Direct Synthesis of 2,4-Diaminoquinazolines from 2-Fluorobenzonitriles

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In a search for new methods for preparing 2,4-diaminoquinazolines having a diversity of substituents in the benzenoid ring, it was found that the reaction of 2,6-difluorobenzonitrile with guanidine carbonate gave 2,4-diamino-5-fluoroquinazoline in excellent yield. Extension of this approach to other 2-fluorobenzonitriles, some of which were elaborated for the first time, showed that this reaction possesses considerable generality. The cyclization was successful even when electron donating groups were present at position six. Only in two cases where a primary or secondary amino group was also present *ortho* to the cyano group was this transformation unsuccessful.

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2,4-Diaminoquinazolines have been prepared by the cyclization of 2-aminobenzonitriles with dicyandiamide, guanidine, or the combination of cyanamide with pyridine hydrochloride [1,2]. In most instances the yields were low using one of these reagents. Considerably better results have been obtained by the reaction of substituted 2-aminobenzonitriles with chloroformamidine hydrochloride in diglyme [3-5]. The synthetic utility of the approach is limited by the availability of the requisite 2-aminobenzonitrile. The reaction of 2-chloro-5-nitrobenzonitrile with guanidine carbonate gave 2,4-diamino-6-nitroquinazoline in excellent yield [3]. However, it appears that only highly activated 2-chlorobenzonitriles undergo this cyclization. It is also possible to prepare 2,4-diaminoquinazolines from the corresponding 2,4(1*H*,3*H*)-quinazolinediones *via* ammonolysis of the intermediate 2,4-dichloroquinazolines at elevated temperature and pressure [6]. This classical transformation has only limited scope due to the drastic conditions which must be employed in the two-step sequence. Finally, it appears that certain 2-amino-4-hydroxyquinazolines can be converted to their 2,4-diamino counterparts using phenylphosphorodiamidate [7]. However, many substituents cannot withstand the harsh conditions required in this reaction and the diversity of potential substrates is also quite restricted.

The nature of the substituent at position five of 2,4-diaminoquinazolines (usually methyl or chloro) often plays a critical role in determining the biological utility of a particular analogue. (The target enzyme for these compounds is usually dihydrofolate reductase). Important examples of this phenomenon can be demonstrated in antibacterial [7], antineoplastic [8,9], antimalarial [10] and antimycobacterial [11] studies. In the last regard, DeGraw and coworkers found that 5-methyl-6-alkyl-2,4-diaminoquinazolines produced synergistic effects against *Mycobacterium* sp. **606** when employed in combination with the standard antileprotic agent, dapsone [11]. In attempting to capitalize upon this observation in an ongoing search for a new folate antagonist suitable for use in the treatment of leprosy, we sought a new economical method for preparing 2,4-diaminoquinazolines having a wide diversity of substitution patterns, particularly at position 5. Our initial studies demonstrated that the reaction of 2,6-difluorobenzonitrile with guanidine carbonate in dimethylacetamide at 140° gave the new compound, 2,4-diamino-5-fluoroquinazoline (**1a**), in excellent yield. This paper is concerned with efforts to expand the scope of this reaction and to gain insight into its mechanism.

