THE SYNTHESIS OF FLUORINE-CONTAINING AZA-MACROCYCLIC COMPOUNDS

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Abstract---Four aza-macrocyclic compounds were synthesized by reactions of phthalaldehydes and phthaloyl chlorides with N,N'-di(2-aminomethyl-3-fluorophenyl)-ethylenediamine(**8**) and their structures were identified. The nucleophilic substitution reaction of 2,6-difluorobenzonitrile(**1**) was discussed.

INTRODUCTION

The aza-macrocyclic compounds have received considerable interest in recent years because of their abilities to form complex with a variety of neutral organic molecules, cations, and anions.[1-5] Many works have been done to synthesize aza-macrocyclic compounds by using two bis-functionalized aliphatic or aromatic compounds as precursors.[6,7] In this paper, we report the synthesis of novel aza-macrocyclic compounds by reactions of phthalaldehydes and phthaloyl chlorides with N,N'-di(2-aminomethyl-3-fluorophenyl)ethylenediamine(**8**) derived from 2,6-difluorobenzonitrile(**1**).

RESULTS AND DISCUSSION

It was reported[8] that 2,6-difluorobenzonitrile(**1**) reacted with a variety of nucleophilic reagents, and we found that **1** reacted with methyl mercaptoacetate in a similar way giving compound (**2**). Treatment of **1** with ethyl glycinate gave product (**3**) with a small amount of compound (**4**), but no indole derivative was formed even in the presence of sodium

ethoxide.

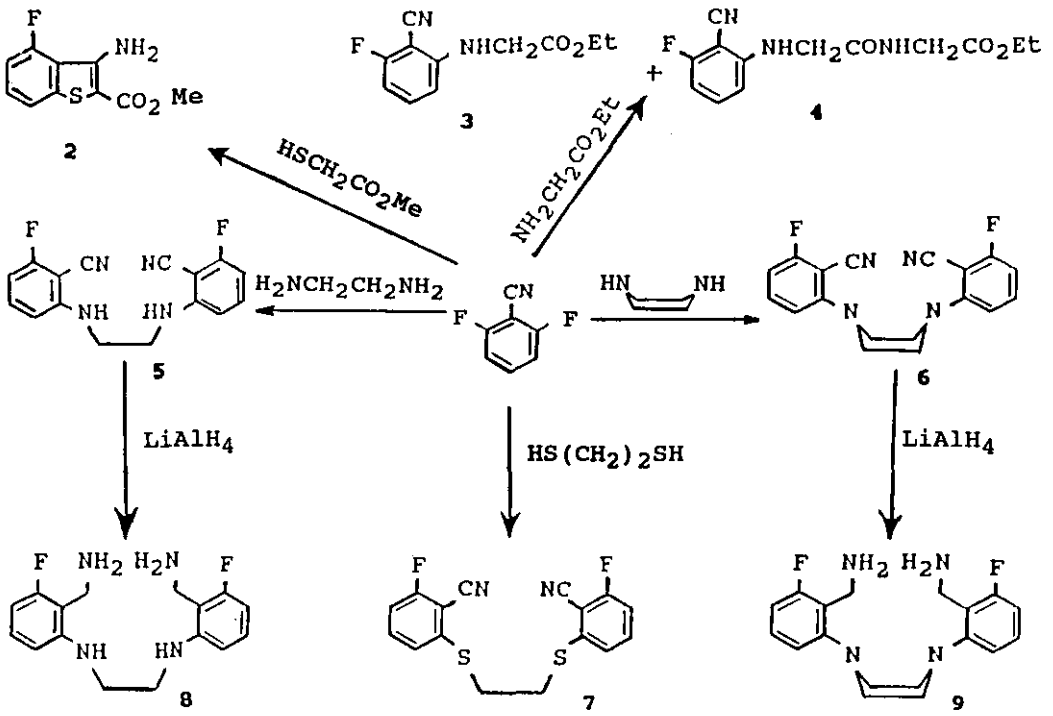
The reaction of **1** with materials with two nucleophilic sites gave di-substituted products in good yields. Thus, treatment of **1** with ethylenediamine and piperazine afforded corresponding compounds (**5**)(75%) and (**6**)(58%), respectively. The reaction of **1** with 1,2-ethanedithiol resulted in the formation of compound (**7**) in 70% yield(see Scheme 1).

In the next step, compounds (**5**) and (**6**) were reduced with $LiAlH_4$ in THF[9] to corresponding diamines (**8**) in 58% yield and (**9**) in 65% yield. However, treatment of **7** with $LiAlH_4$ didn't give a good result because of its low solubility and ir spectrum indicated that CO, NH_2, and unreacted CN groups existed in the crude mixture(see Scheme 1).

