Reduction of 5-(Trifluoromethyl)isoxazoles with Lithium Aluminum Hydride: Synthesis of (2,2,2-Trifluoroethyl)aziridines

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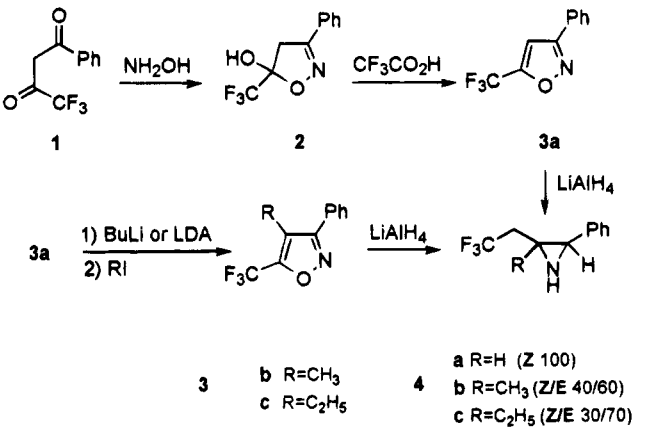
Trifluoromethylated heterocycles are currently of considerable interest, owing to their biological potential.[1,2] During our ongoing research on the synthesis of trifluoromethylated aziridines,[3] we focused our efforts on the preparation of (2,2,2-trifluoroethyl)aziridines **4** (Scheme 1) and some heterocyclic derivatives. Such functionality should enhance the lipophilicity, keeping unchanged the chemical reactivity. In this paper, we report on a specific strategy directed toward the transformation of (trifluoromethyl)isoxazoles into aziridines.

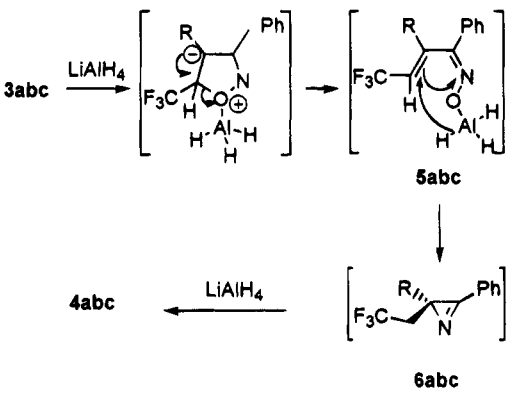
Reduction of the isoxazole ring has been thoroughly described in the literature[4–6] and most often led to N–O bond cleavage. However, only a few examples of the isoxazole ring reduction using $LiAlH_4$ (LAH) were reported.[7,8] When 3,4-diphenylisoxazole was treated with LAH, no aziridine was formed, but the starting material was recovered quantitatively.[7] The reduction of 3,5-dimethylisoxazole and 3,4,5-trimethylisoxazole with LAH yielded a complex mixture.[8] The major component was the result of a hydride attack at the C_5 carbon followed by N–O bond cleavage. Only 2 equiv of hydride is required. More recently, Alberola et al.[9] have shown that 4-cyano-3,5-dimethylisoxazole reduction by LAH produces 5-amino-4-ethyl-3-methylisoxazole. The driving force of this reaction is the stabilization of the negative charge by the nitrile group. This stabilization favors the C_5–O bond cleavage and produces a conjugated oximate, which is the precursor of the 5-aminoisoxazole. Moreover, Kotera[7] has shown that LAH transforms oximates from conjugated ketones to aziridines. So bearing in mind the electron-withdrawing force of a 5-trifluoromethyl group, we thought that a 5-trifluoromethyl group could favor the C–O bond cleavage (Scheme 2) and could produce the conjugate oximate **5a–c** which should be transformed into a (trifluoroethyl)aziridine.

(Trifluoromethyl)isoxazoles are generally obtained via 1,3-dipolarcycloaddition[10,11] or addition of hydroxylamine to conjugated ynone[2] or to β-diketone[12] derivatives. Using this last reaction, we prepared the 5-hydroxyisoxazoline **2** and the corresponding isoxazole **3a**. Further alkylation[13] gave the 4-alkylisoxazoles **3b,c**. When 5-(trifluoromethyl)isoxazoles **3a–c** reacted with LAH, (trifluoroethyl)aziridines **4a–c** were formed in good yields. This reaction represents the first synthesis of (trifluoroethyl)aziridines.