In addition to the seven 2-fluorobenzonitriles which

Scheme I

Routes used to Prepare 2-Fluoro-6-substituted-benzonitriles

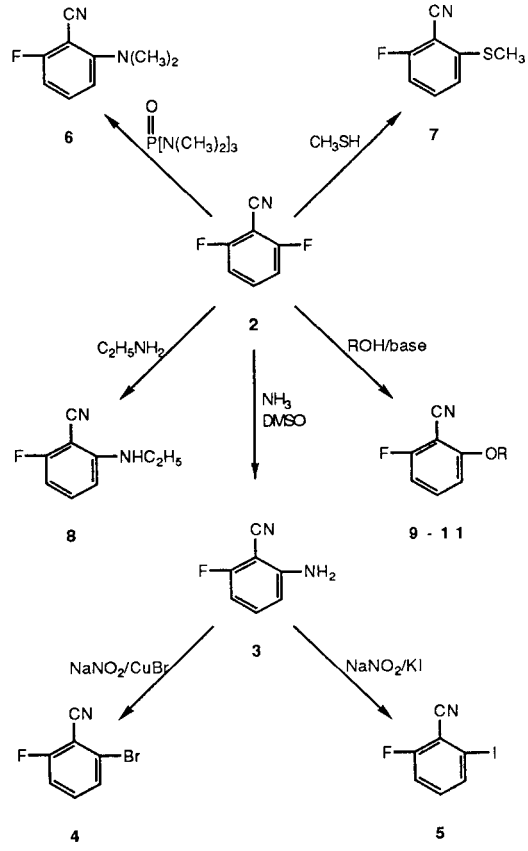
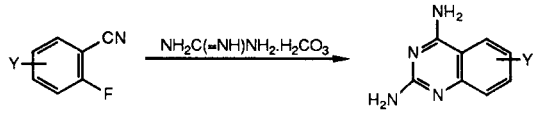


Table 1

Physical and Analytical Data for 2,4-Diaminoquinazolines Prepared from 2-Fluorobenzonitriles



Compound No.	Y Product	Reaction time, hours	Molar ratio of reactants [a]	Yield %	MS m/e	Empirical Formula	Analyses %, Calcd./Found C	H	N	F or Cl
1a	5-F	5	1.67	91	179 [b]	$C_8H_7FN_4 \cdot O \cdot 4H_2O$	51.83	4.30	30.22	10.20
							51.85	4.09	31.14	10.19
1b	5-Cl	7	1.5	92	-	$C_8H_7ClN_4 \cdot H_2O$	45.19	3.22	26.35	16.67
							45.06	3.32	26.05	16.29
1c	5-Br	8	1.5	82	239 [b]	$C_8H_7BrN_4$	40.19	2.95	23.43	
							39.68	2.97	23.41	
1d	5-I	8	1.5	74	287 [b]	$C_8H_7IN_4$	33.59	2.47	19.59	
							33.72	2.38	19.52	
1e	-	3	2	68	-	$C_8H_8N_4$				
1f	6-F	6	2	78	178 [c]	$C_8H_7FN_4$	53.93	3.96	31.45	
							53.86	4.03	31.38	
1g	7-F	4	2	38	178 [c]	$C_8H_7FN_4$	53.93	3.96	31.45	
							53.58	4.22	31.91	
1h	8-F	7	1	83	178 [c]	$C_8H_7FN_4$	53.93	3.96	31.45	
							53.85	4.08	31.48	
1i	5-OCH_3	10	1.5	92	-	$C_9H_{10}N_4O$				
1j	5-SCH_3	24	2	67	206 [c]	$C_9H_{10}N_4S$	52.40	4.89	27.18	
							52.39	4.89	27.08	
1k	5-OC_2H_5	6	1.5	77	204 [c]	$C_{10}H_{12}N_4O \cdot H_2O$	54.04	6.35	25.21	
							54.11	5.61	25.46	
1l	5-OCH_2CF_3	6	1.6	79	259 [b]	$C_{10}H_9F_3N_4O$	46.52	3.51	21.70	22.10
							46.17	3.58	21.62	21.89
1m	5-$N(CH_3)_2$	13	2.6	53	204 [b]	$C_{10}H_{13}N_5 \cdot 0.25H_2O$	57.81	6.54	33.71	
							57.85	6.22	33.93	
1n	5,6,7,8-F_4	4.5	1.42	47	232 [c]	$C_8H_4F_4N_4 \cdot 0.75H_2O$	39.11	2.25	22.81	
							38.89	1.96	22.56	

[a] Moles guanidine carbonate/moles 2-fluorobenzonitrile. [b] FAB (M + 1). [c] Electron impact, off probe.

