A One-Step Approach to 1-(Fluoroalkyl)indolizine Derivatives

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Abstract: A facile one-step method is presented for the synthesis of 1-(fluoroalkyl)-substituted indolizine derivatives in moderate to good yields by reactions of pyridinium, 4-methylpyridinium, isoquinolinium, and pyridazinium ylides with 2-bromo-3,3,3-trifluoropropene and 1-iodo-2-(polyfluoroalkyl)ethenes, respectively, in the presence of base.

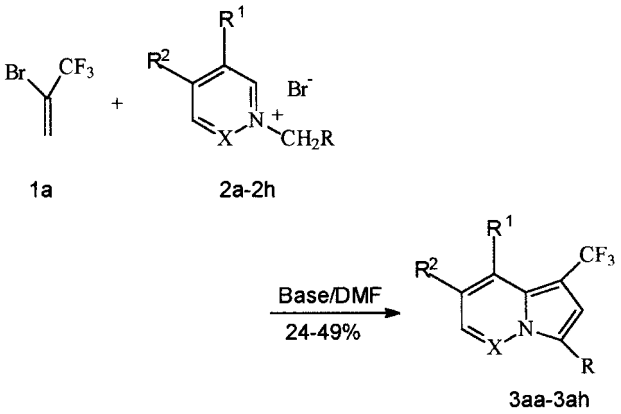
Key words: 1-(fluoroalkyl)indolizines, heteroaromatic *N*-ylides, 1,3-dipolar addition

In recent years, fluorinated heterocycles have received increasing attention due to their potential biological properties and considerable efforts have been paid to the exploitation of new synthetic routes to these fluorinated compounds. Compared with fluorination and halogen exchange reactions,[1,2] the application of fluorine-containing building blocks in organic synthesis is becoming an important strategy for the construction of fluorinated heterocycles because of its higher selectivity and milder conditions.[3] We have previously reported the synthesis of 2-(fluoroalkyl)-substituted indolizine derivatives from the reactions of pyridinium *N*-ylides with 2,2-dihydropolyfluoroalkanoates.[4] In this paper, we will describe a convenient approach to 1-(fluoroalkyl)indolizines.

2-Bromo-3,3,3-trifluoropropene[5] and 1-iodo-2-(polyfluoroalkyl)ethenes[6] are both easily obtained fluorine-containing synthons and can be used directly for the synthesis of fluorinated compounds.[7] 1,3-Dipolar cycloaddition of these building blocks with pyridinium, 4-methylpyridinium, isoquinolinium and pyridazinium ylides provides a convenient one-step route to the construction of fluorinated indolizine derivatives.

In the presence of base, the reaction of pyridinium ylides with 2-bromo-3,3,3-trifluoropropene **(1a)** in dimethylformamide gave 1-(trifluoromethyl)-substituted indolizine derivatives. The reactions of isoquinolinium **2g–2h** and pyridazinium **2f** ylides with 2-bromo-3,3,3-trifluoropropene also gave the corresponding products. The resulting heterocycles were pyrrolo[2,1-a]isoquinoline **3ag**, **3ah** and pyrrolo[1,2-*b*]pyridazine derivatives **3af**, respectively (Scheme 1).

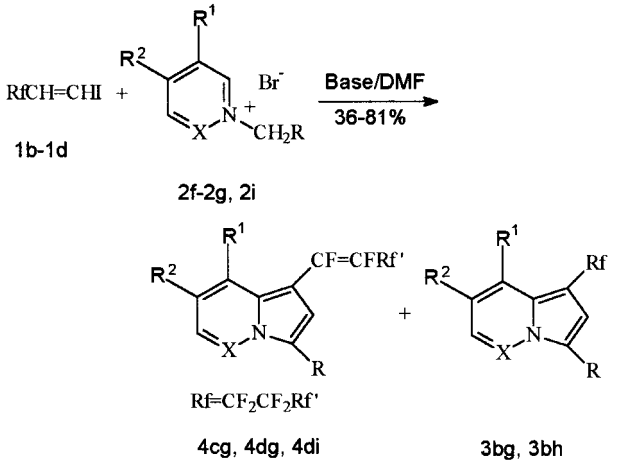
In a similar way, when 1-iodo-2-(polyfluoroalkyl)ethenes were employed to react with isoquinolinium *N*-ylides, the pyrrolo[2,1-*a*]isoquinolines with a fluoroalkyl group at the 1-position were formed.



