Chemistry of Heterocyclic Compounds, Vol. 30, No. 1, 1994

REACTIONS OF POLYHALOPYRIDINES 5.* REACTION OF 2,3,5,6-TETRACHLORO-4-TRIFLUOROMETHYLTHIOPYRIDINE WITH NUCLEOPHILIC REAGENTS

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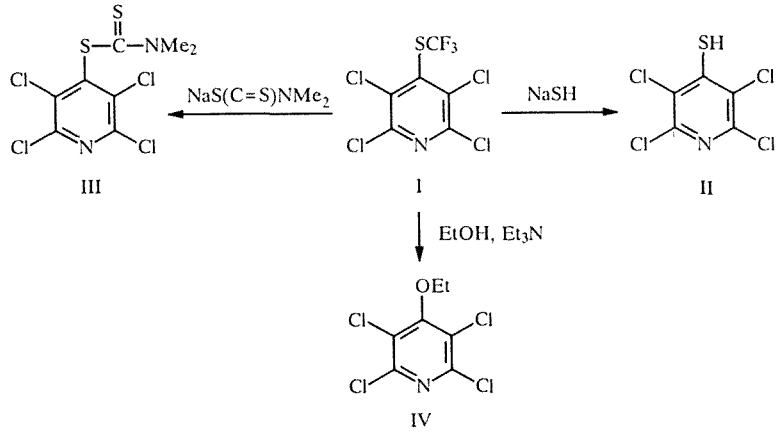
The reaction on 2,3,5,6-tetrachloro-4-trifluoromethylthiopyridine with various nucleophilic reagents has been studied. It was shown that the CF_3S group is readily replaced under the action of O- and S-nucleophiles. Competition was detected between replacement of an α-chlorine atom on the pyridine ring and of the fluorine-containing group under the action of N-nucleophilic reagents. New derivatives of trichlorotrifluoromethylthiopyridine with nitrogen-containing substituents have been synthesized.

In the previous communication we described new compounds, perfluoroalkylpolychloropyridines, which were obtained by the perfluoroalkylation of polychloropyridine thiols with fluorine-containing xenon compounds [1]. The present work is devoted to an investigation of the reactivity of the compounds synthesized. The influence of the perfluoroalkylthio group on the nucleophilic substitution processes characteristic of polychloropyridines has been studied using the reaction of 2,3,5,6-tetrachloro-4-trifluoromethylthiopyridine (I), as an example, with N-, O-, and S-nucleophiles.

We discovered that the point of nucleophilic attack in the pyridine ring depends on the nature of the reagent. The CF_3S group is readily replaced in the presence of S-containing nucleophiles such as sodium hydrosulfide or sodium N,N-dimethyldithiocarbamate. As a result compounds are formed analogous to the product of substitution in pentachloro-pyridine at position 4, viz. 2,3,5,6-tetra-chloropyridinethiol (II) and 2,3,5,6-tetrachloro-4-pyridyl N,N-dimethyldithiocarbamate (III). Similarly, replacement of the CF_3S fragment by an ethoxy group occurs on storing compound (I) in an ethanol solution of triethylamine. On investigating all three reaction mixtures not even traces were detected of the presence of CF_3S-containing pyridines, i.e., products of replacing one of the chlorine atoms.



III I II IV

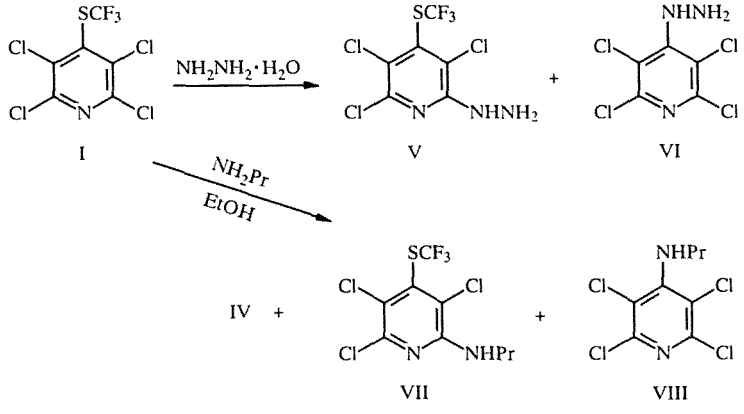
*For Communication 4 see [1].

Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences, Chernogolovka 142432. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 63-67, January, 1994. Original article submitted December 27, 1993.

