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STUDIES ON FLUORINE-CONTAINING HETEROCYCLIC COMPOUNDS. 3. REACTIONS OF 3,5-DINITRO-2-CHLOROBENZOTRIFLUORIDE AND 3,5-DINITRO-4-CHLOROBENZOTRIFLUORIDE WITH SULFUR AND NITROGEN-CONTAINING NUCLEOPHILES

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SUMMARY

The reactions of 3,5-dinitro-4-chlorobenzotrifluoride (1a) and 3,5-dinitro-2-chlorobenzotrifluoride (1b) with sulfur- and nitrogen-containing nucleophiles furnished the substituted benzothiazo-N-oxide(3,5) and S-(5-nitro-2-trifluoromethylphenyl-1,4-dithioglycolic ethyl ester(4). Similarly, the reaction of ethyl aminoacetate with 1b gave substituted imidazol-N-oxide(8) and tetraazacyclooctanol(9). The possible mechanisms for the formation of 9 were discussed.

INTRODUCTION

Many useful developments in medicine and insecticides arise from studies of heterocyclic compounds[1,2]. Because fluorine alters electronic effects, imparts oxidative and thermal stability and leads to an increase in lipid solubility in membranes, many research workers are interested in the synthesis of fluorine-containing heterocyclic compounds[3,5]. Previously, we have studied some reactions of 3,5-dinitro-4-chlorobenzotrifluoride(1a) and 3,5-dinitro-2-chlorobenzotrifluoride(1b) with sulfur-containing nucleo-

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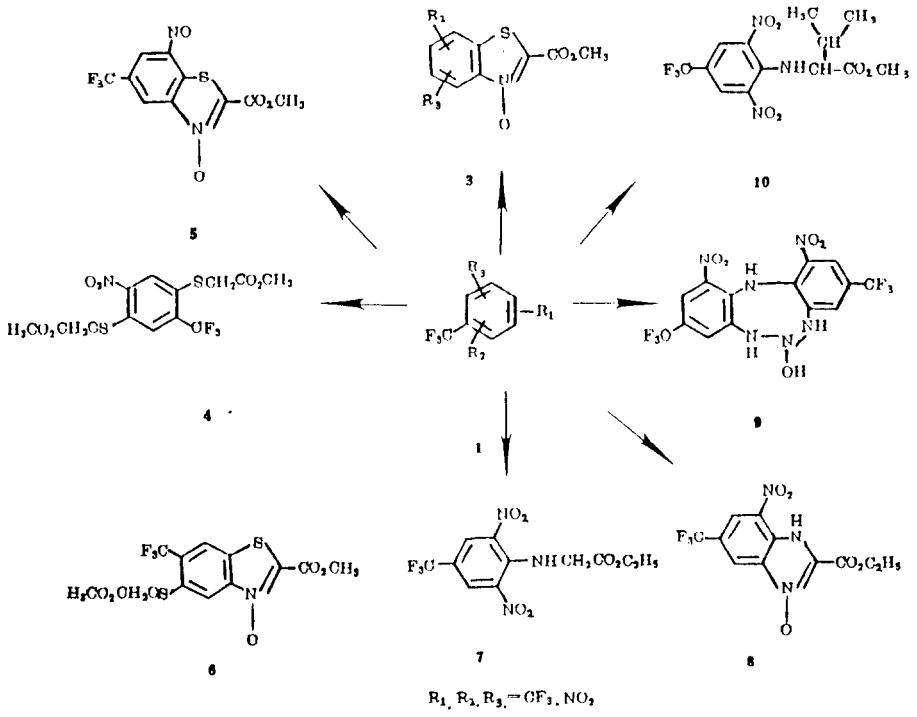
philes[6]. It was found that the reactivity of nitro-groups at different sites on the benzene ring of (1) is quite different and strongly depends on the reaction conditions used. It was interesting to study the reactions of (1) with nitrogen-containing nucleophiles to get novel fluorine-containing biological compounds.