2a X = CH, R = COPh, $R^1 = R^2 = H$
2b X = CH, R = COMe, $R^1 = R^2 = H$
2c X = CH, R = CO_2Et, $R^1 = R^2 = H$
2d X = CH, R = COPh, $R^1 = H$, $R^2 = Me$
2e X = CH, R = COMe, $R^1 = H$, $R^2 = Me$
2f X = N, R = COPh, $R^1 = R^2 = H$
2g X = CH, R = COPh, R^1,$R^2 = –(CH)_4–$
2h X = CH, R = CO_2Et, R^1,$R^2 = –(CH)_4–$

Scheme 1

When Rf = $Cl(CF_2)_2$, the expected adduct was formed as the sole product. When Rf = $Cl(CF_2)_4$ and $Cl(CF_2)_6$, the defluorinated cycloadducts **4** were obtained as the major products accompanied by a trace of the expected ones **3** (Scheme 2).

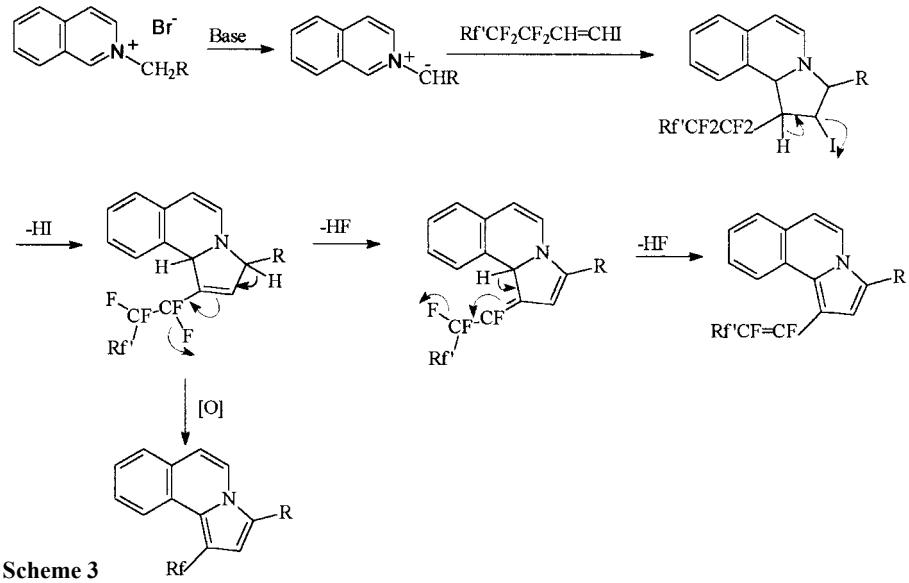


1b **Rf** = $Cl(CF_2)_2$; 1c Rf = $Cl(CF_2)_4$; 1d Rf = $Cl(CF_2)_6$
2i X = CH, R = CN, R^1, $R^2 = –(CH)_4–$

Scheme 2

Table The Isolated Yields of Compounds **3** and **4**

1	Rf	2	X	R	R^1	R^2	3/Yield (%)	4/Yield (%)
1a	CF_3	**2a**	CH	COPh	H	H	**3aa**/40	
1a	CF_3	**2b**	CH	COMe	H	H	**3ab**/24	
1a	CF_3	**2c**	CH	CO_2Et	H	H	**3ac**/35	
1a	CF_3	**2d**	CH	COPh	H	Me	**3ad**/49	
1a	CF_3	**2e**	CH	COMe	H	Me	**3ae**/27	
1a	CF_3	**2f**	N	COPh	H	H	**3af**/36	
1a	CF_3	**2g**	CH	COPh	$-(CH)_4-$		**3ag**/35	
1a	CF_3	**2h**	CH	CO_2Et	$-(CH)_4-$		**3ah**/33	
1b	$Cl(CF_2)_2$	**2g**	CH	COPh	$-(CH)_4-$		**3bg**/55	
1b	$Cl(CF_2)_2$	**2h**	CH	CO_2Et	$-(CH)_4-$		**3bh**/36	
1c	$Cl(CF_2)_4$	**2g**	CH	COPh	$-(CH)_4-$		trace	**4cg**/81
1d	$Cl(CF_2)_6$	**2g**	CH	COPh	$-(CH)_4-$		trace	**4dg**/70
1d	$Cl(CF_2)_6$	**2i**	CH	CN	$-(CH)_4-$		trace	**4di**/60



Scheme 3

From the coupling constant ($^3J_{FF}$ = 145 Hz), we can deduce that the two alkenyl fluorine atoms of defluorinated compounds are *trans*-located.

