Journal of Fluorine Chemistry, 52 (1991) 341–351

Received: November 12, 1990; accepted: February 25, 1991

SYNTHESIS OF 3,4-DIFLUOROBENZONITRILE AND MONOFLUOROBENZONITRILES BY MEANS OF HALOGEN-EXCHANGE FLUORINATION

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SUMMARY

3,4-Difluorobenzonitrile has been prepared by a halogen-exchange reaction between 3,4-dichlorobenzonitrile and spray-dried potassium fluoride in the presence of tetraphenylphosphonium bromide in refluxing 1,3-dimethylimidazolidine-2-one. In the fluorination reaction, 4-chloro-3-fluorobenzonitrile seems to be a key intermediate.

3,4-Difluorobenzonitrile, 2-, 3-, and 4-fluorobenzonitriles have also been produced from the corresponding chlorobenzonitrile derivatives by halogen-exchange at 290 °C in DMI in a pressure reactor.

INTRODUCTION

New syntheses of fluorobenzonitriles are important, because of the widespread and rapidly growing use of the compounds in the synthesis of a number of industrial products, including pharmaceuticals and agrochemicals. For example, 3,4-difluorobenzonitrile (3,4-DFBN) is a useful intermediate in the preparation of fluorophenoxy herbicides [1]. 3,4-Difluoroaniline, 3,4-difluorobenzoic acid, and 3,4-difluorobenzotrifluoride, which are also useful synthetic tools, are easily produced from 3,4-DFBN.

We have recently developed novel synthetic routes to m-fluoroaryl derivatives by means of fluorodenitration and

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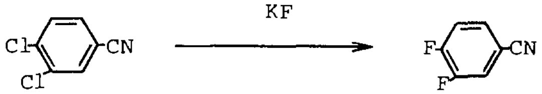
fluorodesulfonylation [2]. Although we were able to prepare various m-fluoroarenes by the application of this method, the development of much more efficient and practical procedures became highly desirable.

Prime concern was to find a simple procedure with low chemicals costs. These factors immediately narrowed our choice of starting materials to aryl chlorides.

The most straightforward method for the introduction of a fluorine atom into an aryl ring involves halogen-exchange with potassium fluoride (KF), Eq.1.



3,4-DCBN 3,4-DFBN

(1)

Such exchange proceeds relatively smoothly for chlorine placed at ortho- and/or para-positions with respect to electron-withdrawing groups such as a CN, giving o- and/or p-fluoroaryl derivatives. However, direct halogen-exchange of meta-chlorine with KF is rarely successful.

We have now found that treatment of 3,4-dichlorobenzonitrile (3,4-DCBN) with KF in the presence of tetraphenylphosphonium bromide (Ph_4PBr) [2,3] as a catalyst in 1,3-dimethylimidazolidine-2-one (DMI) is a convenient, high-yield, one-step method for preparing 3,4-DFBN. We have also shown that DMI is a superior solvent for the synthesis of 3,4-DFBN, and 2-, 3-, and 4-fluorobenzonitriles (FBN) at an elevated temperature (290 °C) in a pressure reactor [4,5].

This report deals with the details of these findings.

RESULTS AND DISCUSSION

In the absence of catalyst, reaction of 3,4-DCBN with 5 equiv. of spray dried KF in a refluxed DMI (225 °C) gave only 11% yield of 3,4-DFBN after 6 h (TABLE 1, Run 1). The yield was unchanged over an additional 6 h. When the Ph_4PBr was employed (0.1 equiv.) as a catalyst, analysis of the reaction mixture revealed a 65% yield (GLC) of 3,4-DFBN , accompanied with a 23% yield of 3-chloro-4-fluorobenzonitrile (3,4-CFBN) (TABLE 1, Run 2). At a short period just after starting the reaction, both 3,4-CFBN and 4-chloro-3-fluorobenzonitrile (4,3-CFBN) isomers were detected by GLC. But 3,4-CFBN was exclusively found after 6 h because the generated 4,3-CFBN was immediately converted to 3,4-DFBN. TABLE 1 lists results on the reaction of 3,4-DCBN with KF under various conditions. Among polar aprotic solvents, the reaction in DMI gave the best result for the formation of 3,4-DFBN. Reactions in 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)pyrimidone (DMPU) and tetrahydrothiophene 1,1-dioxide (sulfolane), afforded a mixture of 3,4-DFBN and CFBN in moderate yields. In dimethylsulfoxide (DMSO), no detectable amount of 3,4-DFBN was observed, due probably to the low boiling point of DMSO.

