METALLATION OF 1-DIALKYLAMINOBENZIMIDAZOLES

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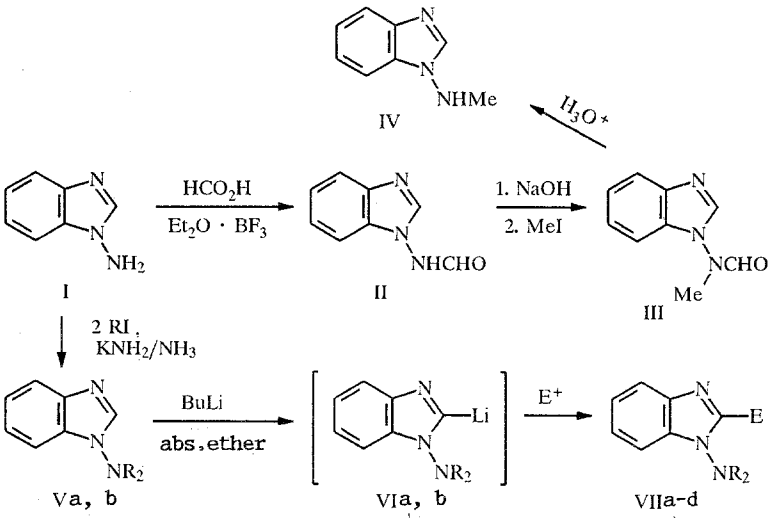
In contrast to 1-amino- and 1-alkylaminobenzimidazoles, 1-di-alkylaminobenzimidazoles are metallated by n-butyl-lithium in absolute either at the 2-position. The subsequent treatment of the lithium derivatives by electrophilic reagents, in which role benzophenone and iodine were used, leads to the formation of the corresponding 2-R-1-dialkylaminobenzimidazoles, which are difficult to obtain by other methods. The possibility was studied of using the N-dialkylamino group as a protective function.

Despite the fact that interest has increased in the last few years in N-aminoazoles [1], their metallation remains uninvestigated up to the present time. It is very difficult to predict beforehand the result of this reaction, since the N-amino group may be eliminated by the action of strong bases [2], while its ionization with the formation of an N-anion [3] may hinder the C-metallation of the hetero ring – the most desirable path of the reaction from the synthetic point of view. In the present work we studied this problem taking N-aminobenzimidazoles as an example.

We selected 1-amino- (I), 1-methyl- amino- (IV) and also 1-dimethylamino- and 1-diethylaminobenzimidazoles (Va,b) as the starting compounds. To prepare compound IV we have developed a more convenient method than that known before [4], consisting in the methylation of the sodium salt of 1-formylaminobenzimidazole (II) by methyl iodide in acetone, followed by the removal of the formyl group. The yields at both stages exceed 80%. 1-Dialkyl-aminobenzimidazoles Va,b were synthesized in a yield of 57 and 36%, respectively, by the action of methyl iodide or ethyl iodide on amine I in liquid ammonia in the presence of potassium amide. It is interesting to note that in all of the experiments, not even traces of the formation of 1-alkylaminobenzimidazoles were detected. A similar phenomenon was also observed during the alkylation of C-aminoazoles under the same conditions [5, 6].



VaR = Me, VbR = Et, VIaR = Me, VIbR = Et, VIIaR = Me, E = $Ph_2C(OH)$, VIIbR = Me, E = I, VIIe R = E = Me, VIIdR = Et, E = $Ph_2C(OH)$