RESULTS AND DISCUSSION

3,5-Dinitro-4-chlorobenzotrifluoride(1a) and 3,5-dinitro-2-chlorobenzotrifluoride(1b) reacted readily with thioglycolic

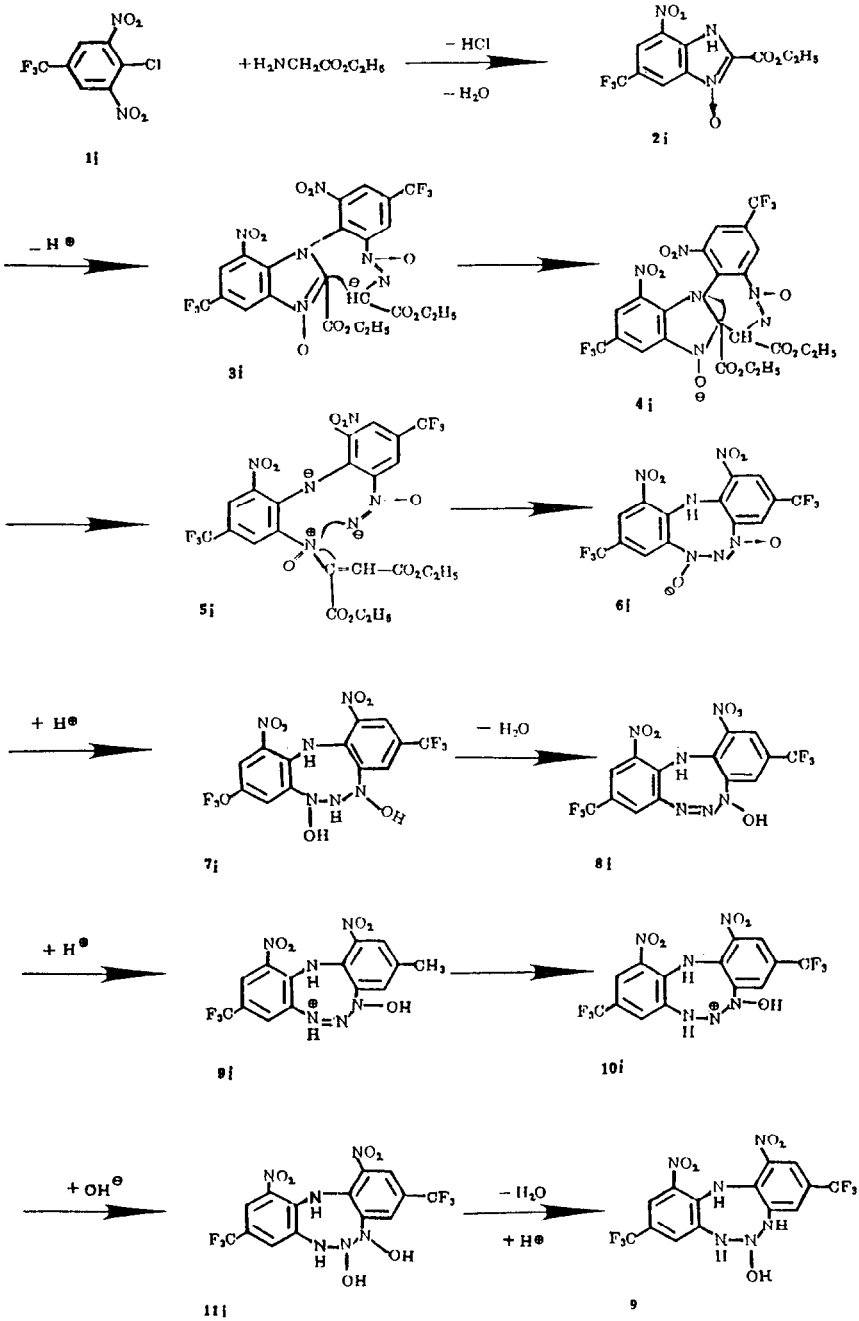


1a: R_1=3-NO_2, R_2=5-NO_2, R_3=4-Cl; 1b: R_1=3-NO_2, R_2=5-NO_2, R_3=2-Cl,
1c: R_1=2-NO_2, R_2=4-NO_2, R_3=5-Cl; 3a: R_1=5-NO_2, R_3=7-CF_3
3b: R_2=5-CF_3, R_3=7-NO_2.

