FACILE SYNTHESIS AND HERBICIDAL ACTIVITIES OF NOVEL FLUOROQUINOXALINES

Kenzi Makino** and Hirosuke Yoshioka*

The Institute of Physical and Chemical Research (RIKEN)

Wako, Saitama 351-01, Japan

**Permanent Address; Central Research Institute, Nissan Chemical Ind., Ltd., Tsuboi-cho, Funabashi, Chiba 274, Japan

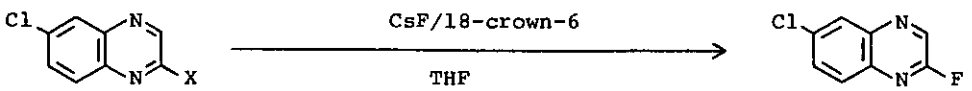
Abstract - The synthesis of new 2-fluoro-, 3-fluoro- and 2,3-difluoroquinoxalines by nucleophilic substitution with cesium fluoride as coupled with 18-crown-6 and their herbicidal activities are described.

The mild and selective introduction of a fluorine atom into heterocycles has become increasingly important because of its potentials in applications for newer designs of bioactive molecules. It seems to date that the most convenient method is the fluorination by nucleophilic substitution of a chlorine atom(s) on heterocyclic ring with a suitable fluoride salt, although relevant examples are quite rare, in which substrates containing a chlorine atom(s) are treated in "a forcing condition" under severe heating in a strongly polar and high boiling solvent[1] and that often results in decreasing chemoselectivity or decomposition of unstable substrates. Our consecutive interest in selective fluorination of N-heterocycles under a mild condition now has focused on the synthesis of new 2-fluoro- and 2,3-difluoroquinoxalines from their chloro analogues for bio-rationalization, since a number of chloro- and bromoquinoxaline derivatives are known to be potent herbicides.[2] We initially attempted nucleophilic substitutions of 2,6-dichloroquinoxaline (1c)[3,4] with a variety of fluoride salts or their modifications such as potassium fluoride (KF) - 18-crown-6,[5-9] silver fluoride (AgF) - dipyridyl[10] and tetra-n-butylammonium fluoride ($n\text{-}Bu_4N^+F^-$),[11] but we could not encounter any appreciable results when conducted in THF or acetonitrile as solvent. In this paper, we now report briefly a facile synthesis of the novel fluoroquinoxalines using CsF as coupled with 18-crown-6.[12]

Firstly, 2,6-dichloroquinoxaline (1c) and 6-chloro-2-p-tosylquinoxaline (2c)[13] were chosen as substrates (Table 1). The nucleophilic substitution of the 2-chlorine atom of 1c readily proceeded with CsF and 18-crown-6 in THF at room temperature, affording 6-chloro-2-fluoroquinoxaline (3c)[14]

in 87% yield (Run 2). The effect of crown ether was best demonstrated in Run 4, where a catalytic amount of 18-crown-6 was employed while no conversion was observed in Run 5 without crown ether. On the other hand, the substitution of the 2-p-tosyl group rather sluggishly proceeded with the modified CsF (Run 7 and 8), resulting in inferior yields to those for the chloro analogues. A variety of 2-fluoroquinoxaline analogues (3a,b,d,e)[15-18] have been prepared by the current procedure in good or fair yields as compiled in Table 2.

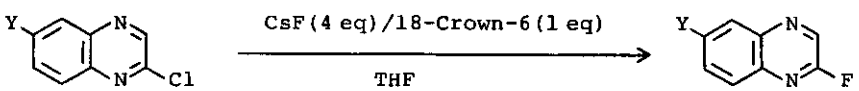
Table 1. Fluorination of 2,6-Dichloroquinoxaline(1c) and 6-Chloro-2-p-tosylquinoxaline(2c) with Cesium Fluoride - Crown Ether



1c or 2c　　3c

Run	Substrate	X	CsF (eq)	18-crown-6 (eq)	React. temp.	React. time, h	Yield %(3c)
1	1c	Cl	4	1	r.t.	20	85
2	1c	Cl	4	0.1	r.t.	20	87
3	1c	Cl	4	1	rfl.	4	70
4	1c	Cl	4	0.1	rfl.	4	73
5	1c	Cl	4	-	rfl.	4	0
6	1c	Cl	1.2	0.1	rfl.	4	81
7	2c	SO_2-C$_6$H$_4$-Me	4	1	r.t.	20	24
8	2c	SO_2-C$_6$H$_4$-Me	4	1	rfl.	4	19

