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Simple method for the introduction of tetrafluoroethyl substituents into nitrogen heterocycles

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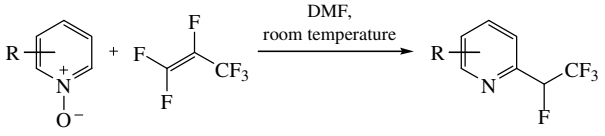
A mild and convenient method for the preparation of 1,2,2,2-tetrafluoroethyl-substituted nitrogen heterocycles *via* a reaction of hexafluoropropene with azine and azole *N*-oxides is reported.

Perfluoroalkyl-substituted heterocyclic rings are present in many pharmaceuticals, plant protection agents, liquid crystalline compounds, *etc.*[1] Thus, methods for the introduction of such substituents into heterocyclic rings are of great interest. We attempted to perform a reaction of azine *N*-oxides activated by acyl or sulfonyl halides with perfluoroisopropyl carbanions generated by the addition of KF to hexafluoropropene (HFP). Surprisingly, in the reaction of quinoline *N*-oxide, benzoyl or tosyl chloride, HFP and $KF_{(s)}$, we isolated 2-(1,2,2,2-tetrafluoroethyl)quinoline in a moderate yield. This unexpected result can be rationalised by assuming a direct reaction between *N*-oxide and HFP, whereas aryl halides and KF did not participate in the process.



1 **2** **3**, **4**

Scheme 1

Table 1 Preparation of tetrafluoroethyl-substituted products **3** and **4**.

Substrate (R)	Reaction time/h	Products (R), yields (%)	Total yield (%)
1a (quinoline)	1.5	**3a**,[3] 73	73
1b (isoquinoline)	24	**3b**, 49	49
1c (3-Me)	2.5	**3c**[2] (5-Me), 48 **4c**[2] (3-Me), 8	56
1d (3-CO_2Me)	48	**3d** (5-CO_2Me), 25 **4d** (3-CO_2Me), 45	70
1e (3-COPh)	48	**3e** (5-COPh), 26 **4e** (3-COPh), 38	64

Indeed, it was reported earlier that pyridine *N*-oxide reacted with HFP at elevated temperatures and pressures (autoclave) to give 2-(1,2,2,2-tetrafluoroethyl)pyridine.[2] This result was later confirmed by Banks *et al.*,[3] who expanded the scope of the reaction and attempted to elucidate its mechanism.

We found that the reaction of *N*-oxides with HFP proceeds under much milder conditions in a glass pressure tube at room temperature and is of a quite general character. Thus, *N*-oxides **1a–e** of typical azines such as quinoline, isoquinoline and substituted pyridines react under mild conditions with HFP to give 1,2,2,2-tetrafluoroethyl derivatives **3** and **4** in good yields without by-products (Scheme 1, Table 1).†

In the reaction of substituted pyridine *N*-oxides **1c–e**, two isomeric products are formed: 2-(1,2,2,2-tetrafluoroethyl)-3-R-pyridines and 2-(1,2,2,2-tetrafluoroethyl)-5-R-pyridines. The ratio between these products depends on the nature of the R substituent.

The reactions were carried out as follows: to ~4 equiv. of HFP condensed in a glass pressure tube at –50 °C, a solution of the substrate in DMF (0.33 M) was added, the tube was closed and the mixture agitated at room temperature for the time indicated in Table 1. After a standard work-up, the products were isolated and purified using column chromatography.

The reaction of *N*-oxides with HFP is not limited to pyridine and quinoline derivatives. We found that the reaction of five-membered heterocyclic *N*-oxides with HFP is also very facile: 1-benzyl-4,5-dimethylimidazole-3-oxide[4] gave 2-(1,2,2,2-tetrafluoroethyl) derivative **3f** in a good yield after a relatively short reaction time (Scheme 2).

The reactivity of *N*-oxides towards HFP depends on the electronic character of the aromatic ring: pyridine derivatives **1d** and **1e** containing electron-withdrawing substituents react

† All new compounds were characterised by elemental analyses, IR, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy (TMS, 400 MHz spectrometer) and mass spectrometry (EI, 70 eV).

