CHEMISTRY LETTERS, pp. 509-512, 1993.

Halogen-Exchange Fluorination of Aromatic Halides with HF or HF-Base

Tsuyoshi FUKUHARA and Norihiko YONEDA*

Department of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo 060

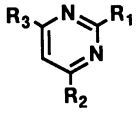
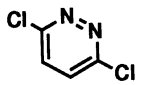
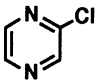
Heteroaromatic halides such as 2-chloropyrimidines and 2-chloropyridines, and 2,4-dinitrochlorobenzene underwent halogen-exchange fluorination with the treatment of HF or HF-base solutions to afford the corresponding fluorides in good yields.

Replacement of halogens by fluorine, namely halogen-exchange fluorination of activated aromatic halides, is known to be one of the most convenient and practical methods available for introduction of fluorine into aromatic rings.[1] Alkali metal salts such as KF are commonly used for this purpose, but it usually requires the severe reaction conditions of high temperature and long reaction time.[1,2] Although HF is an attractive fluorine source because of its inexpensive and ready availability,[3] its application to the halogen-exchange fluorination of aromatic halides has little been studied.[4,5] This is because the halogen-exchange fluorination of aromatic halides with HF is thermodynamically unfavorable to afford aromatic fluorides.[6]

However, as shown in Table 1, we found 2-chloropyrimidine underwent the halogen-exchange fluorination affording readily 2-fluoropyrimidine in 27% isolated yield in an autoclave even at room temperature for some ten minutes (Entry 1). When the reaction was carried out at room temperature in a vessel open to the air to allow liberating the HCl gas spontaneously, the yield of 2-fluoropyrimidine was increased with the duration of time and an equilibrium was attained fairly rapidly to afford 2-fluoropyrimidine in 57 % yield with the reaction time of 30 min (Entry 2). 2-Fluoropyrimidine was obtained in almost quantitative yield by carrying out the reaction at 50 °C with feeding fresh HF continuously (Entry 7).

The reaction may be well explained by assumption of its initial protonation of nitrogen atom in the substrates so as to decrease the electron density at *ipso* carbon bearing a halogen atom to enhance the nucleophilic attack with fluoride ion more readily. The addition of organic bases such as pyridine to HF may be well expected to enhance the halogen-exchange fluorination of 2-chloropyrimidine, since the nucleophilicity as well as the basicity, in other words, the fluorination reactivity of the fluoride ion in HF-base solutions is known

Table 1. Preparation of fluorodiazines

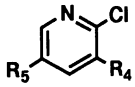
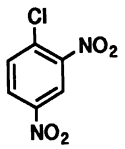
Entry No.	Substrate ArCl	Conditions[a] Temp ℃	Additive (mmol)	ArF yield/%[b]	Not isolated products/%	Recovered ArCl %
1	R_1=Cl, R_2=R_3=H	20[c,d]	-	27	8	65
2	"	20[c]	-	57	2	41
3	 "	20[e]	Pyr.[g] (5)	53	4	43
4	"	20[e]	Pyr. (10)	35	2	63
5	"	20[e]	Pyr. (18)	8	3	89
6	"	20[e]	Pyr. (25)	0	2	98
7	"	50[f]	-	97	2	1
8	R_1=Cl, R_2=R_3=Me	20	-	49	3	48
9	R_1=H, R_2=R_3=Cl	20	-	44	8	48
10	R_1=NH_2, R_2=R_3=Cl	50[f]	-	90[h]	5	5
11	R_1=NH_2, R_2=Cl, R_3=Me	50[f]	-	60	5	35
12		50[f]	-	14	2	84
13		100[f]	-	92[i]	2	6
14		50[f]	-	13	3	84
15		100[f]		61	5	34

a) Conditions: Reaction time, 1 h; Substrate, 10 mmol; HF initial amount, 100 mmol. b) Isolated yield. c) Reaction time, 0.5 h. d) In an autoclave. e) Substrate, 2 mmol. f) Feeding fresh HF, 2 mmol/min. g) Pyridine. h) Product distribution, 4-fluoro- 99%; 4,6-difluoro- 1%. i) Product distribution, 3-fluoro- 44%; 3,6-difluoro- 56%.

to be substantially higher than that of anhydrous HF.[3,8] However, as shown in Table 1, the addition of pyridine to HF was not effective enough for the halogen-exchange fluorination of 2-chloropyrimidine (Entries 3-6). On the contrary, increasing the amount of pyridine in HF hindered remarkably the halogen-exchange fluorination to recover the substrate 2-chloropyrimidine almost quantitatively. This result can be explained by the stronger basicity of pyridine than 2-chloropyrimidine. Namely, pyridine in HF is strongly protonated in preference to 2-chloropyrimidine, and most of substrate remains in a non-protonated state which is unfavorable for the nucleophilic halogen-exchange fluorination with a fluoride ion. The reaction of substituted 2-chloropyrimidines and chlorodiazines with HF also initiates the exchange fluorination of halogens, which exist adjacent to N atom in the ring, to afford the corresponding fluorides in good yields (Entries 8-15).

