Journal of Fluorine Chemistry, *43* (1989) 319–327

Received: May 26, 1988; accepted: October 25, 1988

STUDIES ON FLUORINE-CONTAINING AROMATIC HETEROCYCLIC COMPOUNDS 4. REACTIONS OF 3-TRIFLUOROMETHYLPHENYL- AND 2-CHLORO-5-TRIFLUOROMETHYLPHENYL ISOCYANIDE DICHLORIDES WITH BIFUNCTIONAL NUCLEOPHILES

GUI-DONG ZHU, JIAN-HUA HUANG and CHING-SUNG CHI*

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

SUMMARY

Reactions of fluorine-containing phenyl isocyanide dichloride (1) with different nucleophiles gave a novel series of products, such as 2-chloro-5-trifluoromethylphenylamino-, -perhydropyrimidine (2a), -4,5-dihydrooxazole (2c), -5-trifluoromethylbenzimidazole (4e), hydroxyethyl-2-chloro-5-trifluoromethylphenylcarbamate (7), 2-(2′-chloro-5′-trifluoromethylphenyl)-3-hydroxy-6-trifluoromethylperhydrobenzo-1,2,4-triazine (9). The effect of CF_3 group on the ring-closure and the probable reaction mechanism are discussed.

INTRODUCTION

The reactions of phenyl isocyanide dichloride with bifunctional nucleophiles have been widely discribed [1-8]. To our knowledge, the reactions of fluorine-containing phenyl isocyanide dichlorides have not yet been reported. Many useful developments arise from studies of fluorine-containing compounds since they often give quite novel properties and effects [9]. Fluorine-containing heterocyclic compounds are important in medicine and pesticides. Our major interest was to investigate the reactions

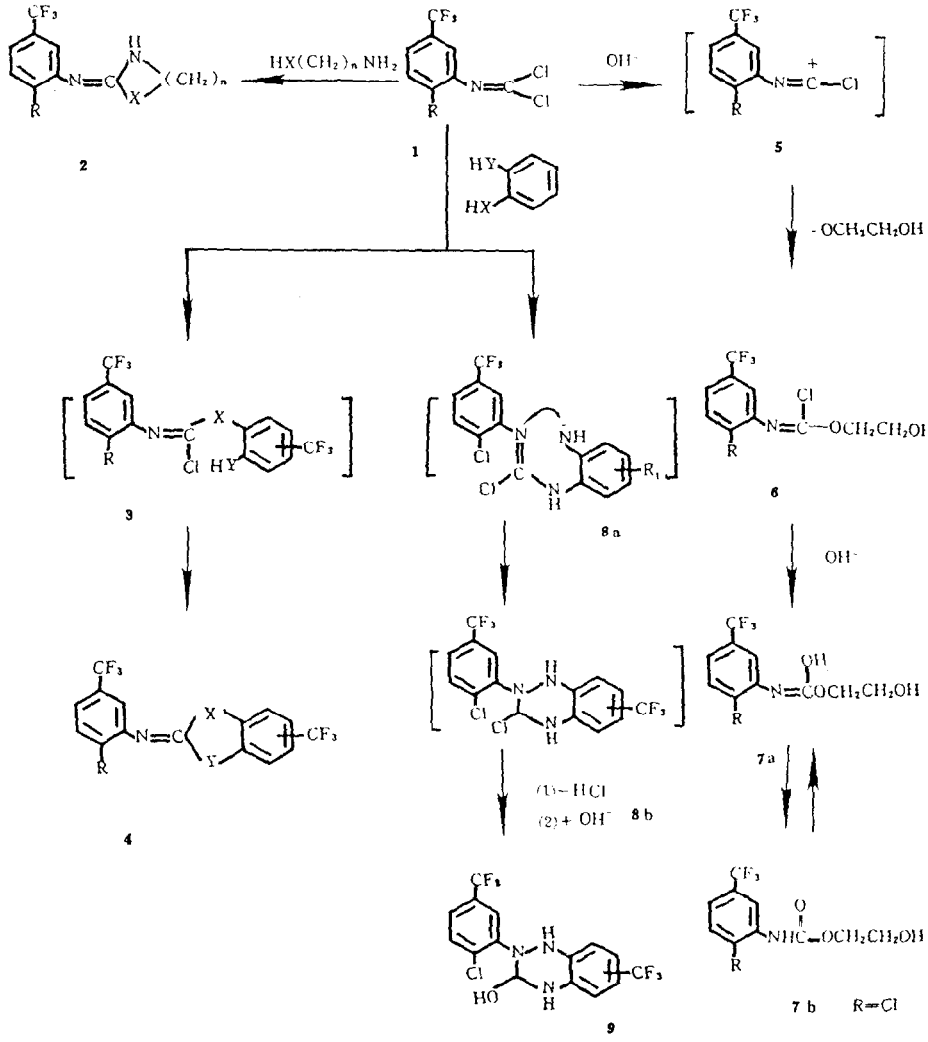
0022-1139/89/$3.50

of fluorine-containing phenyl isocyanide dichloride with bifunctional nucleophiles for preparing novel bioactive compounds and to find the effects of fluorine on those reactions.

