Chemistry of Heterocyclic Compounds, Vol. 32, No. 10, 1996

N-ARYLATION OF 1-AMINOBENZIMIDAZOLE

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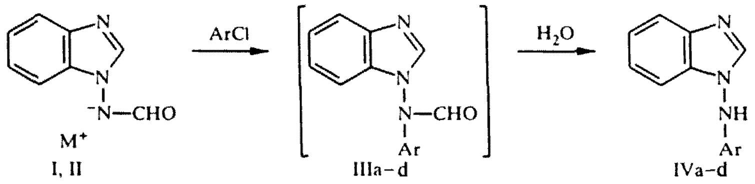
By treatment of the sodium (potassium) salt of 1-formylaminobenzimidazole in acetone or DMF with picryl chloride, 2,4-dinitrochlorobenzene, 2- and 4-nitrochlorobenzenes, we obtained the corresponding 1-arylaminobenzimidazoles. This is the first case of direct arylation of the amino group in N-aminobenzimidazole.

Recently we proposed convenient methods for obtaining 1-dialkylamino- [1] and 1-alkylaminobenzimidazoles [2], based on alkylation of N-anions of respectively 1-amino- and 1-acylaminobenzimidazoles. In developing this work, it seemed of interest to extend this approach to obtaining 1-arylaminobenzimidazoles, which until recently were practically unknown [3]. We should note that the only example of direct arylation of N-aminoazoles before the beginning of this investigation was the synthesis of 2-*o*-nitrophenylaminobenzotriazole described in the patent [4].

As the starting material, we used the sodium or potassium salt of 1-formylaminobenzimidazole I, II, which was reacted with picryl chloride, 2,4-dinitrochlorobenzene, and also with 2- or 4-nitrochlorobenzenes. On stirring the salt I with an equimolar amount of picryl chloride in acetone at room temperature, we isolated in 43% and 36% yield respectively 1-picrylaminobenzimidazole (IVa) and its N-formyl derivative IIIa. Obviously, compound IVa is formed as a result of hydrolysis of the formamido group to the formylamine IIIa by traces of water. Under the same conditions, salt I reacts with 2,4-dinitrochlorobenzene with formation of compound IVb in 52% yield. The corresponding formylamino derivative IIIb could not be isolated in this case. Salt I does not react in acetone with *o*- and *p*-nitrochlorobenzenes; but when it is heated with the potassium salt II in DMF, the reaction occurs and 1-(4-nitrophenyl)amino- and 1-(2-nitrophenyl)aminobenzimidazoles (IVc,d) are formed in 35-40% yield.



I M = Na; II M = K; III—IV a Ar = 2,4,6-$(O_2N)_3C_6H_2$; b Ar = 2,4-$(O_2N)_2C_6H_3$;
c Ar = 4-$O_2NC_6H_4$; d Ar = 2-$O_2NC_6H_4$

1-Arylaminobenzimidazoles IVa-d are rather high-melting crystalline materials of different shades of yellow. They are soluble in dilute aqueous base, forming orange or orange—red solutions. The *o*-nitroarylamino derivative IVd is appreciably more difficult to dissolve in base, which is possibly the result of formation of an intramolecular hydrogen bond with participation of the proton of the NH group and the nitro group. The solubility in base, like the color, suggests conjugation of the electron pair of the amine nitrogen and the nitroaryl substituent.

Interesting information about the structural features of compounds IVa-d are provided by their PMR spectra (Table 1). Thus, the signal from the 2-H proton of the imidazole ring in the spectrum of 1-picrylaminobenzimidazole (9.61 ppm) is located significantly more downfield than in the case of other 1-arylaminobenzimidazoles (8.4-8.5 ppm). This is typical for

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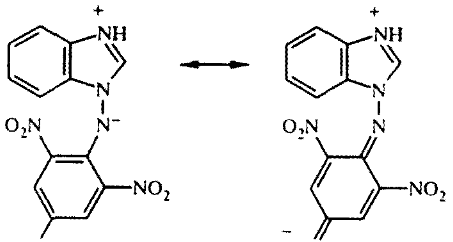
Rostov State University, Rostov-na-Donu 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1347-1351, October, 1996. Original article submitted July 16, 1996.