were obtained commercially, a variety of others were prepared by the synthetic routes summarized in Scheme 1. It will be seen that 2,6-difluorobenzonitrile (**2**) served as the key starting material for preparing many of the 2-fluorobenzonitriles employed in this study. The physical properties of these compounds are presented in Table 2. The reaction of **2** with ammonia at 80-100° in dimethylsulfoxide gave 2-amino-6-fluorobenzonitrile (**3**) in 90% yield. This reaction had formerly been conducted in a sealed vessel using ethanol as the solvent, and the reported yield was considerably lower [12].The diazonium salt derived from **3** then gave 2-bromo-6-fluorobenzonitrile (**4**) and 2-fluoro-6-iodobenzonitrile (**5**) when treated with cuprous bromide or potassium iodide, respectively. The 2-(dimethylamino)-6-fluorobenzonitrile (**6**) was prepared from **2** according to the literature method using hexamethylphosphoric triamide [13]. The reaction of **2** with methanethiol in dimethylacetamide at 0° gave 2-fluoro-6-(methylthio)-benzonitrile (**7**) together with a small amount of the disubstitution product 2,6-di(methylthio)benzonitrile. This mixture was readily resolved by column chromatography over silica gel. Ethylamine reacted readily and cleanly with **2** in dimethyl sulfoxide to afford the 2-ethylamino-6-fluorobenzonitrile (**8**) in excellent yield. The alkoxy derivatives **9** and **10** were obtained by reacting **2** with the appropriate alkoxide. Finally, 2,2,2-trifluoroethanol reacted with **2** in the presence of cesium carbonate at ambient temperature to give 2-fluoro-6-(2,2,2-trifluoroethoxy)benzonitrile in respectable yield. In this instance, it was not necessary to prepare the sodium salt of 2,2,2-trifluoroethanol with

sodium hydride as had been done in earlier related nucleophilic displacement reactions [14].

The next 2-fluorobenzonitrile to be subjected to the aforementioned cyclization conditions was 2-chloro-6-fluorobenzonitrile which afforded 5-chloro-2,4-diaminoquinazoline (**1b**) in excellent yield. This compound had formerly been prepared in three steps in low overall yield beginning with 2,3-dichloronitrobenzene [3]. The fact that the fluorine in this reactant is much less reactive than that of **2** gave impetus for extending the study to other substrates, the results of which are summarized in Table 1. It will be seen that the transformation was successful even when electron donating groups such as alkoxy or dimethylamino were present, although in the latter case the reaction was sluggish and the yield was only 53%. However, with 2-ethylamino-6-fluorobenzonitrile none of the desired 5-ethylaminoquinazoline was obtained in spite of the use of a large excess of guanidine carbonate and prolonged heating. In the case of 2-amino-6-fluorobenzonitrile (**3**), which is an *ortho* aminobenzonitrile as well as a 2-fluorobenzonitrile, a complex product was obtained which was not resolved. The presence of **1a**, however, was indicated by ^{19}F nmr analysis of the crude mixture. The other three commercially available difluorobenzonitriles (the 2,5- 2,4-, and 2,3-isomers) gave the expected 6-, 7-, and 8-fluoroquinazolines **1f-1h** respectively, thus demonstrating the regioselectivity of this reaction. Low yields were obtained in the two instances where the substrate contained an additional fluorine *para* to the cyano function (**1g** and **1n**). Since fluorine located in this position is activated toward nucleophilic displacement, it is believed that competing reactions occured in these two cases.

It is proposed that this cyclization reaction proceeds by the reversible addition of guanidine to the cyano function followed by nucleophilic displacement of fluoride ion as shown below.

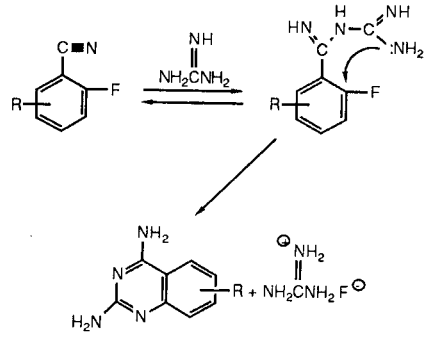
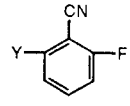


