IMIDAZOLE DERIVATIVES THAT CONTAIN POTENTIALLY LABILE GROUPINGS ATTACHED TO THE N ATOM.

7.* SYNTHESIS OF 1-SUBSTITUTED 2-AMINOBENZIMIDAZOLES BY AMMONOLYSIS OF 1-R-3-METHOXYBENZIMIDAZOLIUM SALTS

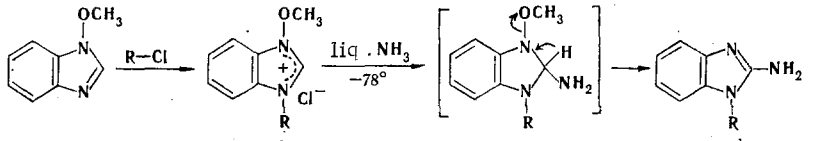
M. M. Medvedeva and A. F. Pozharskii

UDC 547.785.5.07:542.958.3

A new method for the synthesis of 1-substituted 2-aminobenzimidazoles, which are difficult or impossible to obtain by direct amination with sodium amide, is proposed. The method consists in the action of liquid ammonia on 1-R-3-methoxybenzimidazolium salts. The reaction is accompanied by the addition of the amide ion in the 2 position and elimination of a methoxy group.

The best method for the synthesis of 1-R-2-aminobenzimidazoles is the amination of 1-substituted benzimidazoles with sodium amide [2]. However, the method has a number of limitations; in particular, it is unsuitable for the synthesis of 2-aminobenzimidazoles that contain labile groupings, as well as certain substituents with heteroatoms (alkoxymethyl, alkylthiomethyl, etc.), in the 1 position. In view of this, 2-aminobenzimidazoles that contain the indicated substituents in the 1 position have been virtually unknown up until now. Only 1-methoxymethyl-2-aminobenzimidazole, which was obtained by alkylation of the sodium salt of 2-aminobenzimidazole with methoxymethyl chloride in absolute dioxane [1], has been described.

In the present research we developed a general method for the synthesis of 2-aminobenzimidazoles that contain alkoxymethyl and alkylthiomethyl groups in the 1 position. The method is based on the ability of 1-R-2-methoxybenzimidazolium salts to add nucleophiles in the 2 position under mild conditions with the simultaneous elimination of a methoxy group [3]. 1-Alkoxymethyl-3-methoxybenzimidazolium salts (IIa-c) were obtained by the action of alkoxymethyl chlorides on the previously described [4] 1-methoxybenzimidazole.† An amino group adds smoothly to them in the 2 position when they are treated with liquid ammonia, and easily isolable amines IIIa-c are formed in 60-66% yields.



I IIa-f IIIa-d

II, III a $R=CH_3OCH_2$; b $R=C_2H_5OCH_2$; c $R=n\text{-}C_4H_9OCH_2$; d $R=n\text{-}C_5H_{11}SCH_2$; IIe $R=CH_3$; f $R=C_6H_5CH_2$

The previously unknown 1-pentylthiomethyl-2-aminobenzimidazole (IId) was similarly obtained in 82% yield. The method also proved to be suitable for the synthesis of diamines V from salts IV, which previously could not be obtained by the Chichibabin reaction [5].

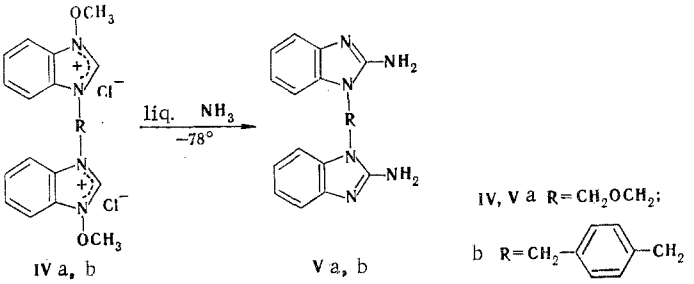
*See [1] for Communication 6.

†Salts IIa-d and IV are extremely hygroscopic and labile; however, they can be stored for a long time without appreciable decomposition over a drying agent (P_2O_5). In our research the salts were not investigated individually but were subjected immediately to reaction with liquid ammonia.