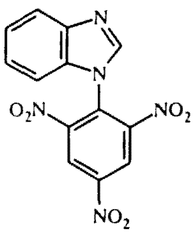
0009-3122/96/3210-1156$15.00

benzimidazolium salts [5], so we can conclude that compound IVa exists in the form of the bipolar ion IVa'. Additional confirmation may be the position of the signals from protons of the picryl group. While in 1-picrylbenzimidazole (V) the 3'-H and 5'-H protons give a singlet at 9.40 ppm, in compound IVa the signal corresponding to these protons is shifted considerably upfield (8.59 ppm), obviously due to their shielding by the amine nitrogen bearing a negative charge.



IVa'

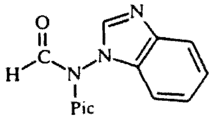
IVa''



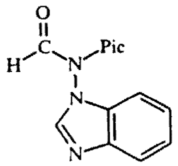
V

Note the weak splitting (by 0.73 Hz) of the signal from the 3'-H and 5'-H protons in the picryl group of compound IVa. This is probably evidence for fixation of the conformation in which these protons become magnetically nonequivalent. It is logical to assume that conjugation of the picryl group and the anionic nitrogen should lead to an increase in the contribution from resonance structures of the type IVa'. In them, the increasing multiple bond character of the N—aryl bond hinders free rotation of the aryl substituent, which also stabilizes the conformation with magnetically nonequivalent protons of the picryl group.

The influence of conformational effects is especially marked in compound IIIa. In its PMR spectrum, the protons of the imidazole ring, the formyl and picryl group give two singlets each with the same intensity ratio, equal to ~2:1. This suggests the existence under the given conditions of two stable conformers (Fig. 1). They probably differ in the position of the substituents about the amide C—N bond (compare with [6]), as was shown in the structures of IIIa' and IIIa''. We think that the form IIIa' predominates in the mixture, since in it the signal from the imidazole proton should be found more downfield due to deshielding by the carbonyl oxygen. It is specifically this signal at 8.59 ppm which is more intense compared with the second peak at 8.28 ppm.

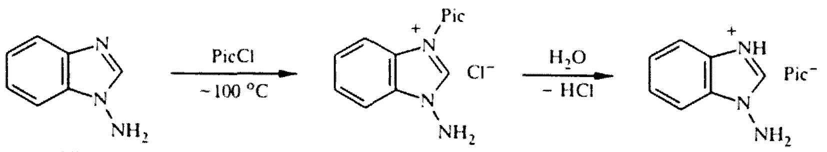


IIIa'



IIIa''

Over the course of the investigation, we also attempted to obtain the 1-amino-3-picrylbenzimidazolium salt (VII) by fusion of 1-aminobenzimidazole (VI) with picryl chloride. As we know, under neutral conditions, the compound VI reacts with alkylating agents at the more nucleophilic pyridinium nitrogen atom [7]. However, in this case we isolated 1-aminobenzimidazolium picrate (VIII) unchanged from the reaction mixture [8]. Probably the N—picryl bond in salts of type VII belong to the class of so-called energy-rich bonds [8] and therefore undergo facile hydrolytic cleavage.