On the contrary, as shown in the Table 2, 2-chloropyridine did not proceed the halogen-exchange fluorina-

Table 2. Preparation of 2-fluoropyridines and 2,4-dinitrofluorobenzene

Entry No.	Substrate ArCl		Conditions[a] Temp ℃	Additive[d]	ArF yield/%[b]	Not isolated products/%	Recovered ArCl %
16	R_4=H,	R_5=H	50[c]	-	0	1	99
17		"	150	-	48	7	45
18		"	150	Pyr.[e]	47	34	19
19		"	150	Et_3N	75	6	19
20		"	150	Coll.[f]	70	6	24
21	R_4=H,	R_5=NO_2	120	-	68	4	28
22		"	120	Coll.	90	3	7
23	R_4=H,	R_5=CF_3	120	Coll.	66	6	28
24	R_4=CF_3,	R_5=H	120	Coll.	80	4	16
25			180	-	<1	4	95
26			180	Pyr.	26	71	3
27			180	Coll.	28	3	69
28			180[c]	Coll.	66	11	23

a) Conditions: Reaction time, 1 h; Substrate, 10 mmol; HF initial amount, 100 mmol; Feeding fresh HF, 2 mmol/min. b) Isolated yield. c) Reaction time, 10 h. d) 5 mmol. e) Pyridine. f) γ-Collidine.

tion at 50 °C for long reaction time (10 hours) (Entry 16). However, when the similar solution of 2-chloropyridine was treated with continuously feeding fresh HF at 150 °C, the corresponding fluoride was produced in fairly good yield (Entry 17). On the contrary, trimethylamine and γ-collidine-HF solutions in the reaction of 2-chloropyridines, which are stronger bases than the substrate exerted their effects highly for the improvement in the yields of the corresponding fluorides (Entries 19-24). However, when the reaction was carried out using the solution of HF with pyridine, the yield of the fluoride was not improved compared to that obtained in the reaction in the presence of HF without bases (Entry 18). In addition to that, the recovered amounts of unreacted 2-chloropyridine was found to be considerably low, as is distinct from the reaction of 2-chloropyrimidine with HF-pyridine (Entries 3-6). This may be due to the basicity of organic bases co-existed in HF. Namely, considerable amount of free pyridine, which can exist under such severe conditions, may react with substrate and product (halopyridines) to form 2-pyridinium pyridine halides. This brings about the decreasing isolated yields of halopyridines.

On the other hand, as shown in the Table 2, chlorobenzenes having strong electron withdrawing

substituents such as 2,4-dinitrobenzene did not take place the reaction with HF even at 180 °C (Entry 25). However, when this substrate was treated with HF-pyridine solution, the corresponding fluoride was produced with expense of the consumption of starting substrate (Entry 26). The yields of desired fluorides were remarkably improved by the use of HF-collidine solution (Entries 27, 28).

The present work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (No. 04650747).

References

1) N. Ishikawa and T. Kitazume, *Yuki Gosei Kagaku Kyokai Shi*, **34**, 258 (1976); Y. Kimura, *ibid.*, **47**, 258 (1989).

2) G. C. Finger, L. D. Starr, D. R. Dickerson, H. S. Gutowsky, and J Hamer, *J. Org. Chem.*, **28**, 1666 (1963).

3) N. Yoneda, *Tetrahedron*, **47**, 5329 (1991).

4) S. C. Carson and R. D. Howard, British Patent, 1272475 (1972) [*Chem. Abstr.*, **77**, 126439 (1972)].

5) E. Kluke, L. Ohlmann, and B. Baasner, *J. Fluorine Chem.*, **21**, 495 (1982); **23**, 301 (1983).

6) The free-energy changes (G°) in the following reactions (1) and (2) can be calculated[7] as -8.1 kcal/mol and 4.7 kcal/mol at 300 K respectively. Even at the temperature of 600 K, $\Delta G°$ of the reaction (2) has a positive value of 3.9 kcal/mol.

$$ArCl + KF \longrightarrow ArF + KCl \quad (1)$$

$$ArCl + HF \longrightarrow ArF + HCl \quad (2)$$

7) R. Fujishiro, *Chem. Today*, **1977**, 63.

8) G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kewewkwa, and J. A. Olah, *J. Org. Chem.*, **44**, 3872 (1979).

(Received November 20, 1992)