CYANOETHYLATION OF 2-CYANOMETHYLBENZIMIDAZOLE

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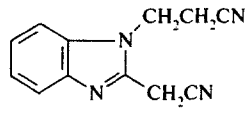
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 33, No. 2, pp. 36 – 39, February, 1999.

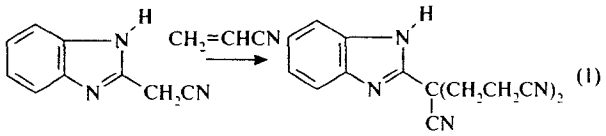
Original article submitted January 27, 1998.

The class of benzimidazole compounds contains some well-known drugs of various groups including spasmolytics (dibazole), neuroleptics (pimozide and droperidol), and antihistamines (astemizole) [1]. Condensation of the pyridine cycle with benzimidazole, that is, the passage to pyridobenzimidazoles, extends the spectrum of biological activity [2, 3]. A convenient intermediate for the synthesis of substituted pyridobenzimidazoles is 1-(2-cyanoethyl)benzimidazol-2-ylacetonitrile (I):



I

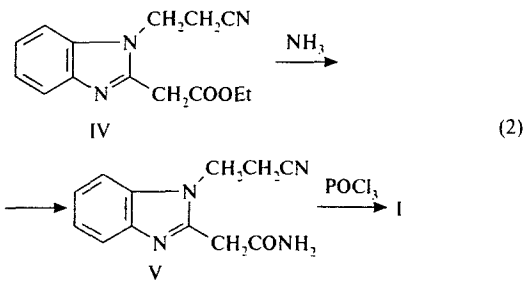
In 1978, Serafin and Konopski [4] performed the condensation of 2-cyanomethylbenzimidazole (II) with excess acrylonitrile (AN) in the presence of a tetraalkylammonium hydroxide catalyst and isolated a product that was assigned the structure of dinitrile I. We have reproduced a procedure described in [4] and obtained the reported product with a melting point of 256 – 257°C, but the subsequent spectroscopic investigations suggest that this compound is α,α-*bis*(2-cyanoethyl)benzimidazol-2-ylacetonitrile (III) rather than dinitrile I:



II III (1)

Indeed, the mass spectra (M^+, $m/z = 263$) suggested that compound III is a product of addition of two AN molecules to compound II. The final assignment of structure III to this product was based on the NMR data (Table 1). The ^1H NMR spectrum of contains a broad singlet of ^1H intensity in the region of weak fields ($\delta = 12.85$ ppm), which is characteristic of the NH proton in N-unsubstituted benzimidazoles. The signals from protons of the benzene ring, represented by doublets of the 4-H and 7-H protons and a multiplet from 5-H and 6-H protons, exhibit strong broadening and pairwise coalescence at high solution concentrations and elevated temperatures. This is explained by accelerated exchange of the NH proton between two equivalent positions. From these data it follows that compound III represents a 2-substituted benzimidazole with both cyanoethyl groups entering into the substituent. This conclusion was confirmed by the ^{13}C NMR spectra, which also elucidated the structure of the substituent as representing a quaternary carbon atom with attached CN group and two equivalent cyanoethyl groups.

Because scheme (1) has proved to be inapplicable for the synthesis of the target dinitrile I, we have used a different scheme (2) proceeding from 1-(2-cyanoethyl)benzimidazol-2-ylacetic acid ethyl ester (IV). The synthesis of ester IV is described in the international patent [5].



IV V (2)

The reactions of ester IV amidation and amide V dehydration proceeded smoothly and yielded 58% of analytically pure dinitrile I (calculated for the initial ester IV); m.p., 151 – 152°C.

The minor products of reaction (1) contained α,α,1-tris(2-cyanoethyl)benzimidazol-2-ylacetonitrile (VI) with a melting point of 171 – 172°C. We have attempted to obtain poly(nitrile) VI by cyanoethylating dinitrile I, but the main product of this reaction (3) was compound III not containing cyanoethyl groups at the cyclic nitrogen atom. According to the ^1H NMR data, the molar ratio of products III and VI is 3 : 1 (see the experimental part below).