The process of defluorination may be depicted as shown in Scheme 3.

The detailed results are shown in the Table.

In conclusion, we have not only provided a one-step approach to 1-(fluoroalkyl)-substituted indolizine derivatives, but also enlarged the scope of utilizing 2-bromo-3,3,3-trifluoropropene and 1-iodo-2-(polyfluoroalkyl)-ethene as building blocks in organic synthesis.

All reagents were of chemically pure or analytical reagent. IR spectra were recorded on a Bio-Rad FTS-20E or FTS 185 spectrophotometer, using KBr pellets. ^{1}H NMR spectra were measured on a Bruker AM 300 (300 MHz) spectrometer, using TMS as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer (56.4 MHz), using TFA as external standard. In ^{19}F NMR spectra, chemical shifts (in ppm) were positive for upfield shifts and the values are reported as $\delta CFCl_3$ ($\delta CFCl_3 = \delta TFA + 76.8$). MS were taken on a Finnigan GC-MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μ.

3-Benzoyl-1-(trifluoromethyl)indolizine (3aa); Typical Procedure for the Preparation of Compounds 3 and 4

A solution of 2-bromo-3,3,3-trifluoropropene **(1a)** (0.18 g, 1.0 mmol), pyridinium salt **2a** (0.33 g, 1.2 mmol), Et_3N (0.20 g, 2.0 mmol) and K_2CO_3 (0.1 g, 1.5 mmol) in DMF (5 mL) was stirred at r.t. for 2 h and then heated to 80 °C for 4 h. After the reaction was completed, the mixture was poured into 1 M HCl solution to make the final solution pH 6. The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was combined and washed with sat. brine, dried (anhyd Na_2SO_4). After removal of solvent, the residue obtained was purified by column chromatography (petroleum ether/EtOAc 6:1) to give the product **3aa** (0.12 g, 40%).

3aa: mp 88–89 °C.

IR (KBr): ν = 1610 (C=O), 1100–1240 cm^{-1} (C–F).

^{1}H NMR ($CDCl_3$): δ = 9.98 (d, 1H, $^3J_{HH}$ = 8 Hz, C5-H), 7.81–7.08 (m, 9H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 289 (M^+, 100.0), 220 (10.6), 212 (59.3), 184 (27.4), 105 (15.2), 77 (27.3).

3ab: mp 119–121 °C.

IR (KBr): ν = 1630 (C=O), 1090–1220 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.87 (m, 1H, C5-H), 7.75–7.00 (m, 4H, Ar-H), 2.58 (s, 3H, $COCH_3$).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 227 (M^+, 7.7), 212 ($M^+ - CH_3$, 11.4), 184 (7.9), 44 (100.0).

3ac: mp 54–56 °C.

IR (KBr): ν = 1700 (C=O), 1090 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.48 (d, 1H, $^3J_{HH}$ = 9 Hz, C5-H), 7.70–6.94 (m, 4H, Ar-H), 4.39 (q, 2H, -OCH_2-), 1.37 (t, 3H, -CH_3).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 257 (M^+, 93.5), 229 (100.0), 212 (88.4).

3ad: mp 136–138 °C.

IR (KBr): ν = 1610 (C=O), 1090–1230 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.87 (d, 1H, $^3J_{HH}$ = 7 Hz, C5-H), 7.79 (s, 1H, C8-H), 7.77 (s, 1H, C2-H), 7.59–7.48 (m, 5H, Ar-H), 6.91 (d, 1H, $^3J_{HH}$ = 7 Hz, C6-H), 2.48 (s, 3H, Ar-CH_3).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 303 (M^+, 100.0), 234 (8.8), 226 (52.1), 198 (29.4), 105 (9.0), 77 (17.9).

3ae: mp 161–163 °C.

IR (KBr): ν = 1630 (C=O), 1090–1230 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.76 (d, 1H, $^3J_{HH}$ = 7 Hz, C5-H), 7.65 (s, 1H, C8-H), 7.48 (s, 1H, C2-H), 6.84 (d, 1H, $^3J_{HH}$ = 7 Hz, C6-H), 2.54 (s, 3H, -Ar-CH_3), 2.46 (s, 3H, -$COCH_3$).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 241 (M^+, 79.9), 226 (100.0), 198 (59.3).

3af: mp 83–85 °C.

IR (KBr): ν = 1650 (C=O), 1090–1260 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 8.54 (d, 1H, $^3J_{HH}$ = 8 Hz, C8-H), 8.23–7.11 (m, 8H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 54.8 (s).