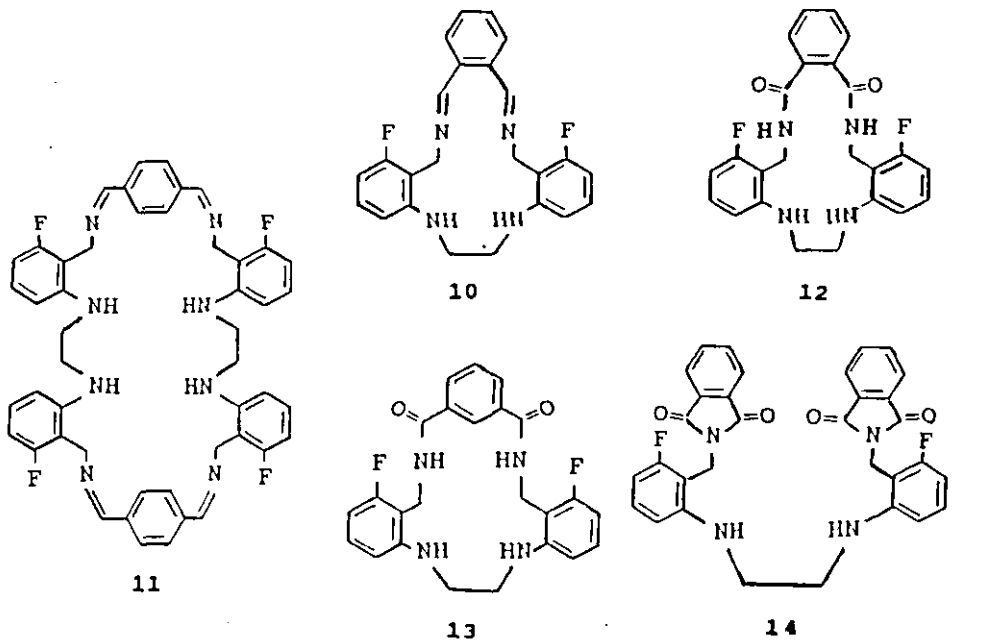
Compound (**8**) contains two NH_2 groups and two NH groups, so it was used to synthesize macrocyclic compounds. Under ordinary reaction conditions,[10] treatment of **8** with phthalaldehydes and phthaloyl chlorides didn't give macrocycles. With high dilution techniques, **8** reacted with o-phthalaldehyde in acetonitrile to give [1+1] cyclic condensation product (**10**) in 18% yield, but when **8** was treated with p-phthalaldehyde, [2+2] condensation product (**11**) was formed in 24% yield but not [1+1] condensation product. The NH groups in **8** were not protected considering their relatively weak nucleophility and greater steric hindrance. No macrocyclic compounds were obtained when treating **8** with m-phthalaldehyde.

Compound (**8**) reacted with o- and m-phthaloyl chlorides in benzene forming cycling products (**12**) and (**13**), respectively, in about 30% yields and the former reaction also produced a small amount of compound (**14**) (5%). It was found that in polar organic solvents such as dichloromethane and acetonitrile, the yields of **12** and **13** were decreased(about 15%). All the azamacrocyclic compounds (**10**, **11**, **12**, and **13**) have high melting points and poor solubility in ordinary organic solvents such as acetone, acetonitrile, and ethyl acetate. When compound (**9**) was treated with phthalaldehydes or phthaloyl chlorides under similar conditions, no macrocycles were obtained probably because the piperazine ring may exist in a chair conformation so as to prevent cyclization reaction but favor linear condensation.

Products (**10** and **11**) show strong molecular ion peaks in ms and distinct



Scheme 1



Scheme 2

C=N peak in ir spectra, and their ^{1}H nmr spectra indicate the existence of CH=N groups. Compounds (**12**, **13**, and **14**) have strong molecular ion peaks in ms spectra, and **14** gave $M^+/2$ peak. Their ir spectra exibit strong C=O frequency.

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EXPERIMENTAL

Melting points are uncorrected. ^{1}H nmr spectra were recorded on Varian EM360 and JEOL FX90Q spectrometers with TMS as an internal standard. ^{19}F nmr spectra were taken on Varian EM360 model instrument with CF_3-COOH as an external standard. Ms spectra were determined on a Finnigan 4021 instrument. Ir spectra were obtained on Shimadzu IR-440 model and Perkin-Elmer 983 model instruments all in potassium bromide pellets. Silica gel(10-40μ) was used for column chromatography.