Table 2

Physical and Analytical Data for 2-Fluoro-6-substituted-benzonitriles



Compound No.	Y	Yield %	Mp°C	^{19}F NMR ppm [a]	Formula	Analyses %, Calcd./Found C	H	N	F
3	NH_2	90	126-127.5 [b]	108.8	$C_7H_5FN_2$				
4	Br	60	57-58.5	103.5	C_7H_3BrFN	42.03 42.04	1.51 1.59	7.00 6.82	
5	I	78	48.5-50.5	102.9	C_7H_3FIN	34.03 34.22	1.22 1.23	5.67 5.68	
6	$N(CH_3)_2$	87	oil [c]	106.7	C_9H_9FN				
7	SCH_3	72	63-64.5	107.0	C_8H_6FNS	57.46 57.46	3.62 3.62	8.38 8.16	
8	NHC_2H_5	97	41.5-43.5	109.0	C_9H_9FN	65.84 66.13	5.53 5.54	17.06 16.99	
9	OCH_3	86	93-95	108.5	C_8H_6FNO	63.57 63.61	4.00 4.40	9.27 9.17	
10	OC_2H_5	79	47-49	107.0	C_9H_8FNO	65.45 63.81	4.88 4.91	8.48 8.19	
11	OCH_2CF_3	80	83-85	106.8 72.9(CF_3)	$C_9H_5F_4NO\cdot0.25H_2O$	48.82 48.36	2.48 2.63	6.33 6.10	34.30 34.00

[a] δ Upfield from fluorotrichloromethane in dimethyl sulfoxide. [b] Ref [12] mp 125-127°. [c] Ref [13] bp 65-70°/0.53 mm.

Indirect evidence for this mechanism stems from the observation that 2-fluorobenzonitrile gave 2,4-diaminoquinazoline (**1e**) under conditions where 2,6-difluorobenzonitrile produced **1a** as the only detectable product. If nucleophilic displacement of fluorine were the initial step in the reaction, one might expect that side products would have been formed in the latter case. The fact that 2-fluorobenzonitriles containing a primary or secondary amino group, which is also *ortho* to the cyano group, did not afford the expected products maybe due to hydrogen bonding between the transient guanidine adduct and the adjacent amino group. The formation of such quasi-cyclic structures could prevent the nucleophilic displacement of fluorine from occurring. Efforts are in progress to expand the synthetic utility of this novel approach to nitrogen heterocycles.

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Analytical samples of compounds **1a-n** were dried under vacuum at 100°. Solvation due to water was confirmed by the presence of a broad peak at *ca.* 3.4 in the ^{1}H nmr spectrum. The ^{1}H and ^{19}F nmr spectra were determined by using a Varian EM 390 spectrometer. The ^{1}H chemical shifts are presented in ppm downfield from tetramethylsilane as the internal standard. The ^{19}F chemical shifts are presented in ppm upfield from fluorotrichloromethane as the internal standard. The relative peak areas are given to the nearest whole number. Fast-atom-bombardment mass spectra (FAB) were obtained on a Finnigan MAT 212 spectrometer using argon bombardment. The electron impact mass spectra were obtained off probe using a Finnigan 4521 mass spectrometer at the Department of Chemistry, University of South Carolina, Columbia, SC. 2,6-Difluorobenzonitrile and 2-chloro-6-fluorobenzonitrile were obtained from Fairfield Chemical Co., while 2,5-, 2,4-, 2,3-difluorobenzonitriles and pentafluorobenzonitrile were purchased from Aldrich Chemical Co.

General Method for Preparing Compounds **1a-n**.

2,4-Diamino-5-fluoroquinazoline (**1a**).

A mixture of 2,6-difluorobenzonitrile (**2**) (106 g, 0.68 mole), guanidine carbonate (184.3 g, 1.02 moles) in 2000 ml of dimethylacetamide was heated at 140-142° for 5 hours. The course of the reaction was monitored by ^{19}F nmr. After refrigeration overnight, the product was separated by filtration and a second crop was obtained by the addition of methylene chloride to the filtrate. The combined solids were recrystallized from aqueous ethanol yielding 98.7 g of white crystalline solid, mp 249-151°; ^{1}H nmr (DMSO-d_6): δ 6.22 (br s, 2H, 2-NH_2), 6.77-7.58 (m, 3H, aromatic), 7.10 (br s, 2H, 4-NH_2). ^{19}F nmr (DMSO): δ 111.9 (m).

