Unusual Reaction of *N*-Arylimines of Hexafluoroacetone with *m*-Chloroperoxybenzoic Acid. New Route to 2,2-Bis(trifluoromethyl)benzoxazolidines†

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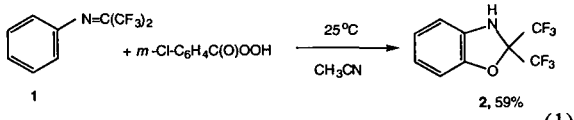
Abstract. Reaction of readily available *N*-arylimines of hexafluoroacetone with anhydrous *m*-chloroperoxybenzoic acid leads to the formation of substituted 2,2-bis(trifluoromethyl)oxazolidines in 30–70% yield as a result of an oxidative cyclization reaction. This process is general and can be used as a synthetic route to the corresponding polyfluorinated oxazolidines.

The oxidation of highly fluorinated *N*-arylimines of hexafluoroacetone, such as *p*-$CF_3C_6F_4N{=}C(CF_3)_2$ and *p*-$NC_5F_4N{=}C(CF_3)_2$, has been demonstrated to proceed with the formation of the corresponding oxaziridines in high yield.[1]

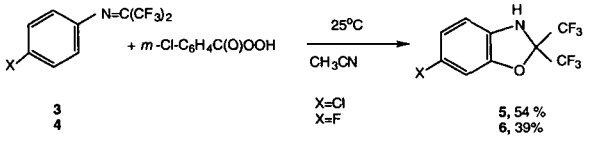
We have found that, in contrast to the above-mentioned reaction, oxidation of *N*-phenylimine of hexafluoroacetone by anhydrous *m*-chloroperoxybenzoic acid (MCPBA) leads to a different result. The reaction proceeds at ambient temperature in a polar solvent with the formation of only one product, which was identified (^1H, ^{19}F NMR, and IR spectroscopy) as 2,2-bis(trifluoromethyl)benzoxazolidine (**2**), previously made by the reaction of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane with 2-aminophenol.[2]



(1)

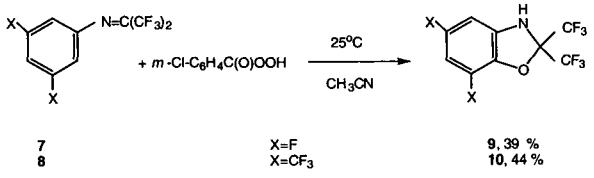
Since starting *N*-arylimines are readily available by the reaction of the corresponding isocyanates with hexafluoroacetone (HFA)[3,4] and the oxidative process is generic, it is used in the synthesis of several previously unknown 2,2-bis-(trifluoromethyl)benzoxazolidines.

For example, the oxidation of imines **3** and **4** with a slight excess of MCPBA at ambient temperature leads to oxazolidines **5, 6** in moderate yield.



(2)

Imines **7** and **8** containing a symmetrically substituted phenyl ring behave similarly, giving oxazolidines **9** and **10**.



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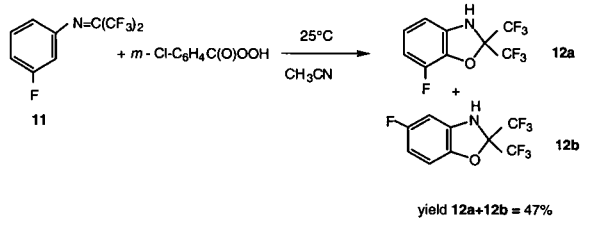
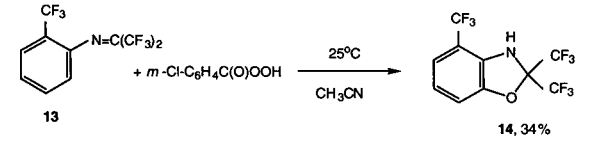
Oxidation of 3-fluorophenylimine **11** with MCPBA results in the formation of a mixture of two isomeric oxazolidines, **12a** and **12b**, in a ratio of 24:76.



(4)

Based on ^1H and ^{19}F NMR spectroscopy data and mechanistic considerations (see the discussion below), the structure **12b** is assigned to the major isomer. The formation of only one regioisomer, oxazolidine **14**, is observed in the reaction of MCPBA with 2-(trifluoromethyl)phenylimine of hexafluoroactetone (**13**).