1-(1,2,2,2-Tetrafluoroethyl)isoquinoline **3b**: oil. ^{1}H NMR ($CDCl_3$) δ: 6.33 (dq, 1H, CHF, $^2J_{HF}$ 44.8 Hz, $^3J_{HF}$ 6.6 Hz), 7.64–7.71 (m, 1H, H_{arom}), 7.72–7.79 (m, 2H, H_{arom}), 7.90 (d, 1H, H_{arom}, $^3J_{HH}$ 8.2 Hz), 8.33 (dm, 1H, H_{arom}, $^3J_{HH}$ 8.8 Hz), 8.59 (d, 1H, H_{arom}, $^3J_{HH}$ 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 90.6 (dq, $^1J_{CF}$ 191.4 Hz, $^2J_{CF}$ 34.5 Hz), 122.4 (qd, $^1J_{CF}$ 282.8 Hz, $^2J_{CF}$ 27.6 Hz), 123.1, 124.8 (d, $^3J_{CF}$ 8.6 Hz), 127.5, 128.2 (d, $^4J_{CF}$ 1.7 Hz), 128.5, 130.6, 136.9, 141.5, 148.6 (d, $^2J_{CF}$ 20.7 Hz). ^{19}F NMR ($CDCl_3$) δ: –195.66 (dq, 1F, CHF, $^2J_{FH}$ 44.8 Hz, $^3J_{FF}$ 13.3 Hz), –75.98 (dd, 3F, CF_3, $^3J_{FF}$ 13.3 Hz, $^3J_{FH}$ 6.6 Hz). IR (neat, ν_{max}/cm^{-1}): 3060, 2969, 1626, 1585, 1557, 1363, 1318, 1276, 1187, 1147, 1102, 852, 830, 750, 643. MS (EI, 70 eV), *m/z* (%): 229 (M^+, 94), 209 (9), 190 (7), 160 (100), 140 (14), 133 (24). HRMS (EI): found, 229.0521; calc. for $C_{11}H_7NF_4$, 229.0515. Found (%): C, 57.57; H, 2.92; N, 6.08. Calc. for $C_{11}H_7NF_4$ (%): C, 57.65; H, 3.08; N, 6.11.

2-(1,2,2,2-Tetrafluoroethyl)-5-methoxycarbonylpyridine **3d**: oil. ^{1}H NMR ($CDCl_3$) δ: 3.99 (s, 3H, OMe), 5.80 (dq, 1H, CHF, $^2J_{HF}$ 44.6 Hz, $^3J_{HF}$ 6.0 Hz), 7.71 (d, 1H, H_{arom}, $^3J_{HH}$ 8.2 Hz), 8.45 (dd, 1H, H_{arom}, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 2.1 Hz), 9.24 (d, 1H, H_{arom}, $^4J_{HH}$ 2.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 52.7, 89.0 (dq, $^1J_{CF}$ 187.9 Hz, $^2J_{CF}$ 34.5 Hz), 121.4 (d, $^3J_{CF}$ 5.2 Hz), 121.6 (qd, $^1J_{CF}$ 282.0 Hz, $^2J_{CF}$ 27.6 Hz), 127.1, 138.3, 150.4 (d, $^4J_{CF}$ 2.6 Hz), 154.2 (d, $^2J_{CF}$ 24.1 Hz), 165.0. ^{19}F NMR ($CDCl_3$) δ: –200.44 (dq, 1F, CHF, $^2J_{FH}$ 44.6 Hz, $^3J_{FF}$ 12.3 Hz), –78.06 (dd, 3F, CF_3, $^3J_{FF}$ 12.3 Hz, $^3J_{FH}$ 5.7 Hz). IR (neat, ν_{max}/cm^{-1}): 2960, 1732, 1601, 1439, 1366, 1299, 1193, 1145, 1121, 1077, 1027, 739, 681. MS (EI, 70 eV), *m/z* (%): 237 (M^+, 56), 218 (12), 206 (100), 178 (45). HRMS (EI): found, 237.0418; calc. for $C_9H_7NO_2F_4$, 237.0413. Found (%): C, 45.30; H, 2.94; N, 5.91. Calc. for $C_9H_7NO_2F_4$ (%): C, 45.58; H, 2.98; N, 5.91.