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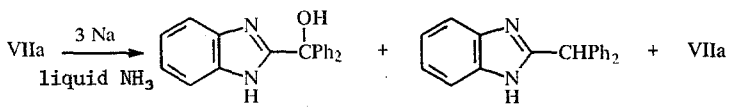
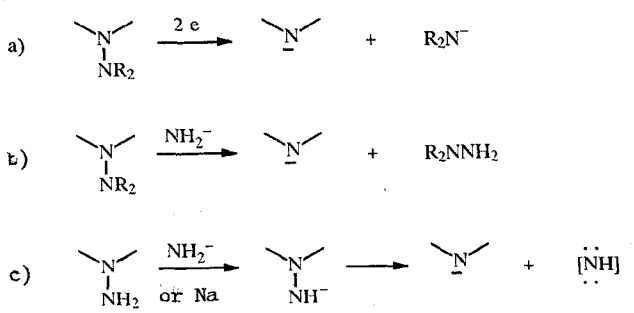
We were also unable to carry out the C-metallation of compounds I and IV by n-butyl-lithium in absolute ether at temperatures from −20°C to −100°C; in all cases, after the addition of benzophenone to the reaction mixture, the starting compound was isolated instead of the expected 1-amino(methylamino)-2-α-hydroxybenzhydrylbenzimidazole. In contrast to this, the experiments with 1-dialkylaminobenzimidazoles gave positive results. First, we have carried out the reactions at −20°C, setting two experiments in parallel: with 1-methylaminobenzimidazole and 1-dimethylaminobenzimidazole. In both cases, the attempts to record the formation of the organolithium compounds by adding benzophenone into the reaction mixture were unsuccessful, and led only to the separation of the starting compounds. It is possible that the 1-R-2-lithium−benzimidazoles are unstable under these conditions. In fact, by decreasing the temperature of the reaction mixture to −100°C, we obtained in the case of 1-methylbenzimidazole the already known [7] 1-methyl-2-α-hydroxybenzhydrylbenzimidazole, and in the case of compounds Va,b — the alcohols VIIa and VIId. The yields of the latter compounds were 74% and 30%, respectively. In a similar way, in treatment of 1-dimethylamino-2-lithiumbenzimidazole (VIa) with iodine, 1-dimethylamino-2-iodobenzimidazole (VIIb) was obtained in a 42% yield. In an attempt to methylate the lithium-derivative VIa with methyl iodide, a mixture of the starting compound Va and 1-dimethylamino-2-methylbenzimidazole (VIIc) was obtained, which, however, could not be separated because of the similarity of the chromatographic mobility and other properties. Judging from the IR spectrum of this mixture, the yield of compound VIIc did not exceed 20%.

It was of interest to study the possibility of using the N-dimethylamino group as a protective function for the organometallic synthesis of 2-substituted benzimidazoles not containing a substituent in the 1-position. Most of the known methods of elimination of the N-amino group (for example, action of nitrous acid) [1] are inapplicable here, because they require the presence of free N−H bonds in the amino group. We therefore tested the reducing methods and the action of strong bases. It was found that the dimethylamino group in compound Va is eliminated both by the action of excess sodium (potassium) in liquid ammonia (the reducing method), and by the action of potassium amide, but the process is slow and cannot be brought to completion. Thus, as the result of stirring compound Va with two equivalents of KNH_2 in liquid ammonia, only 17% of benzimidazole was obtained and about 75% of the starting compound was regenerated. The yield of benzimidazole was higher (40%) by the action of excess sodium in liquid ammonia on compound Va, but also in this case a large portion of the starting compound remained unchanged. Approximately the same results were obtained as a result of the reductive elimination of the dimethylamino group in alcohol VIIa. The starting alcohol, VIIa (35%), 2-α-hydroxybenzhydrylbenzimidazole (VIII) (30%) and also the product of the reduction of the hydroxyl group in the latter compound − 2-benzhydrylbenzimidazole (IX) (35%) were isolated from the reaction mixture.



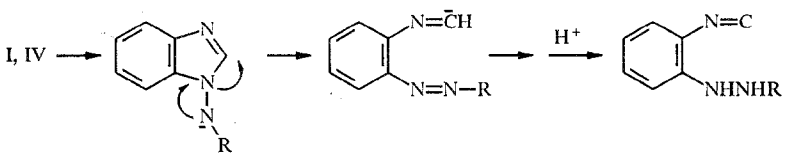
VIII IX

In contrast to the dimethylamino group, the elimination of the N-amino group in compound I, both by the action of metallic sodium and potassium amide in liquid ammonia, proceeds very readily and the yields of benzimidazole reach 70 and 85%, respectively, it is very likely that three possible elimination mechanisms are realized under these conditions: the reducing mechanism (path a), nucleophilic (b) and fragmentation of the anion (c):