Scheme 1



Scheme 2



The reaction from the isoxazole **3a** is completely stereoselective ((*Z*)-**4a**, 100%). This stereoselectivity is in agreement with the literature.[14] But it is interesting to point out that the *Z* aziridine is the minor isomer obtained from azirines **6b,c**. The major one comes from the addition of the hydride on the most hindered side (cis addition vs CF_3–CH_2). We want to recall that a trifluoromethyl group is as large as a phenyl or a cyclohexyl one.[15] A repulsive interaction between the π-electrons of the CN double bond and the electronegative trifluoromethyl group could favor a conformation in which the trifluoromethyl group is far away from the CN bond. The addition of hydride to form the *E* isomer occurs easily.

Further ring transformations of the *N*-carbethoxy derivative (*Z*)-**7a** led to different heterocycles. Thus, treatment of (*Z*)-**7a** with sodium iodide afforded the oxazoline (*E*)-**8a** with total inversion of configuration (Scheme 3). The thermolysis of (*Z*)-**7a** allowed for the formation of the oxazolidinone **9a** with loss of stereo-

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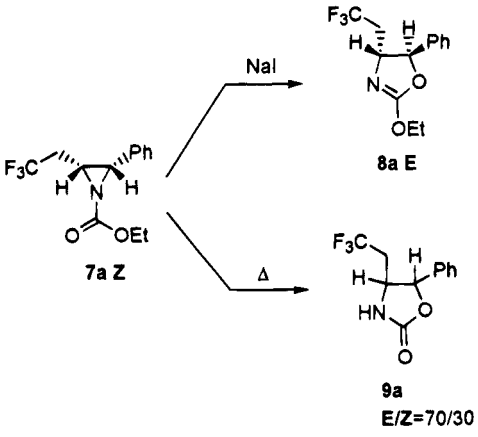
Scheme 3



chemistry. Such reactions have been previously studied and described on N-derivatives of 3-phenyl-2-(trifluoromethyl)aziridines.[16]

In conclusion, the reduction of 5-trifluoromethylated 3-phenylisoxazoles with LAH allows for the synthesis of (2,2,2-trifluoroethyl)aziridines in good yields. This method provides an alternative to the preparation of trifluoroethylated heterocycles. Further studies on the synthesis of such fluorine-containing heterocycles are underway.

Experimental Section

NMR spectra were recorded in $CDCl_3$ unless otherwise noted and at 60 or 200 MHz (^1H), 56.4 MHz (^{19}F), and 75.47 MHz (^{13}C). TMS was used as an internal standard for ^1H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR. Chemical shifts are reported in ppm. Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrometer. Mass spectra were obtained using a Nermag R10-10S instrument operated at 70 eV. Melting points are uncorrected. Merck 60 (0.063–0.200 mm) and Merck 60H silica gels were used for column chromatography. All reactions involving air sensitive materials were conducted under a nitrogen atmosphere.

3-Phenyl-5-hydroxy-5-(trifluoromethyl)isoxazoline (2). A solution of 8.2 g (116.3 mmol) of hydroxylamine hydrochloride in 94 mL of water was made alkaline with 60 mL of a 2 N solution of sodium hydroxide. A solution of 25.0 g (115.7 mmol) of diketone **1** in 280 mL of ethanol was added dropwise to the mixture at room temperature. Stirring was continued for 45 min in refluxing solvent. The reaction mixture was then hydrolyzed with water (600 mL). A precipitate of the isoxazoline **2** was formed, and after filtration, 24.2 g (104.8 mmol, 91%) of **2** was isolated as white crystals: mp 144–145 °C; ^1H NMR (CD_3COCD_3) δ 3.60 and 4.13 (2d, J = 19.0 Hz, 2H), 7.43 (s, 1H), 7.5–8.2 (m, 5H); ^{13}C NMR δ 43.6, 104.9, 123.6, 127.7, 129.5, 129.7, 131.6, 157.7; ^{19}F NMR δ −80.0 (s); IR (Nujol, cm^{-1}) ν 3140, 1610, 1530, 1190–1155; MS m/z (relative intensity) 231 (M^+, 55). Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.95; H, 3.48; N, 6.06. Found: C, 52.13; H, 3.50; N, 5.97.

