Action of Benzyl Chloride on 2-(*N*,*N*-Dimethylamino)pyridine and 2-Benzoylaminopyridine

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The results of the reaction of 2-(*N*,*N*-dimethylamino)pyridine (**1**) and 2-benzoylaminopyridine (**2**) with benzyl chloride (**3**) proved that **3** did not undergo direct reaction with the pyridine ring to form a *C*-benzyl product.

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In relation to my interest in the reactivity of the pyridine ring in electrophilic substitution, I have previously studied the electrophilic benzylation of *N*-unsubstituted and *N*-benzyl substituted 2-aminopyridines [1-4]. Reactivity of the pyridine ring on an electrophilic attack has also been investigated by means of theoretical analysis [4-6].

The present work was undertaken in order to prove the mechanism of the *C*-benzyl derivative of 2-aminopyridines formation in its reaction with benzyl chloride. The reactions of 2-(*N*,*N*-dimethylamino)pyridine (**1**) in the hydrochloride form as well as in the free base form and 2-benzoylaminopyridine (**2**) with benzyl chloride (**3**) were investigated. The reactions were carried out under conditions described for the reactions of 2-amino- and 2-benzylaminopyridines with benzyl chloride, where the *C*-benzylation process of the pyridine ring takes place [1,2]. At the beginning, the reaction mixture was heated for a few hours from the point when the reaction mixture started to boil to a temperature of 250° and then, kept at that temperature during an additional period.

The following compounds were found in the reaction products of **1** hydrochloride with **3**, used in molar ratio of 1:1 and heated at a temperature of 250° during 4 hours (see Scheme 1): *N*-benzyl-*N*-methyl-2-aminopyridine (**4**), 2-(*N*,*N*-dibenzylamino)pyridine (**5**), 2-benzylaminopyridine (**6**), 2-benzylamino-5-benzylpyridine (**7**) and 2-amino-5-benzylpyridine (**8**).

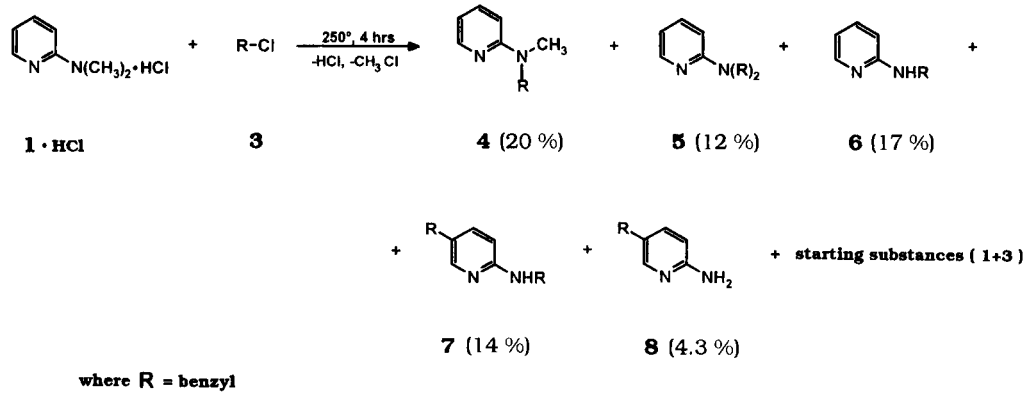
In the case of the reaction of the free base **1** with **3** and the same heating time at 250°, a decrease in the yield of the *C*-benzylation products was noticed (see the experimental).

Fractional distillation of the reaction mixture of **1** or **1** hydrochloride with **3** into three parts facilitated this identification on the basis of high resolution gas chromatography, gc/ms and ^{1}H nmr spectra and by comparison with a reference substance.

