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NUCLEOPHILIC SUBSTITUTION REACTIONS

OF 2,4,6-TRIS(METHYLSULFONYL)-3.5-DICHLOROPYRIDINE

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It was established that hard bases replace the methylsulfonyl groups and that soft bases replace the chlorine atoms in 2,4,6-tris(methylsulfonyl)-3,5-dichloropyridine.

In the present communication we present the results of studies of the competitive nucleophilic substitution of the chlorine atoms and methylsulfonyl groups in sulfone I [1]. Because of the strong electron-acceptor effect of three methylsulfonyl groups and a nitrogen heteroatom, the electron densities on the carbon atoms in the 2, 4, and 6 positions are lower than in the 3 and 5 positions. The 2-C. 4-C. and 6-C atoms should therefore act as hard acids, and the 3-C and 5-C atoms should act as soft acids. In fact, hard bases (sodium methoxide and phenoxide, potassium fluoride, sodium hydroxide, sodiomalonic ester, etc.) react at the 2, 4, and 6 positions, whereas soft bases (ammonia, aniline, morpholine, piperidine, malonic ester, ethanol, etc.) react at the 3 and 5 positions; this is in conformity with Pearson's principle of the reaction of hard and soft acids and bases [2].

The reaction of sulfone I with ammonia and amines at low temperature leads to replacement of one chlorine atom to give the corresponding 3-amino-substituted 5-chloro-2,4,6-tris(methylsulfonyl)pyridines (IIa-d, Table 1). At room temperature the reaction of I with morpholine and aniline gives rise to replacement of two chlorine atoms to give. respectively, 3,5-dimorpholino- and 3.5-bis(phenylamino)-2.4,6-tris(methyl-sulfonyl)pyridines (IIIa, b). The second chlorine atom in any of the products of replacement of one chlorine atom in IIa-d is also replaced by the further action of a soft nucleophile. Thus amine IId reacts with aniline or p-nitrophenol at room temperature to give, respectively, product IIIb and 3-phenylamino-5-(p-nitrophenoxy)-2,4,6-tris(methylsulfonyl)pyridine (IIIc).

An attempt to obtain the corresponding isocyanate by reaction of sulfone I with potassium cyanate yielded amine IIa, the synthesis of which evidently includes the formation of an intermediate reactive isocyanate, which reacts with water to give amine IIa.

The reaction of sulfone I with malonic ester and ethanol also leads to replacement of one chlorine atom to give, respectively, diethyl[2,4.6-tris(methylsulfonyl)-5-chloro-3-pyridyl]malonate (IIe) and 3-ethoxy-5-chloro-2,4,6-tris(methylsulfonyl)pyridine (IIf).

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| Com • pound * | R | mp, °C | Empirical formula | Found, 7/0 | | Calc., % | | Yield |
|-------------------|---------------------------------|-------------------------------|---|-------------------|----------------------|-------------------|----------------------|----------------|
| | | | | CI | S | CI | s | 7/0 |
| IIa | NH ₂ | 289-290 | $C_3H_{11}CIN_2O_6S_3$ | 9,8 | 26,4 | 9,8 | 26,5 | 75 |
| Нb | \bigcirc | 269—271 | $C_{12}H_{17}CIN_2O_7S_3$ | δ.3 | 21,8 | 8,2 | 22.2 | 76 |
| [[c | \checkmark | 239—240 | $C_{13}H_{13}ClN_2O_6S_3$ | 8.4 | 22,3 | ۶,2 | 22.3 | 86 |
| IId 'Ie IIf | NHCeH5 CH(COOC2H5)2 OC2H5 | 245—247 212—214 249—250 | $\begin{array}{c} C_{14}H_{15}ClN_2O_6S_3\\ C_{13}H_{20}ClNO_{10}S_3\\ C_{10}H_{14}ClNO_7S_3 \end{array}$ | 8,3 7,3 9,3 | 21,9 19,0 24,3 | 8,1 7,0 9,1 | 21,9 19,0 24,5 | 80 61 64 |

*Compounds IIa-f were crystallized from aqueous ethanol.

Hard bases react with sulfone I with replacement of the methylsulfonyl groups, and the number of replaced groups also depends on the temperature. Sulfone I undergoes substitution of one methylsulfonyl group on reaction with methylamine and sodium azide at -20°, on heating with sodium hydroxide, and at room temperature with sodium malonate to give, respectively. 4-methylamino-, 4-azido-, and 4-hydroxy-3,5-dichloro-2,6-bis(methylsulfonyl)pyridines (IVa-c, Table 2) and diethyl[3,5-dichloro-2,6-bis(methylsulfonyl)-4-pyridyl]malonate (IVd).



Replacement of the methylsulfonyl group in the 4 position was proved for IVa by alternative synthesis [3] and for IVb-d by the singlet of protons of methylsulfonyl groups at 3.36 ppm in the PMR spectra.