3-Phenyl-5-(trifluoromethyl)isoxazole (3a). A solution of 11.6 g (50.4 mmol) of **2** in 230 mL of trifluoroacetic acid was stirred for 24 h in refluxing acid. After neutralization of the acid with an aqueous solution of sodium carbonate, the crude mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 9.8 g (45.9 mmol, 91%) of **3a** which was further crystallized in petroleum ether to yield 8.8 g (41.2 mmol, 82%) of pure **3a** as white crystals: mp 80–81 °C; ^1H NMR δ 6.9 (s, 1H), 7.2–8.1 (m, 5H); ^{13}C NMR δ 103.5, 118.0, 127.0, 127.5, 129.3, 131.0, 159.3, 162.7; ^{19}F NMR δ −65.0 (s); IR (CH_2Cl_2, cm^{-1}) ν 1680, 1190–1150; MS m/z (relative intensity) 213 (M^+, 100). Anal. Calcd for $C_{10}H_6F_3NO$: C, 56.34; H, 2.83; N, 6.57. Found: C, 56.40; H, 2.80; N, 6.45.

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General Procedure for the Alkylation of the 3-Phenyl-5-(trifluoromethyl)isoxazole (3a). A solution of 10 mmol of **3a** in 15 mL of THF was added dropwise at 0 °C to a solution of 12 mmol of *n*-butyllithium in 10 mL of THF. After 30 min, a solution of 12 mmol of the appropriate alkyl iodide in 5 mL of THF was added dropwise over a 15 min period. The mixture was then allowed to warm to room temperature and was stirred for 2 h. After this time, the reaction mixture was hydrolyzed with brine and extracted with diethyl ether (3 × 50 mL). The combined organic solutions were dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent petroleum ether/methylene chloride (4:1)) to afford pure **3b,c**.

3-Phenyl-4-methyl-5-(trifluoromethyl)isoxazole (3b): yield 64%; mp 41–42 °C; ^1H NMR δ 2.28 (s, 3H), 7.4–8.2 (m, 5H); ^{13}C NMR δ 7.5, 114.9, 118.9, 127.8, 128.4, 129.0, 130.3, 154.6, 163.7; ^{19}F NMR δ −63.3 (s); IR (CH_2Cl_2, cm^{-1}) ν 1640, 1580, 1140–1170. Anal. Calcd for $C_{11}H_8F_3NO$: C, 58.15; H, 3.55; N, 6.16. Found: C, 57.98; H, 3.51; N, 6.04.

3-Phenyl-4-ethyl-5-(trifluoromethyl)isoxazole (3c): yield 53%; ^1H NMR δ 1.10 (t, J = 7.5 Hz, 3H), 2.65 (q, J = 7.5 Hz, 2H), 7.6 (s, 5H); ^{13}C NMR δ 14.8, 15.3, 119.0, 121.3, 128.1, 128.4, 129.1, 130.3, 154.3, 163.6; ^{19}F NMR δ −63.5 (s); IR (film, cm^{-1}) ν 1630, 1200–1125; MS m/z (relative intensity) 241 (M^+, 26). Anal. Calcd for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.80. Found: C, 59.59; H, 4.35; N, 5.57.

General Procedure for the Reduction of Isoxazoles 3a–c with LAH. A solution of 5 mmol of isoxazole **3a–c** in 15 mL of THF was added dropwise at room temperature to a solution of 30 mmol of LAH in 15 mL of THF. The solution was stirred in refluxing solvent for 2 h. The mixture was then hydrolyzed with water (50 mL) and extracted with diethyl ether. The organic layer was washed with brine (3 × 35 mL) and then dried over magnesium sulfate. After removal of the solvent under reduced pressure, the products (colorless liquids) (**4a**, 72%; **4b**, 92%; **4c**, 69%) were pure enough to determine the *E*/*Z* ratios by NMR and to perform further reactions. A small part of each aziridine was purified by column chromatography (eluent petroleum ether/methylene chloride (3:1)) to obtain good analyses.

