2,2-difluoropropanoate (8c)**

Ester **8c** was obtained from **7c** (6 g, 19 mmol, 1 equiv) and zinc enolate **1** prepared according to the general procedure. The mixture was stirred for 3 h at 25 °C. Work-up furnished **8c** (5.02 g, 86%) as a colorless oil which can be further used without purification. An analytical sample was obtained by column chromatography (silica gel, hexane–EtOAc, 9:1; R<sub>f</sub> 0.61).

IR (film): 1771 cm<sup>-1</sup> (C=O).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.22–7.37 (m, 10 H<sub>arom</sub>), 4.89 (s, 1 H, Ph<sub>2</sub>CH), 4.34 (q, 2 H, <sup>3</sup>J = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.18 (t, 2 H, <sup>3</sup>J<sub>H-F</sub> = 13.2 Hz, CH<sub>2</sub>CF<sub>2</sub>), 1.35 (t, 3 H, <sup>3</sup>J = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 163.6 (t, <sup>2</sup>J<sub>C-F</sub> = 32 Hz, CF<sub>2</sub>C=O), 142.5, 128.5, 127.3, 127.2, 115.2 (t, <sup>1</sup>J<sub>C-F</sub> = 251 Hz, CF<sub>2</sub>), 64.5 (s, Ph<sub>2</sub>CH), 62.7 (s, OCH<sub>2</sub>), 49.7 (t, <sup>2</sup>J<sub>C-F</sub> = 26 Hz, CH<sub>2</sub>CF<sub>2</sub>), 13.9 (s, CH<sub>3</sub>).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ = -110.0 (t, <sup>3</sup>J<sub>H-F</sub> = 13.2 Hz).

MS (CI/CH<sub>4</sub>-N<sub>2</sub>O): *m/z* (%) = 319.2 ([M]<sup>+</sup>, 3), 318.2 ([M - H]<sup>+</sup>, 15), 167.2 ([M - NHCH<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>Et]<sup>+</sup>, 100), 152.2 ([M - Ph<sub>2</sub>CH]<sup>+</sup>, 11).

HRMS: *m/z* calcd for C<sub>18</sub>H<sub>19</sub>F<sub>2</sub>NO: 319.1361; found: 319.1383.

Anal. Calcd for C<sub>18</sub>H<sub>19</sub>F<sub>2</sub>NO: C, 67.69; H, 5.99; N, 4.38. Found: C, 67.37; H, 5.94; N, 4.23.

**Cyclization of 8 to Azetidinones 3; General Procedure**

In a dried glassware and under argon, *tert*-butylmagnesium chloride (2 M solution in anhyd Et<sub>2</sub>O, 1.3 equiv) was added at 0 °C under stirring to a solution of compound **8** (1 equiv) in anhyd Et<sub>2</sub>O (4.8 mL, [8] = 0.25 M). After 1 h, a second portion of *tert*-butylmagnesium chloride (2 M solution in Et<sub>2</sub>O, 0.7 equiv) was added and the mixture was brought to 20 °C. After completion of the reaction (<sup>19</sup>F NMR, ca. 2 h), the mixture was treated with sat. aq NH<sub>4</sub>Cl (very slow addition!) and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 ×). The organic phases were combined, dried (MgSO<sub>4</sub>) and evaporated under vacuum. The solid obtained was then purified by column chromatography on silica gel.

**3,3-Difluoro-1-(4'-methoxyphenyl)azetidin-2-one (3b)**

Starting from **8b** (300 mg, 1.2 mmol, 1 equiv), 140 mg (45%) of **3b** were obtained as a white solid after chromatography (silica gel, hexane–EtOAc, 8:2; R<sub>f</sub> 0.4); mp 88–90 °C.

IR (KBr): 1763 cm<sup>-1</sup> (C=O).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.3 (d, 2 H<sub>arom</sub>, *J* = 9 Hz), 6.92 (d, 2 H<sub>arom</sub>, *J* = 9 Hz), 4.01 (q, 2 H, <sup>3</sup>J<sub>H-F</sub> = 6.3 Hz, CH<sub>2</sub>CF<sub>2</sub>), 3.82 (s, 3 H, PhOCH<sub>3</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 157.3 (t, <sup>2</sup>J<sub>C-F</sub> = 30.8 Hz, CF<sub>2</sub>C=O), 155.8, 129.9, 119.4 (t, <sup>1</sup>J<sub>C-F</sub> = 235 Hz, CF<sub>2</sub>), 118.5, 114.6, 55.5 (s, PhOCH<sub>3</sub>), 54.4 (t, <sup>2</sup>J<sub>C-F</sub> = 18 Hz, CH<sub>2</sub>CF<sub>2</sub>).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ = -115.1 (t, <sup>3</sup>J<sub>H-F</sub> = 6.3 Hz).