VI

VII

VIII

EXPERIMENTAL

The IR spectra of the compounds were taken on UR-20 (for IIIa, IVb,c, and VIII), IKS-40 (IVa), and Specord IR-75 (for IVd) instruments in Vaseline oil. The PMR spectra were recorded on a Unity-300 instrument in a DMSO-D_6 solution. The

TABLE 1. Proton Chemical Shifts in PMR Spectra of 1-(Nitroaryl)aminobenzimidazoles IVa-d

Compound	Aryl	PMR spectrum, δ, ppm, *J*, Hz			
		2-H (1H, s)	benzene ring	N-aryl	NH (1H, s)
IVa	2,4,6-$(NO_2)_3C_6H_2$	9,61	7,68 (2H, m, 5-H, 6-H), 7,84 (2H, m, 4-H, 7-H)	8,58 (2H, d, 3'-H, 5'-H, $^{4}J_{3'5'}$ = 0,73)	6,49 (broad s)
IVb	2,4-$(NO_2)_2C_6H_3$	8,48	7,32 (2H, m, 5-H, 6-H), 7,45 (1H, m, 7-H), 7,79 (1H, м, 4-H)	6,34 (1H, d, 6'-H, $^{3}J_{5'6'}$ = 9,38), 8,27 (1H, d.d, 5'-H, $^{3}J_{5'6'}$ = 9,67, $^{4}J_{3'5'}$ = 2,35), 8,95 (1H, d, 3'-H, $^{4}J_{3'5'}$ = 2,35)	11,46
IVc	2-$NO_2C_6H_4$	8,46	7,29 (3H, m, 5-H — 7-H), 7,76 (1H, m, 4-H)	6,57 (2H, d, 2'-H, 6'-H, $^{3}J_{2'3'}$ = $^{3}J_{5'6'}$ = 8,79), 8,12 (2H, d, 3'-H, 5'-H, $^{3}J_{2'3'}$ = $^{3}J_{5'6'}$ = 9,16)	10,74
IVd	4-$NO_2C_6H_4$	8,43	7,27 (2H, m, 5-H, 6-H), 7,35 (1H, m, 7-H), 7,76 (1H, m, 4-H)	6,09 (1H, d.d, 6'-H, $^{3}J_{5'6'}$ = 8,43), 6,99 (1H, d.t, $^{4}J_{4'6'}$ = 1,10, $^{3}J_{3'4'}$ = 8,42), 7,48 (1H, d.t, 5'-H, $^{4}J_{3'5'}$ = 1,47, $^{3}J_{4'5'}$ = 7,32), 8,22 (1H, d.d, 3'-H, $^{4}J_{3'5'}$ = 1,46, $^{3}J_{3'4'}$ = 8,42)	10,56

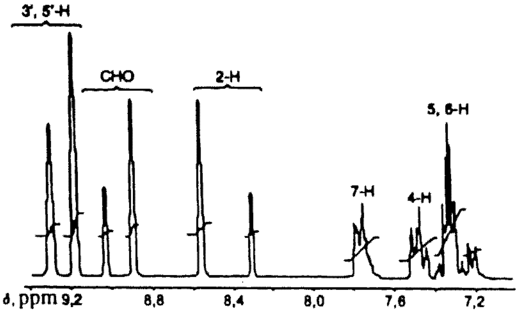


Fig. 1. Proton chemical shifts in PMR spectra of 1-(nitroaryl)aminobenzimidazoles IVa-d.

course of the reactions and the purity of the compounds obtained were monitored by TLC on plates with Al_2O_3 (Brockmann activity IV), eluent chloroform, visualization by iodine vapors. The melting points were measured on a PTP instrument in sealed glass capillaries and were uncorrected.

Salts of 1-Formylaminobenzimidazole (I, II). A solution of 1.1 g (6.8 mmoles) 1-formylaminobenzimidazole [10] and 0.3 g (7.5 mmoles) NaOH or 0.42 g (7.5 mmoles) KOH in 3 ml water was evaporated to dryness under vacuum. The residue was dried for 1.5 h at 100°C. The salts obtained were immediately introduced into the arylation reaction without additional purification.