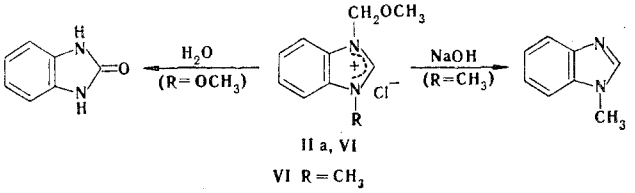
Stavropol State Pedagogical Institute, Stavropol 355009. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1086-1088, August, 1982. Original article submitted November 3, 1981.

 0009-3122/82/1808-0830$07.50 © 1983 Plenum Publishing Corporation

The proposed scheme is also suitable for the synthesis of 1-alkyl- and 1-benzyl-2-aminobenzimidazoles; this was demonstrated in the case of amines IIIe, f. However, these amines, as we have already mentioned, are more simply obtained via the Chichibabin reaction [2].



It should be noted that the direction of ammonolysis of salts II and IV cannot be predicted, since they contain not only methoxy but also alkoxymethyl and alkylthiomethyl groups, which are potentially labile with respect to bases. Thus, for example, splitting out of a methoxymethyl group and the formation of 1-methylbenzimidazole are observed when 1-methyl-3-methoxybenzimidazolium salt IVa is heated in water. The reaction is complete in 12 h. The same reaction under the influence of 10% aqueous NaOH solution is complete after 10 min.



It seemed of interest to extend the indicated method also to the synthesis of benzimidazolones that contain labile groups in the 1 position. However, the only reaction product (in 60% yield) was benzimidazolone when 1-methoxymethyl-3-methoxybenzimidazolium chloride (IVb) was heated in water.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CF_3COOH were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

General Method for the Synthesis of 1-Alkoxymethyl-3-methoxybenzimidazolium Chlorides (IIa-c, IVa) and 1-n-Pentylthiomethylbenzimidazolium Chloride (IId). A 0.035-mole sample of the corresponding alkoxymethyl chloride (or the chloromethyl pentyl sulfide in the case of the synthesis of (IId)) was added dropwise with stirring to a solution of 4 g (0.027 mole) of 1-methoxybenzimidazole in 15 ml of absolute ether, and the mixture was stirred for 1 h. The precipitated salt was removed by filtration, washed with 25 ml of absolute ether, and dried over P_2O_5. The product was obtained in quantitative yield. In the preparation of salt IVa, 0.026 mole of bischloromethyl ether was used for 0.04 mole of 1-methoxybenzimidazole. The formation of salt IVa proceeded slowly, and the reaction flask was allowed to stand in a desiccator over P_2O_5 for completion of the reaction.

ω,ω'-Bis(3-methoxybenzimidazolia-1-yl)-o-xylene Dichloride (IVb). A mixture of 7 g (0.05 mole) of 1-methoxybenzimidazole and 6 g (0.034 mole) of p-xylylene dichloride was heated on an oil bath at 110-115°C for 15-20 min, after which it was cooled, and the melt was triturated with absolute ether. The solvent was decanted, and the viscous mass was dried over P_2O_5. The substance was then ground to a powder and drenched with absolute benzene for 24 h. The quaternary salt was removed by filtration and again dried over P_2O_5. The yield was 6.5 g (60%).

General Method for the Synthesis of 1-Alkoxymethyl-2-aminobenzimidazoles (IIIa-c). The corresponding 1-alkoxymethyl-3-methoxybenzimidazolium chloride was added in portions (0.025 mole) to 200 ml of liquid ammonia, and the mixture was stirred at −78°C for 1 h, after which the ammonia was evaporated to dryness. The residue was triturated with ether, and the precipitate was removed by filtration and recrystallized.

1-Methoxymethyl-2-aminobenzimidazole (IIIa). This compound was obtained in 66% yield as white crystals with mp 147-148°C (from water), in agreement with the data in [1]. IR spectrum: 3490, 3400, and 1625 cm^{-1}. The hydrochloride was obtained as white crystals with mp 159-160°C (from alcohol with ether). Found: C 46.3; H 6.2; Cl 15.8; N 17.6%. $C_9H_{14}ClN_3O_2 \cdot H_2O$. Calculated: C 46.6; H 6.1; Cl 15.3; N 18.1%.

1-Ethoxy-2-aminobenzimidazole (IIIb). This compound was obtained in 62% yield as white crystals with mp 130-131°C (from benzene). IR spectrum: 3475, 3395, and 1635 cm^{-1}. Found: C 62.5; H 7.0; N 22.6%. $C_{10}H_{13}N_3O$. Calculated: C 62.9; H 6.9; N 22.0%.