The reaction of 3,4-DCBN with KF in DMI proceeded well at the reflux temperature of DMI (225 °C), giving 3,4-DFBN in good yield. When the reaction temperature was set at 215 °C, the yield of 3,4-DFBN dramatically decreased to 11% (TABLE 1, Run 4). It was noticeable that the viscosity of the reaction mixture was quite different between 215 and 225 °C, and indeed, the measurement of the viscosity of DMI containing KF showed a steep change at around 220 °C (Fig. 1). This finding demonstrates that the solubilities of KF in DMI increase with increasing temperature, though we cannot directly relate the decreasing of viscosity with the increasing of solubility.

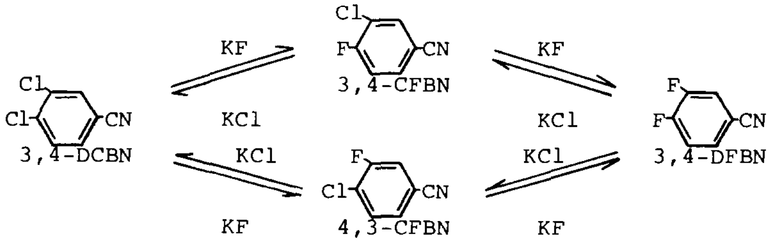
Next, we attempted halogen-exchange of 3-chloro-4-fluorobenzonitrile (3,4-CFBN) with KF in order to utilize the reaction intermediate. Surprisingly, fluorination of 3,4-CFBN separated from the previous reaction (TABLE 1, Run 2) was very slow at the reflux temperature of DMI. This prompted us to investigate the reaction in detail, because we had assumed that 3,4-CFBN was a reaction intermediate en route from 3,4-DCBN to 3,4-DFBN.

TABLE 1

Reaction of 3,4-dichlorobenzonitrile with potassium fluoride in various solvents

Run	Solvent[a]	KF (equiv.)	Ph_4PBr (equiv.)	Temp.[b] °C	Time h	Yield/%[c]	
						3,4-DFBN	CFBN
1	DMI	5	--	Reflux[e]	6	11	78
2	"	5	0.1	Reflux[e]	6	65(61)	23
3	"	3	0.1	Reflux[e]	6	25	43
4	"	5	0.1	210-215	6	11	68
5	"	7	0.1	Reflux[e]	6	56	25
6	DMPU	5	0.1	220-225	6	47	30
7	Sulfolane	5	0.1	220-225	6	38	43
8	DMSO	5	0.1	Reflux[f]	6	trace	46

[a] DMI = 1,3-dimethylimidazolidine-2-one; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)pyrimidone; Sulfolane = tetrahydrothiophene 1,1-dioxide; DMSO = dimethylsulfoxide. [b] Internal temperature. [c] Yield was determined by GLC using internal standard technique. A number in parentheses refer to isolated product. [d] 3,4-CFBN exclusively. [e] 225 °C. After several hours the reflux temperature fell to 220 °C. [f] 190 °C.



A sample of 3,4-CFBN was prepared from 3,4-DCBN using 1.1 equiv. of KF in sulfolane in 84% yield. Analysis of the sample by capillary gas chromatography showed it to be almost pure, and final purification was achieved by recrystallization from ethanol. When the 3,4-CFBN was heated (reflux, 6 h) with 3 equiv. of KF in the presence of Ph_4PBr in DMI, 3,4-DFBN was obtained in only 10% yield. If 3,4-CFBN is a real intermediate to 3,4-DFBN, more than 60% yield of 3,4-DFBN should have been obtained under these conditions. When the reaction was repeated in the presence of 1 equiv. of potassium chloride, a dramatic yield enhancement was observed (TABLE 2, Run 3). This and related results are given in TABLE 2. This finding makes an immediate path from 3,4-CFBN to 3,4-DFBN very unlikely, and suggests that there may be a reverse reaction in which KCl which has been generated by the halogen-exchange reaction of 3,4-DCBN with KF converts 3,4-CFBN back to 3,4-DCBN.