(*Z*)-2-Phenyl-3-(2,2,2-trifluoroethyl)aziridine (4a): ^1H NMR δ 1.5 (m, 1H), 1.90 (dxq, J_{HH} = 6.1 Hz, J_{HF} = 10.8 Hz, 2H), 2.57 (dxt, J_{HH} = 6.1 Hz, J_{HH} = 6.1 Hz, 1H), 3.37 (d, J_{HH} = 6.1 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR δ 30.6, 33.4, 35.5, 126.7, 127.3, 127.7, 128.2, 136.2; ^{19}F NMR δ −65.7 (t, J_{HF} = 10.3 Hz); IR (CH_2Cl_2, cm^{-1}) ν 3320, 1160–1110; MS m/z (relative intensity) 201 (M^+, 22). The elemental analysis was performed on the N-benzoylated derivative of **4a**. Anal. Calcd for $C_{17}H_{14}F_3NO$: C, 66.87; H, 4.62; N, 4.58. Found: C, 67.11; H, 4.72; N, 4.47.

2-Phenyl-3-methyl-3-(2,2,2-trifluoroethyl)aziridine (4b). A 3:2 mixture of *E*/*Z* aziridine was obtained. **(*E*)-4b:** ^1H NMR δ 1.01 (s, 4H), 2.48 and 2.55 (dxq, J_{HH} = 14.4 Hz, J_{HF} = 10.4 Hz, 2H), 3.16 (s, 1H), 7.2–7.5 (m, 5H); ^{13}C NMR δ 18.0, 36.1, 44.2, 44.7, 126.8, 127.3, 127.6, 128.3, 136.7; ^{19}F NMR δ −63.5 (t, J_{HF} = 10.8 Hz); IR (CH_2Cl_2, cm^{-1}) ν 3310, 1120–1080; MS m/z (relative intensity) 215 (M^+, 33). **(*Z*)-4b:** ^1H NMR δ 1.52 (s, 3H), 2.15 and 2.23 (dxq, J_{HH} = 14.4 Hz, J_{HF} = 10.9 Hz, 2H), 2.32 (s, 1H), 3.07 (s, 1H), 7.2–7.5 (m, 5H); ^{13}C NMR δ 25.0, 37.0, 37.2, 44.7, 126.3, 127.6, 127.7, 128.3, 136.8; ^{19}F NMR δ −62.7 (t, J_{HF} = 10.8 Hz). Anal. Calcd for $C_{11}H_{12}F_3N$: C, 61.40; H, 5.62; N, 6.50. Found: C, 61.16; H, 5.77; N, 6.10.

2-Phenyl-3-ethyl-3-(2,2,2-trifluoroethyl)aziridine (4c). A 7:3 mixture of *E*/*Z* aziridine was obtained. **(*E*)-4c:** ^1H NMR δ 0.87 (t, J_{HH} = 7.4 Hz, 3H), 1.0–1.5 (m, 3H), 2.32 and 2.59 (dxq, J_{HH} = 15.0 Hz, J_{HF} = 11.0 Hz, 2H), 3.21 (s, 1H), 7.31 (s, 5H); ^{13}C NMR δ 9.30, 23.6, 40.3, 40.7, 44.6, 126.3, 127.2, 127.7, 128.2, 136.6; ^{19}F NMR δ −63.6 (t, J_{HF} = 10.8 Hz); IR (CH_2Cl_2, cm^{-1}) ν 3300, 3225, 1600, 1270–1230; MS m/z (relative intensity) 229 (M^+, 48). **(*Z*)-4c:** ^1H NMR δ 1.25 (t, J_{HH} = 7.5 Hz, 3H), 3.17 (s, 1H); ^{13}C NMR δ 9.40, 25.3, 40.5, 43.1, 125.6, 127.7, 127.8, 134.1; ^{19}F NMR δ −62.7 (t, J_{HF} = 11.3 Hz). The elemental analysis was performed on the N-benzoylated derivative of **4c**. Anal. Calcd for $C_{19}H_{18}F_3NO$: C, 68.45; H, 5.44; N, 4.20. Found: C, 68.14; H, 5.84; N, 3.97.