RESULTS AND DISCUSSION

Non-fluorine-containing phenyl isocyanide dichloride undergoes a smooth ring-closure reaction with glycol, diamine, or aminoalkanols to give a series of ring-closed products in high yields [1]. However we found that the reactions of fluorine-containing phenyl isocyanide dichloride with the same nucleophiles gave both monosubstituted products and addition products in addition to ring-closed products (see scheme 1).

For example, treatment of 2-chloro-5-trifluoromethylphenyl isocyanide dichloride (1a) and 3-trifluoromethylphenyl isocyanide dichloride (1b) with aminopropanol, phenyldiamine, or glycol gave a novel series of ring-closure products 2,4 which were confirmed by analysis, NMR, IR, and Mass spectroscopy. Interestingly, treatment of 1 with glycol afforded only the monosubstituted product 7. ^1H NMR spectra in deuteriated acetone showed a keto: enol ratio of about 3:1. This reaction of 1 with glycol is in contrast to that of non-fluorine-containing phenyl isocyanide dichlorides, which gave only a ring-closed product; no monosubstituted product was obtained [2]. By using meta-trifluoromethylphenyl diamine instead of phenyl diamine, it was found that CF_3 group on the nucleophile has also a profound effect on the ring-closure. For example, treatment of 1 with meta-trifluoromethylphenyl diamine yielded an unexpected addition product 9 in addition to the expected ring-closed product (4e). However the reaction of 1 with o-phenylenediamine afforded only the expected ring-closed product (4a). The mechanism of reaction of 1 with nucleophiles should involve unimolecular C-Cl bond cleavage giving initially the azocarbonium ion 5[10], which would be more unstable than the corresponding non-fluorine-containing species due to the electron withdrawing effect of the CF_3. The nucleophilic attack by OH- and $-OCH_2CH_2OH$ on 5 proceeds simultaneously or stepwise, resulting in the formation of compound 7.



2a: R= Cl, n= 3, X= NH. 2b: R= H, n= 3, X= NH.
2c: R= Cl, n= 2, X= 0. 2d; R= Cl, n= 3, X= 0.
4a: R= Cl, R'= H, X=Y=NH. 4b: R= Cl, R'= H, X=Y=0.
4c: R= H, R'= H, X=Y=0. 4d: R= Cl, R'= H, X= NH, Y=0.
4e: R= Cl, R'= m-CF_3, X=Y=NH.

Scheme 1

The intramolecular addition reaction of the H_2N-group in 3 to the -N=C- group is still not clear. Possibly, in amines, the bonds to nitrogen are pyramidal. In consequence of this, the intramolecular nucleophilic substitution or nucleophilic addition are dependent on the orientation of the nucleophilic species. The orientation of the HN-group in 3 is favourable to the formation of 4, and of the HN-group in 8a would favour intramolecular nucleophilic addition, resulting in compound 9 through elimination and addition. On the other hand, in 4-trifluoromethyl-o-phenylenediamine, the electron withdrawing activity of the CF_3 -group would weaken the nucleophilic activity of the NH_2-group at the 1 position,but have little influence on the other H_2N-group, and the smaller nucleophilic activity favours nucleophilic addition resulting in the intermediate 8.

EXPERIMENTAL

Melting points were determined on a X-4 melting point apparatus and were uncorrected. Routine NMR spectra were recorded on Varian EM-360A and Varian XL-200 spectrometers. TMS was used as internal reference, acetone-d_6 as solvent. IR spectra were measured on a Perkin-Elmer 983 spectrometer. Mass spectra were measured on a Finnigan 4021 spectrometer.

2-Chloro-5-trifluoromethylphenyl isocyanide dichloride (1a) and 3-trifluoromethylphenyl isocyanide dichloride (1b) were prepared according to the literature [3].