In order to get a further evidence that the reaction proceeds by way of 4,3-CFBN, an unambiguous characterization of 4,3-CFBN was next attempted. An authentic 4,3-CFBN was obtained and characterized by GC-MS from a reaction of 3,4-DFBN with 10 equiv. of KCl. The structure could not be surely identified because the 4,3-CFBN was obtained in only 4 % yield

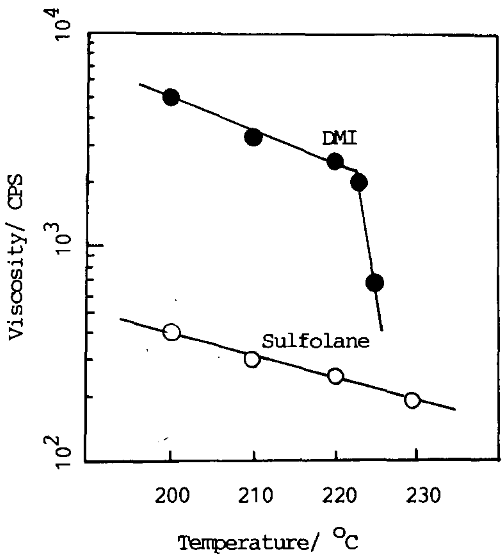


Fig. 1. Relationship between viscosity of a DMI solution containing KF versus temperature.

TABLE 2

Reaction of 3-chloro-4-fluorobenzonitrile with potassium fluoride in DMI[a]

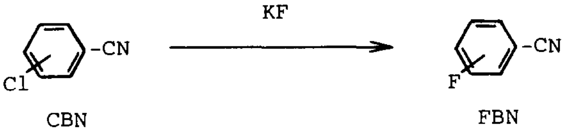
Run	KF (equiv.)	Additive (equiv.)	Yield/%[b]		
			3,4-DFBN	3,4-CFBN	3,4-DCBN
1	1.5	-	9	67	0
2	3.0	-	10	69	0
3	3.0	KCl (1.0)	39	47	4
4	3.0	KCl (0.2)	16	64	-[c]
5	5.0	KCl (1.0)	39	57	-[c]

[a] Reaction of 0.15-0.50 mol of KF suspended in 0.10 mol of 3,4-CFBN in DMI in the presence of 0.01 mol of Ph_4PBr at 225 °C for 4 h. [b] GLC yield. [c] Not determined.

and could not be isolated in the pure form. (see the Experimental Section) A reaction of 3,4-DCBN with 1 equiv. of KF in the presence of 0.1 equiv. of Ph_4PBr in boiling DMI was conducted. We observed a formation of a significant amount of 4,3-CFBN in a short period just after starting the reaction. After 10 min, formation of 5% of 4,3-CFBN and 30% of 3,4-CFBN could be detected by capillary gas chromatographic analysis, along with 65% of the unreacted 3,4-DCBN. After 6 h, the reaction provided 3,4-DFBN, 3,4-CFBN, 4,3-CFBN, and 3,4-DCBN in 0.5, 40, 7, and 50% yield, respectively. If a large excess of KF exists, 4,3-CFBN would be quickly converted to 3,4-DFBN, there by displacing the equilibrium. Our observation does not disprove a path via 3,4-CFBN, but strongly suggests that 4,3-CFBN is a key intermediate to 3,4-DFBN.

As disclosed above, DMI is very good solvent for halogen-exchange fluorination. With the aim of developing an efficient synthetic method for producing 3,4-DFBN, we next attempted a high-temperature halogen-exchange fluorination in a pressure reactor. DMI proved to be a stable solvent for exchange fluorination at a temperature of 290 °C. Thus, 3,4-DCBN was treated with 3 equiv. of KF in DMI at 290 °C in a Hastelloy 'C' pressure reactor. GLC analysis of the organic layer revealed 64% formation of 3,4-DFBN. In this case, the yield was not affected by the presence of Ph_4PBr.

Other polar aprotic solvents such as N-methyl-pyrolidone (NMP), DMPU, and sulfolane clearly were not suitable (TABLE 3) at such elevated temperatures.



