Preliminary Note

Reaction of quinoxalin-2-ones with difluorocarbene

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(Received May 30, 1992; accepted June 20, 1992)

Abstract

The reaction of quinoxalin-2-ones (**1**) with difluorocarbene derived from chlorodifluoromethane($CHClF_2$) has afforded 2-difluoromethoxyquinoxalines (**2**), 1-difluoromethylquinoxalin-2-ones (**3**) and 2-fluoroquinoxalines (**4**), and with difluorocarbene from dibromodifluoromethane (CBr_2F_2) afforded 2-bromodifluoromethoxyquinoxalines (**5**), (**2**) and (**4**). Compounds **2** and **5** were readily converted into **4** under basic conditions. The reaction of 2-bromodifluoromethoxyquinoxaline (**5a**) with poly(hydrogen fluoride) pyridine afforded 2-trifluoromethoxyquinoxaline (**6a**).

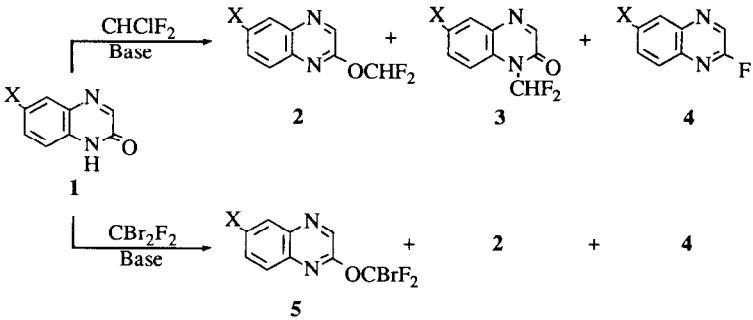
The introduction of a fluorine atom or fluorinated group into heterocycles has become increasingly important because of the potential for activity improvement in applications to newer designs of bioactive molecules. For the synthesis of heterocycles substituted with a fluorine atom or fluorinated group, two methods are mainly reported. One of them is the nucleophilic substitution of a chlorine atom on heterocycles with a suitable fluoride salt, and the other is the use of synthons originally containing a fluorine atom or fluorinated group when constructed [1–3]. However, we considered the difluorocarbene reaction [4–6] to be one of the most attractive methods. We have recently reported the reaction of ethyl pyrazole-4-carboxylate with difluorocarbenes derived from chlorodifluoromethane ($CHClF_2$) and dibromodifluoromethane (CBr_2F_2), and have directly introduced a difluoromethyl or bromodifluoromethyl group onto the endocyclic sp^3 nitrogen in a pyrazole ring [7]. As an evolution of the difluorocarbene reaction, we were interested in the application of this reaction to heterocycles containing an amide moiety [8, 9] and selected quinoxalin-2-ones (**1**), which are useful intermediates for agrochemicals [10, 11], as substrates. We now report the reaction of **1** with difluorocarbenes derived from $CHClF_2$ and CBr_2F_2.

Firstly, quinoxalin-2-one (**1a**) was reacted with an excess of $CHClF_2$ in the presence of anhydrous potassium carbonate (K_2CO_3, 3 equiv.) in DMF

0022-1139/92/$5.00

TABLE 1

Reaction of quinoxalin-2-ones with difluorocarbenes derived from $CHClF_2$ and CBr_2F_2



Run	Substrate	X	Reaction type[a]	Relative ratio (%)[b,c]				Yield (%)[c,d]
				2	**3**	**4**	**5**	
1	**1a**	H	i	82	12	6	–	71 (**2a**+**3a**+**4a**)
2	**1b**	MeO	i	88	12	–	–	61 (**2b**+**3b**)
3	**1c**	CF_3	i	62	13	25	–	12 (**2c**+**3c**+**4c**)
4	**1d**	Cl	i	50	4	46	–	32 (**2d**+**3d**+**4d**)
5	**1d**	Cl	ii	7	10	83	–	45 (**2d**+**3d**+**4d**)
6	**1a**	H	iii	10	–	10	80	43 (**2a**+**4a**+**5a**)
7	**1d**	Cl	iii	9	–	68	23	38 (**2d**+**4d**+**5d**)

[a] i; $CHClF_2/K_2CO_3$ (3 equiv.) in DMF, 90 °C, 1 h.
ii; $CHClF_2$/CsF (3 equiv.) in DMF, 90 °C, 1 h.
iii; CBr_2F_2/K_2CO_3 (3 equiv.) in DMF, 90 °C, 5 h.
[b]Relative ratio determined by GLC methods.
[c]Each substituent in the 6-position of the quinoxaline ring in Runs 1–7 was identical to that of the substrate used.
[d]Yield is that of **2**–**5** combined.