Table 2. Fluorination of 6-Substituted 2-Chloroquinoxalines With Cesium Fluoride - Crown Ether

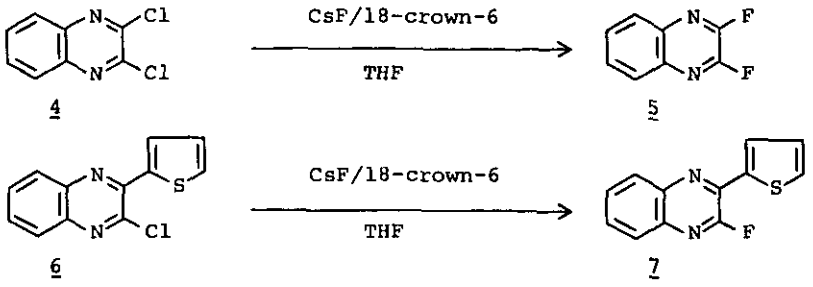


1　　3

Run	Substrate	Y	React. temp.	React. time, h	Yield %(3)
1	1a	H	r.t.	20	38 (3a)
2	1a	H	rfl.	4	70 (3a)
3	1b	F	r.t.	40	64 (3b)
4	1d	Br	r.t.	20	87 (3d)
5	1e	CF_3	r.t.	20	58 (3e)

2,3-Dichloroquinoxaline (4) and 3-(2-thienyl)-2-chloroquinoxaline (6) were similarly converted to 2,3-difluoroquinoxaline (5)[19] and 3-(2-thienyl)-2-fluoroquinoxaline (7)[20] in 64 and 82% yields

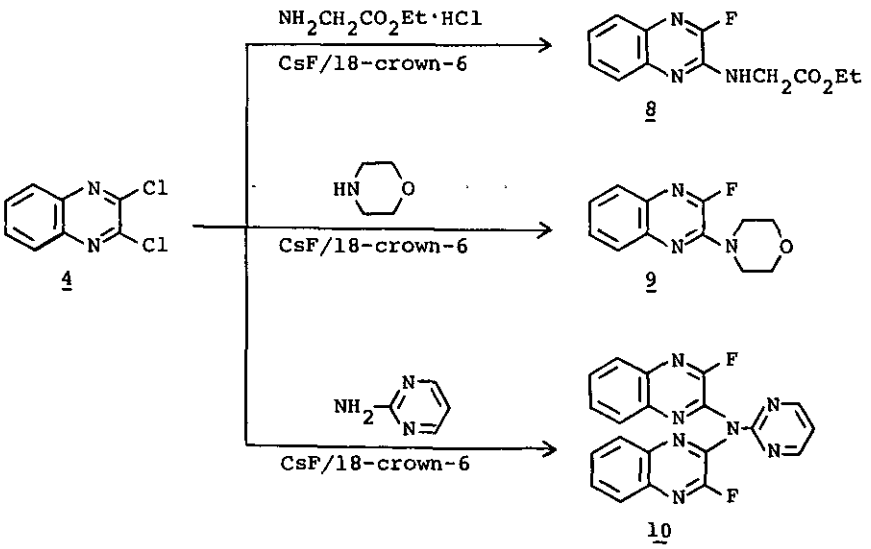
respectively (Scheme 1).



4 5 6 7

Scheme 1.

Furthermore, we found that the current procedure could be modified into a one-pot synthesis of 2-substituted 3-fluoroquinoxalines from 4 by subsequent nucleophilic substitution with various synthons with a primary or secondary amino group. For example, 4 (1 eq) was treated with glycine ethyl ester hydrochloride (1 eq) in the presence of CsF (4 eq) - 18-crown-6 (1 eq) in THF at room temperature, yielding N-(3-fluoro-2-quinoxalinyl)glycine ethyl ester (8)[21] in 61% yield. N-(3-fluoro-2-quinoxalinyl)morpholine (9)[22] (78% yield) and 2-[N,N-bis(3-fluoro-2-quinoxalinyl)-amino]pyrimidine (10)[23] (64% yield) were similarly prepared from morpholine (1 eq) and 2-aminopyrimidine (0.5 eq) respectively (Scheme 2).



4 8 9 10

Scheme 2.

Herbicidal activities of 7 against important weeds were shown in Table 3, exhibiting nearly equal potencies to those for the chloro analogue 6.