Methyl 3-Amino-4-fluoro-1-benzothiophene-2-carboxylate(2)

A solution of **1**(1.39 g, 10 mmol), methyl mercaptoacetate(1.06 g, 10 mmol), and K_2CO_3(1.38 g, 10 mmol) in 10 ml of DMSO was stirred at room temperature for 10 h, and then poured into 30 ml of water. The mixture was extracted with benzene(20 mlx3) and the organic phase was washed with water several times and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography using benzene as an eluent. 1.51 g(67%) of **2** was obtained. mp 83-85°C. Anal. Calcd for $C_{10}H_8NO_2FS$: C, 53.32; H, 3.59; N, 6.22; F, 8.44; S, 14.23. Found: C, 53.35; H, 3.39; N, 6.14; F, 8.53; S, 14.27. Ir ν_{max}: 3400(NH_2), 1690(C=O), 1600, 1280, and 780 cm^{-1}. ^{1}H Nmr(acetone-d_6) δ: 3.9(3H, s), 4.7(2H, s), 7.4(3H, m) ppm. ^{19}F Nmr(acetone-d_6) δ: 46.0 ppm. Ms m/z(%): 225(M^+, 34.1), 194(100.0).

Ethyl 2-Cyano-3-fluorophenylaminoacetate(3) and N-Ethoxylcarbonylmethyl 2-Cyano-3-fluorophenylaminoacetamide(4)

A mixture of **1**(1.39 g, 10 mmol), ethyl glycinate hydrochloride(1.40 g, 10 mmol), and 3 ml of NEt_3 was added with stirring to 10 ml of ethyl alcohol. The solution was stirred at 80°C for 40 h. After removal of

the solvent, the residue was purified by column chromatography using petroleum ether/ethyl acetate(3:1) as an eluent. 1.55 g(60%) of **3** and 0.075 g(5%) of **4** were obtained. **3**: mp 98-99°C. Anal. Calcd for $C_{11}H_{11}N_2O_2F$: C, 59.44; H, 5.00; N, 12.61; F, 8.55. Found: C, 59.85; H, 4.79; N, 12.69; F, 8.44. Ir ν_{max}: 3380(NH), 2205(CN), 1742(C=O), and 1210 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 1.4(3H, t, 6 Hz), 4.0(2H, s), 4.3(2H, q, 6 Hz), 5.3(1H, s), 6.5-7.3(3H, m) ppm. ^{19}F Nmr($CDCl_3$) δ: 28.6 ppm. Ms m/z(%): 222(M^+, 32.4), 149(100.0). **4**: mp 144-145°C. Anal. Calcd for $C_{13}H_{14}N_3O_3F$: C, 55.90, H, 5.06; N, 15.05. Found: C, 56.20; H, 4.45; N, 15.60. ^1H Nmr($CDCl_3$) δ: 1.3(3H, t, 6 Hz), 4.0(6H, m), 5.5(1H, s), 6.5-7.2(3H, m) ppm. ^{19}F Nmr($CDCl_3$) δ:29.4 ppm. Ms m/z(%): 280(M^++1, 14.5), 149(100).

N,N'-(2-Cyano-3-fluorophenyl)ethylenediamine(5)

A solution of **1**(5.56 g, 40 mmol), ethylenediamine(1.20 g, 20 mmol), and NEt_3(6 ml) in 50 ml of DMSO was heated with stirring at 80°C for 20 h and then poured into 100 ml of NaOH solution(5%). The mixture was filtered and washed with water. After dried, the residue was crystallized from pyridine. 4.5 g(75%) of **5** was obtained. mp 256-258°C. Anal. Calcd for $C_{16}H_{12}N_4F_2$: C, 64.61; H, 4.06; N, 18.79; F, 12.74. Found: C, 64.42; H, 3.55; N, 18.43; F, 12.24. Ir ν_{max}: 3370(NH), 2170(CN), 1620, 1570, 1295, and 1180 cm^{-1}. ^1H Nmr(acetone-d_6) δ: 3.7(4H, s), 4.1(2H, s), 6.6-7.3(6H, m) ppm. ^{19}F Nmr(acetone-d_6) δ: 28.0 ppm. Ms m/z(%): 299 (M^++1, 65.4), 163(14.0), 149(100.0).

N,N'-Di(2-cyano-3-fluorophenyl)piperazine(6)

The reaction was similar to that for compound (**5**). Product (**6**) was obtained in 58% yield. mp 241°C. Anal. Calcd for $C_{18}H_{14}N_4F_2$: C, 66.65; H, 4.36; N, 17.28; F, 11.72. Found: C, 66.58; H, 3.87; N, 17.32; F, 11.76. Ir ν_{max}: 2200(CN), 1610, 1570, and 790 cm^{-1}. ^1H Nmr(acetone-d_6) δ: 3.5 (8H, s), 6.6-7.2(6H, m) ppm. ^{19}F Nmr(acetone-d_6) δ: 28.1 ppm. Ms m/z (%): 324(M^+, 100.0), 175(54.3), 162(14.7), 148(79.2), 121(83.2).