2-(2-Chloro-5-trifluoromethylphenylamino)-perhydropyrimidine(2a)

5.4g(0.075mol) of 1,3-propanediamine in 25ml ether was cooled to 0°C and stirred, then 2.00g(0.0072mol) 1a in 15ml ether was added dropwise. The reaction mixture was stirred at room temperature for 2h. The solvent was removed by evaporation and the residual oil was washed with 2M NaOH and dried. 1.85g of a white

powder was obtained in a yield of 92.2%. m.p 161-162°C. IR(KCl): 3459(m, NH); 1648(s, N=C); 1593, 1568(s,Ar)cm^{-1}; ^1H NMR: δH (CD_3COCD_3): 1.30(4H, m, 2×N-H, $-CH_2-$); 2.70(4H, m, 2×N-CH_2); 6.70(3H, m, Ar-H)ppm. Anal. calcd for $C_{11}H_{11}ClF_3N_3$. C, 47.57; H, 3.96; Cl, 12.79; F, 20.54; N, 15.16; M^+, 278. Found: C, 47.88; H, 4.16; Cl, 12.71; F, 20.93; N, 15.23. M^+, 278.

2-(3-Trifluoromethylphenylamino)-1,4,5,6-tetrahydropyrimidine (2b)

The process was similar to the preparation of 2a; yield 92.0% m.p 124-125°C. IR(KCl): 3452(m, NH); 1646(s, N=C); 1594, 1580 (s, Ar)cm^{-1}. ^1H NMR: δH(CD_3COCD_3): 1.45(3H, m, $-CH_2-$, NH); 2.65 (4H, m, 2×N-CH_2); 4.6(1H, m, -NH); 6.6(4H, m, ArH)ppm. Anal. calcd for $C_{11}H_{12}F_3N_3$. C, 54.32; H, 4.94; F, 23.46; N, 17.28; M^+, 243. Found: C, 54.54; H, 5.13; F, 22.88; N, 17.23; M^+, 243.

2-(2-Chloro-5-trifluoromethylphenylamino)-4,5-dihydrooxazole (2c)

To a stirred solution containing 4.5g(0.074mol) ethanolamine in 25ml THF, 2.00g(0.0072mol) 1a in 15ml THF was added dropwise at 0°C. The mixture was stirred for 0.5h. at room temperature. Then the solvent was evaporated and the residue was washed with 2M NaOH, water and dried. 1.87g of white powder was obtained in a yield of 97.8%. m.p 153.0-153.5°C. IR(KCl): 3185(w, NH), 1675 (s, N=C); 1594, 1574(s, Ar-H)cm^{-1}. ^1H NMR: δH(CD_3COCD_3): 2.5(1H, m, NH), 3.1(2H, m, N-CH_2), 3.9(2H, m, OCH_2), 6.8(3H, m, ArH)ppm. Anal. calcd for $C_{10}H_8ClF_3N_2O$. C, 45.37; H,3.05; Cl, 13.42; F, 21.55; N, 10.59; M^+, 265. Found: C, 45.84; H, 3.02; Cl,13.25; F, 21.72; N, 10.65; M^+,265.

2-(2-Chloro-5-trifluoromethylphenylamino)-4,5,6-trihydrooxazine (2d)

To a stirred solution containing 5.4g(0.072mol) 3-amino-1-propanol in 25ml THF. 2.00g(0.0072mol) 1a in 15ml THF was added

dropwise at 0°C. The reaction mixture was stirred at room temperature for 1h. and the solvent was evaporated under vacum when a colourless oil was obtained. This oil was dissolved in ether, washed with 2M NaOH, dried and evaporated, the residue was separated through a column (80x2cm), which was eluted with light petroleum and ethylacetate, 50mg of a rhombic colourless crystalline solid was obtained in a yield of 2.5%. m.p 151.5-152.0°C. IR(KCl): 3286(w, NH); 1654(s, N=C); 1594, 1574(m, Ar-H)cm^{-1}. ^1H NMR: δ H(CD_3COCD_3): 2.1(3H, m, NH, CH_2); 3.4(2H, t, NCH_2); 4.2(2H, t, OCH_2); 7.2(1H, m, Ar-H); 7.5(2H, m, Ar-H)ppm. Anal. calcd for $C_{11}H_{10}ClF_3N_2O$. C, 47.40; H, 3.59; F, 20.47; N, 10.05; M^+, 278. Found: C, 47.40; H, 3.73; F, 20.64; N, 9.97; M^+, 278.