Finally, extension to monochlorobenzonitriles was explored. The results are summarized in TABLE 4. A boiling DMI solution of 3-CBN afforded no detectable 3-FBN after vigorous stirring with 5 equiv. of KF, even in the presence of Ph_4PBr. In sharp contrast, treatment of 3-CBN with 1.5 equiv. of KF in DMI at 290 °C gave 3-FBN in 70% yield; benzonitrile was produced as a by-product in 9% yield. Though halogen-exchange fluorination of 2-CBN or 4-CBN was accomplished in refluxing DMI, it took a long time. For example, treatment of 4-CBN with 3 equiv. of KF in DMI at 225 °C for 15 h gave a 60% yield of 4-FBN. At 290 °C in pressure reactor, the starting materials were consumed after 2 h, giving 4-FBN and 2-FBN in 91 and 76% yield, respectively.

In conclusion, the fluorination reaction in DMI described here is anticipated to be a very practical route to fluorobenzonitriles.

TABLE 3

Reaction of 3,4-DCBN with KF in a pressure reactor[a]

Run	Solvent[b]	Temp. °C	Time h	P^c kg/cm^2	Yield%[d]	
					3,4-DFBN	3,4-CFBN
1	DMI	290	4	5	64	4
2	DMI	260	8	2	43	21
3	NMP	290	4	8	5[e]	-
4	DMPU	290	1	>30	f)	
5	Sulfolane	290	1	>30	f)	
6	BN	290	4	10	2	27

[a] Reaction of 25.8 g (0.15 mol) of 3,4-DCBN with 3 equiv. of KF in 150 ml of solvent in the absence of Ph_4PBr. [b] DMI = 1,3-dimethylimidazolidine-2-one; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)pyrimidone; Sulfolane = tetrahydrothiophene 1,1-dioxide; BN = benzonitrile [c] Autogenous pressure. [d] GLC yield. [e] Plus tarry materials. [f] Decomposition occurred.

TABLE 4

Fluorination of various benzonitrile derivatives in DMI at 290 °C in a pressure reactor

Substrate	KF (equiv.)	Time h	P kg/cm^2	Product (Yield)[a]
3-CBN	1.5	8	4	3-FBN (70), BN (9)
3-CBN	3	8	6	3-FBN (57), BN (20)
4-CBN	3	2	6	4-FBN (91)
2-CBN	3	2	3	2-FBN (76)

[a] Yields are for isolated products.

EXPERIMENTAL

All melting points were determined with a Mettler FP61 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO FT/IR-5M infrared spectophotometer. Mass spectra were taken with a Hewlett Packard model 5988A. GC-Mass spectroscopic analysis was achieved using a 0.20 mm x 28 m column of Ultra 2 (5% phenylmethylsilicone). Product mixtures were analyzed by GLC on a Shimadzu Model GC-7A gas chromatograph using a 3 mm x 2 m column of Dexsil 400GC on Chromosorb W AW DMCS (with phenanthrene as an internal standard) or a 1.2 mm x 20 m column of G205 (5% phenylmethylsilicone). Viscosity was measured with a Tokyo Keiki meter type B, using No 4 rotor, 60 RPM.

The temperature of the oil bath used was controlled with the aid of Ricoh Mini Heater Electric Controller Model MH-10.

Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. Spray-dried potassium fluoride was purchased from Morita Kagaku Kogyo Co. or Reidel de Haen Co. and dried in a microwave oven before use. Sulfolane and 1,3-dimethylimidazolidine-2-one were purchased from Sumitomo Seika Co. and Mitsui Toatsu Co., respectively and dried over molecule sieves 4A before use.

Preparation of 3,4-Dichlorobenzonitrile

A 1-L four-necked flask equipped with a mechanical stirrer, a thermometer, and a water separator was charged with 102 g (1.5 mol) of 25% aqueous ammonia and 500 ml of water. To the stirred reaction mixture was added 104.7 g (0.5 mol) of 3,4-dichlorobenzoyl chloride over 1 h. The reaction mixture was then stirred at room temperature for 1 h. Crude 3,4-dichlorobenzamide was collected by filtration. To the solution of 3,4-dichlorobenzamide in 250 ml of chlorobenzene was added dropwise 89.3 g (0.75 mol) of thionyl chloride over 1 h. The stirred mixture was then heated at reflux for 15 h, then cooled to room temperature before chlorobenzene and the excess of thionyl chloride were evaporated in vacuo. The residue was recrystallized from hexane, to give 3,4-DCBN (80 g, 93%) with mp 74-75 °C (lit.[6], mp 70-71 °C).