1-Picrylaminobenzimidazole (IVa). 1.6 g (6.8 mmoles) picryl chloride were added all at once to a suspension of 1.25 g (6.8 mmoles) of the sodium salt of 1-formylaminobenzimidazole (I) in 10 ml absolute acetone with stirring. The bright red reaction mixture was stirred for 2 h at room temperature, after which the precipitate formed was filtered off and washed with 30 ml water. Obtained: 1.05 g (43%) of compound IVa. Light yellow crystals with mp 215-217°C (from ethanol). IR spectrum: 1322 (s) and 1549 (s, NO_2), 1603 (m), and 1629 (m, ring), 3345 cm^{-1} (m, NH). Found, %: C 45.34, H 2.32, N 24.31. $C_{13}H_8N_6O_6$. Calculated, %: C 45.36, H 2.34, N 24.41.

The acetone mother liquor was evaporated to dryness and 0.85 g (36%) 1-picrylformylaminobenzimidazole (IIIa) was obtained. Brown crystals with mp 158-160°C (from butanol). IR spectrum: 1345 (s) and 1545 (s, NO_2), 1600 (m, ring), 1715 (s, CO), 3105 cm^{-1} (s, NH). PMR spectrum: 7.33 (3H, m, 5-H...7-H), 7.75 (1H, m, 4-H), 8.28 (1H, s, 2-H of the conformation IIIa''), 8.59 ppm (1H, s, 2-H of the conformation IIIa'), 8.91 (1H, s, CHO of the conformation IIIa'), 9.02 (1H, s, CHO of the conformation IIIa''), 9.19 ppm (2H, s, 3'-H, 5'-H of the conformation IIIa'), 9.31 ppm (2H, s, 3'-H, 5'-H of the conformation IIIa''). Found, %: C 45.50, H 2.40, N 22.34. $C_{14}H_8N_6O_7$. Calculated, %: C 45.17, H 2.17, N 22.58.

1-(2,4-Dinitrophenyl)aminobenzimidazole (IVb). Obtained similarly to compound IVa from 0.6 g (3.28 mmoles) of the salt and 0.67 g (3.28 mmoles) of 2,4-dinitrochlorobenzene. Yield of compound IVb, 0.51 g (52%). Pale yellow crystals with mp 262-263°C (from DMF—butanol, 3:1). IR spectrum: 1350 (s) and 1500 (s, NO_2), 1585 (m), and 1610 (m, ring), 3110 cm^{-1} (m, NH). Found, %: C 51.83, H 3.26, N 23.21. $C_{13}H_9N_5O_4$. Calculated, %: C 52.18, H 3.03, N 23.40.

1-(4-Nitrophenyl)aminobenzimidazole (IVc). 0.8 g (5.1 mmoles) 4-nitrochlorobenzene were added all at once to a solution of 1 g (5 mmoles) of the potassium salt II in 10 ml absolute DMF. The reaction mixture was stirred for 8 h at 80-85°C, in this case its color gradually changes from colorless to dark red. The solvent was driven off under vacuum, the residue was treated with 15 ml hot chloroform and the insoluble residue was filtered off. The chloroform solution was passed through a column with Al_2O_3 (l = 15 cm, d = 2 cm), eluent chloroform, collecting the yellow fraction with R_f 0.22. Yield, 0.5 g (40%). Yellow crystals with mp 228-229°C (from ethanol). IR spectrum: 1340 (s) and 1490 (s, NO_2), 1590 (m, ring), 3200 cm^{-1} (m, NH). Found, %: C 61.74, H 3.80, N 22.21. $C_{13}H_{10}N_4O_2$. Calculated, %: C 61.41, H 3.96, N 22.04.

1-(2-Nitrophenyl)aminobenzimidazole (IVd). 0.8 g (5.1 mmoles) o-nitrochlorobenzene were added to a solution of 1 g (5 mmoles) of salt II in 10 ml absolute DMF. The mixture was stirred for 8 h at 75-80°C. The solvent was driven off to dryness under vacuum, the residue was treated with 30 ml chloroform and the insoluble residue was filtered off. It was dissolved in 10 ml water and neutralized with concentrated HCl to pH 7. The precipitate of 1-formylaminobenzimidazole was filtered off and washed with 3 ml of water. Yield, 0.25 g (31%). Colorless platelets with mp 204-206°C (from water). There was no depression of the melting point when a sample was mixed with a known sample.