1,2-Di(2-cyano-3-fluorophenylthio)ethane(7)

1,2-Ethanedithiol(0.94 g, 10 mmol) and K_2CO_3(1.52 g, 11 mmol) were added to DMSO(20 ml). After stirring for 0.5 h, **1**(2.78 g, 20 mmol) was added and then stirred at room temperature for 50 h. After hydrolysis and workup as above, 2.32 g(70%) of **7** was obtained. mp > 180°C.

Anal. Calcd for $C_{16}H_{10}N_2F_2S_2$: C, 57.78; H, 3.04; N, 8.43; F, 11.43; S, 19.28. Found: C, 57.86; H, 2.70; N, 8.46; F, 11.02; S, 18.76. Ir ν_{max}: 2205(CN), 1600, 1570, 1460, 1225, and 905 cm^{-1}. ^1H Nmr(acetone-d_6) δ: 2.8(4H, s), 6.9-7.4(6H, m) ppm. ^{19}F Nmr(acetone-d_6) δ: 36.8 ppm. Ms m/z (%): 332(M^+, 42.2), 180(100.0), 152(21.2).

N,N'-Di(2-aminomethyl-3-fluorophenyl)ethylenediamide(8) and N,N'-Di(2-aminomethyl-3-fluorophenyl)piperazine(9)

A THF solution(400 ml) of **5**(2.98 g, 20 mmol)(heated for complete dissolution) was added slowly(2 h) to a suspension of $LiAlH_4$(0.94 g, 22 mmol) in 200 ml of THF. After stirring for another 3 h at room temperature, saturated aqueous ammonium chloride solution was added dropwise until no gas was evolved. 2 ml of 20% aqueous KOH solution were then added. The mixture was allowed to stand overnight. The mixture was filtered and the organic layer was dried over $MgSO_4$, and then evaporated in vacuo. The residue was purified by column chromatography using $CHCl_3$ /MeOH/NEt_3(10:3:1) as an eluent to give 1.80 g(58%) of **8**. Compound (**9**) was synthesized similarly in 65% yield. **8**: mp 95-96°C. Anal. Calcd for $C_{12}H_{20}N_4F_2$: C, 62.72; H, 6.59; N, 18.29; F, 12.40. Found: C, 62.25; H, 6.25; N, 18.04; F, 12.13. Ir ν_{max}: 3400, 3200(NH_2, NH), 1620, 1585, 1530, 1470, 925, and 780 cm^{-1}. ^1H Nmr(acetone-d_6) δ: 1.7(4H, w), 3.5 (4H, s), 3.9(4H, s), 4.4(2H, s), 7.0(6H, m) ppm. ^{19}F Nmr(acetone-d_6) δ: 39.2 ppm. Ms m/z(%): 307(M^++1, 12.2), 166(64.2), 154(28.3), 136(100.0), 109(41.8). **9**: mp 165-167°C. Anal. Calcd for $C_{18}H_{22}N_4F_2$: C, 65.03; H, 6.68; N, 16.86; F, 11.43. Found: C, 64.62; H, 6.24; N, 16.92; F, 10.94. Ir ν_{max}: 3360(NH_2), 1605, 1575, 1450, and 785 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 1.8(4H, s), 3.7(8H, s), 4.0(4H, s), 7.1(6H, m) ppm. ^{19}F Nmr($CDCl_3$) δ: 40.0ppm. Ms m/z(%): 333(M^++1, 10.8), 179(38.5), 166(78.2), 163(36.3), 136(100.0).

3,4-Benzo-8,9-(2-fluorobenzo)-14,15-(5-fluorobenzo)-1,6,10,13-tetraaza-1,5-cyclohexadecadiene(10) and 3,6,21,24-Diphenylene-11,12,28,29-di(2-fluorophenylene)-17,18,34,35-di(5-fluorophenylene)-1,8,12,15,19,26,30,-33-octaaza-1,7,19,25-cyclohexatriacontatetraene(11)

A solution of **8**(0.612 g, 2 mmol) and o-phthalaldehyde(0.268 g, 2 mmol) in 2000 ml of acetonitrile was stirred at room temperature for 12 h and then allowed to stand overnight. The solvent was removed and the residue was purified directly by column chromatography using $CHCl_3$/MeOH