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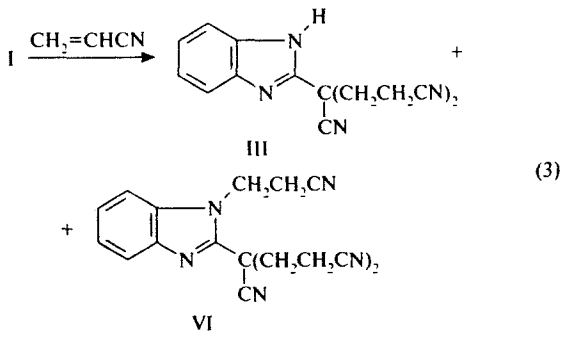
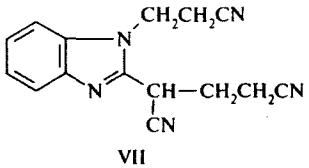


(3)

The results of reactions (1) and (3) prompted us to study the interaction of nitriles I and II with AN in more detail by NMR techniques. The reaction was carried out in pyridine-d_5 (catalyst, $Bu_4N^+OH^-$) at 100°C and at lower temperatures, which allowed us to follow the formation and transformations of intermediate reaction products, including trinitrile VII not isolated from the reaction mixture.



The results of these investigations showed that a primary product in the multistep reaction of nitrile II with AN is dinitrile I. The signals of this compound can be observed in the ^1H NMR spectra of the reaction mixture within 10 – 15 min after adding catalyst to this mixture at room temperature. Dinitrile I (formed both at 100°C and at room temperature) is subject to further conversion and is not accumulated in the reaction mass: the maximum molar fraction of dinitrile I with respect to the initial nitrile II did not exceed 10% (Table 2).

According to the sequence of new signals appearing in the ^1H NMR spectra of the reaction mixture II + AN, the next product in the chain under consideration is trinitrile VII formed as a result of cyanoethylation of the intermediate dinitrile I. Compound VI was identified by the ^1H and ^{13}C NMR spectra of the reaction mixtures II + AN and I + AN (Table 1) measured in various stages of the process. Similarly to dinitrile I, trinitrile VII is formed even at room temperature. Upon a prolonged (30 day) interaction of compound I with AN at room temperature and low concentration of catalyst, the content of product VII exceeded 20%, as confirmed by data on the reaction mass composition presented below:

Compound	I	VII	VI	III
Content, mol %	45	22	22	8

Under the conditions of reactions (1) and (3), trinitrile VII is subject to cyanoethylation with the formation of tetranitrile VI. If the reactions are conducted at a moderate temperature (< 50°C) with a considerable excess of AN, the molar fraction of tetranitrile VI may reach up to 30 in reaction (1) and 80% in reaction (3), after which the value drops in the course of attaining a thermodynamic equilibrium

$$VI \rightleftharpoons III + CH_2{=}CHCN, \quad (4)$$

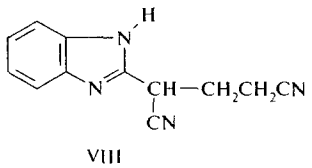
which can be considered as a final stage in the sequence of transformations. The reversible character of reaction (4) is indicated by the appearance of a signal from the protons of compound VI in the NMR spectra measured upon heating a mixture of trinitrile III with AN in pyridine-d_5 in the presence of a catalyst. On the other hand, the spectra of a solution of tetranitrile VI heated under the same conditions without AN show signals due to the protons of compounds III and AN. At an initial tetranitrile VI concentration of 0.068 M, the solution heated to 100°C for 3.5 h comprises a mixture of products with the molar ratio III : VI equal to 4 : 1 and showing a tendency to increase. Thus, at reasonable concentrations of the reagents, the equilibrium (4) is shifted to the right in agreement with the results of syntheses according to schemes (1) and (3).