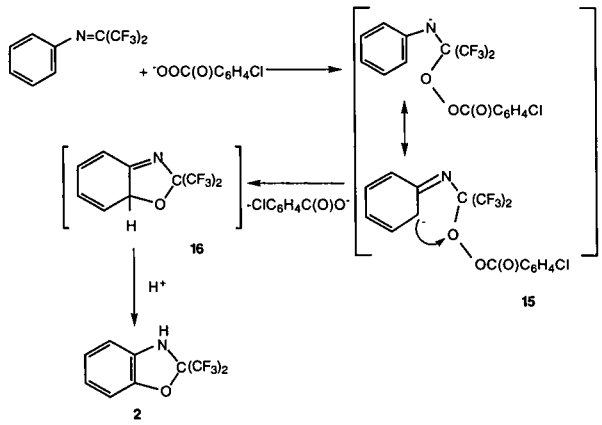
(5)

It is noteworthy that all oxidation reactions are clean and, according to ^{19}F NMR spectroscopy data, after 12–16 h at ambient temperature, the reaction mixture contains only the corresponding oxazolidine, along with a small amount (5–10%) of starting imine. For reasons not yet fully understood, it is difficult to achieve a complete conversion of the imine, even when excess oxidant and extended reaction time are used. The necessary separation of the product from the starting material entails lower yields, typically 30–60%.

Presence of a polar solvent, such as CH_3CN or sulfolane, is essential for the oxidation since no formation of compound **2** is observed in the reaction of *N*-phenylimine of hexafluoroacetone with MCPBA in a dry methylene chloride solvent. On the other hand, the reaction is limited to polyfluorinated imines because, as demonstrated in the control experiment, the reaction of *N*-benzylideneaniline and MCPBA under the conditions used in oxidation of imines **1**, **3**, **4**, **7**, **8**, **11**, and **13** results in the formation of a complex mixture of products, a major component being benzaldehyde (^1H NMR). This is not surprising since limited stability of Schiff bases and hydrocarbon oxaziridines to protic acids is well documented[5,6] and consistent with several reported unsuccessful attempts to prepare the corresponding oxaziridines of imines bearing an aryl group at nitrogen[7,8] by oxidation using peroxyacids. Despite the fact that conversion of imines to oxaziridines is usually carried out by reaction with peroxyacids, most of the known *N*-aryloxaziridines have been prepared by such different procedures as, for example, photochemical isomerization of nitrones,[8,9] thereby avoiding the use of protic acids.

IR spectra of benzoxazolidines **2**, **5**, **6**, **9**, **10**, **12a,b**, and **14** exhibit strong absorption around 3400 cm^{-1}, assigned to the N–H group. In ^1H NMR spectra, all of them contain broad resonances at 4.7–5.0 ppm typical of an N–H fragment. ^{19}F NMR spectra of oxazolidines show a resonance at –80 ppm, along with the resonances of aromatic fluorines in compounds **6**, **9**, **12a,b**, and CF_3 groups in **10** and **14**. In mass spectra of all oxazolidines, a parent ion of high intensity is present along with a variety of other fragment ions.

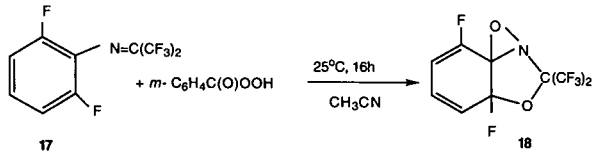
We believe that the mechanism of this reaction involves several steps. As proposed earlier for polyfluorinated imines,[10] the reaction starts with a nucleophilic attack on the carbon of the C=N bond by peroxyanion, resulting in formation of mesomeric anion **15**.



Scheme 1

The ring closure reaction occurs as a result of nucleophilic attack by *carbanion* on the oxygen of the peroxy group yielding imine **16**, which further rearranges into the final product through a protonation–deprotonation sequence. This reaction is mechanistically similar to the oxidation, reported a few years ago,[11] of 4,4-bis(trifluoromethyl)-1,3-diazabutadienes-1,3 by MCPBA producing 5,5-bis(trifluoromethyl)-1,2,4-oxadiazol-3-ines.

Interestingly, the oxidation of 2,6-difluorophenylimine of HFA (**17**), having both hydrogens in the α-position of the aromatic ring replaced with fluorine substituents, proceeds in a different manner. This process leads to the formation of a compound which is believed to be oxaziridine **18**.