at 90 °C [A]* which afforded 2-difluoromethoxyquinoxaline (**2a**) [B] as the major product together with 1-difluoromethylquinoxalin-2-one (**3a**) [E] and 2-fluoroquinoxaline (**4a**) [H] as minor products in a ratio of 82:12:6 in a combined yield of 71% (Run 1 in Table 1). Under the same conditions, 6-methoxyquinoxalin-2-one (**1b**) gave 2-difluoromethoxy-6-methoxyquinoxaline (**2b**) [C] as the major product together with 1-difluoromethyl-6-methoxy-quinoxaline-2-one (**3b**) [F] as the minor in a ratio of 88:12 in a combined yield of 61%, but 2-fluoro-6-methoxyquinoxaline (**4b**) was not detected (Run 2). When a trifluoromethyl or chlorine atom was introduced onto the 6-position of the quinoxaline ring, the relative ratio of 2-fluoroquinoxalines (**4c, d**) increased (Runs 3 and 4) [A]. The use of anhydrous cesium fluoride (CsF, 3 equiv.) as a base afforded **4a** as the major product (Run 5).

*Refers to Experimental notes, see below.

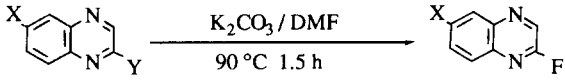
Next, **1a** was reacted with an excess of CBr_2F_2 in place of $CHClF_2$ under the same conditions and afforded 2-bromodifluoromethoxyquinoxaline (**5a**) as the major product together with **2a** and **4a** as the minor in the ratio of 80:10:10 a combined yield of 43% (Run 6) [I]. However, 6-chloroquinoxalin-2-one (**1d**) gave **4d** as the major product (Run 7).

The stability of **2a, b, d** and **5a, d** under the above reaction conditions was examined (Table 2). The difluoromethoxy group of **2a** and the bromodifluoromethoxy group of **5a** were replaced by a fluorine atom, yielding **4a** in 8% and 24% yields, respectively. Compounds **2d** and **5d** were more easily converted into **4d** in 50% and 95% yields, respectively [K]. However, **2b** remained intact under these conditions. The reactivity of the bromine atom of the bromodifluoromethoxy group in **5a** was also investigated. The reaction of **5a** with an excess of poly(hydrogen fluoride) pyridine coupled with mercuric oxide in diisopropyl ether at room temperature afforded 2-trifluoromethoxyquinoxaline (**6a**) (Scheme 1) [L].

In this study, quinoxalin-2-ones (**1**) were reacted with the difluorocarbene derived from $CHClF_2$ and afforded 2-difluoromethoxyquinoxalines (**2**), 1-difluoromethylquinoxalin-2-ones (**3**) and 2-fluoroquinoxalines (**4**), and with the difluorocarbene from CBr_2F_2 yielding 2-bromodifluoromethoxyquinoxalines (**5**), (**2**) and (**4**). These compounds could be easily isolated via column chromatography (silica gel, $CHCl_3$). We have found that **2** and **5** are readily

TABLE 2

Conversion of 2-difluoromethoxy and 2-bromodifluoromethoxyquinoxalines into 2-fluoroquinoxalines under basic conditions

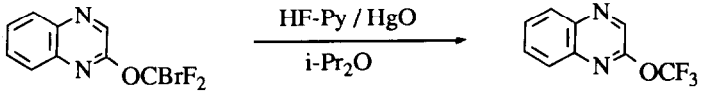


2; Y=$OCHF_2$
5; Y=$OCBrF_2$

4

Run	Substrate	X	Y	Yield (%)[a]
1	**2a**	H	$OCHF_2$	8 (**4a**)
2	**5a**	H	$OCBrF_2$	24 (**4a**)
3	**2d**	Cl	$OCHF_2$	50 (**4d**)
4	**5d**	Cl	$OCBrF_2$	95 (**4d**)
5	**2b**	MeO	$OCHF_2$	0

[a]Each substituent in the 6-position of the quinoxaline ring in Runs 1–5 was identical to that of the substrate used.



5a **6a**

Scheme 1.

converted into **4** under basic conditions, and that the bromodifluoromethoxy group in the 2-position of **5a** can be converted into a trifluoromethoxy group. It has been deduced that the yield of **4** increases as a result of an increase in the electron-withdrawing effect of the substituent in the 6-position of the quinoxaline ring, and by the use of a suitable basic nucleophilic fluorinating agent as a source for the fluoride anion. It is notable that a fluorine atom can be introduced into heterocycles via the difluorocarbene reaction and that this reaction proceeds in basic conditions, in comparison to synthesis of 2-chloroquinoxalines from quinoxalin-2-ones (**1**) which occurs under acidic conditions [12].