Another reversible process is the reaction

$$II + CH_2{=}CHCN \rightleftharpoons I \quad (5)$$

Indeed, upon heating an 0.05 M solution of dinitrile I in pyridine-d_5 (with 0.01 M of a $Bu_4N^+OH^-$ — catalyst) for 10 min at 100°C, the ^1H NMR spectrum of the reaction mixture shows signals due to the protons of mononitrile II and AN (the amount of these products relative to dinitrile I being 2 and 1 mol.%, respectively). In addition, the spectrum displays new signals due to the protons of trinitrile VII (0.6 mol.% relative to I). The ratio between the products virtually does not change upon prolonged heating (70 min at 100°C). From this we infer that equilibrium (5) is shifted toward the cyanoethylation product (dinitrile I) – in contrast to reaction (4).

Based on the data obtained, in particular, taking into account the reversibility of reactions (4) and (5), we may conclude that, of the two competitive pathways of the interaction between nitrile II and AN, the reaction of addition at the nitrogen atom is preferred from the kinetic standpoint. On the other hand, the products of cyanoethylation at the carbon atoms of the CH_2CN group are thermodynamically more stable. At the same time, the presence of a cyanoethyl substituent at the nitrogen atom facilitates the AN addition at the carbon atom of the cyanomethyl group, as evidenced, first, by the easy formation of the trinitrile VII and thermodynamically unstable tetranitrile VI in the reactions of I and II with AN and, second, by the absence of any significant amount of product VIII in the reaction mixtures II + AN under both mild and rigid conditions.



It should be noted that the presence of $R_4N^+OH^-$ in the reaction mixture is a necessary factor for the above processes

TABLE 1. Parameters of the NMR Spectra of Compounds I – VII

Compound	Nucleus	Chemical shifts (δ, ppm) for nuclei in positions					
		2	4	7	5.6	1-R	2-R
I[a]	^1H	–	7.70d	7.66d	7.24 – 7.29	4.56 (t, NCH_2), 3.05 (t, CH_2CN)	4.58 (s, CH_2)
	^{13}C	145.5	119.1	110.7	122.9, 122.4	38.9 (NCH_2), 17.9 ($\underline{C}H_2CN$)	17.7 (CH_2), 116.3 (CN)
II[b]	^1H	–		7.69	7.23	[c]	4.53 (s, CH_2)
	^{13}C	144.6		115.0	122.0	–	18.5 (CH_2), 116.0 (CN)
III[a]	^1H	–	7.65d	7.53d	7.19 – 7.29	12.85 (bs, NH)	2.45 – 2.65 (CH_2CH_2)
	^{13}C	148.4	119.3	112.1	123.3, 122.1		43.2 ($\underline{C}CN$), 32.8 ($\underline{C}CH_2$), 13.6 ($\underline{C}H_2CN$)
IV[a]	^1H	–	7.66d	7.58d	7.20 – 7.27	4.58 (t, NCH_2), 3.01 (t, CH_2CN)	4.16 (s, CH_2CO), 4.13 (q, CH_2), 1.20 (t, CH_3)
V[a]	^1H	–	7.65d	7.56d	7.16 – 7.25	4.59 (t, NCH_2), 3.06 (t, CH_2CN)	3.91 (c, CH_2), 7.82 (bs, NH_2)
	^{13}C	150.2	118.7	110.5	122.2, 121.9	39.0 (NCH_2), 17.9 ($\underline{C}H_2CN$)	34.8 (CH_2), 169.5 ($CONH_2$)
VI[a]	^1H	–	7.81d	7.71d	7.28 – 7.35	4.81 (t, NCH_2), 3.13 (t, CH_2CN)	2.55 – 2.75 (CH_2CH_2)
	^{13}C	146.5	119.7	11.6	123.7, 122.9	40.0 (NCH_2), 17.5 ($\underline{C}H_2CN$)	41.0 ($\underline{C}CN$), 32.3 ($C\underline{C}H_2$), 13.0 ($\underline{C}H_2CN$)
VII[b]	^1H	–	7.88	7.62	7.25 – 7.30	4.8 – 4.9 (NCH_2), 3.22 (CH_2CN)	5.33 (CH), 2.6 – 3.0 (CH_2CH_2)
	^{13}C	[d]	119.9	110.2	123.5 [d]	39.3 (NCH_2), 17.9 ($\underline{C}H_2CN$)	28.5 (CH), 27.4 ($CH\underline{C}H_2$), 14.3 ($\underline{C}H_2CN$)