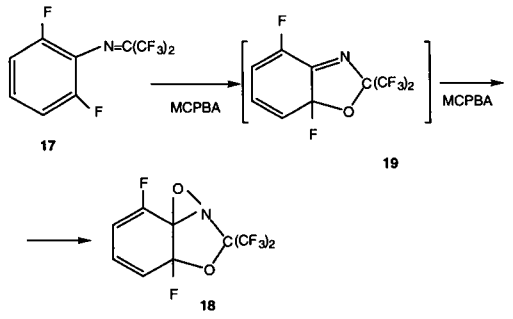


(6)

Although compound **18** was not isolated (it rapidly decomposes during isolation), all experimental data support the formation of the oxaziridine structure. In contrast to oxazolidines **5**, **6**, **9**, **10**, **12a,b**, and **14**, which do not possess any oxidative properties, a solution of compound **18** in CH_2Cl_2 (after MCPBA is removed) releases iodine from a KI solution, typical of oxaziridines which are known to be strong oxidizers.[5,6,12] Data of ^{19}F, ^1H NMR spectroscopy are also in agreement with oxaziridine structure **18**. For example, the ^{19}F NMR spectrum of a mixture of imine **17** and MCPBA in CH_3CN (after 1 h at 25 °C) contains a new set of signals at –74.7, –75.4, –77.8, and –126.3 ppm integrated as 3:1:3:1, along with signals of the starting material (26%). In oxaziridine **18**, trifluoromethyl groups are expected to be nonequivalent due to the presence of asymmetrical centers in the ring (resonances at –74.70 and –77.83 ppm). A significant difference in the chemical shifts betweeen the signals pertaining to two fluorine substituents (–75.39 and –126.30 ppm) suggests that the two atoms have different environments, with the signal at –75.39 ppm being assigned to the fluorine in the α-position to oxygen in the oxazolidine ring. The ^1H NMR spectrum, although quite complex, is also consistent with the proposed structure.

Scheme 2 presents a mechanism for the formation of oxaziridine **18**.

The process starts with the formation of adduct **19** as a result of the reaction between MCPBA and imine **17.** Due to the absence of hydrogen in the α-position to oxygen, this compound cannot be converted to the corresponding oxazolidine; it further reacts with excess MCPBA to form cyclic oxaziridine **18.**



Scheme 2

EXPERIMENTAL SECTION

Starting Materials

All isocyanates, triphenyl phosphine oxide, anhydrous acetonitrile, and hexafluoroacetone were obtained from commercial sources and used without further purification. *m*-Chloroperoxybenzoic acid (60%, Aldrich) was concentrated and dried by a known method.[12] *N*-arylimines of hexafluoroacetone were prepared using a slightly modified procedure[3,4] by the reaction of the corresponding isocyanates with HFA, catalyzed by $(C_6H_5)_3PO$.

Caution: Hexafluoroacetone is a highly toxic material and should be handled in a well-ventilated hood to avoid contact with its vapors.

^{19}F and ^1H NMR spectra were recorded on a QE-300 (General Electric, 200 MHz) or Brucker DRX-400 instrument (400.5524 and 376.8485 MHz, respectively) using $CFCl_3$ or $(CH_3)_4Si$ as internal standard and chloroform-*d* or aceton-d_6 as a lock solvent. IR spectra were recorded on a Perkin-Elmer 1600 FT spectrometer in a liquid film. Compounds **1**,[3] **3**, and **4**[4] were identified by comparison of their boiling points and NMR data with the values reported.

General Procedure for the Preparation of N-Arylimines of Hexafluoroacetone

Isocyanate (0.08–1 mol), triphenylphosphine oxide (1.0–3.0 g), and hexafluoroacetone (0.08–1 mol) were loaded into a Hastelloy reactor, and the reaction mixture kept at 200 °C for 16–24 h. The gases were released and the residual liquid distilled under vacuum to give the corresponding imine in the form of a yellow liquid. Compounds **7**, **8**, **11**, **13**, and **17** are characterized below.

N-(3,5-Difluorophenyl)-Hexafluoroisopropylidenimine (7)

Yield 80%, bp 37.6 °C at 20 mmHg; IR: 1711 (w), 1609 (s) cm^{-1}; ^1H NMR: 6.93 (m); ^{19}F NMR: –65.50 (3F, br s), –69.99 (3F, br s), –111.39 (1F, m), –120.99 (1F, s). MS *m/e* 277.0092 (M^+ $C_9F_8H_3N^+$, Calcd 277.0138); Anal. Calcd for $C_9F_8H_3N$: C, 39.01; N, 5.05. Found: C, 39.08; N, 5.07.