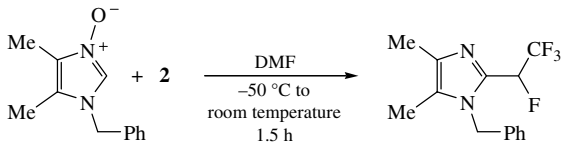
2-(1,2,2,2-Tetrafluoroethyl)-5-benzoylpyridine **3e**: mp 39–40 °C. ^{1}H NMR ($CDCl_3$) δ: 5.85 (dq, 1H, CHF, $^2J_{HF}$ 44.6 Hz, $^3J_{HF}$ 5.9 Hz), 7.55 (tm, 2H, COPh, $^3J_{HH}$ 7.3 Hz), 7.68 (tt, 1H, COPh, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz), 7.77 (d, 1H, H_{arom}, $^3J_{HH}$ 8.1 Hz), 7.82–7.86 (m, 2H, COPh), 8.25 (dd, 1H, H_{arom}, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 2.2 Hz), 9.02 (d, 1H, H_{arom}, $^4J_{HH}$ 2.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 89.1 (dq, $^1J_{CF}$ 188.8 Hz, $^2J_{CF}$ 34.5 Hz), 121.4 (d, $^3J_{CF}$ 4.3 Hz), 121.7 (qd, $^1J_{CF}$ 281.9 Hz, $^2J_{CF}$ 27.6 Hz), 128.7, 130.0, 133.5, 134.1, 136.2, 138.3, 150.3 (d, $^4J_{CF}$ 1.7 Hz), 153.5 (d, $^2J_{CF}$ 24.1 Hz), 194.0. ^{19}F NMR ($CDCl_3$) δ: –200.38 (dq, 1F, CHF, $^2J_{FH}$ 44.2 Hz, $^3J_{FF}$ 12.2 Hz), –78.10 (dd, 3F, CF_3, $^3J_{FF}$ 12.2 Hz, $^3J_{FH}$ 6.1 Hz). IR (neat, ν_{max}/cm^{-1}): 3069, 2981, 1648, 1595, 1449, 1360, 1290, 1266, 1188, 1158, 1148, 1084, 882, 841, 704, 693. MS (EI, 70 eV), *m/z* (%): 283 (M^+, 83), 264 (10), 214 (8), 206 (35), 182 (93), 178 (27), 105 (100), 77 (33). HRMS (EI): found, 283.0614; calc. for $C_{14}H_9NOF_4$, 283.0620. Found (%): C, 58.81; H, 2.98; N, 4.91. Calc. for $C_{14}H_9NOF_4$ (%): C, 59.37; H, 3.20; N, 4.95.

1-Benzyl-2-(1,2,2,2-tetrafluoroethyl)-4,5-dimethylimidazole **3f**: oil. ^{1}H NMR ($CDCl_3$) δ: 2.00 (d, 3H, Me, $^6J_{HF}$ 2.1 Hz), 2.22 (s, 3H, Me), 5.11 (d, 1H, NCH_2, $^2J_{HH}$ 16.9 Hz), 5.30 (d, 1H, NCH_2, $^2J_{HH}$ 16.9 Hz), 5.86 (dq, 1H, CHF, $^2J_{HF}$ 43.9 Hz, $^3J_{HF}$ 5.8 Hz), 6.94 (m, 2H, Ph), 7.27–7.36 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$) δ: 8.7, 12.5, 47.7, 83.6 (dq, $^1J_{CF}$ 186.2 Hz, $^2J_{CF}$ 37.1 Hz), 121.5 (qd, $^1J_{CF}$ 281.0 Hz, $^2J_{CF}$ 30.2 Hz), 125.6, 126.8, 127.7, 128.8, 134.3 (d, $^2J_{CF}$ 24.1 Hz), 134.9, 135.7. ^{19}F NMR ($CDCl_3$) δ: –192.39 (m, 1F, CHF), –76.43 (dd, 3F, CF_3, $^3J_{FF}$ 15.7 Hz, $^3J_{FH}$ 6.3 Hz). IR (neat, ν_{max}/cm^{-1}): 3067, 3035, 2952, 2926, 2864, 1590, 1497, 1473, 1453, 1361, 1288, 1189, 1141, 1047, 897, 866, 723, 682. MS (EI, 70 eV), *m/z* (%): 286 (M^+, 39), 91 (100). HRMS (EI): found, 286.1100; calc. for $C_{14}H_{14}N_2F_4$, 286.1093. Found (%): C, 58.37; H, 4.86; N, 8.83. Calc. for $C_{14}H_{14}N_2F_4$ (%): C, 58.74; H, 4.93; N, 9.79.