Table 3. Pre-emergence Herbicidal Activities of 3-(2-Thienyl)-2-fluoroquinoxaline(7) Compared with Those of 3-(2-Thienyl)-2-chloroquinoxaline(6) and 2-(2-Thienyl)-quinoxaline(11)

Weed	Compound		
	6	7	11
Echinocloa crus-galli	6	4	3
Digitaria adscendence	8	8	2
Cyperus difformis	8	7	2
Solanum nigrum	9	9	7
Galinsoga ciliata	9	9	8
Rorippa indica	9	9	8

Rate; 25 g/a. 10; 100% Kill, 0; No Effect.

ACKNOWLEDGMENT

We are thankful to Mr. T. Nawamaki, Biological and Chemical Research Laboratory of Nissan Chemical Ind., Ltd., for herbicidal activity test.

REFERENCES AND FOOTNOTES

1. 2,6-Dichloropyrimidine and its derivatives were converted to corresponding fluoro analogues with KF and 18-crown-6 in tetraglyme at 150-160 °C.[24]
2. H. Takahashi, I. Yashima, T. Oya, T. Ikai, and K. Suzuki (Nissan Chem. Ind., Ltd.): Jpn. Kokai Tokkyo Koho Jp 54-36285 (1979); Chem. Abstr., 91, 108000t (1979).
3. G. Sakata, K. Makino, and K. Morimoto, Heterocycles, 1985, 23, 143.
4. G. Sakata and K. Makino, Chem. Lett., 1984, 323.
5. J. H. Clark and J. Emsley, J. Chem. Soc. Dalton, 1975, 2129.
6. J. H. Clark, Chem. Rev., 1980, 80, 429.
7. M. Gerstenberger and A. Haas, Angew. Chem. Int. Ed. Engl., 1981, 20, 647.
8. J. M. Miller and J. H. Clark, Chem. Comm., 1982, 1318.
9. G. G. Yakobson and N. E. Akmentova, Synthesis, 1983, 169.
10. K. Yamagishi, S. Matsuoka, T. Fukuhara, N. Yoneda, and A. Suzuki, 10th Meeting of Fluorine Chemistry of Japan, 1985, Abstr., No. 2C01.
11. M. Shimizu, Y. Nakahara, and H. Yoshioka, Tetrahedron Lett., 1985, 26, 4207.

12. The first modification of CsF with crown ethers was recently reported as applied to the fluorination of polychlorinated aromatic hydrocarbons and pyridines in CH_3CN at 80 °C,[25] where the fluorination proceeded in a moderate rate without crown ether.
13. 2c was synthesized from 1c with sodium p-toluenesulfinate in DMF at 110-120 °C.
14. A typical reaction procedure is described for the synthesis of 3c: To a suspension of CsF (866 mg, 5.70 mmol) and molecular sieves 4A (1.5 g) in 5 ml of dry THF, was added 18-crown-6 (38 mg, 0.14 mmol) at room temperature under stirring in nitrogen. After stirring for 1 h, 1c (284 mg, 1.43 mmol) was added and stirred for 20 h at room temperature. After celite-filtration of the mixture followed by washing with a small amount of THF, the solvent was evaporated and ethyl acetate (30 ml) was added. The ethyl acetate 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 to obtain 227 mg (87%) of 3c, mp 120-120.5 °C; ir(KBr): 3055, 1585, 1492, 1442, 1389, 1324, 1298, 1204, 1180, 1075, 993, 922, and 843 cm^{-1}; pmr($CDCl_3$) δ 7.74(1H, d d, J=2.0, 9.0 Hz), 7.92(1H, d, J=9.0 Hz), 8.16(1H, d, J=2.0 Hz), and 8.71(1H, d, J=7.7 Hz); ms m/z 182(M^+, base peak), 163, 155, 147, 137, and 110.
15. 3a: colorless oil. ir(KBr): 3425, 3060, 1583, 1498, 1469, 1402, 1335, 1298, 1265, 1213, 1200, 1134, 990, 906, and 760 cm^{-1}; pmr($CDCl_3$) δ 7.68-8.22(4H, m) and 8.71(1H, d, J=7.9 Hz); ms m/z 148(M^+, base peak), 129, 121, 103, and 76.
16. 3b: mp 72.5-74 °C. ir(KBr): 3430, 3055, 1620, 1589, 1500, 1332, 1302, 1216, 1201, 1153, 1111, 1095, 994, 914, and 842 cm^{-1}; pmr($CDCl_3$) δ 7.48-8.10(3H, m) and 8.72(1H, d, J=7.9 Hz); ms m/z 166(M^+, base peak), 147, 139, 121, and 94.
17. 3d: mp 133-134 °C. ir(KBr): 3025, 1597, 1577, 1480, 1435, 1379, 1312, 1291, 1200, 1174, 1129, 1055, 989, 910, and 833 cm^{-1}; pmr($CDCl_3$) δ 7.87(2H, br s), 8.33(1H, br s), and 8.70(1H, d, J=7.7 Hz); ms m/z 226(M^+, base peak), 147, 127, and 120.
18. 3e: mp 112.5-114 °C. ir(KBr): 3425, 3060, 1597, 1464, 1400, 1329, 1305, 1219, 1197, 1158, 1130, 1070, 998, 943, and 858 cm^{-1}; pmr($CDCl_3$) δ 7.98(1H, d d, J=1.8, 9.0 Hz), 8.12(1H, d, J=9.0 Hz), 8.48(1H, br s), and 8.81(1H, d, J=7.7 Hz); ms m/z 216(M^+, base peak), 197, 189, 171, 166, 149, and 144.
19. 5: mp 94-95 °C. ir(KBr): 3410, 1492, 1451, 1388, 1347, 1329, 1239, 1193, 1168, 1144, and 762 cm^{-1}; pmr($CDCl_3$) δ 7.70-8.10(4H, m); ms m/z 166(M^+, base peak), 147, 146, 139, 121, and 116.
20. 7: mp 135-135.5 °C. ir(KBr): 3425, 1550, 1522, 1488, 1427, 1395, 1349, 1328, 1232, 1192, 1138, 1057, 952, 849, 769, 760, and 708 cm^{-1}; pmr($CDCl_3$) δ 7.19(1H, d d, J=3.7, 5.1 Hz), 7.58(1H, d d, J=1.1, 5.1 Hz), and 7.60-8.20(5H, m); ms m/z 230(M^+, base peak), 211, 186, 185, 102.
21. A typical reaction procedure is described for the synthesis of 8: To a suspension of CsF