MS (CI/CH<sub>4</sub>-N<sub>2</sub>O): *m/z* (%) = 213.8 ([M + H]<sup>+</sup>, 100).

HRMS: *m/z* calcd for C<sub>10</sub>H<sub>10</sub>F<sub>2</sub>NO<sub>2</sub>: 214.0683; found: 214.0679.

Anal. Calcd for C<sub>10</sub>H<sub>9</sub>F<sub>2</sub>NO<sub>2</sub>: C, 56.34; H, 4.25; N, 6.57. Found: C, 56.06; H, 4.22; N, 6.34.

**1-Benzhydryl-3,3-difluoroazetidin-2-one (3c)**

Starting from **8c** (4 g, 0.013 mol, 1 equiv), 2.311 g (65%) of **3c** was obtained as a white solid after chromatography (silica gel, hexane–EtOAc, 99:1, then 95:5) and recrystallization from propan-2-ol; mp 92–93 °C.

IR (KBr): 1784 cm<sup>-1</sup> (C=O).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.15–7.39 (m, 10 H<sub>arom</sub>), 6.26 (s, 1 H, Ph<sub>2</sub>CH), 3.64 (t, 2 H, <sup>3</sup>J<sub>H-F</sub> = 6.3 Hz, CH<sub>2</sub>CF<sub>2</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 160.3 (t, <sup>2</sup>J<sub>C-F</sub> = 30.7 Hz, CF<sub>2</sub>C=O), 137.0, 128.9, 128.3, 127.9, 119.9 (t, <sup>1</sup>J<sub>C-F</sub> = 284.5 Hz, CF<sub>2</sub>), 59.5 (s, Ph<sub>2</sub>CH), 53.7 (t, <sup>2</sup>J<sub>C-F</sub> = 26.4 Hz, CH<sub>2</sub>CF<sub>2</sub>).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ = -116.07 (t, <sup>3</sup>J<sub>H-F</sub> = 6.3 Hz).

MS (CI/CH<sub>4</sub>-N<sub>2</sub>O): *m/z* (%) = 274.0 ([M + H]<sup>+</sup>, 14), 166.9 ([Ph<sub>2</sub>CH]<sup>+</sup>, 100).

HRMS: *m/z* calcd for C<sub>16</sub>H<sub>14</sub>F<sub>2</sub>NO: 274.1045; found: 274.1043.

Anal. Calcd for C<sub>16</sub>H<sub>13</sub>F<sub>2</sub>NO: C, 70.32; H, 4.79; N, 5.12. Found: C, 70.07; H, 4.91; N, 5.15.

**Benzotriazole Derivatives 7; General Procedure**

The appropriate amine (1 equiv) and formaldehyde (37% aq solution, 1.2 equiv) were successively added to a solution of benzotriazole (1 equiv) dissolved in a minimum amount of MeOH. The mixture was then stirred at r.t. until a precipitate appeared. After evaporation under vacuum, the solid obtained was recrystallized from MeOH.

***N*-(4'-Methoxybenzyl)-1*H*-benzotriazolyl-1-methylamine (7a)**

This compound was unstable and characterized only by <sup>1</sup>H NMR of the crude mixture.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.1–7.3 (m, 8  $\text{H}_{\text{arom}}$ ), 6.9 (d,  $J$  = 9 Hz, 2 H,  $\text{CH}_2$ ), 5.68 (s, 2 H,  $\text{CH}_2\text{PhOMe}$ ), 3.81 (s, 3 H,  $\text{OCH}_3$ ).

#### ***N*-(Benzhydryl)-1*H*-benzotriazolyl-1-methylamine (7c)**

Starting from diphenylmethanamine (8.87 mL, 0.047 mol), 13.38 g (97%) of **7c** was obtained as a white solid; mp 101–103 °C.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 7.43–7.02 (m, 14  $\text{H}_{\text{arom}}$ ), 5.50 (s, 2 H,  $\text{CH}_2$ ), 4.65 (s, 1 H,  $\text{CHPh}_2$ ), 2.96 (br s, 1H, NH).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz):  $\delta$  = 145.7, 141.9, 133.1, 128.6, 128.5, 127.4, 127.3, 127.2, 123.8, 119.8, 118.2, 109.3, 62.9, 59.8.

MS ( $\text{CI}/\text{CH}_4\text{-N}_2\text{O}$ ):  $m/z$  (%) = 362.4 ( $[\text{Ph}_2\text{CHCH}_2\text{NHCHPh}_2]^+$ , 31), 196.0 ( $[\text{CH}_2=\text{NCHPh}_2]^+$ , 35), 167.0 ( $[\text{Ph}_2\text{CH}]^+$ , 100), 119.9 ( $[\text{1H-benzotriazole}]^+$ ).

Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_4$ : C, 76.41; H, 5.77; N, 17.82. Found: C, 76.27; H, 5.54; N, 17.96.

#### **Acknowledgment**

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