The reaction of sulfone I with excess sodium methoxide. sodium phenoxide, and potassium fluoride leads to replacement of three methylsulfonyl groups to give, respectively, 2,4,6-trimethoxy-, 2,4,6-triphenoxy-, and 2,4,6-trifluoro-3,5-dichloropyridines (Va-c).

The reaction of sulfone I with methylamine and sodium azide at room temperature proceeds in two directions. In addition to substitution of a methylsulfonyl group, a chlorine atom is also replaced to give 3,4-diazido-5-chloro-2,6-bis(methylsulfonyl)pyridine (VIa) in the case of sodium azide; in the case of methylamine, two products - 2.4-bis(methylamino)-3,5-dichloro-6-methylsulfonylpyridine (VII) and 3,4-bis(methylamino-5-chloro-2,6-bis(methylsulfonyl)pyridine (VIb) - are formed. The IR spectra of VIb and VII contain distinct absorption bands at 1130 and 1300 cm⁻¹, which are characteristic for symmetrical and asymmetrical vibrations of the SO₂ group. Differences with respect to both the form of the spectra and the absorption frequency are observed in the region of the absorption of the NH groups. A doublet with absorption maxima at 3390 and 3460 cm⁻¹ is observed for VII; a single broad intense band at 3330-3340 cm⁻¹ is observed for VIb. Thus in our case sodium azide and methylamine occupy intermediate positions [4] in the series of hard and soft bases.

According to the data in [5, 6], a halogen atom in the β position of the pyridine ring reacts with nucleophiles only under severe conditions. The introduction of three strong electron-acceptor substituents has made it possible for the first time to effect nucleophilic substitution of the chlorine atom in the 3 position at low temperatures.



*According to the data in [3], this compound has mp 179-180°. †Found: N 16.3%. Calculated: N 16.2%.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were recorded at room temperature with a Tesla BS-487 B spectrometer (80 MHz with hexamethyldisiloxane as the external standard). The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer.

<u>3-Amino-5-chloro-2,4,6-tris (methylsulfonyl)pyridine (IIa).</u> A) A solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF was saturated at -20° for 10 min with dry ammonia gas, after which the mixture was allowed to stand for 30 min. The ammonia and the solvent were removed by vacuum evaporation, and the residue was treated with dioxane. The NH₄Cl was removed by filtration, and the product was precipitated by the addition of heptane to give 0.27 g (75%) of IIa. Compounds IIa-d were similarly obtained (Table 1).

B) A solution of 0.38 g (1 mmole) of potassium cyanate in 3 ml of water was added to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF, after which the mixture was stirred at 20° for 2 h. It was then treated with 60 ml of water and cooled to 0°, and the precipitated product was removed by filtration to give 0.29 g (80%) of IIa.

<u>3,5-Dimorpholino-2,4,6-tris (methylsulfonyl)pyridine (IIIa).</u> Morpholine (2 ml) was added at 20° to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF, after which the mixture was allowed to stand at this temperature for 2 days. It was then worked up to give 0.29 g (60%) of a product with mp 114-115° (dec., from benzene-heptane). Found: N 8.7; S 19.4%. $C_{16}H_{25}N_3O_8S_5$. Calculated: N 8.7; S 19.8%.

3,5-Bis (phenylamino)-2,4,6-tris (methylsulfonyl)pyridine (IIIb). A) Aniline (2 ml) was added at 20° to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF, after which the mixture was allowed to stand at this temperature for 3 days. It was then worked up to give 0.45 g (91%) of a product with mp 237-238° (dec., from aqueous ethanol). Found: N 8.5; S 19.4%. $C_{20}H_{21}N_3O_6S_3$. Calculated: N 8.5; S 19.4%.

B) Compound IIIb was similarly obtained in 95% yield from IId and aniline.

<u>3-Phenylamino-5-(p-nitrophenoxy)-2,4,6-tris(methylsulfonyl)pyridine (IIIc).</u> A solution of 0.3 g (2.1 mmole) of p-nitrophenol in 2 ml of DMF and 1 ml of triethylamine were added to a solution of 0.22 g (0.5 mmole) of IId in 3 ml of DMF, and the mixture was allowed to stand at 20° for 2 days. It was then treated with 50 ml of water and acidified with HCl, and the precipitated product was removed by filtration to give 0.16 g (59%) of IIIc with mp 247-248° (dec., from methanol). Found: N 7.9; S 17.3%. $C_{20}H_{20}N_3O_9S_8$. Calculated: N 7.8; S 17.7%.

Diethyl [2,4,6-Tris(methylsulfonyl)-5-chloro-3-pyridyl]malonate (IIe). Malonic ester (1 ml) and 1 ml of triethylamine were added to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF, after which the mixture was allowed to stand at 20° for 2 days. It was then treated with 50 ml of water, acidified with HCl, and cooled, and the precipitated product was removed by filtration to give 0.31 g (61%) of IIe (Table 1).

3-Ethoxy-5-chloro-2,4,6-tris (methylsulfonyl)pyridine (IIf). Triethylamine (1 ml) was added to a solution of 0.38 g (1 mmole) of sulfone I in 100 ml of absolute ethanol, and the mixture was refluxed for 5 h until sulfone I dissolved completely. The alcohol was then removed by vacuum distillation, and the residue was treated with 50 ml of water acidified with HCl and worked up to give 0.25 g (64%) of IIf (Table 1).

