Journal of Fluorine Chemistry, 49 (1990) 99–106

Received November 15, 1989, accepted. March 19, 1990

REACTIONS OF AMINES OR AMIDES WITH PHTHALOYL CHLORIDE. SYNTHESIS OF FLUORINE-CONTAINING N,N-DIMETHYL-N'-SUBSTITUTED AMIDINES AND RELATED COMPOUNDS

MEI-JIN CHEN,CHING-SUNG CHI and QING-YUN CHEN*

Shanghai Institute of Organic Chemistry,Academia Sinica,
345 Lingling Lu, Shanghai 200032 (China)

SUMMARY

The appropriate diamines reacted with phthaloyl chloride to yield 1,2-bis(2-N,N-dimethylaminomethyleneamino-4-trifluoromethylphenylthio)ethane and 1,2-bis[2'-(3''-phthaleneamino)-4'-trifluoro-methylphenylthio]ethane.Similarly,2,6-dinitro-4-trifluoromethylaniline gave N,N-dimethyl-N'-(2,6-dinitro-4-trifluoromethylphenyl)formamidine. 2-Fluorobenzoic hydrazide and 2,6-difluorobenzamide gave 3-hydro-2-(2'-fluorobenzoyl)-1,4-phthalazinedione and N-(2,6-difluorobenzoyl)phthalimide. A single crystal of (3) was monoclinic, and a trans configuration about the C=N bond was determined by X-ray analysis.

INTRODUCTION

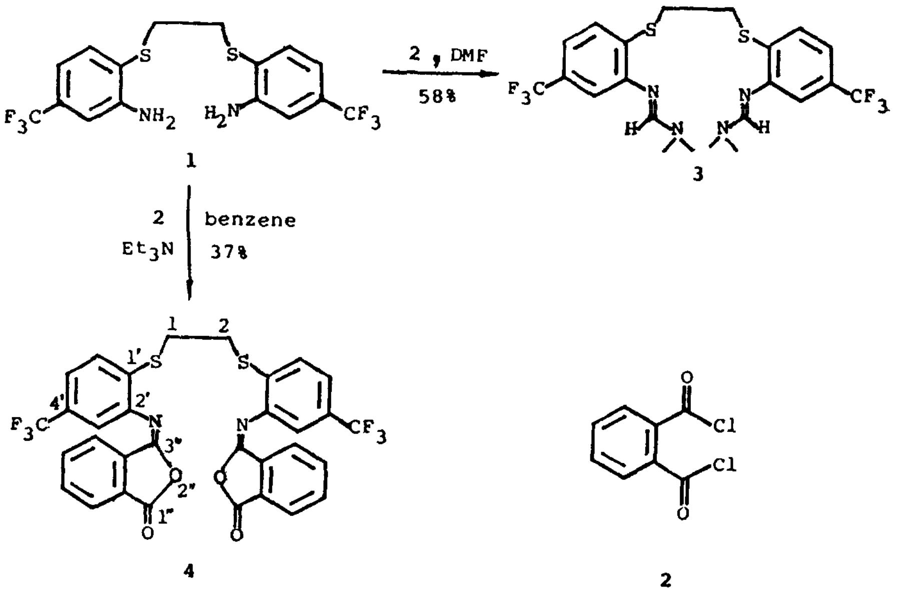
Heterocyclic compounds are useful in medicine and insecticides[1] and substituted amidines have been used as fungicides and bactericides[2]. Because fluorine alters electronic effects, imparts oxidative and thermal stability, fluorine-containing heterocyclic compounds are of interest[3]. We have previously synthesized a macrocycle from a diamine and

0022-1139/90/$3.50

aliphatic carbonyl dichloride [4], however, when an aromatic phthaloyl chloride was used, different behaviour was observed. The results will be reported here in detail.

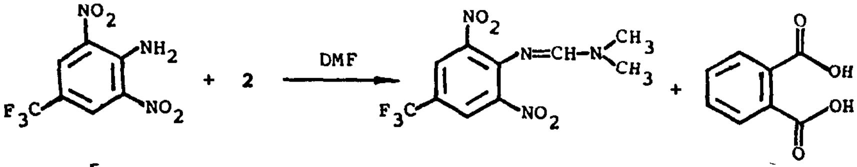
RESULTS AND DISCUSSION

The reaction of diamine (**1**) in N,N-dimethylformamide in the presence of phthaloyl chloride (**2**) at room temperature generated a trans-substituted amidine (**3**), which was identified by X-ray single crystal analysis. **1** and **2** with triethylamine also gave product **3**, however treatment of **1** with triethylamine in benzene instead of DMF resulted in the formation of a five-membered cycle **4** containing phthaloyl groups(**Scheme**). This condensation reaction also took place when **1** is replaced by the substituted aniline **5**, giving N,N-dimethyl-N'-(2,6-dinitro-4-trifluoromethylphenyl)formamidine(**6**) and phthalic acid (**7**) (**eq.1**). 2-Fluorobenzoic hydrazide (**8**) reacted with **2**, in the presence as well as in the absence of