Notes. ^1H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, otherwise, multiplet; ^{13}C NMR spectra: δ = 117 – 120 ppm (CN), 141.0 – 142.5 ppm (C3a), 132.5 – 136.0 ppm (C7a); [a] solvent, DMSO-d_6; [b] solvent, pyridine-d_5; [c] signal vanishes because of proton exchange with water traces in solvent; [d] assignment hindered by close signals from other components; [e] overlap with the signal of solvent.

to take place. In the absence of the catalyst, significant changes in the initial reagent mixture are observed only at a high temperature (100°C) and are probably related to degradation of the benzimidazole nucleus. Apparently, the role of the catalyst consists in ionization of the benzimidazole NH group of molecule II, which leads to the formation of N-anions subjected to the electrophylic attack of AN molecules. However, the process of N-cyanoethylation, in contrast to the C-cyanoethylation, is reversible [6]. Therefore, the thermodynamically controlled interaction of 2-cyanomethylbenzimidazole (II) with AN involves the following sequence of processes:

$$II + CH_2{=}CHCN \rightleftharpoons I \xrightarrow{AKH} VII \xrightarrow{AKH} VI \rightleftharpoons III + CH_2{=}CHCN$$

TABLE 2. Variation of the Content of Cyanoethyl Derivatives of Benzimidazole in the Course of Reaction between 2-Cyanomethylbenzimidazole (II) and Acrylonitrile

Compound	Relative content in reaction mixture (mol.%) at various reaction times			
	0	20 min	50 min	80 min
I	1.5	10	9	8
II	98	60	41	33
III	0	19	34	39
VI	0	6	11	15
VII	0	5	5	5

Notes. Solvent, pyridine-d_5; temperature, 100°C; concentrations, 0.2 M (II), 0.5 M (AN), 0.004 M ($Bu_4N^+OH^-$).

in which the main thermodynamically stable product is α,α-bis(2-cyanoethyl)benzimidazol-2-ylacetonitrile (III).

EXPERIMENTAL PART

The IR spectra of samples prepared as nujol mulls were recorded on a Perkin-Elmer Model 450 spectrophotometer. The NMR spectra (Table 1) were measured on a Varian Unity +400 spectrometer operated at a working frequency of 400 and 100 MHz in the ^1H and ^{13}C modes, respectively. The mass spectra were obtained with a Finnigan SSQ-710 instrument using an ionizing electron beam energy of 70 eV and an ion source temperature of 150°C.

Tetrabutylammonium hydroxide (TBAH) was used in the form of a 1 M solution in dry pyridine. The data of elemental analyses f compounds I, III, V, and VI agree with the results of analytical calculations according to the empirical formulas.

2-Cyanomethylbenzimidazole (II). A mixture of 16.2 g (0.15 mole) of *o*-phenylenediamine, 25.4 g (0.225 mole) of cyanoacetic ester, and 100 ml of *o*-xylene was boiled for 8 – 10 h in a flask equipped with a Dean – Stark trap. Then the mixture was cooled and allowed to stand overnight at room temperature. The precipitate was filtered off and recrystallized from 370 ml of water to obtain 14.2 g (60%) of compound II; m.p. = 207 – 211°C (209 – 210°C [7]); IR spectrum (ν_{max}, cm^{-1}): 2250 (CN), 745 (CH_{arom}); mass spectrum, m/z (I_{rel}): M^+, 157 (100), 156 (30).