5-Chloro-2,4-diaminoquinazoline (**1b**).

This compound was obtained as cream colored plates (ethanol-water), mp 186-188° (lit [3] mp 183-185°); ^{1}H nmr (DMSO-d_6): δ 6.22 (br s, 2H, 2-NH_2), 6.96-7.59 (m, 3H, aromatic), 6.97 (br s, 2H, 4-NH_2).

5-Bromo-2,4-diaminoquinazoline (**1c**).

This compound was obtained as cream colored needles (ethanol-water), mp 202-204°; ^{1}H nmr (DMSO-d_6): δ 6.20 (br s, 2H, 2-NH_2), 7.22-7.40 (m, 3H, aromatic), 7.33 (br s, 2H, 4-NH_2).

2,4-Diamino-5-iodoquinazoline (**1d**).

This compound was obtained as cream colored crystals (ethanol-water), mp 192-193°; ^{1}H nmr (DMSO-d_6): δ 6.13 (br s, 2H, 2-NH_2), 6.9-7.6 (m, 3H, aromatic), 7.20 (br s, 2H, 4-NH_2).

2,4-Diaminoquinazoline (**1e**).

This compound was obtained as white needles (water), mp 254-258° (lit [3] mp 248-252°); ^{1}H nmr (DMSO-d_6): δ 6.03 (br s, 2H, 2-NH_2), 6.90-8.00 (m, 3H, aromatic), 7.22 (br s, 2H, 4-NH_2).

2,4-Diamino-6-fluoroquinazoline (**1f**).

This compound was obtained as off white crystals (ethanol-water), mp 315-320°; ^{1}H nmr (DMSO-d_6): δ 6.07 (br s, 2H, 2-NH_2), 7.11-7.86 (m, 3H, aromatic), 7.28 (br s, 2H, 4-NH_2); ^{19}F nmr (DMSO): δ 121.6 (m).

2,4-Diamino-7-fluoroquinazoline (**1g**).

This compound was obtained as cream colored crystals (ethanol-water), mp 274-277°; ^{1}H nmr (DMSO-d_6): δ 6.30 (br s, 2H, 2-NH_2), 6.73-8.12 (m, 3H, aromatic), 7.40 (br s, 2H, 4-NH_2); ^{19}F nmr (DMSO): δ 107.8 (m).

2,4-Diamino-8-fluoroquinazoline (**1h**).

This compound was obtained as a white crystalline powder (ethanol-water), mp 285-287°; ^{1}H nmr (DMSO-d_6): δ 6.22 (br s, 2H, 2-NH_2), 6.81-7.83 (m, 3H, aromatic), 7.37 (br s, 2H, 4-NH_2); ^{19}F nmr (DMSO): δ 128.8 (m).

2,4-Diamino-5-methoxyquinazoline (**1i**).

This compound was obtained as a white crystalline powder (water), mp 200-202° (lit [2] mp 208-209°); ^{1}H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 5.91 (br s, 2H, 2-NH_2), 7.44-8.43 (m, 3H, aromatic), 7.30 (br s, 2H, 4-NH_2).

2,4-Diamino-5-(methylthio)quinazoline (**1j**).

This compound was obtained as cream colored crystals (ethanol-water), mp 170-172°; ^{1}H nmr (DMSO-d_6): δ 3.22 (s, 3H, SCH_3), 5.93 (br s, 2H, 2-NH_2), 6.98-7.45 (m, 3H, aromatic), 7.50 (br s, 2H, 4-NH_2).

2,4-Diamino-5-ethoxyquinazoline (**1k**).