The reductive elimination, which most likely occurs by the action of alkali metals, obviously proceeds slowly, since the NH_2^- and NR_2^- anions are poor leaving groups. Judging from the experimental results with compound IVa, the nucleophilic elimination, during which N-aminobenzimidazole acts as an electrophilic aminating agent with respect to the base (a corresponding hydrazine should thus be formed), also proceeds with difficulty. From the fact that the unsubstituted amine is most smoothly dominated, it can be concluded that the most readily proceeding process is the fragmentation of the N-anion. During its course, the aminic nitrogen is probably split off in the form of nitrene, which then disproportionates according to one of the known scheme [8]. Already previously during the study of the NH-acidity of N-aminoazoles, we have noted the instability of their N-anions [3]. Also in the present work, we have noted that if during the alkylation of compound I a pause is made before the introduction of the alkylating agent into the reaction mixture, the corresponding 1-alkylbenzimidazole is formed as a by-product, as a result of the alkylation of benzimidazole, obtained during the fragmentation of the 1-aminobenzimidazole anion.

There are grounds for assuming that the 1-aminobenzimidazole N-anions also partially decompose by the opening of the imidazole ring, leading to the formation of isonitriles:



The odor of isonitriles is always noted in the reaction mixture when strong bases act on N-aminobenzimidazoles. It is probable that a degradation of this type is particularly characteristic for the N-anions of monoalkyl derivatives of type IV, since when compound IV was reacted with one equivalent of KNH_2 in liquid ammonia, only 13% of the starting compound was regenerated. At the same time, only traces of benzimidazole were isolated and a complex mixture of difficulty separable oily products with an isonitrile odor was obtained.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-487C spectrometer with a working frequency of 80 MHz, using HMDS as internal standard. The IR spectra were measured on a Specord 75 IR spectrophotometer in a thin layer of mineral oil. The course of the reaction and the purity of the compounds obtained were monitored by TLC on plates with Al_2O_3 of Iv-th grade of activity according to Brockman, with development by iodine vapors. The melting points were measured in a sealed capillary in a melting point apparatus and were not corrected.

The elemental analysis data of the synthesized compounds for C, H, N corresponded to the calculated values.

1-Formylaminobenzimidazole (II). A solution of 4.0 g (0.03 mole) of 1-aminobenzimidazole and 1 ml of boron trifluoride etherate in 50 ml of a 98% formic acid was boiled for 2 h, then the excess of the acid was distilled off under reduced pressure, and the residue was treated with 30 ml of water. After neutralization of the solution with a 22% ammonia solution, the precipitate that separated out was filtered off and washed with water. Yield, 4.0 g (83%). Colorless flakes, mp 204-205°C (from water), which corresponds to the literature data [9].

1-Methylaminobenzimidazole (VI, $C_8H_9N_3$). A solution of 1.1 g (6.8 moles) of 1-formylaminobenzimidazole and 0.3 g (7.5 mmoles) of sodium hydroxide in 3 ml of water was evaporated to dryness under reduced pressure. To the residue consisting of the sodium salt of compound II, 8 ml of acetone and 0.5 ml (8.1 mmoles) of methyl iodide were added. The mixture was stirred at room temperature for 2 h, whereby the suspension completely dissolved towards the end. Acetone was evaporated, the residue was dissolved in 15 ml of chloroform, and the solution was passed through a column containing Al_2O_3, eluting with chloroform. The fraction with R, 0.25, containing 1-methylformylaminobenzimidazole (III), was collected. Yield 1.0 g (84%). Colorless oil. IR spectrum (thin film): 1610, 1713 (C = 0) cm^{-1}. Picrate – bright yellow crystals, mp 212...213°C (from isopropanol).