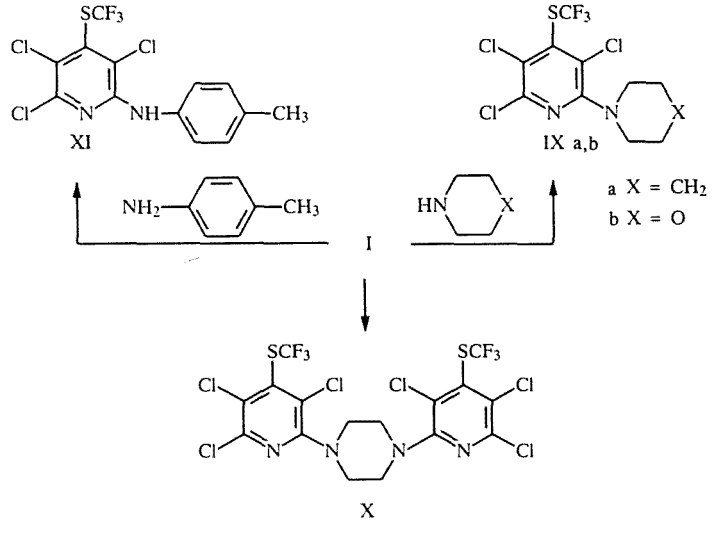
 0009-3122/94/3001-0056$12.50

Compound (II)-(IV) corresponded completely in physicochemical characteristics with samples obtained by the alternative synthesis from pentachlorpyridine.

A different picture was observed on reacting compound (I) with N-nucleophilic reagents. In this case the mobility of the CF_3S group is clearly reduced and a whole series of new pyridine derivatives retaining the fluorine-containing fragment was successfully obtained. Of special interest was the competition between replacement of a chlorine atom and of the CF_3S in several cases. A mixture of compounds (V) and VI) was obtained by the action of hydrazine hydrate on compound (I) with a significant predominance of the fluorine-containing derive. This result confirms the higher stability of the CF_3S group at position 4 of the pyridine ring to the action of hydrazine hydrate compared to a chlorine atom in the pentachloropyridine molecule since it is known that in the latter case the opposite order of nucleophilic attack is observed (predominantly at position 4) [2]. In the case of aliphatic amines such as propylamine, competition is observed between processes of O and N substitution of CF_3S in addition to replacement of the α-chlorine atom. No. predominance for any one of the three reaction was detected.



The main reaction products when reacting cyclic secondary amines (piperidine, morphiline) were compounds retaining the fluorine−containing group (IXa,b). The symmetrical derivative (X) was obtained in the case of piperazine.



The replacement of a chlorine atom occurs on reaction with p-toluidine similarly to the cyclic amines. Only traces of 2,3,5,6-tetrachloro-4-(4-tolylamino)pyridine were detected in the reaction mixture.

Compounds (V), (VI), (IX), (X), and (XI) contain singlets at 38 ppm in the ^{19}F NMR spectra and quartets at 128-130 ppm in the ^{13}C NMR spectra, characteristic for CF_3S. Intense molecular ions were observed in the mass spectra and the presence of a trifluoromethyl group in the molecule was detected by the presence of ions linked with a loss of 69 mass units.

The stability of the CF_3S group in compound (I) to the action of nitrogen-containing nucleophilic reagents may be represented by the series, cyclic secondary amines > arylamines > hydrazine hydrate > primary aliphatic amines. It must also be noted that compound (I) is like pentachloropyridine in reactivity in nucleophilic substitution reactions when conditions, reaction times, and yields of final products are compared [2-6].

EXPERIMENTAL

The IR spectra of compounds were measured on a Specord M-80 instrument in chloroform and nujol mulls. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solution on a Bruker AC-200 instrument with an operating frequency of 200 MHz spectral measurements were made on a Finningan-4021 (^1H), 188 MHz (^{19}F), and 50 MHz (^{13}C), internal standard was TMS, external standard was trifluoroacetic acid (^{19}F). Mass instrument (direct insertion, ionization energy 70 eV).

Reaction of Compound (I) with NaHS. A solution of NaHS (0.3 g) in methanol (2 ml) was added with stirring at room temperature to compound (I) (1.1 g: 0.00347 mole) in methanol (20 ml). The mixture was stirred for a further 10-15 min, the solvent evaporated, and the residue dissolved in water (10 ml). The aqueous layer was extracted with chloroform, filtered, and acidified with dilute hydrochloric acid. A white solid was precipitated. This was filtered off, washed with water, dried, and recrystallized from ethanol. 2,3,5,6-Tetrachloro-4-mercaptopyridine (0.6 g: 69.4%) was obtained having mp 159-161°C (lit. 157.5-160.5°C [3]).

Reaction of Compound (I) with a Solution of Triethylamine in Ethanol. A mixture of compound (I) (1.05 g: 0.0033 mole) in abs. ethanol (10 ml) to which had been added triethylamine (1 g 0.01 mole) was stored at room temperature for 30 days. The solvent and triethylamine were then removed by evaporation and the residue chromatographed on a column of silica gel (eluent was benzene–hexane, 1:3). 2,3,5,6-Tetrachloro-4-ethoxypyridine (IV) (0.6 g: 70%) was obtained and had mp 54-56° (lit. 56-58°C [4]). PMR spectrum: 1.50 (3H, t, Me); 4.20 ppm (2H, q, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 259 (26) M^+, 231 (100) $[M-C_2H_4]^+$.