In the mass spectra (gc/ms system) of all the fractions, the molecular and fragmentation ions coming up from compounds **1, 3-8** were detected respectively. Also, in the ^{1}H nmr spectra the signals characteristic for the analyzed substances were observed. For example, in the second fraction (the reaction of **1** hydrochloride with **3**) the singlet signals at δ 3.09 ppm and δ 4.84 ppm corresponding to -CH_3 and -CH_2- groups of **4**, a signal at δ 4.46 ppm (doublet) corresponding to -CH_2- group of **6** [2] and a signal at δ 3.80 ppm (singlet) of the methylene group in **8** [2] were observed.

The evolution of hydrogen chloride from the reaction mixture was established by the fact that a quantity of the aqueous ammonium hydroxide used for alkalizing the hydrogen chloride produced during the reaction was *ca.* 40% of the theoretical amount. The methyl chloride evolution was determined by the analysis of the gases emitted during the reaction after its absorption in deuteriochloroform. In the ^{1}H nmr spectra, a singlet signal at δ 3.04 ppm

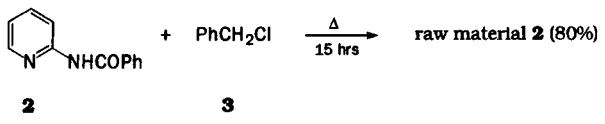
Scheme 1



corresponded to the methyl group of methyl chloride [7].

In contrast to the reaction of **1** with **3**, the reaction of 2-benzoylaminopyridine (**2**) with **3** did not show progress during heating. The temperature of the mild boiling reaction mixture, *ca.* 190°, did not increase during 15 hours of heating and 80% of the starting **2** was recovered after the reaction (see Scheme 2).

Scheme 2



The experimental results of the reactions of **1** and **2** with **3** proved that the *C*-benzylation process of the 2-aminopyridine ring did not take place in the direct reaction with the use of benzyl chloride, because in the products I found neither the *C*-benzyl derivatives of 2-(*N,N*-dimethylamino)pyridine nor 2-benzoylaminopyridine.

The results of the reaction of **1** with **3** suggest that at the beginning the displacement of the methyl group in 2-(*N,N*-dimethylamino)pyridine (**1**) by the benzyl substituent occurred and the formation of the *N*-benzyl-*N*-methyl-2-aminopyridine (**4**) took place. This fact is confirmed by the analysis of the reaction products of **1** hydrochloride with **3** after 2 hours heating, when the temperature of the reaction mixture reached *ca.* 205°. In this case **1** and **4** was found in the reaction mixture in the ratio of 1:1. The displacement of the methyl group in **4** by the benzyl substituent leads to the formation of 2-(*N,N*-dibenzylamino)pyridine (**5**) and the rearrangement of the latter causes 2-benzylamino-5-benzylpyridine (**7**) formation according to the scheme proposed previously [1]. Thermolysis of the aminomethylene bond in **5** and **7** under the reaction conditions, causes 2-benzylaminopyridine (**6**) and 2-amino-5-benzylpyridine (**8**) formation [1,2].

The reactivities of the reaction mixtures of **1** and **3**, followed by the yield and the ratio of the products obtained, are different in the presence and in the absence of the hydrogen chloride, which indicates the important role of hydrogen chloride. This proves conclusively that the processes takes place *via* the ionic structures, which influences the polar reaction mixture.

EXPERIMENTAL

Elemental analyses were performed on a Perkin-Elmer 240 analyzer, gc/ms mass spectra were carried out with Hewlett Packard apparatus consisting of gas chromatograph 5890 and mass detector 5971A. The ^{1}H nmr spectra were recorded in deuteriochloroform with a Tesla 487C spectrometer; the chemical shifts are expressed in δ values downfield from tetramethylsilane (TMS) as an internal standard. Chromatographic analyses were performed on a Carlo Erba 6330-50 capillary gas chromatograph. Melting points are uncorrected.