A solution of 1.0 g (5.7 mmoles) of compound III in 10 ml of hydrochloric acid (1:1) was boiled for 10 min. After neutralization with ammonia, the 1-methylaminobenzimidazole obtained was extracted with chloroform (2 × 15 ml) and purified on a chromatographic column containing Al_2O_3 (eluent – chloroform). The fraction with R_f, 0.4 was collected. Yield, 0.75 g (89%). Paleflesh colored prisms, mp 71-73°C (from an octane-benzene mixture). IR spectrum: 1610, 3205 (NH) cm^{-1}. PMR

spectrum ($CDCl_3$): 7.89 (1H, s, 2-H), 7.68 (1H, m, 4-H), 7.25 (3H, m, 5,7-H), 5.15 (1H, br. s, NH), 2.92 (3H, s, N-CH_3) (DMSO-d_6): 8.29 (1H, s, 2-H), 7.60 (2H, m, 4,7-H), 7.20 (2H, m, 5,6-H), 6.69 (1H, q, J = 5.4 Hz, NH), 2.81 (3H, d, J = 5.4 Hz, N-CH_3).

1-Dimethylaminobenzimidazole (Va) was obtained by the method described previously in [3] in a yield of 57%.

1-Diethylaminobenzimidazole (Vb, $C_{11}H_{15}N_3$). A 7,5 g portion (0.056 mole) of 1-aminobenzimidazole was added at −78°C to the solution of potassium amide obtained by dissolution of 4.3 g (0.112 mole) of potassium in 90 ml of liquid ammonia, and after 10 min, 9.2 ml (0.112 mole) of ethyl iodide was added dropwise. The mixture was stirred for 30 min at −78°C, and then the ammonia was allowed to evaporate freely. The oily residue was extracted with ether (2 × 30 ml). 1-Diethylaminobenzimidazole which passed into the ether usually contains an admixture of 1-ethylbenzimidazole. For their separation the concentrated ether extract was passed through a column containing Al_2O_3 (40 × 2 cm), eluting successively with ether, firstly, compound Vb (R_f 0.46) and then 1-ethylbenzimidazole (R_f 0.16).

Yield of compound Vb − 3.9-4.5 g (37-42%). Slightly yellowish oil with n_D^{20} 1.546. PMR spectrum (CCl_4): 7.82 (1H, s, 2-H), 7.60 (1H, m, 7-H), 7.30 (1H, m, 4-H), 7.08 (2H, m, 5,6-H), 3.18 (4H, q, J = 7.2 Hz, CH_2CH_3), 0.80 (6H, t, J = 7.2 Hz, CH_2CH_3). Picrate − bright-yellow crystals, mp 142-144°C (from ethanol).

1-Dimethylamino-2-(α-hydroxybenzhydryl)benzimidazole (VIIa, $C_{22}H_{21}N_3O$). The experiment was carried out in an argon atmosphere. A solution of 1.61 g (0.01 mole) of 1-dimethylaminobenzimidazole in 15 ml of ether was added dropwise in the course of 15 min, with cooling to −100°C to a solution of n-butyl-lithium, prepared from 0.28 g (0.04 mole) of lithium and 2.1 ml (0.04 mole) of dry butyl bromide in 25 ml of absolute diethyl ether. The mixture was stirred for 1 h at −100°C and then a solution of 3.64 g (0.02 mole) of benzophenone in 15 ml of ether was added. The mixture was stirred for another 20 min at −100°C and then for 1 h at room temperature. On increasing the temperature of the mixture a voluminous white precipitate separated out. To the suspension 22 ml of hydrochloric acid (1:1) was added, the aqueous layer was separated, washed with ether and neutralized with aqueous 22% ammonia. The oil that separated out crystallized after some time; the precipitate was filtered off, and washed with cold water. Yield, 2.55 g (74%). Colorless crystals, mp 154-156°C (from alcohol). R_f 0.8 ($CHCl_3$), IR spectrum: 1590, 1600, 3365 (w) cm^{-1}. PMR spectrum ($CDCl_3$): 7.75 (1H, m, 7-H), 7.30 (13H, m, 2 × C_6H_5, 4,6-H), 6.68 (1H, s, OH), 2.75 (6H, s, $(NCH_3)_2$).