1-n-Butoxy-2-aminobenzimidazole (IIIc). This compound was obtained in 62% yield as white crystals with mp 99-100°C (from benzene). IR spectrum: 3475, 3395, and 1630 cm^{-1}. Found: C 66.2; H 8.0; N 19.0%. $C_{12}H_{17}N_3O$. Calculated: C 65.7; H 7.8; N 19.2%. The hydrochloride was obtained as white crystals with mp 169-170°C (from alcohol with ether). Found: C 56.1; H 7.1; Cl 14.5; N 16.0%. $C_{12}H_{18}ClN_3O$. Calculated: C 56.5; H 7.1; Cl 14.0; N 16.5%.

1-n-Pentylthiomethyl-2-aminobenzimidazole (IIId). This compound was obtained by the general method. After evaporation of the liquid ammonia, the residue was treated with 50 ml of water, removed by filtration, and dried to give 1.4 g (82%) of a product with mp 80-81°C (from aqueous alcohol). IR spectrum: 3470, 3370, and 1639 cm^{-1}. Found: C 62.7; H 7.8; N 16.7; S 12.6%. $C_{13}H_{19}N_2S$. Calculated: C 62.6; H 7.7; N 16.9; S 12.8%.

1,3-Bis(2-aminobenzimidazol-1-yl)dimethyl Ether (Va). This compound was obtained by the general method. After evaporation of the ammonia, the residue was triturated with ether, removed by filtration, and treated with 20 ml of water to give 2.3 g (93%) of a mustard-colored precipitate, which was recrystallized from a large amount of water with activated charcoal. The diamine was then washed to remove the yellow impurity by repeated refluxing with chloroform (in 5-ml portions) and removed by filtration. The product had mp 234-235°C (dec.). PMR spectrum (in CF_3COOH): 5.5 (s, 4H, 2-CH_2) and 7.0 (m, 8H). Found: C 62.5; H 5.3; N 27.8%. $C_{16}H_{16}N_6O$. Calculated: C 62.3; H 5.2; N 27.3%.

ω,ω'-Bis(2-aminobenzimidazol-1-yl)-p-xylene (Vb). This compound was obtained by the usual method. After evaporation of the liquid ammonia, the residue was treated with 100 ml of water, removed by filtration, and dried. The diamine was triturated with acetone (50 ml) and removed by filtration to give 3 g (64%) of product. As in the case of other 1-R-2-aminobenzimidazoles, Vb gave a bright-red coloration with a solution of sodium hypochlorite. We were unable to purify Vb because of its limited solubility.

1-Methyl-3-methoxymethylbenzimidazolium Chloride (VIa). A 1.6-h (0.02 mole) sample of methoxymethyl chloride was added to a solution of 2.64 g (0.02 mole) of 1-methylbenzimidazole in absolute benzene (50 ml), during which we observed heating up of the mixture and the formation of a white crystalline precipitate. The latter was removed by filtration, washed with benzene, and dried in a vacuum desiccator over $CaCl_2$. The yield was quantitative. The colorless hygroscopic crystals had mp 88-90°C (from absolute alcohol with ether). Found: Cl 13.2; N 17.0%. $C_{10}H_{13}ClN_2O$. Calculated: Cl 13.2; N 16.7%.

Hydrolysis of 1-Methoxymethyl-3-methoxybenzimidazolium Chloride (VI). A solution of 1.5 g (6 mmole) of salt VI was refluxed for 5 h with 30 ml of water, after which the solution was concentrated to 10 ml, and the precipitated benzimidazolone was removed by filtration, washed with water, and dried. The yield of the benzimidazolone, with mp 299-300°C (from alcohol) was 0.5 g (60%). No melting-point depression was observed for a mixture of this product with a genuine sample, and the IR spectra of the two substances were identical.

LITERATURE CITED

1. T. P. Filipskikh, A. F. Pozharskii, V. N. Koroleva, A. M. Simonova, and É. A. Zvezdina, Khim. Geterotsikl. Soedin., No. 6, 809 (1972).
2. A. F. Pozharskii, A. M. Simonov, and V. N. Doron'kin, Usp. Khim., 47, No. 11, 1933 (1978).
3. S. Takahashi and H. Kano, Chem. Pharm. Bull., 14, 375 (1966).
4. S. Takahashi and H. Kano, Chem. Pharm. Bull., 11, 1375 (1963).
5. M. M. Medvedeva, A. F. Pozharskii, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 10, 1418 (1972).