Reaction of Compound (I) with Sodium N,N-Dimethyldithiocarbamate. Compound (I) (1.1 g: 0.00347 mole) and sodium N,N-dimethyldithiocarbamate dihydrate (0.724 g: 0.004 mole) were dissolved in solvent with stirring at room temperature. Stirring was continued for 2 h and the solvent evaporated. The residue was washed with water, extracted with chloroform, and the extract dried. The solid residue after removing the solvent was recrystallized from methanol. Yellow crystalline compound (III) (0.63 g: 60%) was obtained having mp 166-168°C, identical to that described previously for 2,3,5,6-tetrachloro-4-pyridyl N,N-dimethyldithiocarbamate [5].

Reaction of Compound (I) with Hydrazine Hydrate. Hydrazine hydrate (0.5 g: 0.01 mole) was added dropwise with stirring at room temperature to a solution of compound (I) (1.585 g: 0.005 mole) in methanol (30 ml). The mixture was left for a day while bright beige needle-shaped crystals formed. These were separated by filtration 2,3,5,6-Tetrachloro-4-hydrazinopyridine (VI) (0.3 g) was obtained having mp 182-183°C (lit. 160-162°C [2]). Found: M^+ 245 (100%). The alcoholic solution was evaporated, the residue washed with water, and dried. The solid was extracted twice with portions (30 ml) of boiling hexane. The hexane solution was cooled to room temperature, filtered, evaporated to the start of crystallization, and cooled. The solid was separated by filtration and compound (V) (0.766 g) obtained.

3,5,6-Trichloro-2-hydrazino-4-trifluoromethylthiopyridine (V) $\mathbf{C_6H_3Cl_3F_3N_3}$. Yield 49%, mp 133.5-135.5°C (hexane). IR spectrum: 3436 cm^{-1} (NH). PMR spectrum: 3.98 (2H, br. s, NH_2); 6.75 ppm (1H, br. s, NH). ^{19}F NMR: 38.2 ppm (SCF_3). ^{13}C NMR: 119.21; 123.92 ($C_{(3)}$, $C_{(5)}$); 128.52 (q, J_{CF} = 310.2 Hz CF_3); 134.21 ($C_{(6)}$); 146.64 ($C_{(4)}$); 153.88 ppm ($C_{(2)}$). Mass spectrum, *m/z* (I_{rel}, %): 311 (100) M^+, 281 (80.5) $[M-N_2H_2]^+$, 212 (34) $[M-N_2H_2-CF_3]^+$, 177 (58.5).

Reaction of Compound (I) with Propylamine. Propylamine (1.4 g: 0.0237 mole) was added with stirring at room temperature to a solution of compound (I) (1.585 g: 0.005 mole) in ethanol. The mixture was stored for 7 days until complete disappearance of the initial (I) from the reaction mixture. The solvent and the excess of propylamine were removed in vacuum and the residue chromatographed on a column of silical gel (eluent was benzene–hexane, 1:6). Three compounds were isolated. First, compound (VII) was eluted. After removing the solvent 0.4 g was obtained as a yellow oil, which gradually crystallized. The second compound eluted was (IV) (0.35 g), white needle-shaped crystals. The third substance was compound (VIII) (0.33 g), isolated as a yellow oil, which gradually crystallized on standing.

3,5,6-Trichloro-2-propylamino-4-trifluoromethylthiopyridine (VII) $\mathbf{C_9H_8Cl_3F_3N_2S}$. Yield 23.1%, mp 41.5-43.5°C. IR spectrum: 3440, 3420 cm^{-1} (NH). PMR spectrum: 1.0 (3H, t, Me); 1.67 (2H, m, Me–$\underline{CH_2}$–CH_2); 3.35 (2H, m, $\underline{CH_2}$–NH); 5.35 ppm (1H, br. s, NH); ^{19}F NMR: 38.12 ppm (s, SCF_3). Mass spectrum, m/z (I_{rel}, %): 338 (28) M^+, 309 (97) $[M-Et]^+$, 269 (4) $[M-CF_3]^+$, 240 (24) $[M-Et-CF_3]^+$.