Scheme 1

methyl ester in the presence of triethylamine, giving 2-methoxycarbonyl-5-nitro-7-trifluoromethylbenzothiazo-N-oxide(3a)(R_2=5-NO_2,R_3=7-CF_3) and 2-methoxycarbonyl-7-nitro-5-trifluoromethylbenzothiazo-N-oxide(3b)(R_2=7-NO_2,R_3=5-CF_3) respectively. An attempt was made to substitute the 5-NO_2 group of 3a for thioglycolic ester at reflux temperature, but 5-nitrosyl-7-trifluoromethyl-benzothiazo-N-oxide(5) was obtained. The 5-NO_2 of 3a could not be removed by thioglycolic ester. By using 2,4-dinitro-5-chlorobenzotrifluoride (1c) instead of 1a, according to the same procedure, the disubstituted compound 4 was obtained. Interestingly, 4 did not cyclize to 6. This is probably due to the presence of the sulfur-containing moiety, which would deactivate nitro-group. The reactivity of aminoacetic ester with 1a is much lower than that of thioglycolic ester. Heat evolution of the former reaction was lower than that of the latter. Treatment of 1a with ethyl aminoacetate(2b) at room temperature only furnished the product 7. However, when the reaction of 1a with 2b was carried out at reflux temperature, the expected product 8 and the unexpected product 9 were obtained respectively. Proof of their structures was based on analyses, NMR, IR and Mass Spectroscopy. In order to confirm the unusual structure 9 we discuss the deduction of 9 in more detail. The parent ion 454 and elemental analyses demonstrate the molecular formula: $C_{14}H_8F_6N_6O_5$. ^{1}HNMR displays 6 signals at 9.065, 9.057, 8.526, 8.502, 8.385, 8.376. Two protons at 8.385 and 8.376 were exchangeable with deuterated water, showing four aromatic protons and four active protons. The absorptions at 3500 and 3400 cm^{-1} in the infrared spectra indicate the presence of OH and NH. The presence of two ^{19}FNMR single signals at -15.3 and -15.6 is a clear indication that there are two CF_3 groups attached to two unequal aromatic rings. The ^{13}CNMR shows only 12 aromatic carbons and no primary, secondary, tertiary and quarternary carbons, thus, leaving 9 as the reasonable structure being consistent with the observed data.

The proposed mechanism for the formation of compound 9 involves intermolecular nucleophilic attack at the chlorine



Scheme 2

by the anion of 2b and 1a in the first two stages, i.e. 1i to 2i and 2i to 3i. The intermediate generated (3i) has an acidic site ($-CH_2-$) due to the influence of the nearby heteroatom and carbonyl group, forming carbanion ($-\bar{C}H-$) in the presence of triethylamine. The next stages would proceed via intramolecular nucleophilic attack, rearrangement, protonation and elimination, giving the intermediate 8i. Further attack of proton could then occur at nitrogen in intermediate(9i), followed by OH- nucleophilic addition, eliminating water, furnishing the observed product 9 as shown in the scheme 2.

EXPERIMENTAL

Melting points were taken in open glass capillaries and are uncorrected, ^{1}HNMR and ^{19}FNMR spectra in $CDCl_3$ or DMSO-d_6 were taken on a Varian XL-200 NMR spectrometer. The chemical shifts are reported in ppm, using TMS or CF_3COOH as an internal references respectively. The infrared spectra were obtained with a Zeiss-Jena specord 75-IR spectrophotometer.