α,α-Bis(2-cyanoethyl)benzimidazol-2-ylacetonitrile (III). As recommended in [4], a mixture of 75 ml pyridine, 5.7 g (36 mmole) of compound II, 5.5 ml (83 mmole) of acrylonitrile, and 2 ml of the 1 M TBAH solution (2 mmole) was

boiled for 1.5 h. Then the mixture was cooled to 50 – 60°C, poured into 700 ml of cold water, and allowed to stand for 2 h. The precipitate was filtered off and washed on the filter with water and ethanol. According to the ^{1}H NMR data, the product (8.85 g) comprises a mixture of 93 mol.% trinitrile III and 7 mol.% tetranitrile VI. Recrystallization of the product from 390 ml of acetonitrile yielded 6.3 g (66%) of compound III; m.p. = 256.5 – 257.0°C (257 – 259°C [4]); $C_{15}H_{13}N_5$; IR spectrum (ν_{max}, cm^{-1}): 2240 (CN), 765, 750 (CH_{arom}); mass spectrum, m/z (I_{rel}): M^+, 263 (20), 209 (15), 170 (100).

1-(2-cyanoethyl)benzimidazol-2-ylacetamide (V). A solution of 12.9 g (0.05 mole) of ester IV [5] in 175 ml of methanol was saturated with ammonia to a weight gain of 22 – 23 g (1.3 mole NH_3) and allowed to stand overnight at room temperature in a hermetically sealed flask. This yields 9.4 g (82%) of amide V. The sample for analysis was recrystallized from acetonitrile; m.p. = 203 – 205°C; $C_{12}H_{12}N_4O$; IR spectrum (ν_{max}, cm^{-1}): 3340 (NH), 2240 (CN), 1675, 1610 (C=O), 745 (CH_{arom}); mass spectrum, m/z (I_{rel}): M^+, 228 (40), 211 (20), 185 (40), 184 (15), 144 (15), 132 (100).

1-(2-cyanoethyl)benzimidazol-2-ylacetonitrile (I). To a solution of 4.5 g (20 mmole) of amide V in 170 ml of boiling dioxane was gradually added (over 10 min) a solution of 5.4 ml (60 mmole) of $POCl_3$ in 30 ml dioxane and the mixture was boiled with stirring for 1 h. The resulting suspension was evaporated in vacuum. The residue was treated with a solution of 20 g $NaHCO_3$ in 350 ml water. The aqueous solution was repeatedly extracted with chloroform. The chloroform was distilled off and the residue recrystallized from 96% ethanol to obtain 3 g (71%) of dinitrile I; m.p. = 151 – 152°C; $C_{12}H_{10}N_4$; IR spectrum (ν_{max}, cm^{-1}): 2245 (CN), 770, 750 (CH_{arom}); mass spectrum, m/z (I_{rel}): M^+, 210 (40), 170 (100).

α,α,1-Tris(2-cyanoethyl)benzimidazol-2-ylacetonitrile (VI). A mixture of 2.1 g (10 mmole) of dinitrile I, 2 ml (30 mmole) of acrylonitrile, 20 ml pyridine, and 1 ml of the 1 M TBAH solution (1 mmole) was boiled for 2 h (110 – 112°C), poured hot into 175 ml of water with crushed ice, and allowed to stand for 2 h. The precipitate (2.2 g) was filtered off; according to the ^{1}H NMR data, the product comprises a mixture of 75 mol.% of trinitrile III and 25 mol.% tetranitrile VI. Recrystallization of the product from acetonitrile yielded 1.0 g (38%) of compound III; m.p. = 255 – 256°C. The mother liquor was evaporated, the residue treated with ethanol, and the precipitate filtered off and separated by fractional distillation to obtain 0.3 g of compound VI; $C_{18}H_{16}N_6$; m.p., 170.5 – 171.5°C (from acetonitrile – ethanol mixture); IR spectrum (ν_{max}, cm^{-1}): 2245 (CN), 765, 745 (CH_{arom}); mass spectrum, m/z (I_{rel}): M^+, 316 (20), 276 (10), 223 (100).

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