This compound was obtained as light gray crystals (ethanol-water), mp 214-216°; ^{1}H nmr (DMSO-d_6): δ 1.40 (t, 3H, CH_3), 4.13 (q, 2H, OCH_2), 5.86 (br s, 2H, 2-NH_2), 6.44-7.41 (m, 3H, aromatic), 7.18 (br s, 2H, 4-NH_2).

2,4-Diamino-5-(2,2,2-trifluoroethoxy)quinazoline (**1l**).

This compound was obtained as a white cyrstalline powder (ethanol-water), mp 245-246°; ^{1}H nmr (DMSO-d_6): δ 4.91 (q, 2H, OCH_2), 6.01 (br s, 2H, 2-NH_2), 6.57-7.48 (m, 3H, aromatic), 7.02 (br s, 2H, 4-NH_2); ^{19}F nmr (DMSO): δ 72.7 (t, CF_3).

2,4-Diamino-5-(dimethylamino)quinazoline (**1m**).

This compound was obtained as a yellow crystalline solid (ethanol-water), mp 204-205°; ^{1}H nmr (DMSO-d_6): δ 2.61 (s, 6H, $N(CH_3)_2$), 5.92 (br s, 2H, 2-NH_2), 6.77-7.43 (m, 3H, aromatic), 7.17 (br s, 1H, 4-NH), 8.80 (br s, 1H, 4-NH hydrogen bonded).

2,4-Diamino-5,6,7,8-tetrafluoroquinazoline (**1n**).

This compound was obtained as a white crystalline powder (water), mp 215-220°; ^{1}H nmr (DMSO-d_6): δ 5.78 (br s, 2 and 4-NH_2); ^{19}F nmr DMSO: δ 139.3 (m, 2F), 150.0 (m, 2F).

2-Amino-6-fluorobenzonitrile (**3**).

A solution of 100 g (0.72 mole) of 2,6-difluorobenzonitrile in 1500 ml of dimethylsulfoxide was placed in a 3 liter 3-necked flask equipped with a gas inlet tube, thermometer, and a dry ice condenser. Gaseous ammonia was added and the solution was maintained between 75-90°. After approximately 24 hours the reaction was judged to be >95% complete by ^{19}F nmr. The solution was added to a large volume of water and refrigerated. The resulting white crystalline solid was separated by filtration, washed with water and dried under vacuum at ambient temperature over phosphorous pentoxide to yield 88.0 g of product; ^{1}H nmr (acetone-d_6): δ 5.82 (br s, 2H, NH_2), 6.35-7.48 (m, 3H, aromatic).

2-Bromo-6-fluorobenzonitrile (**4**).

To a solution containing 6.81 g (0.050 mole) of **3** in 250 ml of 5*N* hy-

drobromic acid maintained at 0 to −5° was added portionwise 3.80 g (0.055 mole) of sodium nitrite in 15 ml of water. After stirring for 1.5 hours, the diazonium salt solution was added slowly to a cold (0°) of solution of cuprous bromide (14.35 g, 0.10 mole) in 60 ml of 48% hydrobromic acid. The resulting mixture was allowed to warm to ambient temperature and stirred for 15 hours. Next, the mixture was extracted with 2 x 250 ml of methylene chloride and the combined organic layers were washed successively with 5% aqueous sodium bicarbonate, water, and then dried over anhydrous magnesium sulfate. After solvent removal under vacuum, the crude product was purified by column chromatography over silica gel (Baker 60-200 mesh) using hexanes-benzene (4:1) as the eluent. The fractions homogeneous by tlc were pooled and evaporated at reduced pressure to yield 5.97 g of **4**; ^{1}H nmr (acetone-d_6): δ 6.60-7.72 (m, aromatic).

2-Fluoro-6-iodobenzonitrile (**5**).