2,3,5,6-Tetrachloro-4-propylaminopyridine (VIII) $\mathbf{C_8H_8Cl_4N_2}$. mp 30-31°C. PMR spectrum: 0.95 (3H, t, Me); 1.63 (2H, m, $\underline{CH_2}$–Me); 3.65 ppm (2H, m, $\underline{CH_2}$–NH). ^{13}C NMR: 1089 (Me); 24.15 ($\underline{CH_2}$–Me); 47.99 ($\underline{CH_2}$–NH); 114.38 ($C_{(3)}$,$C_{(5)}$); 146.24 ($C_{(2)}$, $C_{(6)}$; 150.17 ppm ($C_{(4)}$). Found; M^+ 272.

Reaction of Compound (I) with Cyclic Secondary Amines. The amine (0.01 mole) was added with stirring at room temperature to a solution of compound (I) (1.585 g: 0.005 mole) in ethanol (30 ml). The reaction mixture was stored for 3 days and the solvent then removed. The residue was washed with water, extracted with chloroform, the organic layer dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel (eluent was hexane–benzene). The product was obtained as a bright yellow oil which crystallized with time.

3,5,6-Trichloro-2-piperidino-4-trifluoromethylthio-pyridine (IXa) $C_{11}H_{10}Cl_3F_3N_2OS$. Eluent was benzene–hexane, 1:6. Yield 92%, mp 59.5-61°C. PMR spectrum: 1.88 (2H, m) 3.34 ppm (3H, m). ^{19}F NMR: 38.24 ppm (s, SCF_3). ^{13}C NMR: 24.57; 26.08; 50.83 (piperidine); 127.14 ($C_{(3)}$); 128.45 ($C_{(5)}$); 129.78 (q, J_{CF} = 310 Hz, CF_3), 136.4 ($C_{(4)}$); 145.49 ppm ($C_{(6)}$). Mass spectrum, *m/z* (I_{rel}, %): 364 (36) M^+, 329 (5) $[M-Cl]^+$, 295 (60), $[M-CF_3$.

3,5,6-Trichloro-2-morpholino-4-trifluoromethylthiopyridine (IXb) $C_{10}H_8Cl_3N_2OS$. Eluent was benzene–hexane, 1:1. Yield 79%, mp 78-79°C. PMR spectrum: 3.43 (2H, q), 3.78 ppm (2H, q). ^{19}F NMR: 38.24 ppm (SCF_3). Mass spectrum, *m/z* (I_{rek}, %): 366 (55) M^+, 335 (47) 297 (24) $[M-CF_3]^+$.

N,N′-Bis(3,5,6-trichloro-4-trifluoromethylthio-2-pyridyl)piperazine (X) $C_{16}H_8Cl_6F_6N_4S_2$. Eluent was benzene–hexane, 1:4. Yield 7.4%, mp 185-187°C. PMR spectrum: 3.57 ppm (s, piperazine). ^{19}F NMR: 38.24 ppm (s, SCF_3). Mass spectrum, *m/z* (I_{rel}, %): 644 (13) M^+, 577 (17) $[M - CF_3]^+$, 348 (71), 335 (100).

Reaction of Compound (I) with p-Toluidine. p-Toluidine (1 g: 0.0093 mole) was added to a solution of compound (I) (1.05 g: 0.0033 mole) in ethanol (20 ml) and the mixture boiled under reflux for 50 h. The solvent was removed, the residue washed with dilute hydrochloric acid solution, then extracted with chloroform, and the extract dried. After removing the solvent the residue was chromatographed on a column of silica gel (eluent was benzene–hexane, 1:6). Compound (XI) (1.11 g) was obtained as a yellow solid. In addition, elution of the column with a mixture of benzene–hexane (1:2) gave 2,3,5,6-tetrachloro-4-(4-tolylamino)pyridine (15 mg) of mp 128.5-129.5°C (Lit. 125-126°C [6]).

3,5,6-Trichloro-2-(4-tolylamino)-4-trifluoromethylthiopyridine (XI) $C_{13}H_8Cl_3F_3N_2S$. Yield 86%, mp 128.5-129.5°C. IR spectrum: 3420 cm^{-1} (NH). PMR spectrum: 2.34 (3H, s, Me); 7.15 (1H, br. s, NH); 7.17 (2H, m, Ph); 7.44 ppm (2H, m, Ph). ^{13}C NMR: 20.78 (Me); 122.13; 124.34 ($C_{(3)}$, $C_{(5)}$); 120.07 ($C_{(3')}$); 128.56 (q, J_{CF} = 310.0 Hz, CF_3); 129.51 ($C_{(2')}$); 133.78 ($C_{(4')}$); 133.92 ($C_{(6)}$); 135.46 ($C_{(1')}$); 145.92 ($C_{(4)}$); 149.01 ppm ($C_{(2)}$). Mass spectrum, *m/z* (I_{rel}, %): 386 (56) M^+, 385 (31) $[M - H]^+$, 316 (8) $[M - H-CF_3]^+$, 281 (16) $[M - C_7H_7NH]^+$, 91 (100) $[C_7H_7]^+$.

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