General procedure for 3,4-difluorobenzonitrile (TABLE 1, Run 2)

A 1-L four-necked flask equipped with a mechanical stirrer, a thermometer, and a water separator was charged with spray dried potassium fluoride (145.3 g, 2.5 mol), Ph_4PBr (21 g, 0.05 mol), and toluene (200 ml). The flask was immersed in an oil bath maintained at 140 °C, and the mixture was stirred to remove toluene azeotropically. After the flask had been cooled to 50 °C, DMI (250 ml) and 3,4-dichlorobenzonitrile (86 g, 0.5 mol) were added and the whole mixture was heated at reflux for 6 h with stirring under a nitrogen atmosphere. The mixture was then cooled to room temperature and ether (500 ml) was added. Filtration, washing with water, and concentration followed by distillation gave pure 3,4-difluorobenzonitrile (42.4 g, 61%) having bp 95 °C/45 mmHg and mp 51.0-51.2 °C (lit.[3e], mp 51-53 °C). IR(KBr): 2340cm^{-1}. MS: m/z=139(M^+).

3-Chloro-4-fluorobenzonitrile

A mixture of 3,4-DCBN (172 g, 1 mol) and KF (63.9 g, 1.1 mol) in sulfolane (600 g) was stirred at 220 °C for 15 h. After cooling, filtration and distillation afforded 130 g (84%) of 3-chloro-4-fluorobenzonitrile having boiling point 135 °C/65 mmHg. A part of this sample was recrystallized from ethanol to afford an analytical sample, mp 70-71 °C.

4-Chloro-3-fluorobenzonitrile

A mixture of 3,4-DFBN (7.0 g, 0.05 mol), potassium chloride (37.3 g, 0.5 mol), and Ph_4PBr (2.1 g, 0.005 mol) in DMI (50 ml) was heated at reflux for 6 h. Direct analysis of the reaction mixture by gas chromatography using a 20 m-G205 column (initial temp. 80 °C, final temp. 200 °C; temperature raised at 5 °C/min). 4-Chloro-3-fluorobenzonitrile was presented in 4% yield. The retention times of 4-chloro-3-fluorobenzonitrile and 3-chloro-4-fluorobenzonitrile were 3.44 and 3.57 minute, respectively. Both products were analyzed by GC-MS, which showed the same molecular weight (m/z 155).

Preparation of 3,4-DFBN in pressure reactor

A 300ml Hastelloy 'C' pressure reactor equipped with a mechanical stirrer was charged with 3,4-DCBN (25.8 g, 0.15 mol), KF (26.1 g, 0.45 mol), and DMI (150 ml). The reaction mixture was heated up to 290 °C during 1 h, and then the reaction was continued at 290 °C for 4 h. The mixture was cooled to room temperature and filtered to remove inorganic materials. The residue was extracted with ether. The ether extract was washed with water three times, and dried over Na_2SO_4. Filtration and concentration in vacuo gave a residue, which was distilled to afford 13.3 g (64%) of 3,4-DFBN having bp 95 °C/45 mmHg. The IR and MS spectra of this sample were identical with those of an authentic sample.

REFERENCES

1 G.R. Pews, L.A. Jackson, C.M. Carson, Japan Kokai Tokkyo Koho, **Jap. Pat. 64-66156 (1989).**

2 H. Suzuki, N. Yazawa, Y. Yoshida, O. Furusawa and Y. Kimura, Bull. Chem. Soc. Jpn., 63 (1990) 2010.

3 a) J.H. Clark and D.J. Macquarrie, Tetrahedron Lett., 28 (1987) 111; b) Y. Yoshida and Y. Kimura, Chem. Lett., (1988) 1355. c) Y. Yoshida and Y. Kimura, J. Fluorine Chem., 44 (1989) 291; d) S. Kumai, M. Sasabe and H. **Matsuo, Japan Kokai Tokkyo Koho, Jap. Pat. 60-228 436 (1985); e) N. Yazawa, H. Suzuki, Y. Yoshida, O. Furusawa and Y. Kimura, Chem. Lett. (1989) 2213.**

4 Part of this work has been submitted in the form of a **patent. [H. Suzuki and Y. Kimura, Jap. Pat. Appl. (Filed: Oct. 27, 1989)].**

5 After completion of this work, similar results were reported by P.G. Pews, J.C. Little and J.M. Gall, Japan Kokai Tokkyo Koho, **Jap. Pat. 2-218 629 (1990).**

6 P. Oxley, M.W. Partridge, T.D. Robson and W.F. Short, J. Chem. Soc., (1946) 763.