N-(3,5-Ditrifluoromethylphenyl)-Hexafluoroisopropylidenimine (8)

Yield 81%, bp 58.0–59.0 °C at 20 mmHg; IR 1714 (w), 1619 (w) cm^{-1}; ^1H NMR 7.79 (1H, s), 7.32(2H, s); ^{19}F NMR: –60.48 (3F, q; 6.5), –62.00 (6F, s), –68.70 (3F, q; 6.5). MS *m/e* 377.0059 (M^+, $C_{11}F_{12}H_3N^+$, Calcd 377.0074); Anal. Calcd for $C_{11}F_{12}H_3N$: C, 35.03; N, 3.71. Found: C, 35.77; N, 3.86.

N-(3-Fluorophenyl)-Hexafluoroisopropylidenimine (11)

Yield 93%, bp 28.9–30.8 °C at 10 mmHg; IR: 1710 (w), 1607 (s) cm^{-1}; ^1H NMR: 7.37 (1H, m), 6.97 (1H, m), 6.63 (2H, m); ^{19}F NMR: –61.80 (3F, d; 6.3), –69.78 (3F, d; 6.60), –111.21 (1F, q; 7.1); MS *m/e* 259.0284 (M^+, $C_9F_7H_4N^+$, Calcd 259.0232); Anal. Calcd for $C_9F_7H_4N$: C, 41.72; F, 51.32; N, 5.41. Found: C, 42.23; F, 51.40; N, 5.23.

N-(2-Trifluoromethylphenyl)-Hexafluoroisopropylidenimine (13)

Yield 92%, bp 47.0–48.0 °C at 20 mmHg; IR:1720 (m), 1604 (m) cm^{-1}; ^1H NMR 7.71(1H, d; 5.0), 7.56 (1H, t; 5.0), 7.34 (1H, t; 5.0), 6.76 (1H, d; 5.2); ^{19}F NMR: –62.14 (3F, s),

–63.34 (3F, br s), –70.62 (3F, br s). MS *m/e* 309.0198 (M^+, $C_{10}F_9H_4N^+$, Calcd 309.0200); Anal. Calcd for $C_{10}F_9H_4N$: C, 38.85; F, 55.31; N, 4.53. Found: C, 38.10; F, 55.13; N, 4.61.

N-(2, 6-Difluorophenyl)-Hexafluoroisopropylidenimine (17)

Yield 98%, bp 36.6–37.9 °C at 20 mmHg; IR: 1620 (w), 1593 (s) cm^{-1}; ^1H NMR 7.00 (2H, m), 7.19 (1H, m). ^{19}F NMR –68.04 (3F, br s), –69.98 (3F, br s), –123.08 (2F, br s).

Preparation of 2,2-Bis(trifluoromethyl)benzoxazolidine (2). Typical Procedure

Imine **1** (8.0 g, 33.2 mmol) was slowly added to a solution of MCPBA (9.66 g, 56.0 mmol) in dry CH_3CN (60 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred overnight. The white solid formed was filtered and washed with 10 mL of cold CH_3CN. Water (200 mL) was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layer was then washed with a 5% $NaHCO_3$ solution (2 × 100 mL) and water (1 × 20 mL), and dried over $MgSO_4$. The residue left after removal of the solvent under vacuum was distilled under reduced pressure to give 5.0 g (59%) of **2**, bp 89.5–90.7 °C at 40 mmHg.

2,2-Bis(trifluoromethyl)-7-chlorobenzoxazolidine (5)

In the reaction of **3** (10.0 g, 36.3 mmol) and MCPBA (7.8 g, 45.4 mmol) 5.67 g (54%) of **5** was obtained; bp 68.1–72.2 °C at 28 mmHg; IR: 3395 (m), 1650 (m) cm^{-1}; ^1H NMR 6.92 (2H, m; 7.6; 1.9), 6.74 (1H, m; 8.2), 4.70 (1H, br s); ^{19}F NMR –83.79 (s); MS *m/e* 290.9934 (M^+, $C_9H_4ClF_6NO^+$, Calcd 290.9886); Anal. Calcd for $C_9H_4ClF_6NO$: C, 37.07; F, 39.09; N, 4.80. Found: C, 36.83; F, 39.41; N, 4.96.

2,2-Bis(trifluoromethyl)-7-fluorobenzoxazolidine (6)

In the reaction of **4** (8.0 g, 30.9 mmol) and MCPBA (8.2 g, 47.5 mmol) 3.3 g (39%) of **6** was obtained, bp 59.2–63.0 °C at 10 mmHg; IR: 3408 (m), 1644 (m) cm^{-1}; ^1H NMR 6.73 (3H, m), 4.55 (1H, br s); ^{19}F NMR –80.33 (6F, s), –118.27 (1F, q; 8.6 Hz); MS *m/e* 275.0203 (M^+, $C_9H_4F_7NO^+$, Calcd 275.0181) Anal. Calcd for $C_9F_7H_4NO$: C, 39.29; N, 5.09. Found: C, 39.47; N, 4.87.