S-(5-Nitro-2-trifluoromethylphenyl-1,4-dithioglycolic ethyl ester(4)

To a stirred solution containing 4.05g(0.015 mol) 2,4-dinitro-5-chlorobenzotrifluoride and 3.33g(0.033 mol) triethyl amine in 30 ml ethanol, 3.18g(0.03 mol) thioglycolic ethyl ester in 5 ml ethanol was added dropwise. The yellow crystalline was precipitated overnight. The solid was collected by filtration, washed with water and air-dried at room temperature. The crude 4 was recrystallized from alcohol. 4.5g of a pale yellow crystalline solid was obtained in the yield of 75% m.p. 89-90°C. IR (KBr): 1745(S, CO_2CH_3), 1535(S, Ar-NO_2), 1135(S, C-F) cm^{-1}, ^{1}HNMR: δH($CDCl_3$): 2.90(6H, S, OCH_3), 2.93(4H, S, CH_2), 8.03(1H, S, Ar-H), 8.43(1H, S, Ar-H) ppm. ^{19}FNMR δF(CF_3COOH) (-15.5, CF_3)ppm. Anal. calcd for $C_{13}H_{12}F_3NO_6S_2$. C, 39.09; H, 3.01; N, 3.50; S, 16.04; F, 14.28; M^+, 399. Found: C, 39.25; H, 2.75; N, 3.45; S, 16.01; F, 14.10; M^+, 399.

2-Methoxycarbonyl-5-nitrosyl-7-trifluoromethylbenzothiazo-N-oxide(5)

To a stirred solution containing 0.53g(5 mmol)thioglycolic methyl ester in 15 ml ethanol, 2.70g(10 mmol)3,5-dinitro-4-chlorobenzotrifluoride was added in one portion. The stirred reaction mixture was heated at reflux temperature for 8 hours. In addition to 2-methoxycarbonyl-5-nitro-7-trifluoromethyl-benzothiazo-N-oxide(3)[3,6], small quantities (100 mg) of 5 were obtained by column chromatography on silica gel using benzene as eluant, m.p. 101-102°C, IR(KBr): 1720(s, C=O), 1320(s, C-F) cm^{-1}. Laser Raman Spectrum: 1510(S, N=O), 1356(S, Ar-N-O)cm^{-1}. ^{1}HNMR δH (DMSO): 3.10(3H, S, OCH_3), 8.85(1H, S, Ar-H), 9.23(1H, S, Ar-H). ^{19}FNMR, δF(CF_3COOH): -16.6(S, CF_3). Anal. calcd for $C_{10}H_5F_3N_2SO_4$: C, 39.22; H, 1.63; N, 9.15; F, 18.62; M^+, 306. Found:C, 39.45; H, 1.56; N, 9.08; S, 10.74; F, 18.58; M+1, 307.

N-(4-Trifluoromethyl-2,6-dinitrophenyl)imidoacetic ethyl ester(7)

To a stirred solution of 1.03g(0.01 mol) ethyl amino-acetate in 20ml ethanol at room temperature, was added 2.70g(0.01 mol) of 3,5-dinitro-4-chlorobenzotrifluoride in one portion. 2.22g(0.022 mol) triethylamine was then added dropwise. An exothermic reaction set in causing a tempera-ture rise from 18° up to 26°C and the formation of a thick pre-cipitate. The solid was collected by filtration, washed with water until the washing was neutral to litmus and air-dried at room temperature. 1.50g cry-stalline product (needles) was obtained in the yield of 44.3% m.p. 84.5-86° IR(KBr): 3250(W, NH), 1720(S, C=O), 1535(Ar-NO_2). ^{1}HNMR δH($CDCl_3$): 9.41(d, 1H, Ar-H), 8.99(d, 1H, Ar-H), 8.74(m, 1H, NH), 4.69(s, 2H, CH_2), 4.42(s, 2H, CH_2CO). ^{19}FNMR, δF:(CF_3CO_2H), -15.5(s, CF_3)ppm. Anal. calcd for $C_{11}H_{10}F_3N_3O_6$: C, 39.17; H, 2.97; F, 16.91; N, 12.46; M^+, 337; Found: C, 39.40; H, 3.19; F, 16.69; N, 12.30; M^+, 337.