Reference standards and reagents: benzyl chloride (**3**) was a commercial product, 2-(*N,N*-dimethylamino)pyridine (**1**) [8] and 2-benzoylaminopyridine (**2**) [9] were prepared according to the literature data. 2-(*N,N*-Dibenzylamino)pyridine (**5**), 2-benzylaminopyridine (**6**), 2-benzylamino-5-benzylpyridine (**7**) and 2-amino-5-benzylpyridine (**8**) were obtained according to the procedures described previously [1-3]. *N*-Benzyl-*N*-methyl-2-aminopyridine (**4**) was obtained by the reaction of 2-benzylaminopyridine with methyl iodide carried out in toluene in the presence of sodium amide in 64% yield, bp 170-173°/1 mm; ^{1}H nmr δ 3.07 (s, 3 H, CH_3), 4.82 (s, 2 H, CH_2), 6.47-6.66 (m, 2 H, 3-H and 5-H), 7.25-7.55 (m, 6 H, 4-H and 5 phenyl protons), 8.20 ppm (dd, 1 H, 6-H, $J_{5,6}$ = 5.9 Hz, $J_{4,6}$ = 1.0 Hz); ms: m/z (I%), M, 198 (71), M-CH_3, 183 (100), 120 (30), 107 (87), 91 (58), 78 (59).

Anal. Calcd. for $C_{13}H_{14}N_2$ (198.26): C, 78.75; H, 7.12; N, 14.13. Found: C, 78.66; H, 7.24; N, 14.01.

Reaction of 2-(*N,N*-Dimethylamino)pyridine (1) with Benzyl Chloride (3).

Reaction of 2-(*N,N*-dimethylamino)pyridine (**1**) with benzyl chloride (**3**) was prepared and carried out in the manner described for the reaction of 2-aminopyridines with benzyl chloride [1-3]; 4.9 g (0.04 mole) of **1** and 5.1 g (0.04 mole) of **3** were used. The temperature of the reaction mixture was inxreased to 182° in 3-4 minutes (reaction mixture started to boil). Next, during 5 hours the temperature was gradually increased to 250° and the reaction mixture was kept at that temperature during an additional 4 hours. The reaction products were distilled into 3 fractions.

The first fraction was collected at 80-90°/2 mm, with the weight of 1.1 g, contained starting substances **1** and **3** in the ratio of 9:1. The second fraction was collected at 170-185°/2 mm, with the weight of 2.8 g, contained substances **4** and **6** in the ratio of 3:2 and their yields were 21 and 15%, respectively. The third fraction was collected at 240-255°/2 mm, with the weight of 2.6 g, contained compounds **5** and **7** in the ratio of 4:1 and their yields were 19 and 4.7%, respectively.

Reaction of 2-(*N,N*-Dimethylamino)pyridine (1) Hydrochloride with Benzyl Chloride (3).

The reaction of 2-(*N,N*-dimethylamino)pyridine (**1**) hydrochloride with benzyl chloride (**3**) was carried out in the manner described for the reaction of **1** with **3**. Instead of the free base **1**, 6.3 g (0.04 mole) of **1** hydrochloride was used. The reaction mixture started to boil at 181°. Next, during 4 hours, the temperature was inxreased to 250° and kept at that temperature during an additional 4 hours. The reaction products were distilled into 3 fractions. They were collected at the same range of temperature and pressure as the respective fractions obtained in the reaction of **1** with **3**.

The first fraction, with the weight of 0.9 g, contained substances **1** and **3** in the ratio of 9:1.

The second fraction, with the weight of 3.2 g, contained substances **4, 6** and **8** in the ratio of 5:4:1. The yields were 20, 17 and 4.3%, respectively.

The third fraction, with the weight of 2.9 g, contained compounds **5** and **7** in the ratio of 4.5:5.5. The yields were 12 and 14%, respectively.

Reaction of 2-Benzoylaminopyridine (**2**) with Benzyl Chloride (**3**).

A mixture of 9.9 g (0.05 mole) of 2-benzoylaminopyridine (**2**) and 6.3 g (0.05 mole) of benzyl chloride (**3**) was subjected to heating. The temperature of the mild boiling reaction mixture after 15 hours heating did not increase above 190°. Crude starting 2-benzoylaminopyridine (**2**) was recovered in 80% yield, mp 84-86° (lit [9] mp 87°).

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