<u>4-Methylamino-3,5-dichloro-2,6-bis (methylsulfonyl)pyridine (IVa).</u> A solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF was saturated at -20° for 20 min with dry gaseous methylamine, after which the excess methylamine was removed rapidly in vacuo, and the solution was treated with 50 ml of water and acid-ified with HCl. Workup gave 0.27 g (81%) of IVa (Table 2).

4-Azido-3,5-dichloro-2,6-bis(methylsulfonyl)pyridine (IVb). A solution of 0.13 g (2 mmole) of sodium azide in 2 ml of water was added at -10° to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF. and the mixture was allowed to stand at this temperature for 10 min. It was then treated with 50 ml of water and worked up to give 0.33 g (96%) of IVb (Table 2).

 $\frac{4-\text{Hydroxy-3.5-dichloro-2,6-bis(methylsulfonyl)pyridine(IVc).} A 0.38-g (1 \text{ mmole}) \text{ sample of sulfone I}}{\text{was added to a solution of 0.4 g (10 mmole) of NaOH in 15 ml of water, after which the mixture was refluxed for 10 min. It was then cooled, acidified with concentrated HCl, and extracted with ether. Workup gave 0.1 g (31%) of IVc (Table 2).}$

Diethyl [3,5-Dichloro-2,6-bis (methylsulfonyl)-4-pyridyl]malonate (IVd). A solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF was added to a solution of 0.23 g (0.01 g-atom) of sodium in a mixture of 2 ml of malonic ester and 10 ml of tetrahydrofuran (THF), and the mixture was allowed to stand at 20° for 2 days. The solvents were then removed by vacuum distillation, and the residue was treated with aqueous alcohol. The mixture was cooled to precipitate 0.33 g (71%) of IVd (Table 2).

2,4,6-Trimethoxy-3,5-dichloropyridine (Va). A solution of 0.23 g (0.01 g-atom) of sodium in 50 ml of absolute methanol was added to a solution of 0.38 g (1 mmole) of sulfone I in 50 ml of absolute methanol, after which the mixture was stirred at 20° for 6 h until sulfone I dissolved completely. It was then allowed to stand at this temperature for another 12 h. The solvent was then removed by vacuum distillation, and the residue was treated with water acidified with HC1. Workup gave 0.23 g (97%) of a product with mp 92-93° (from aqueous ethanol) (mp 93-94° [7]).

2,4,6-Triphenoxy-3,5-dichloropyridine (Vb). A solution of 1 g (9 mmole) of sodium phenoxide in 10 ml of DMF was added to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF. and the mixture was allowed to stand at 20° for 24 h. It was then treated with 20 ml of water acidified with HCl, and the reaction product was extracted with ether. Workup gave 0.3 g (71%) of a product with mp 105-107° (from aqueous ethanol). Found: C 65.2; H 3.5; Cl 16.5%. C₂₃H₁₅Cl₂NO₃. Calculated: C 65.1; H 3.5; Cl 16.7%.

2,4,6-Trifluoro-3,5-dichloropyridine (Vc). This compound, with bp 155° (bp 156° [8]), was similarly obtained in 70% yield from sulfone III and potassium fluoride.

<u>3.4-Diazido-5-chlor-2,6-bis (methylsulfonyl)pyridine (VIa)</u>. A solution of 0.2 g (3 mmole) of sodium azide in 5 ml of water was added to a solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF, and the mixture was allowed to stand at 20° for 1 h. Workup gave 0.26 g (74%) of a product with mp 139-141° (dec., from ethanol). Found: Cl 9.8; N 28.3%. $C_7H_6ClN_7O_4S_2$. Calculated: Cl 10.1; N 27.9%.

2,4-Bis (methylamino)-3,5-dichloro-6-methylsulfonylpyridine (VII) and 3,4-Bis (methylamino)-5-chloro-2,6-bis (methylsulfonyl)pyridine (VIb). A solution of 0.38 g (1 mmole) of sulfone I in 10 ml of DMF was saturated for 30 min at 20° with dry methylamine gas, after which it was allowed to stand at 20° for 4 days. The methylamine and DMF were removed in vacuo, and the residue was treated with 10 ml of water acidified with HCl. The mixture of products VII and VIb was removed by filtration, and the compounds were separated by means of their different solubilities in propanol. The yield of VII, with mp 145-147° (from aqueous propanol), was 0.12 g (43%). Found: Cl 24.7; N 14.8; S 11.4%. C₈H₁₁Cl₂N₃O₂S. Calculated: Cl 25.0; N 14.8; S 11.3%. The yield of VIb, with mp 201-203° (dec., from propanol), was 0.1 g (30%). Found: Cl 11.0; N 12.6%. C₉H₁₄ClN₃O₄S₂. Calculated: Cl 10.8; N 12.8%.

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