2-(1,2,2,2-Tetrafluoroethyl)-3-methoxycarbonylpyridine **4d**: mp 32–33 °C. ^{1}H NMR ($CDCl_3$) δ: 3.98 (s, 3H, OMe), 7.07 (dq, 1H, CHF, $^2J_{HF}$ 44.7 Hz, $^3J_{HF}$ 5.9 Hz), 7.53 (dd, 1H, H_{arom}, $^3J_{HH}$ 8.0 Hz, $^3J_{HH}$ 4.7 Hz), 8.40 (ddd, 1H, H_{arom}, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.8 Hz, $^5J_{HF}$ 1.1 Hz), 8.91 (dd, 1H, H_{arom}, $^3J_{HH}$ 4.8 Hz, $^4J_{HH}$ 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 84.1 (dq, $^1J_{CF}$ 188.0 Hz, $^2J_{CF}$ 34.5 Hz), 122.0 (qd, $^1J_{CF}$ 282.8 Hz, $^2J_{CF}$ 28.4 Hz), 124.6, 126.1, 139.0, 150.1 (d, $^2J_{CF}$ 16.4 Hz), 152.7, 165.2. ^{19}F NMR ($CDCl_3$) δ: –200.08 (dq, 1F, CHF, $^2J_{FH}$ 44.2 Hz, $^3J_{FF}$ 12.4 Hz), –76.49 (dd, 3F, CF_3, $^3J_{FF}$ 12.4 Hz, $^3J_{FH}$ 5.4 Hz). IR (neat, ν_{max}/cm^{-1}): 3021, 2968, 1720, 1587, 1429, 1377, 1273, 1180, 1135, 1057, 826, 775, 741, 683, 629. MS (EI, 70 eV), *m/z* (%): 237 (M^+, 11), 217 (100), 206 (85), 202 (13), 178 (52), 128 (47). HRMS (EI): found, 237.0416; calc. for $C_9H_7NO_2F_4$, 237.0413. Found (%): C, 45.09; H, 2.85; N, 5.77. Calc. for $C_9H_7NO_2F_4$ (%): C, 45.58; H, 2.98; N, 5.91.

2-(1,2,2,2-Tetrafluoroethyl)-3-benzoylpyridine **4e**: oil. ^{1}H NMR ($CDCl_3$) δ: 6.28 (dq, 1H, CHF, $^2J_{HF}$ 44.1 Hz, $^3J_{HF}$ 5.9 Hz), 7.48–7.55 (m, 3H, COPh, H_{arom}), 7.66 (tt, 1H, COPh, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.4 Hz), 7.77 (dd, 2H, COPh, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 1.2 Hz), 7.81 (ddd, 1H, H_{arom}, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.6 Hz, $^5J_{HF}$ 1.0 Hz), 8.89 (dd, 1H, H_{arom}, $^3J_{HH}$ 4.7 Hz, $^4J_{HH}$ 1.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 85.0 (dq, $^1J_{CF}$ 188.8 Hz, $^2J_{CF}$ 34.5 Hz), 121.9 (qd, $^1J_{CF}$ 282.8 Hz, $^2J_{CF}$ 28.4 Hz), 123.8 (d, $^3J_{CF}$ 1.7 Hz), 128.7, 130.1, 134.1, 134.6, 136.2, 137.3, 148.2 (d, $^2J_{CF}$ 19.0 Hz), 151.1, 194.8. ^{19}F NMR ($CDCl_3$) δ: –198.16 (dq, 1F, CHF, $^2J_{FH}$ 44.2 Hz, $^3J_{FF}$ 13.2 Hz), –76.19 (dd, 3F, CF_3, $^3J_{FF}$ 13.2 Hz, $^3J_{FH}$ 6.2 Hz). IR (neat, ν_{max}/cm^{-1}): 3062, 1742, 1668, 1598, 1582, 1450, 1317, 1284, 1186, 1144, 1064, 930, 855, 711, 655, 631. MS (EI, 70 eV), *m/z* (%): 283 (M^+, 43), 263 (4), 214 (29), 206 (16), 178 (9), 128 (10), 105 (100), 77 (43). HRMS (EI): found, 283.0615; calc. for $C_{14}H_9NOF_4$, 283.0620. Found (%): C, 59.00; H, 2.82; N, 4.81. Calc. for $C_{14}H_9NOF_4$ (%): C, 59.37; H, 3.20; N, 4.95.