2-(2-Chloro-5-trifluoromethylphenylamino) benzimidazole (4a)

To a stirred solution containing 0.94g(0.0087mol) o-phenylene diamine and 3.7g(0.036mol) triethylamine in 25ml THF, 2.00g (0.0072mol) 1a in 15ml THF was added dropwise at 0°C under N_2. The reaction mixture was stirred at room temperature for 5h. The solvent was evaporated under reduced pressure and the residual oil was washed with 1M HCl, water and dried. 2.08g of a white powder was obtained in a yield of 92.4%. m.p 214-215°C. IR(KCl): 3320(m, NH); 1628(m, N=C); 1598, 1571(s, Ar)cm^{-1}. ^1H NMR: δ H (CD_3COCD_3): 2.7(1H, m, N-H); 3.5(1H, m, NH); 6.8-7.3(7H,m, ArH) ppm. Anal. calcd for $C_{14}H_9ClF_3N_3$. C, 53.93; H, 2.89; Cl,11.40; F, 18.30; N, 13.48; M^+, 311. Found: C, 53.70; H, 2.81;Cl, 11.45; F, 18.30; N, 13.44; M^+,311.

2-(2-Chloro-5-trifluoromethylphenylamino)benzo-1,3-dioxolane(4b).

The sodium salt of o-dihydroxybenzene was prepared by heating 4.0g(0.036mol) of o-dihydroxybenzene with 0.85g(0.037mol) sodium in 45ml THF. To this mixture, 2.00g(0.0072mol) 1a in 15ml THF was added dropwise at 0°C under N_2 atmosphere. The reaction

mixture was stirred at room temperature for 3h. then filtered. The solvent of the filtrate was removed by evaporation and the residual brown oil was washed with 2M NaOH, water and dried. 2.20g of a white powder (4b) was obtained in a yield of 96.9%. m.p 92-93°C. IR(KCl): 1719(s, N=C); 1597, 1575(s,ArH)cm^{-1}. ^1H NMR: δ H(CD_3COCD_3): 6.8(7H, m, ArH)ppm. Anal. calcd for $C_{14}H_7ClF_3NO_2$. C, 53.59; H, 2.33; Cl,11.32; F, 18.18; N, 4.47; M^+, 313. Found: C, 53.84; H, 2.33; Cl, 10.90; F, 17.84; N,4.59; M^+, 313.

2-(3-Trifluoromethylphenylamino)-benzo-1,3-dioxolane (4c)

The process was similar to the preparation of 4b. yield 81.3%. m.p 78.5-79.0°C. IR(KCl): 1741, 1716(s, N=C); 1602, 1587(w, ArH) cm^{-1}. ^1H NMR: δH(CD_3COCD_3): 6.8(4H, m, ArH); 7.0(4H, m, Ar-H)ppm. Anal. calcd for $C_{14}H_8F_3NO_2$. C, 60.22; H, 2.87; F, 20.43; N, 5.02; M^+, 279. Found: C, 60.22; H, 2.54; F,20.39; N, 4.67; M^+, 279.

2-(2-Chloro-5-trifluoromethylphenylamino)-benzooxazole (4d)

The sodium salt of 2-aminophenol was prepared by heating 4.0g(0.037mol) 2-aminophenol with 0.8g(0.035mol) sodium in 40ml THF. To this mixture, 2.00g(0.0072mol) 1a in 15ml THF was added dropwise at 0°C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2h. and the solvent was evaporated under reduced pressure. The residual oil was dissolved in ether and washed with 2M NaOH, water and the solvent was removed by evaporation. 1.90g of a white powder was obtained in a yield of 84.0%. m.p 97.2-97.5°C. IR(KCl): 3407(m, NH); 1637(s, N=C); 1607, 1617, 1595, 1580(s, ArH)cm^{-1}. ^1H NMR: δ H(CD_3COCD_3): 2.7 (1H, m, NH); 7.0(6H, m, ArH); 8.6(1H, m, ArH)ppm. Anal. calcd for $C_{14}H_8ClF_3N_2O$. C, 53.76; H, 2.56; Cl, 11.36; F, 18.24; N, 8.96; M^+, 312. Found: C, 53.68; H, 2.55; Cl, 11.09; F, 17.95; N, 9.00, M^+, 312.