2,2-Bis(trifluoromethyl)-5,7-difluorobenzoxazolidine (9)

In the reaction of **7** (8.5 g, 30.7 mmol) and MCPBA (10.62 g, 61.5 mmol) was obtained 3.5 g (39%) of **9** as yellow liquid, bp 49.8–52.2 °C at 10 mmHg; IR: 3403 (s), 3320 (m), 1681.0 (m), 1646 (s); ^1H NMR: 6.51 (2H, m), 4.60 (1H, br s,); ^{19}F NMR: –81.29 (6F, s), –116.13 (1F, t; 8.5), –128.75 (1F, d; 9.6). MS: *m/e* 293.0092 (M^+, $C_9H_3F_8NO^+$, Calcd 293.0087) Anal. Calcd for $C_9H_3F_8NO$: C, 36.88; F, 51.85; N, 4.78. Found: C, 36.94; F, 51.98; N, 4.67.

6,8-Tetrakis(trifluoromethyl)benzoxazolidine (10)

In the reaction of **9** (5.0 g, 13.3 mmol) and MCPBA (2.9 g, 16.6 mmol) was obtained 2.3 g (44%) of **10** as yellow liquid, bp 32.5–33.3 °C at 0.075 mmHg; IR: 3437 (s), 1762 (m), 1658 (m) cm^{-1}; ^1H NMR: 7.39 (1H, s), 7.19 (1H, s), 5.11 (1H, br s); ^{19}F NMR: –62.55 (3F, br s), –62.98 (3F, br s), –81.92 (6F, s). MS: *m/e* 393.0023 (M^+, $C_{11}H_3F_{12}NO^+$, Calcd 393.0023). Anal. Calcd for $C_{11}F_{12}H_3NO$: C, 33.61; N, 3.56. Found: C, 33.88; N, 3.80.

2,2-Bis(trifluoromethyl)-8-fluorobenzoxazolidine (12)

In the reaction of **11** (8.0 g, 30.9 mmol) and MCPBA (8.2 g, 47.5 mmol) was obtained 4.0 g (47%) of mixture **12 a** and **12b** (ratio 1:3) as yellow liquid, bp 70.3–70.9 °C at 13 mmHg; IR (mixture of isomers): 3422 (m), 1651 (m) cm^{-1}; ^1H NMR: 6.87 (1H, m), 6.61 (2H, m), 4.77 (1H, br s); ^{19}F NMR: **12a**: –80.04 (6F, s), –118.09 (1F, m), **12b**: –79.82 (6F s), –136.31(1F m); MS (mixture of isomers) *m/e:* 275.0204 (M^+, $C_9H_4F_7NO^+$, Calcd 275.0181). Anal. Calcd for $C_9F_7H_4NO$: C, 39.29; N, 5.09. Found: C, 39.47; N, 4.87.

2,2,4-Tris(trifluoromethyl)benzoxazolidine (14)

In the reaction of **13** (6.8 g, 22.0 mmol) and MCPBA (5.0 g, 29.0 mmol) was obtained 2.4 g (34%) of **14** as yellow liquid, bp 48.9–49.8 °C at 20 mmHg; IR: 3445 (s), 1646.0 (m), 1616 (s) cm^{-1}; ^1H NMR: 7.08 (2H, dd; 7.9), 6.82 (1H m; 7.96), 5.09 (1H br. s); ^{19}F NMR: –60.98 (3F, s), –80.99 (6F, s); MS *m/e*: 325.0122 (M^+, $C_{10}H_4F_9NO^+$, calc. 325.0149). Anal. Calcd for $C_{10}F_9H_4NO$: C, 36.94; N, 4.31. Found: C, 36.73; N, 4.55.

Reaction of 17 with MCPBA

1 g (3.6 mmol) of **17** was added to a solution of 1.89 g (10.8 mmol) of MCPBA in dry CH_3CN at 0–5 °C, the reaction mixture was warmed to 25 °C and stirred for 3 h. Precipitate was filtered and the reaction mixture stored overnight in a refigerator, filtered again, diluted with water, precipitated oil was extracted with CH_2Cl_2, washed twice with a 5% solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated to the volume of 1 mL (temperature <15 °C). The isolated product according to ^1H and ^{19}F NMR was about 90% purity **18**. ^{19}F NMR: –74.70 (3F, quint.; 10), –75.39 (1F, quint.; 12), –77.83 (3F, q, 9), –126.30 (1F, br s); ^1H NMR: 6.30–6.55 (m).

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