Experimental notes

A: The reaction procedure of **1d** with $CHClF_2$ is described (Run 4 in Table 1). To a suspension of **1d** (10.0 g, 55.4 mmol) and anhydrous K_2CO_3 (23.0 g, 167 mmol) in DMF (300 ml) was introduced $CHClF_2$ (100 g, 1160 mmol) at 90 °C for 1 h under efficient stirring. After cooling, the mixture was poured into water (1000 ml) and toluene (500 ml) was added. After stirring for 15 min, the insoluble solid was filtered off and the toluene layer was separated. Then the water layer was extracted with toluene (300 ml). The combined toluene solution was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with chloroform as an eluent to obtain 2.06 g (16%) of **2d**, 0.17 g (1%) of **3d** and 1.52 g (15%) of **4d**, respectively. **2d**: m.p., 106–107 °C. IR(KBr) (cm^{-1}): 3050; 1600; 1580; 1485; 1325; 1210; 1180; 1135; 1125; 1070; and 830. ^1H NMR ($CDCl_3$) δ: 7.47 (1H, t, $J=71.3$ Hz); 7.56 (1H, d d, $J=2.0$, 9.0 Hz); 7.72 (1H, d, $J=9.0$ Hz); 7.95 (1H, d, $J=2.0$ Hz); 8.45 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -87.6 (d, $J=71.3$ Hz) ppm. MS *m/z*: 230 (M^+, base peak); 180; 152; 124. **3d**: m.p., 126–127 °C. IR(KBr) (cm^{-1}): 3045; 1685 (C=O); 1118; 1075; and 1055. ^1H NMR ($CDCl_3$) δ: 7.38 (1H, d d, $J=2.0$, 9.0 Hz); 7.59 (1H, d, $J=9.0$ Hz); 7.73 (1H, d, $J=2.0$ Hz); 7.82 (1H, t, $J=57.2$ Hz); 8.10 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -103.8 (d, $J=57.2$ Hz) ppm. MS *m/z*: 230 (M^+, base peak); 202 ($M^+-C=O$); 183; 152; 124. **4d**: m.p. 120–120.5 °C. IR(KBr) (cm^{-1}): 3055; 1585; 1492; 1442; 1389; 1324; 1298; 1204; 1180; 1075; 993; 922; and 843. ^1H NMR ($CDCl_3$) δ: 7.74 (1H, d d, $J=2.0$, 9.0 Hz); 8.16 (1H, d, $J=2.0$ Hz); 8.71 (1H, d, $J=7.7$ Hz) ppm. MS *m/z*: 182(M^+, base peak); 163; 155; 147; 137; 110.

B: **2a**: m.p., 68–69 °C. IR(KBr) (cm^{-1}): 3030; 1575; 1500; 1405; 1300; 1212; 1102; 1065; 915; and 762. ^1H NMR ($CDCl_3$) δ: 7.40–8.15 (4H, m); 7.51 (1H, 6, $J=72.0$ Hz); 8.43 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -87.5 (d, $J=72.0$ Hz) ppm. MS *m/z*: 196 (M^+, base peak); 146; 130; 118; 100.

C: **2b**: m.p., 83–84 °C. IR(KBr) (cm^{-1}): 1620; 1503; 1343; 1330; 1305; 1221; 1205; 1130; 1115; 1100; 1070; 1020; and 833. ^1H NMR ($CDCl_3$) δ: 3.88 (3H, s); 7.14–7.36 (2H, m); 7.45 (1H, t, $J=72.0$ Hz); 7.64 (1H, d, $J=9.6$ Hz); 8.38 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -87.1 (d, $J=72.0$

Hz) ppm. MS *m/z*: 226 (M^+, base peak); 176; 183; 161; 148; 133; 120; 105.

D: **2c**: m.p., 62–63 °C. IR(KBr) (cm^{-1}): 3045; 1580; 1495; 1320; 1292; 1215; 1185; 1160; 1130; 1070; 935; and 840. ^1H NMR ($CDCl_3$) δ: 7.53 (1H, t, $J=70.8$ Hz); 7.87 (2H, br s); 8.28 (1H, br s); 8.55 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -60.2(s); -87.8 (d, $J=70.8$ Hz) ppm. MS *m/z*: 264 (M^+, base peak); 214; 197; 186; 167; 158; 136.