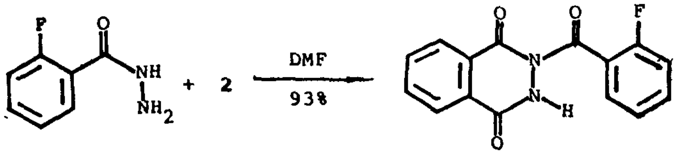


Scheme.

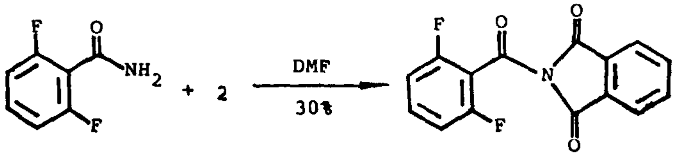
triethylamine to afford the fluorine-containing substituted 1,4-phthalazinedione (**9**). Apparently **8** can be used both as a substrate and a base (eq.2). Tricarbonyl benzamide (**11**) was obtained from the reaction of 2,6-difluorobenzamide(**10**) with phthaloyl chloride (eq.3).



5 6 7 (1)



8 9 (2)



10 11 (3)

Proof of structures was based on analysis,NMR,IR and MS. In the mass spectrum of **4** a weak M+1 ion(673) is observed. A peak at 279 (100%) resulting from the loss of CO_2 from the fragment 323 demonstrates that **4** is a lactone.Furthermore,**4** is characterized by its stretching C=N vibration at 1695cm^{-1},and by the stretching lactone C=O vibration that appears at 1820 cm^{-1}. The crystal structure of **3** has been determined by X-ray analysis:the C=N bond was found to have a trans-configuration, which might be formed due to the thermodynamical stability.

TABLE

Bond Distances(Å) And Angles(deg) For $C_{22}H_{24}N_4F_6S_2$(3)[a,b]

S-C1	1.764(5)	N1-C9	1.276(6)	C2-C3	1.391(7)
S-C8	1.817(5)	N2-C9	1.333(6)	C3-C4	1.389(7)
F1-C7	1.251(9)	N2-C10	1.444(7)	C4-C5	1.362(7)
F2-C7	1.272(7)	C2-C11	1.452(7)	C4-C7	1.497(7)
F3-C7	1.258(9)	C1-C2	1.406(6)	C5-C6	1.391(8)
N1-C2	1.408(6)	C1-C6	1.380(7)	C8-C8pp	1.521(9)
C1-S-C8	102.8(2)	N1-C2-C3	124.6(4)	F1-C7-F2	106.0(6)
C2-N1-C9	119.3(4)	C1-C2-C3	118.7(4)	F1-C7-F3	103.7(6)
C9-N2-C10	123.5(4)	C2-C3-C4	120.7(5)	F1-C7-C4	114.0(5)
C9-N2-C11	121.2(4)	C3-C4-C5	120.0(5)	F2-C7-F3	103.4(6)
C10-N2-C11	115.2(4)	C3-C4-C7	119.1(5)	F2-C7-C4	115.4(5)
S-C1-C2	115.2(3)	C5-C4-C7	120.9(5)	F3-C7-C4	113.1(5)
S-C1-C6	125.2(4)	C4-C5-C6	120.3(5)	S-C8-C8pp	106.4
C2-C1-C6	119.6(4)	C1-C6-C5	120.5(5)	N1-C9-N2	123.4(4)
N1-C2-C1	116.5(4)				

[a] symmetry operation: 0.5-x, +y, -z.

[b] The standard deviation in the last digit is in parentheses.

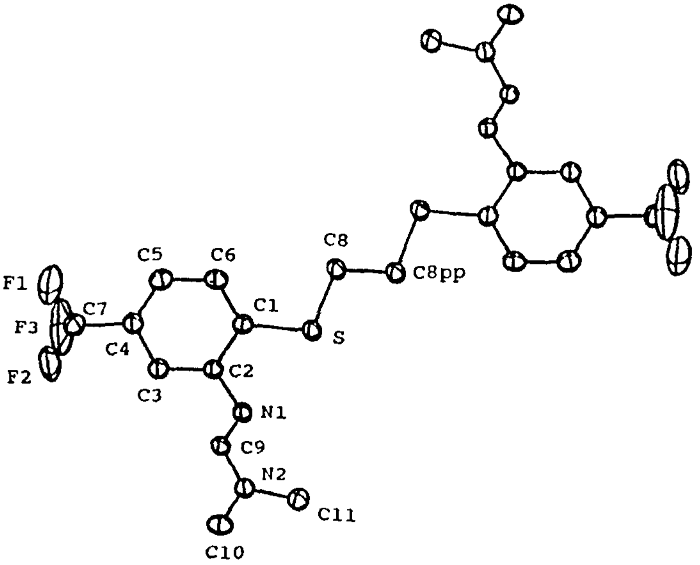


Fig. **ORTEP** diagram for **3** with labelling scheme.