The chloroform solution was chromatographed on a column with Al_2O_3 (l = 15 cm, d = 2 cm), eluent chloroform, collecting the fraction with R_f 0.35. Yield of compound IVd, 0.45 g (35%). Bright yellow prisms with mp 235-236°C (from butanol). IR spectrum: 1335 (s) and 1494 (s, NO_2), 1611 (s, ring), 3338 cm^{-1} (m, NH). Found, %: C 61.27, H 3.72, N 21.93. $C_{13}H_{10}N_4O_2$. Calculated, %: C 61.41, H 3.96, N 22.04.

1-Picrylbenzimidazole (V). Obtained according to the technique in [11]. Orange-yellow crystals with mp 211-212°C (from ethanol). PMR spectrum: 7.33 (3H, m, 4-H—6H), 7.79 (1H, m, 7-H), 8.54 (1H, s, 2-H), 9.40 ppm (2H, s, 3'-H, 5'-H). Found, %: C 47.21, H 2.17, N 21.46. $C_{13}H_7N_5O_6$. Calculated, %: C 47.43, H 2.14, N 21.27.

Attempt at Synthesis of 1-Amino-3-picrylbenzimidazolium Chloride (VII). A mixture of 1.07 g (8 mmoles) 1 aminobenzimidazole (VI) [1] and 0.2 g (8 mmoles) picryl chloride were stirred at 95-100°C for 30 min. The mass at first melted, but after 15 min it solidified. On cooling, the dark brown melt was triturated with 15 ml of a mixture of chloroform and ethanol (1:1), the residue was filtered off. Obtained: 0.9 g (30%) picrate of 1-aminobenzimidazole (VIII). The rich brown crystals with mp 213-216°C (from ethanol). Lit. data: 223-226°C [8]. IR spectrum of the sample obtained was identical to the IR spectrum of the picrate of 1-aminobenzimidazole.

REFERENCES

1. A. F. Pozharskii, V. V. Kuz'menko, A. A. Bumber, É. S. Petrov, M. I. Terekhova, N. L. Chikina, and I. M. Nanavyan, Khim. Geterotsikl. Soedin., No. 2, 221 (1989).
2. O. V. Dyablo, A. F. Pozharskii, and V. V. Kuz'menko, Izv. Akad. Nauk, Ser. Khim., No. 11, 2231 (1995).
3. V. V. Kuz'menko and A. F. Pozharskii, Adv. Heterocycl. Chem., **53**, 85 (1992).
4. R. A. Carboni, US Pat. 3184472; Chem. Abstr., **63**, 4306 (1965).
5. A. F. Pozharskii, V. V. Kuz'menko, C. Foces-Foces, A. L. Llamas-Saiz, R. M. Claramunt, D. Sanz, and J. Elguero, J. Chem. Soc., Perkin Trans. II, No. 3, 841 (1994).
6. L. Salazar, M. Espada, C. Arendano, R. M. Claramunt, D. Sanz, and J. Elguero, J. Org. Chem., **57**, 1563 (1992).
7. V. V. Kuz'menko, V. N. Komissarov, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 6, 814 (1980).
8. R. M. Claramunt and D. Sanz, J. Chem. Soc. Perkin Trans. II, No. 9, 1687 (1993).
9. A. F. Pozharskii, Theoretical Principles of Heterocyclic Chemistry [in Russian], Khimiya, Moscow (1985), p. 160.
10. V. V. Kuz'menko, I. A. Filatova, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 9, 1196 (1992).
11. A. M. Simonov, N. D. Vitkevich, and S. Ya. Zheltonozhko, Zh. Obshch. Khim., **30**, 2688 (1960).