2-Phenyl-3-(trifluoromethyl)-*N*-carbethoxyaziridine (7a). This aziridine derivative was prepared from **4a** as described in the literature[16] with 65% yield: ^1H NMR δ 1.23 (t, J = 8.0 Hz, 1H), 1.6–2.5 (m, 2H), 2.96 (dxt, J = 7.0 Hz, 1H), 3.75 (d, J = 7.0 Hz, 1H), 4.21 (q, J = 8.0 Hz, 2H), 7.43 (m, 5H); ^{13}C NMR δ

14.20, 32.52, 37.46, 42.64, 63.0, 126.0, 127.50, 128.20, 128.53, 133.41, 162.92; ^{19}F NMR δ −65.66 (t, J_{HF} = 10.34 Hz); IR (CH_2Cl_2, cm^{-1}) ν 1720, 1300−1190; MS *m/z* (relative intensity) 200 ($M^{\bullet+}$ − CO_2Et, 19). Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.13; H, 5.16; N, 5.12. Found: C, 56.89; H, 5.45; N, 4.72.

2-Ethoxy-4-(2,2,2-trifluoroethyl)-5-phenyl-Δ²-oxazoline (8a). A solution of aziridine derivative **7a** (520 mg, 1.9 mmol) and sodium iodide (300 mg, 2.0 mmol) in 40 mL of butanone was stirred for 22 h in refluxing solvent. The reaction mixture was hydrolyzed with water (50 mL) and extracted with diethyl ether (3 × 30 mL). The organic layer was dried over magnesium sulfate. After removal of the solvent under reduced pressure, the crude product (500 mg) was purified by column chromatography (eluent petroleum ether/diethyl ether (9:1)) to exclusively afford the oxazoline derivative (***E***)**-8a** (1.05 mmol, 55 %): ^{1}H NMR δ 1.36 (t, J = 7.0 Hz, 3H), 2.0−2.9 (m, 2H), 4.1−4.5 (m, 3H), 5.3 (d, J = 6.0 Hz, 1H), 7.4 (m, 5H); ^{13}C NMR δ 14.3, 40.2, 66.5, 67.3, 86.2, 125.7, 125.9, 128.9, 129.0, 139.1, 162.6; ^{19}F NMR δ −63.6 (t, J_{HF} = 11.9 Hz).

4-(2,2,2-Trifluoroethyl)-5-phenyloxazolidin-2-one (9a). A solution of **7a** (1.05 g, 3.8 mmol) in toluene (2.0 mL) was stirred in refluxing solvent for 8 h. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (eluent petroleum ether/acetone (2:1)) to afford a 7:3 mixture of *E*/*Z* oxazolidinone **9a** (420 mg, 45%). (***E***)**-9a:** ^{1}H NMR δ 2.46−2.59 (m, 2H), 4.06 (dxdxd, J = 6.2 Hz, 1H), 5.18 (d, J = 6.09 Hz, 1H), 6.64 (s, 1H), 7.26−7.46 (m, 5H); ^{13}C NMR δ 38.8, 55.2, 82.6, 125.4, 126.0, 129.2, 129.6, 136.7, 158.6; ^{19}F NMR δ −64.5 (t, J_{HF} = 11.4 Hz); IR (CH_2Cl_2, cm^{-1}) ν 3270−3440, 1770, 1165−1135; MS *m/z* (relative intensity) 245 (M^+, 19). Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.59; H, 4.07; N, 5.64. (***Z***)**-9a:** ^{1}H NMR δ 1.69−1.95 (m, 2H), 4.41 (m, 1H), 5.78 (d, J = 8.18 Hz, 1H), 6.45 (s, 1H), 7.26−7.46 (m, 5H); ^{13}C NMR δ 36.5, 51.2, 79.9, 126.0, 126.1, 129.1, 129.4, 133.9, 158.7; ^{19}F NMR δ −64.6 (t, J_{HF} = 11.5 Hz).

Supplementary Material Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra of (***E***)**-8a** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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