MS: *m/z* (%) = 290 (M^+, 100.0), 262 (50.6), 213 (71.4), 105 (38.2), 77 (28.2).

3ag: mp 128–130 °C.

IR (KBr): ν = 1625 (C=O), 1185–1275 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.67 (d, 1H, $^3J_{HH}$ = 8 Hz, C10-H), 8.52 (m, 1H, C5-H), 7.85–7.29 (m, 10H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 339 (M^+, 100.0), 262 (61.1), 234 (37.4), 105 (39.1), 77 (41.2).

3ah: mp 106–108 °C.

IR (KBr): ν = 1700 (C=O), 1090–1230 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.36 (d, 1H, $^3J_{HH}$ = 8 Hz, C10-H), 8.45 (d, 1H, $^3J_{HH}$ = 8 Hz, C5-H), 7.75–7.16 (m, 5H, Ar-H), 4.40 (q, 2H, -OCH_2-), 1.41 (t, 3H, -CH_3).

^{19}F NMR ($CDCl_3$): δ = 55.5 (s).

MS: *m/z* (%) = 307 (M^+, 100.0), 279 (80.0), 262 (58.2), 235 (83.3).

3bg: mp 107–110 °C.

IR (KBr): ν = 3147, 1622 (C=O), 1537, 1115–1267 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.62 (d, 1H, $^3J_{HH}$ = 7 Hz, C10-H), 8.52 (d, 1H, $^3J_{HH}$ = 6 Hz, C5-H), 7.82–7.18 (m, 10H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 67.1 (m, 2F), 97.5 (m, 2F).

MS: *m/z* (%) = 405 (M^+, 22.5), 320 (10.6), 216 (11.6), 105 (9.4), 77 (10.5).

3bh: mp110–112 °C.

IR (KBr): ν = 1705 (C=O), 1085–1230 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.38 (m, 1H, C10-H), 8.40 (m, 1H, C5-H), 7.73–7.13 (m, 5H, Ar-H), 4.41 (q, 2H, -OCH_2-), 1.44 (t, 3H, -CH_3).

^{19}F NMR ($CDCl_3$): δ = 67.8 (m, 2F), 98.1 (m, 2F).

MS: *m/z* (%) = 373 (M^+, 43.4), 319 (43.4), 288 (100.0), 260 (79.8).

4cg: mp 118–120 °C.

IR (KBr): ν = 3136, 1691, 1621 (C=O), 1104–1297 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.62 (d, 1H, $^3J_{HH}$ = 7.6 Hz, C-10H), 8.22 (s, 1H, C2-H), 7.88–7.25 (m, 10H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 71.0 (s, 2F), 114.7 (m, 2F), 124.2 (d, 1F, $^3J_{FF}$ = 146 Hz), 164.0 (d, 1F, $^3J_{FF}$ = 146 Hz).

MS: *m/z* (%) = 467 (M^+, 96.06), 382 (31.41), 332 (57.39), 302 (71.42), 105 (100.0), 77 (46.08).

4dg: mp 88–90 °C.

IR (KBr): ν = 3144, 1699, 1627 (C=O), 1137–1299 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 9.62 (d, 1H, $^3J_{HH}$ = 7.5 Hz, C10-H), 8.21–7.25 (m, 11H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 68.0 (s, 2F), 116.5–123.0 (m, 6F), 124.5 (d, 1F, $^3J_{FF}$ = 145 Hz), 161.0 (d, 1F, $^3J_{FF}$ = 145 Hz).

MS: *m/z* (%) = 567 (M^+, 43.12), 382 (32.44), 332 (28.50), 105 (100.0), 77 (44.24).

4di: mp 74–76 °C.

IR (KBr): ν = 2219 (-CN), 1500, 1138–1205 cm^{-1} (C–F).

^1H NMR ($CDCl_3$): δ = 8.41 (d, 1H, $^3J_{HH}$ = 7.7 Hz, C10-H), 7.79–7.17 (m, 6H, Ar-H).

^{19}F NMR ($CDCl_3$): δ = 68.5 (s, 2F), 115.5–122.0 (m, 6F), 126.0 (d, 1F, $^3J_{FF}$ = 144 Hz), 161.0 (d, 1F, $^3J_{FF}$ = 144 Hz).

MS: *m/z* (%) = 488 (M^+, 47.57), 453 (20.34), 303 (85.66), 283 (61.36), 253 (77.60), 223 (100.0), 205 (60.63).

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