Bis(5,13-ditrifluoromethyl-7,11-dinitrobenzo)(c,f)-1,2,9,16-tetraazacyclooctanol(9) and 5-nitro-7-trifluoromethylimidazol-N-oxide(8)

To a stirred solution of 2.70g(0.01 mol) 3,5-dinitro-4-chlorobenzotrifluoride in 30ml ethanol was added 1.03g(0.01 mol)ethylaminoacetate at room temperature in one portion. Triethylamine 1.10g(0.01 mol) was then added dropwise. An exothermic reaction set in causing a temperature rise up to 40°C. The reaction mixture was stirred at 20-25°C for 4 hours and the stirring was continued at reflux temperature for 4 hours. The yellow crystalline precipitate appeared overnight. The solid was collected by filtration, washed with water and air-dried at room temperature. 1.50g crude 9 was obtained m.p. 216-217°C. IR(KBr): 3500(w, OH), 3400(w, NH), 1625(m, Ar-H), 1230(S, C-F), 1125(S, C-O) cm^{-1}. ^{1}HNMR, δH(DMSO-d_6): 9.06(1H, S, Ar-H), 9.05(1H, S, Ar-H), 8.52(1H, S, Ar-H), 8.38(1H, S, Ar-H), 8.37(3H, S, NH), 8.38(1H, S, OH). ^{19}FNMR, δF(CF_3COOH): -15.30(S, CF_3). -15.6(S, CF_3). Anal. calcd for $C_{14}H_8F_6N_6O_5$: C, 37.00; H, 1.76; F, 25.11; N, 18.50; M^+, 454. Found: C, 37.37; H, 1.51; F, 24.95; N, 18.41; M^+, 454.

The minor component was separated from the mother liquor mentioned above by chromatography on silica, using benzene as eluant and recrystallized from alcohol. 100 milligram of 2-ethoxy carbonyl-5-nitro-7-trifluoromethylimidazol-N-oxide(8) was obtained. m.p. 251-252°C. IR(KBr): 3205(W, NH), 1540(S, Ar-NO_2)cm^{-1}. ^{1}HNMR δH(DMSO-d_6): 1.80 (3H, t, CH_3), 4.20(2H, q, CH_2), 8.80(1H, m, NH), 9.10(1H, d, Ar-H), 9.52(1H, d, Ar-H). ^{19}FNMR(CF_3COOH), δF: -15.80(S, CF_3). Anal. calcd for $C_{11}H_8F_3N_3O_5$: C, 41.38; H, 2.50; N, 13.16; F, 17.86; M^+, 319. Found: C, 41.05; H, 2.41; N, 13.02; F, 17.62; M^+, 319.

N-(2,6-dinitro-4-trifluorophenyl)-Valine methylester(10)

To a stirred suspension at 20°C of 1.0g(8.5mmol) L-valine in 15 ml methanol anhydrous hydrochloride was bubbled until the solid L-valine was dissolved. 2.30(8.5mmol) 3,5-dinitro-4-chlorobenzotrifluoride in 10 ml methanol was then added

in one portion and an exothermic reaction set in causing a temperature rise from 20° to 40°C. Triethylamine was added dropwise until basic to litmus. An exothermic reaction set in causing a temperature rise up to 50°C. A solid precipitate appeared. The solid was collected by filtration, washed with diluted hydrochloric acid and water, crystallized from alcohol. A 2.10g of 10 was obtained in 59% yield, m.p. 86-87°C. IR(KBr): 3300(w, NH), 1720(S, C=O), 1120(S, CF_3) cm^{-1}. ^{1}HNMR, δH($CDCl_3$): 8.35(S, 2H, Ar-H), 3.72(3H, S, CO_2CH_3), 2.42 (S, 1H, CH), 2.15(S, 1H, CH), 1.01(d, 6H, CH_3). ^{19}FNMR, δF(CF_3COOH): -15.8 (S, CF_3)ppm. Anal. calcd for $C_{13}H_{14}O_6N_3F_3$:C, 42.73; H, 3.83; F, 15.62; M^+, 365. Found: C, 42.67; H, 3.60; F, 15.45; M^+, 365.

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