1-Dimethylamino-2-iodobenzimidazole (VIIb, $C_9H_{10}N_3$). A solution of 0.75 g (0.0045 mole) of 1-dimethylaminobenzimidazole in 10 ml of absolute ether was added in the course of 10 min with cooling to −100°C to a solution of n-butyl-lithium, prepared from 0.14 g (0.02 mole) of lithium and 1.05 ml (0.02 mole) of butyl bromide in absolute diethyl ether. The mixture was stirred for 1 h at −100°C, and then a solution of 1.27 g (0.01 mole) of iodine in 15 ml of ether was added rapidly. After 20 min, the cooling bath was removed, and stirring of the mixture was continued for 1 h at room temperature. A 10 ml portion of water and sodium metabisulfite were added (to decolorize the solution). The mixture was acidified with 5 ml of concentrated hydrochloric acid. A voluminous precipitate of the hydrochloride of compound VIIb separated out, which was filtered off, suspended in 30 ml of water and neutralized with sodium hydrocarbonate. Thus, 0.4 g of base VIIb was obtained, which was separated out and washed on the filter with water. Neutralization of the aqueous filtrate with 22% ammonia and subsequent extraction with chloroform (2 × 25 ml) gave another 0.6 g of a mixture of product VIIb and the starting compound. They were separated on a column containing Al_2O_3, eluting with ether. First, the fraction with R_f 0.8 was collected consisting of the 2-iodo derivative VIIb, and then the fraction with R_f 0.68 − the starting compound (0.4 g, 53%). The overall yield of compound VIIb was 0.55 g (42%). Colorless prisms, mp 98-100°C (from isooctane). PMR spectrum ($CDCl_3$): 7.6 (2H, m, 4,7-H), 7.18 (2H, m, 5,6-H), 2.95 ppm (6H, s, $N(CH_3)_2$).

Attempt to obtain **1-dimethylamino-2-(methylbenzimidazole (VIIc).** The experiment was carried out analogously with the preparation of compound VIIb with the only difference being that instead of iodine, 0.62 ml (0.1 mole) of methyl iodide was added to the solution of lithium derivative VIa. The mixture was held for 20 min at −100°C and for another 1 h at room temperature. Then 15 ml of hydrochloric acid (1:1) was added, the aqueous layer was separated, washed with ether (50 ml), and neutralized with a 22% aqueous ammonia. The oily layer was extracted with chloroform and purified on a column with Al_2O_3 (eluent − chloroform). Thus, 0.35 g of a mixture was obtained, which according to PMR spectroscopy data, consisted of 60% of the starting compound and 40% of 1-dimethylamino-2-methylbenzimidazole (VIIc).

1-Diethylamino-2-(α-hydroxybenhydryl)benzimidazole (VIId) was obtained in analogy with compound VIIa. However, after the neutralization of the aqueous layer with ammonia, an oil separated out which was extracted with chloroform. The residue remaining after the evaporation of chloroform was ground with alcohol, yielding compound VIId in the form of colorless crystals, mp 178-179°C (from alcohol). Yield, 30%, R_f 0.8 ($CHCl_3$). PMR spectrum ($CDCl_3$): 7.7 (1H, m, 7-H), 7.2 (14H, m, 2 × C_6H_5, 4.6-H, OH), 3.1 (4H, q, J = 7.2 Hz, CH_2CH_3), 0.75 ppm (6H, t, J = 7.2 Hz, CH_2CH_3).

Deamination of 1-dimethylaminobenzimidazole. A. A 0.8 g portion (0.005 mole) of compound Va was added to a solution of KNH_2, obtained from 0.4 g (0.01 mole) of potassium in 20 ml of liquid ammonia. The mixture was stirred for 1 h at −78°C, and then ammonia was allowed to evaporate freely. The residue was treated with 10 ml of cold water (cautiously!) and extracted with chloroform (2 × 20 ml). The chloroformic solution was passed through a column containing Al_2O_3 (chloroform). First, the fraction with R_f 0.6 was collected (eluent − chloroform) consisting of the starting compound. Pale-yellow oil, which in its spectral characteristics was identical with an authentic sample of Va. Then, 0.1 g (17%) of benzimidazole was eluted with ethyl acetate. Colorless prisms, mp 169-170°C (from water), do not give depression of the melting point with an authentic sample.