To a solution containing 10 g (0.073 mole) of **3** in 200 ml of 6*N* hydrochloric acid maintained at 0 to −5° was added portionwise 5.59 g (0.081 mole) of sodium nitrite in 22.5 ml of water. After stirring for 1 hour, the mixture was added slowly (30 minutes) to a cold (0 to −5°) solution of 24.2 g (0.146 mole) of potassium iodide in 80 ml of water. The resulting mixture was allowed to warm to ambient temperature and stirring was continued for 15 hours. Next, it was extracted with 3 x 350 ml of methylene chloride and the organic layer was then washed successively with 5% aqueous sodium bisulfite, 10% aqueous sodium hydroxide, and water. After drying over anhydrous magnesium sulfate, the methylene chloride was removed under reduced pressure. Column chromatography over silica gel (Baker 60-200 mesh) using hexanes-toluene (3:1) yielded 14.0 grams of **5** after solvent evaporation and drying under vacuum; ^{1}H nmr (deuteriochloroform): δ 6.85-7.72 (m, aromatic).

2-Fluoro-6-(methylthio)benzonitrile (**7**).

To a stirred mixture of **2** (2.78 g, 0.020 mole) and potassium bicarbonate (2.0 g, 0.020 mole) in 50 ml of dimethylacetamide maintained at 0°, was added methanethiol until the ^{19}F nmr indicated that all of **2** had been consumed. The reaction mixture was poured into 200 ml of cold water and the resulting solid was isolated by filtration, washed with water and air dried. Purification by column chromatography over silica gel (Baker 60-200 mesh) using hexanes-toluene (1:1) as the eluent yielded 2.4 g of pure product. A small quantity of slow runner mp 164-167° was obtained and identified as 2,6-di(methylthio)benzonitrile by mixed melting point with an authentic sample; ^{1}H nmr (acetone-d_6): δ 2.65 (s, 3H, SCH_3), 7.02-7.81 (m, 3H, aromatic).

2-Ethylamino-6-fluorobenzonitrile (**8**).

In a reaction set-up similar to that employed for the preparation of **3** was placed 8.0 g (0.057 mole) of **2** in 94 ml of dimethyl sulfoxide. Excess ethylamine was added through a gas addition tube at ambient temperature. After 4 hours, the reaction mixture was poured into 250 ml of water and the resultant solution placed in a refrigerator for 15 hours. The white crystals were isolated by filtration, washed with water, and dried under vacuum to yield 9.5 g of product; ^{1}H nmr (acetone-d_6): δ 1.27 (t, 3H, CH_3), 3.36 (q, 2H, CH_2N), 5.60 (br s, 2H, NH_2), 6.20-7.53 (m, 3H, aromatic).

2-Fluoro-6-methoxybenzonitrile (**9**).

To a solution of 11.17 g (0.072 mole) of **2** in 150 ml of methanol maintained at 0° was added sodium methoxide in methanol (nitrogen purge). The reaction was monitored by ^{19}F nmr until all the **2** had been consumed. The reaction mixture was then added to 800 ml of water and refrigerated. The product was separated by filtration, dried, and recrystallized from carbon tetrachloride to yield 10.4 g of white crystals; ^{1}H nmr (acetone-d_6): δ 3.97 (s, 3H, OCH_3), 6.81-7.81 (m, 3H, aromatic).

2-Ethoxy-6-fluorobenzonitrile (**10**).

This compound was prepared in an analogous fashion to **9** and was recrystallized from *n*-hexane; ^{1}H nmr (acetone-d_6): δ 1.40 (t, 3H, CH_3), 4.24 (q, 2H, CH_2O), 6.80-7.78 (m, 3H, aromatic).

2-Fluoro-6-(2,2,2-trifluoroethoxy)benzonitrile (**11**).

A mixture containing 7.0 g (0.050 mole) of **2**, 13.84 g (0.14 mole) of 2,2,2-trifluoroethanol, 16.29 g (0.050 mole) of cesium carbonate and 25 ml of dimethylacetamide was stirred at ambient temperature for 24 hours. The contents of the flask were poured into 800 ml of cold water and refrigerated for 24 hours. The white crystalline solid was separated by filtration, washed with water, and dried under vacuum to yield 8.80 g of product; ^{1}H nmr (acetone-d_6): δ 4.41 (q, 2H, CH_2O), 6.67-7.61 (m, 3H, aromatic).

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