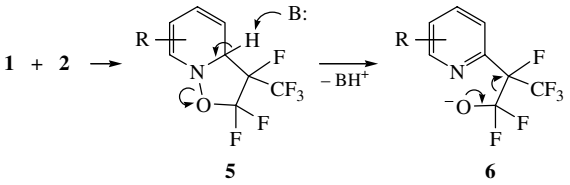
‡ *Isoxazolidine* **5a**: oil. ^{1}H NMR ($CDCl_3$) δ: 5.11 (d sept., 1H, NCH, $^3J_{HF}$ 44.0 Hz, $^4J_{HF}$ 5.6 Hz), 7.62 (ddd, 1H, H_{arom}, $^3J_{HH}$ 8.1 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.2 Hz), 7.76 (ddd, 1H, H_{arom}, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.9 Hz, $^4J_{HH}$ 1.4 Hz), 7.84 (dd, 1H, H_{arom}, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.3 Hz), 8.00 (d, 1H, H_{arom}, $^4J_{HH}$ 1.8 Hz), 8.15 (d, 1H, H_{arom}, $^3J_{HH}$ 8.5 Hz), 8.80 (d, 1H, H_{arom}, $^4J_{HH}$ 2.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 77.1 (d, $^2J_{CF}$ 19.8 Hz), 84.7 (dm, $^1J_{CF}$ 202.7 Hz, $^2J_{CF}$ 35.4 Hz), 118.0 (td, $^1J_{CF}$ 271.6 Hz, $^2J_{CF}$ 22.4 Hz), 120.0 (qd, $^1J_{CF}$ 282.0 Hz, $^2J_{CF}$ 25.9 Hz), 126.5, 127.7, 127.8, 129.5, 129.7, 142.2, 145.4, 146.5. ^{19}F NMR ($CDCl_3$) δ: –211.78 (dm, 1F, C*F*CF_3, $^3J_{FH}$ 43.8 Hz, $^3J_{FF}$ 11.1 Hz), –79.73 (dm, 1F, CF_2, $^2J_{FF}$ 147.3 Hz), –78.08 (dm, 1F, CF_2, $^2J_{FF}$ 146.3 Hz), –75.36 (m, 3F, CF_3). IR (neat, ν_{max}/cm^{-1}): 3070, 2957, 1607, 1499, 1386, 1334, 1292, 1191, 1115, 986, 890, 848, 788, 751, 708. MS (EI, 70 eV), *m/z* (%): 295 (M^+, 100), 163 (12), 145 (28), 128 (24), 116 (67). HRMS (EI): found, 295.0427, calc. for $C_{12}H_7NOF_6$, 295.0432.



1f **3f** (72%)

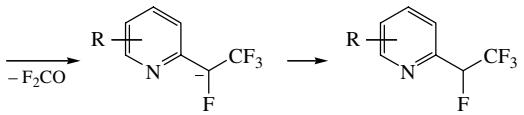
Scheme 2

much slower than relatively electron-rich **1a**, **1f** or **1c** (a lower yield in the last case results from volatility of the product and partial losses during isolation).



5 **6**

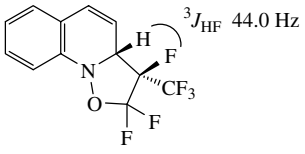
B: = DMF or *N*-oxide



7 **3**

Scheme 3

It was suggested[2,3] that the reaction proceeded *via* initial cycloaddition (probably, stepwise) of HFP to *N*-oxide with the formation of isoxazolidine derivative **5** (Scheme 3). Subsequent elimination and rearomatization gives oxy anion **6**, which undergoes a retro-aldol type fragmentation to provide the final product. This supposition was supported by the formation of difluorophosgene, but isoxazolidine **5** was never observed, perhaps because under harsh conditions it rapidly reacted further. Working in much milder conditions, we were able to isolate and characterise intermediate isoxazolidine **5a**,‡ although in a low yield of 5%. This result gives credit to the mechanism depicted in Scheme 3.



5a

The successful isolation of compound **5a** may be attributed to a lower resonance energy hence lower driving force for aromatization in the quinoline ring system than in the pyridine series. Interestingly, **5a** is stable at room temperature and it does not undergo spontaneous transformation into **3a**, although the reaction of **1a** with **2** proceeds readily at room temperature. Apparently, the presence of a basic solvent (DMF) is necessary to initiate the elimination process. Note that HFP reacts similarly with nitrones to give stable isoxazolidines.[5] Azine *N*-oxides are the analogues of nitrones; however, due to loss of aromaticity in the adduct, they are unstable and convert to substituted azines.

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