The bond distances and angles are listed in **Table** and the **ORTEP** diagram is shown in the **Figure**.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Infrared spectra were measured on Shimadzu IR-440 spectrophotometer (KCl pellets). ^{1}H and ^{19}F NMR were performed on Varian XL-200 and EL-360L spectrometers using TMS and TFA as external standards for ^{1}H and ^{19}F respectively. Mass spectral data were recorded on Finning-402 spectrometer. All chemical shifts are reported in ppm and wave numbers in cm^{-1}.

X-Ray crystallography. Compound **3**. (a) Crystal data $C_{22}H_{24}N_4F_6S_2$, Mr=522.57, a=7.559(1), b=10.810(4), c=29.353(8)Å, β=89.78(2)°, V=2398(1)Å^3, monoclinic, space group I2/a, Z=4, Mo-Kα radiation(λ = 0.71069Å), F(000)=1080.00, μ =2.38cm^{-1}.

(b) Data collection and processing. The intensity data were measured on a Nicolet R_3 four circle diffractomer using Mo-Kα radiation and ω scanning and were corrected for Lp factors. Of the 2405 data collected, 1352 had F>5 σ(F), where σ is the standard deviation of the background count based on counting statistics, and were used in structure solution and refinement.

(c) Structure solution and refinement. The coordinates of non-hydrogen atoms were determined by direct methods (MULTAN 84). The hydrogen atoms were subsequently located on a series of difference Fourier maps. With the inversion center (0.5,0,0) at the midpoint of C8-C8pp, the one half molecule was obtained by inversing the other half which lay in the independent area. Refinement of data was carried out with anisotropic temperature factors only for the non-hydrogen atoms. At convergence, the discrepancy factors R and R_w were 0.0699 and 0.0635 respectively.

1,2-Bis(2-N,N-dimethylaminomethyleneamino-4-trifluoromethylphenylthio)ethane(3)

To a stirred solution containing 2.06g (5mmole) (**1**) in 30ml DMF, 1.50g(7.4mmole) phthaloyl chloride in 10ml DMF was added.

The reaction mixture was stirred at 20-25°C for 36h, then, DMF was removed *in vacuo*.After addition of 50ml water, a yellowish crystalline precipitate appeared. The solid was collected by filtration,washed with water and air dried at room temperature. The crude solid was recrystallized from acetone. 1.52g crystalline solid was obtained in 58% yield. m.p.148-149°C.IR:1100(s, C-F),1640(s,C=N);NMR:$\delta^1H(CDCl_3)$: 3.40(12H,s,CH_3),3.56(4H,s,CH_2), 7.40(2H,s,N=CH),7.60(4H,s, ArH,ortho- and meta- to N), 7.93(2H, s,ArH,para- to N); $\delta^{19}F(CDCl_3)$:15.3;MS:523(M^++1); Anal. Calcd for $C_{22}H_{24}N_4F_6S_2$:C,50.57; H,4.59;N,10.73;F,21.84;S,12.26;Found: C,50.49;H,4.45;N,10.59;F,21.85;S,12.36%. When 1.22g(10.2mmole) triethylamine was added to the reaction mixture (in DMF) at the outset of the reaction,the product (**3**) was obtained only in 23% yield.

1,2-Bis[2'-(3''-phthaleneamino)-4'-trifluoromethylphenylthio) ethane(**4**)

A similar procedure was used except that dry benzene was used as the solvent.The yellow solid was recrystallized from acetone. 0.91g solid was obtained in 37% yield.m.p.191-192°C. IR:1695(vs, C=N),1820(vs,C=O);NMR: $\delta\ ^1H$(acetone-d_6):3.10(4H,s,CH2),7.30(3H,s, ArH), 7.76(4H,s,ArH);$\delta^{19}F$(acetone-d_6):-13.3;MS:279($C_{15}H_8NF_3O_2S^+$), 323(279+CO_2),653(M^++1); Anal.Calcd for $C_{32}H_{18}N_2F_6O_4S_2$:C,57.14;H, 2.39;N,3.72;F,16.96;S,9.52; Found:C,56.96;H,2.50;N,3.93;F,17.12; S,9.69%.