2-(2'-Chloro-5'-trifluoromethylphenylamino)-5-trifluoromethyl benzimidazole (4e) and 3-hydroxy-6-trifluoromethyl-2-(2'-chloro-5'-trifluoromethylphenyl)-perhydrobenzo-1,2,4-triazine (9)

To a stirred solution containing 1.40g(0.0086mol) 4-trifluoromethyl-o-phenylenediamine and 3.7g(0.036mol) triethylamine in 25ml THF, 2.00g(0.0072mol) 1a in 15ml THF was added dropwise at 0°C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 9h. The reaction mixture was filtered and the filtrate was evaporated, the dark red oil was separated through a column (80x2cm) which was eluted with light petroleum and ethyl acetate. 930mg of colourless crystalline needles (4e) were obtained in a yield of 33.8%. m.p 158-160°C. IR(KCl): 3404 (w,NH);1638(m, N=C); 1599, 1572(s,Ar)cm^{-1}. ^1H NMR: $\delta H(CD_3COCD_3)$: 3.5(2H, m, 2xNH);7.5(6H, m, Ar-H)ppm.Anal. calcd for $C_{15}H_8ClF_6N_3$ C, 47.43; H, 2.11; Cl, 9.35; F, 30.24; N, 11.07. M^+, 379. Found: C, 47.82; H,2.18; Cl, 9.67; F,29.77; N, 10.95. M^+,379.

410mg of light yellow crystalline needles (9) were obtained in a yield of 14.3%. m.p 182-183°C. IR(KCl): 3391(w, NH); 3299 (w, OH); 1643, 1619, 1591, 1564(s, Ar)cm^{-1}.^1H NMR: $\delta H(CD_3COCD_3)$: 1.29 (1H, s, OH; 3.27(2H, m, 2xNH); 7.0-7.7(6H, m, ArH); 8.8(1H, m, C-H)ppm. Anal. Calcd for $C_{15}H_{10}ClF_6N_3O$. C, 45.34; H, 2.52; Cl, 8.94; F, 28.72; N, 10.58. M^+, 397. Found: C, 45.57; H, 2.46; Cl, 8.91; F, 28.77; N, 10.74. M^+, 397.

Hydroxyethyl-2-chloro-5-trifluoromethylphenylcarbamate (7)

The sodium salt of glycol was prepared by heating 4.5g (0.075mol) glycol with 1.6g(0.07mol) sodium in 25ml dioxane. To this mixture, 2.00g(0.0072mol) 1a in 15ml dioxane was added dropwise. The reaction mixture was stirred at room temperature for 0.5h. and the solvent was evaporated under vacuum to give a colourless oil. This oil was dissolved in ether, washed with 2M NaOH and dried. The solvent was evaporated and the residue was separated through a column (80x20cm) which was eluted with light

petroleum and ethyl acetate. 490mg of colourless crystalline needles were obtained in a yield of 23.9%. m.p 77.5-78.0°C. IR(KCl): 3550(m, NH); 3320(br, OH); 1730(s, C=O); 1610,1560(s, ArH)cm^{-1}. ^1H NMR: $\delta H(CD_3COCD_3)$: 1.2(1H, t, OH); 3.4(1H,d, NH); 3.8(2H, m, CH_2O); 4.3(2H, m, CH_2OC=); 7.7(2H, m, ArH); 3.5(1H, m, ArH)ppm. Anal. calcd for $C_{10}H_9ClF_3NO_3$. C, 42.32; H, 3.17; Cl, 12.52; F, 20.10; N, 4.94; M^+, 284. Found: C, 42.25; H, 3.07; Cl, 12.78; F, 19.72; N, 4.82. M^+, 284.

ACKNOWLEDGEMENT

We are greatly indebted to Prof. Chen Qing-Yun for his helpful discussions.

REFERENCES

1 E. Kuhle, Angew. Chem. (Internat. ed.), 8 (1969) 20.
2 T. Mukaiyama, T. Fujisawa and T. Hyugaji, Bull. Chem. Soc. Jap., 35 (1962) 687.
3 K. Zeile, K. Heinz, Hauptamnn and Helmutstahle, U.S. Pat. 3 202 660
4 R. E. Klem, H. F. Skinner, H. Walba and R. W. Isensee, J. Heterocycl. Chem., 7 (1970) 403.
5 W. Hanson, Ger. Offen. 2 652 821.
6 B. Rouot, G. Leclerc, A.-G. Wermuth, F. Miesch and J.Schwartz. J. Med. Chem., 19 (1976) 1049.
7 J. T. Suh., R. A. Schnettler. U.S. Pat. 3 849 400.
8 Masaaki Matsuo, Kiyoshi Taniguchi, Yousuke Katsura, Toshiharu Kamitani and Ikuo Ueda, Chem. Pharm. Bull., 33 (1985) 4409.
9 R. Filler, Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha, Tokyo, 1982.
10 A. F. Hegarty and K. J. Dignam, J. Chem. Soc. Perkin Trans, (1975) 1046.