(50:1) as an eluent. 0.15 g(19%) of **10** was obtained. Compound (**11**) was synthesized similarly in 24% yield. **10**: mp 168-171°C. Anal. Calcd for $C_{24}H_{22}N_4F_2$: C, 71.26; H, 5.49, N, 13.85; F, 9.40. Found: C, 71.66; H, 6.13; N, 13.44; F, 9.02. Ir ν_{max}: 3320(NH), 1620(CH=N), 1608, 1470, and 770 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 3.4(4H, s), 4.5(4H, s), 5.1(2H, s), 6.4-7.4 (10H, s), 8.2(2H, s) ppm. ^{19}F Nmr($CDCl_3$) δ: 40.2 ppm. Ms m/z(%): 404 (M^+, 59.8), 266(27.9), 253(13.5), 151(15.4), 136(64.7), 124(33.3), 57 (100.0). **11**: mp >210°C. Anal. Calcd for $C_{48}H_{44}N_8F_4$: C, 71.26; H, 5.49; N, 13.85; F, 9.40. Found: C, 70.87; H, 5.01; N, 13.72; F, 9.65. Ir ν_{max}: 3300(NH), 1620(CH=N), 1575, and 765 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 3.4(8H, s), 3.7(8H, s), 5.0(4H, s), 6.4-7.2(20H, s), 7.7(4H, s) ppm. ^{19}F Nmr ($CDCl_3$) δ: 39.8 ppm. Ms m/z: 809(M^++1), 808(M^+).

N,N'-[2,3-(2-Fluorobenzo)-8,9-(5-fluorobenzo)-4,7-diazadecamethylene]-phthalic Diamide(12), N,N'-Di(2-phthalimidomethyl-3-fluoro)phenyl Ethylenediamine(14) and N,N'-[2,3-(2-Fluorobenzo)-8,9-(5-fluorobenzo)-4,7-diazadecamethylene]-m-phthalic Diamide(13)

A solution of o-phthaloyl chloride(0.31 g, 1.5 mmol) in 200 ml of anhydrous benzene was added dropwise for about 3 h to **8**(0.46 g, 1.5 mmol) and NEt_3(1.5 ml) in 1500 ml of anhydrous benzene at room temperature. The reaction mixture was then stirred for 3 h and allowed to stand overnight. After removal of the solvent, the residue was directly purified by column chromatography using $CHCl_3$/MeOH(100:1) as an eluent. 0.2 g(30%) of **12** and 0.023 g(5%) of **14** were obtained. Similarly, compound (**13**) was synthesized in 30% yield. **12**: mp >230°C. Anal. Calcd for $C_{24}H_{22}N_4O_2F_2$: C, 66.03; H, 5.09; N, 12.84; F, 8.71. Found: C, 65.99; H, 4.93; N, 12.51; F, 8.61. Ir ν_{max}: 3420, 3300(NH), 1635(C=O), 1600, 1525, and 780 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 2.6(2H, s), 3.6(4H, s), 4.6(4H, s), 6.4(6H, m), 7.0-7.6(6H, m) ppm. ^{19}F Nmr($CDCl_3$) δ: 39.5 ppm. Ms m/z (%): 436(M^+, 47.9), 284(14.5), 151(46.6), 136(100.0), 109(51.8). **14**: mp 160°C. Anal. Calcd for $C_{32}H_{24}N_4O_4F_2$: C, 67.83; H, 4.28; N, 9.89. Found: C, 67.69; H, 4.36; N, 10.00. Ir ν_{max}: 3300(NH), 1703(C=O) cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 2.6(2H, s), 3.5(4H, s), 4.8(4H, s), 6.4(4H, m), 7.1-7.6(10H, m) ppm. ^{19}F Nmr($CDCl_3$) δ: 39.2 ppm. Ms m/z(%): 566(M^+, 13.4), 283(M^+/2, 72.2), 160(26.4), 136(100.0), 109(58.3). **13**: mp 228°C. Anal. Calcd for $C_{24}H_{22}N_4O_2F_2$: C, 66.03; H, 5.09; N, 12.84; F,8.71. Found: C, 65.99; H, 4.93; N, 12.50; F, 8.29. Ir ν_{max}: 3300(NH), 1630(C=O), 1530, 1470, and 775 cm^{-1}. ^1H Nmr($CDCl_3$) δ: 2.4(2H, s), 3.5(4H, s), 4.6(4H. s), 6.6-7.5 (12H, m) ppm. ^{19}F Nmr($CDCl_3$) δ: 40.2 ppm. Ms m/z(%): 436(M^+, 36.4), 284

(13.1), 136(100.0), 124(21.7), 109(50.9).

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