E: **3a**: m.p., 66–68 °C. IR(KBr) (cm^{-1}): 3050; 1675(C=O); 1595; 1560; 1462; 1330; 1130; 1110; 1065; 750; 710; and 538. ^1H NMR ($CDCl_3$) δ: 7.16–7.94 (4H, m); 7.89 (1H, t, $J=57.1$ Hz); 8.11 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -104.2 (d, $J=57.1$ Hz) ppm. MS *m/z*: 196 (M^+, base peak); 168; 149; 118.

F: **3b**: m.p., 103–104 °C. IR(KBr) (cm^{-1}): 1675(C=O); 1588; 1560; 1495; 1440; 1288; 1248; 1140; 1112; 1065; 1028; 808; and 737. ^1H NMR ($CDCl_3$) δ: 3.82 (3H, s); 6.93–7.59 (3H, m); 7.80 (1H, t, $J=58.6$ Hz); 8.04 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -104.2 (d, $J=58.6$ Hz) ppm. MS *m/z*: 226 (M^+, base peak); 198; 183; 176; 155; 133; 105.

G: **3c**: m.p., 77–78 °C. IR(KBr) (cm^{-1}): 1695(C=O); 1620; 1330; 1285; 1185; 1158; 1127; and 1080. ^1H NMR ($CDCl_3$) δ: 7.73 (2H, br s); 7.87 (1H, t, $J=57.4$ Hz); 8.04 (1H, br s); 8.18 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -60.3 (s); -104.3 (d, $J=57.4$ Hz) ppm. MS *m/z*: 264 (M^+, base peak); 236; 216; 186; 167; 136.

H: **4a** and **4c** [1].

I: The reaction procedure of **1a** with CBr_2F_2 is described (Run 6 in Table 1). CBr_2F_2 (12.0 g, 57.1 mmol) was added to a suspension of **1a** (2.00 g, 13.7 mmol) and anhydrous K_2CO_3 (5.70 g, 41.3 mmol) in DMF (20 ml), and the mixture was stirred at 90 °C for 5 h. After the same work-up as described in A, the crude product was chromatographed on silica gel with chloroform as an eluent to obtain 0.99 g (26%) of **5a**, 0.30 g (11%) of **3a** and 0.12 g (6%) of **4a**, respectively. **5a**: colorless oil. IR(KBr) (cm^{-1}): 1596; 1500; 1400; 1300; 1180; 1140; 1130; 1022; 789; and 760. ^1H NMR ($CDCl_3$) δ: 7.50–8.15 (4H, m); 8.52 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -15.8 (s) ppm. MS *m/z*: 276 (M^+); 274; 129 (base peak); 102; 90.

J: **5d**: m.p., 38–39 °C. IR(KBr) (cm^{-1}): 3030; 1605; 1575; 1490; 1440; 1298; 1175; 1140; 1023; 845; 825; and 772. ^1H NMR ($CDCl_3$) δ: 7.59 (1H, d d, $J=2.0$, 9.0 Hz); 7.85 (1H, d, $J=9.0$ Hz); 7.98 (1H, d, $J=2$ Hz); 8.49 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: -16.1(s) ppm. MS *m/z*: 309 (M^+); 307; 163 (base peak); 136; 124; 100.

K: The conversion of **5d** into **4d** is described (Run 4 in Table 2). A suspension of **5d** (400 mg, 1.29 mmol) and anhydrous K_2CO_3 (540 mg, 3.91 mmol) in DMF (5 ml) was stirred at 90 °C for 1.5 h. After cooling, the mixture was poured into water (20 ml) and extracted twice with toluene (15 ml). The toluene solution was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with chloroform as an eluent to obtain 223 mg (95%) of **4d**.

L: The synthesis of **6a** is described. Mercuric oxide (200 mg, 0.92 mmol) was added portion-wise to a solution of **5a** (160 mg, 0.58 mmol) and 70% poly(hydrogen fluoride) pyridine (0.3 ml) in isopropyl ether (1.0 ml) at room temperature for 4 h with stirring under nitrogen. After stirring at room temperature for 4 h, the mixture was poured into aqueous 25% potassium fluoride (20 ml) and the insoluble solid was filtered off. The filtrate was extracted twice with ether (20 ml), the ether solution washed with saturated aqueous sodium chloride and dried over magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with chloroform as an eluent to obtain 36 mg (29%) of **6a** as a colorless oil. IR(KBr) (cm^{-1}): 1585; 1495; 1405; 1254; 1219; 1196; 1160; and 763. ^1H NMR ($CDCl_3$) δ: 7.65–8.20 (4H, m); 8.60 (1H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: −54.5 (s) ppm. MS *m/z*: 214 (M^+, base peak); 145 ($M^+ - CF_3$); 90. HRMS: 214.0357 (M^+, calcd. for $C_9H_5F_3N_2O$: 214.0354).

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