B. A 0.135 g portion (0.006 mole) of sodium was gradually added at −78°C to a solution of 0.4 g (0.0025 mole) of 1-dimethylaminobenzimidazole in 25 ml of liquid ammonia. Each successive portion of sodium was added after the disappearance of the dark-blue color of the solution. The mixture was held for 1 h at −100-°C, and then ammonia was evaporated. The dry residue was dissolved in 10 ml of water, and the unreacted 1-dimethylaminobenzimidazole was extracted with ether (2 × 10 ml). Yield, 0.2 g (50%). A pale yellow oil, which according to spectral characteristics was identical with compound Va.

The aqueous layer was neutralized with acetic acid to pH 7 and evaporated to dryness. Benzimidazole was extracted with hot ethyl acetate. Yield, 0.1 g (40%), Colorless crystals, mp 168-170°C (from water). A mixed melting point with an authentic sample of benzimidazole is 169-170°C.

Deamination of 1-methylaminobenzimidazole. A 0.75 g portion (0.005 mole) of 1-methylaminobenzimidazole was added to a grey-colored solution of KNH_2 obtained from 0.2 g (0.005 mole) of potassium in 20 ml of liquid ammonia. The solution thus became dark-brown in color. The mixture was stirred for 1 h at −78°C and ammonia was evaporated. The dark-brown solid residue with a strong isonitrile odor was treated with 10 ml of water, and extracted with chloroform (2 × 15 ml). The chloroformic extract was passed through a column containing Al_2O_3 (3 × 20 cm). and the fraction with R_f 0.4 of the starting compound IV was eluted with chloroform. Yield, 0.1 g (13%). Flesh colored prisms, mp 71-73°C (from benzene with octane). No depression was observed of the mixed melting point with an authentic sample of methylamine IV.

The complex caramel-like mixture of compounds with R_f from 0.15 to 0.05 which was eluted with ethyl acetate, could not be separated or purified. Yield, 0.13 g.

No compounds could be separated or identified also from the aqueous layer.

Deamination of Carbinol VIIa. Sodium (0.2 g, 0.009 mole) was added in portions in the course of 15 min to a suspension of 1.0 g (0.003 mole) of carbional VIIa in 30 ml of liquid ammonia, whereby the color of the solution changed from blue, through brown to pink. The mixture was stirred for 30 min at −78°C to the complete decoloration of the solution, and ammonia was evaporated. To the residue 20 ml of cold water was added, and the precipitate (0.95 g) was filtered off. According to TLC on Al_2O_3 (chloroform) the precipitate consisted of a mixture of three compounds with R_f 0.2, 0.35, and 0.7. The compound with R_f 0.2 was separated by grinding with 30 ml of chloroform. The yield of 2-benzhydrylbenzimidazole (IX) was 0.3 g (35%). Colorless prisms, mp 219-221°C (dec., from alcohol), which corresponds to the literature data [10]. IR spectrum: 1604, 1624 cm^{-1}. PMR spectrum (DMSO-d_6): 12.3 (1H, br. s, NH, disappears after deuteration), 6.9-7.70 (14H, m, arom. protons) and 5.74 ppm (1H, s, CNH) Mass spectrum, m/z (%): $M^{+\cdot}$284 (40), 283 (70), 206 (4), 165 (11), 141 (4).

After the evaporation of chloroform, the residue was ground with 20 ml of ether and the precipitate of compound with R_f 0.7 was filtered off. The yield of 2-α-hydroxybenzhydrylbenzimidazole (VII) was 0.3 g (30%). Colorless prisms, mp 218-220°C (dec., from alcohol), which corresponds to the literature data [7]. IR spectrum: 1600, 3394 cm^{-1} (N−H).

The residue after evaporation of ether (0.35 g, 35%) consisted of an oily substance with R_f 0.35 and was the starting carbinol VIIa. Colorless prisms, mp 154-155°C (from alcohol), which gave no mixed mp depression with a sample of carbinol VIIa.

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