(1855 mg, 12.2 mmol) and molecular sieves 4A (1.5 g) in 5 ml of dry THF, was added 18-crown-6 (404 mg, 1.53 mmol) at room temperature under stirring in nitrogen. After stirring for 1 h, 4 (304 mg, 1.53 mmol) and glycine ethyl ester hydrochloride (213 mg, 1.53 mmol) were added and the mixture was stirred for 24 h at room temperature. After the same working-up as described for 3c, the resultant crude product was purified by column chromatography on silica gel with chloroform to give 232 mg (61%) of 8, mp 169-170 °C; ir(KBr): 3365, 2980, 1722, 1630, 1599, 1540, 1478, 1462, 1440, 1402, 1368, 1308, 1266, 1230, 1190, 1139, 1110, 1020, and 760 cm^{-1}; pmr($CDCl_3$) δ 1.33 (3H, t, J=7.2 Hz), 4.29(2H, q, J=7.2 Hz), 4.38(2H, d, J=5.3 Hz), 5.71(1H, br s), and 7.30-7.90(4H, m); ms m/z 249(M^+), 203, 176(base peak), 148, 147, and 129.

22. 9: mp 96-97 °C. ir(KBr): 3420, 2940, 2895, 2840, 1555, 1497, 1474, 1442, 1380, 1366, 1330, 1308, 1280, 1258, 1231, 1209, 1182, 1162, 1105, 1038, 951, 918, 905, 848, and 769 cm^{-1}; pmr($CDCl_3$) δ 3.60-4.00(8H, m) and 7.35-7.85(4H, m); ms m/z 233(M^+, base peak), 218, 202, 188, 176, 175, 162, and 148.
23. 10: mp 229-230 °C. ir(KBr): 3420, 3040, 1568, 1498, 1449, 1410, 1370, 1343, 1328, 1308, 1245, 1220, 1209, 1201, 1141, 936, 805, 770, and 759 cm^{-1}; pmr($CDCl_3$) δ 7.12(1H, t, J=4.8 Hz), 7.50-8.10(8H, m), and 8.58(2H, d, J=4.8 Hz); ms m/z 387(M^+), 368(base peak), 240, and 200.
24. P. I. Svirskaya, V. Yedidia, and C. C. Leznoff, J. Heterocyclic Chem., 1985, 22, 149.
25. V. V. Aksenov, V. M. Vlasov, I. M. Moryakina, P. P. Rodionov, V. P. Fadeeva, V. S. Chertok, and G. G. Yakobson, J. Fluorine Chem., 1985, 28, 73.

***All the new fluoroquinoxalines gave satisfactory data on elemental analysis.

Received, 12th February, 1987