NUCLEOPHILIC FLUORINATION OF CHLORINATED *N*-HETEROCYCLES WITH TETRABUTYLPHOSPHONIUM HYDROGENDIFLUORIDE AND DIHYDROGENTRIFLUORIDE

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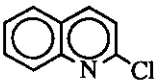
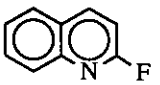
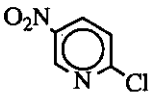
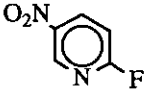
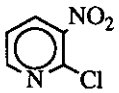
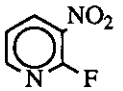
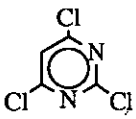
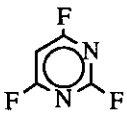
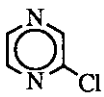
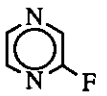
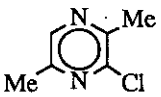
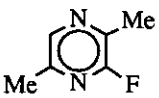
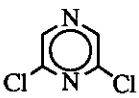
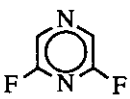
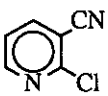
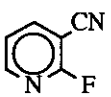
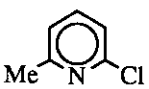
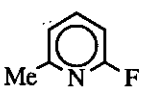
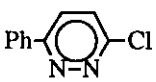
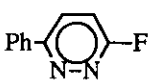
Abstract-Fluorination of various chlorinated *N*-heterocycles with tetrabutylphosphonium hydrogendifluoride (**1**) or dihydrogentrifluoride (**2**) readily proceeded in high yields under mild conditions.

Fluorination by nucleophilic substitution of a chlorine atom(s) on heterocyclic ring with suitable fluoride salts such as KF[1] is one of the most convenient methods, but examples of fluorination of the chlorinated heterocycles are rare and the fluorination often needs such a forcing condition as heating at over 200°C in a high polar and high boiling solvent such as DMF, *N*-methylpyrrolidone, dimethyl sulfone or sulfolane, which often result in decomposition of unstable substrates. More recently, improved methods employing alkali or alkali earth metal fluorides in the presence of Crown ethers have been reported for fluorination of 2,4-dichloropyrimidines with KF,[2] chloroquinoxalines and chloropyrazoles with CsF[3] under mild conditions. In this paper, we report a facile and selective method for fluorination of various chlorinated *N*-heterocycles with tetrabutylphosphonium hydrogendifluoride (**1**) and dihydrogentrifluoride (**2**) which we have recently developed for fluorination of various aliphatic substrates,[4] and halogenated or nitrated aromatics.[5]

We carried out fluorination of a variety of ring-chlorinated *N*-heterocycles with **1** or **2** and summarized the results in Table 1 showing that these materials were readily converted the *N*-heterocycles under mild to moderate conditions to the corresponding fluorides mostly in high yields. For a typical example, 2-chloroquinoline (818 mg, 5 mmol) was treated with **1** (4.477 g, 15 mmol) in xylene (2 ml) at 140°C for 2 h under N_2, affording 2-fluoroquinoline in 99% yield (after usual working-up including quenching with H_2O). Comparison is made to the conditions (KF, DMSO, 190~200°C, 3~4 days, 60% yield) previously reported for the preparation of 2-

fluoroquinoline by Hamer *et al.*[6] 2-Fluoro-3,6-dimethylpyrazine (practically pure by gc) was first prepared by this procedure (see run 9), although it took 50 h for the complete conversion.

Table 1 Fluorination of *N*-Heterocycles with **1** or **2**[a)]

Run	Substrate	Reagent	Solvent	Temp(°C)	Time(h)	Product	Yield(%)[b)]
1		**1**	xylene	140	2		99
2		**1**	toluene	80	1.5		(tar)
3		**2**	toluene	110	2		95
4		**1**	toluene	80	2		(tar)
5		**2**	toluene	110	11		36
6		**1**[c)]	none	50	4		85
7		**1**	none	100	2		93
8		**2**	none	140	23		81
9		**1**	none	100	50		91
10		**1**[d)]	none	80	1		85
11		**1**	none	80	2		88
12		**1**	none	140	96		72
13		**1**	none	100	2		89

a) Each substrates (5 mmol) was treated with **1** or **2** (15 mmol) in the solvent (2 ml) or without solvent.

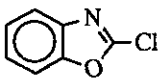
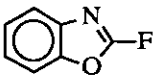
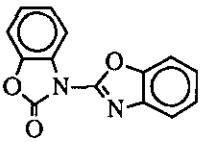
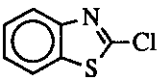
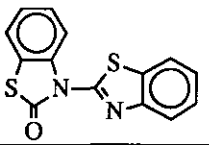
b) Yields were determined by gc with internal standard.

c) Six mol equiv. of **1** was used.

d) Four mol equiv. of **1** was used.

It was impossible to fluorinate certain chloronitropyridines with **1**. For example, 2-chloro-5-nitropyridine was collapsed into a tarry matter when treated with **1** at 80°C (see run 2), but was readily converted with **2** to 2-fluoro-5-nitropyridine in 95% yield. The results in runs 4 and 5 show a similar trend. As is similar to the description in the previous reports,[4,5] **2** is sometimes more effective to specific substrates owing to its basicity lower than that of **1**. Xylene as well as toluene seems to be the best of all the common solvents. Besides, the fluorination was equally conductible on every substrate without any solvent, which served as a merit to isolate fluorinated products of low boiling points such as 2,4,6-trifluoropyrimidine boiling at 98°C (see run 6). Previously, Ivin *et al.* reported that the conversion from 2,4,6-trichloropyrimidine gave a mixture of trifluoro- and dichlorofluoropyrimidines, in 48% and 8% yields respectively, after treatment with KF at 280°C for 1.5 h.[7]

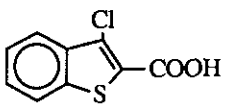
Table 2 Fluorination of *N*-Heterocycles with **1** or **2**[a)]

Run	Substrate	Reagent	Time(h)	Temp(°C)	Product	Yield(%)[b)]
14		**2**	11	50		74
15		**1**	24	r.temp		65
16		**1**	2.5	100		67
17		**2**	13	100		33

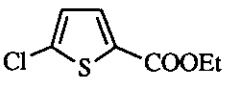
a) A substrate (5 mmol) was treated with **1** or **2** (15 mmol) without solvent.

b) Yields after isolation.

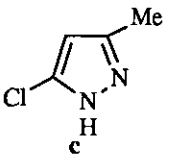
Compounds not affected with **1**:



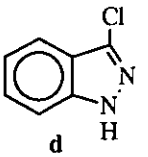
a



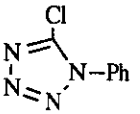
b



c



d



e

Treatment of 2-chlorobenzoxazole with **2** at 50°C gave the 2-fluoro derivative, but a run at room temperature resulted in the formation of 1-(2-benzoxazolyl)benzopyrazolone (see runs 14, 15 in Table 2). It appears that 2-chlorobenzoxazole was partly converted to the 2-fluoro derivative that promptly underwent hydrolysis and coupling with each other or with the substrate during working-up. 2-Chlorobenzothiazole was also converted to a similar coupling product or 1-(2-benzothiazolyl)benzothiazolone even after treatment at higher temperature (see runs 16 and 17). A group of the chlorinated heterocycles (**a** through **e**) in Table 2 remained unaffected when treated with **1** at 100~140°C for several hours (without solvents).

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Received, 6th May, 1992