N,N-Dimethyl-N'-(2,6-dinitro-4-trifluoromethylphenyl)formamidine(**6**)

To a stirred solution of 2.51g(10mmole) 2,6-dinitro-4-trifluoromethyl aniline(**5**) in 25ml DMF,2.64g(13mmole) of **2** was added. The reaction mixture was stirred at room temperature for 17h and at 60°C for 44h.After adding 30ml water,a yellow solid precipitate appeared.After adding 10ml concentrated hydrochloric acid,the water phase was allowed to stand overnight.1.6g phthaloyl acid (**7**) crystallized in 74% yield (based on **2**).

(**6**),m.p.89-90°C.IR:1130(s,C-F),1320(s,NO_2),1660(s,N=C); NMR: $\delta\,^1H(CDCl_3)$:3.46, 3.56(6H,d,CH_3),7.90(1H,s,N=CH),8.60(2H,s,ArH); $\delta\,^{19}F(CDCl_3)$:-14.6; MS:44($C_2H_6N^+$),306(M^+),307(M^++1); Anal.Calcd for $C_{10}H_9N_4F_3O_4$:C,39.22;H,2.94;N,18.30;F,18.63;Found:C,38.84;H, 2.69;N,18.37;F,18.96%.

3-Hydro-2-(2'-fluorobenzoyl)-1,4-phthalazinedione(**9**)

To a stirred solution containing 2.22g(22mmole)triethylamine and 1.54g(10mmole)2-fluorobenzoic hydrazide (**8**) dissolved in 15ml DMF,2.03g of **2** was added. An exothermic reaction took place causing a temperature rise to 70°C.The reaction mixture was stirred for 1.5h,then,30ml water was added.A solid precipitate appeared. The solid was collected by filtration,washed with water,and recrystallized from DMF/H_2O. 2.64g of **9** was obtained in 93% yield. When this reaction was repeated without triethylamine, 1.30g of **9** was obtained in 46% yield.m.p.177-178°C. IR: 920(s,C-F),1660 (m,C=O),1700(s,C=O),1795(s,C=O), 3400(w,NH); NMR: $\delta\,^1H(DMSO-d_6)$: 7.53-7.83(4H,m,ArH),8.03-8.13(4H,m,ArH);$\delta\,^{19}F(DMSO-d_6)$:30.6; MS: 123($C_7H_4FO^+$); Anal. Calcd for $C_{15}H_9N_2FO_3$:C,63.38;H,3.21;N,9.86; F,6.69;Found:C,63.31;H,3.01;N,9.85;F,5.99%.

N-(2,6-Difluorobenzoyl)phthalimide(**11**)

To a refluxing solution containing 1.57g(10mmole) of 2,6-difluorobenzamide and 2.22g (22mmole) of triethylamine in 20ml dry benzene, 2.24g(11mmole) of phthaloyl chloride was added under stirring.The reaction mixture was then stirred under reflux for 4h.After the solution was cooled and water was added,the benzene layer separated was washed with aqueous NaCl solution and dried by sodium sulphate. Removal of the solvent gave a solid,recrystallized from alcohol to give 0.87g of product 11 in 30% yield.

m.p.136-137°C. IR:1280-1310(s,C-F).1750(vs,asy.C=O),1760(vs,sym C=O),1800(vs,C=O, attached to F-Ar); NMR:δ ^{1}H(DMSO-d_6):6.90-7.30 (3H,m,ArH),7.86,7.90(4H,d,ArH); δ ^{19}F(DMSO-d_6): 38.0; MS: 141 ($C_7H_3F_2O^+$),287(M^+),288(M^++1);Anal.Calcd for $C_{15}H_7NF_2O_3$:C,62.72; H,2.44; N,4.88;F,13.24; Found: C,62.74;H,2.24;N,4.78;F,13.08%.

ACKNOWLEDGEMENT

We thank Prof.Qing-Chuan Yang(Department of Chemistry,Beijing University) for X-ray analysis.

REFERENCES

1 C.-S.Chi,M.-J.Chen,S.-Q.Liang and D.-H.Chen,J.Fluorine Chem. 38 (1988) 327.

2 CIBA Ltd. Fr.Pat. 1 573 904 cited from Chem.Abstr., 73 (1970) 25101d.

3 R.Filler,Y.Kobayashi,'Biomedicinal Aspects of Fluorine Chemistry,'Kodansha, Tokyo, 1982.

4 M.-J.Chen,C.-S.Chi and Q.-Y. Chen, to be published.