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Alternative and efficient method for the preparation of 2-acetamidobenzimidazoles

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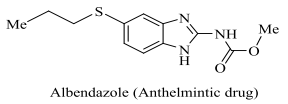
Abstract

An alternative method for the synthesis of acetamidobenzimidazoles (**3**-**6**) has been developed, including the reacylation of methylbenzimidazol-2-ylcarbamate (carbendazim, MBC, **1**) under the action of aliphatic and aromatic carboxylic acids. It was shown that with an increase in the size of the alkyl group and the reaction temperature (in the case of butyric acid), due to the decomposition of the resulting product, the yield of the target acyl products sharply decreases. The obtained compounds are homologues of the anthelmintic drug - N-(1H-benzimidazol-2-yl) acetamide (2-acetylaminobenzimidazole, **3**). A possible mechanism of reacylation is presented.

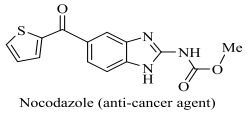
Keywords: methylbenzimidazol-2-yl carbamate, 2-aminobenzimidazole, carboxylic acids, 2-acetylaminobenzimidazole, reacylation, crystal structure, x-ray diffraction

Introduction

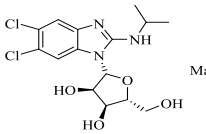
Benzimidazoles, their derivatives and anologues are important from both theoretical and practical points of view. To date, a sufficient number of biologically active compounds have been found among them, which are widely used in veterinary and medical practice as anthelmintic [1, 2], anticancer [3], cholinesterase inhibitors [4], anti-inflammatory [5], antimalarial [6], antiviral [7] and antimicrobial [8] agents. Analysis of the literature data shows that 2-aminobenzimidazole (**2**) is an interesting and important object in terms of studying chemical modifications of an ambifunctional group with endocyclic amino groups at positions 1 and 3, benzene ring, exocyclic amino group, and searching for potential biologically active compounds [9-11]:



Albendazole (Anthelmintic drug)



Nocodazole (anti-cancer agent)



Maribavir (antiviral drug)

Studies have shown that some alkyl esters of benzimidazolyl-2-carbamic acid have fungicidal activity against fungal diseases of various plants. It was found that the introduction of substituents into the benzene ring decreases its activity.

The acylation of 2-aminobenzimidazole (**2**) with acid chlorides was studied. Depending on the conditions, these reactions can proceed in two directions: at endocyclic and at exocyclic nitrogen atoms [12]. According on the electron density of the 2-aminobenzimidazole molecule on nitrogen atoms, nitrogen in position 1 has the highest basicity of the imidazole ring [13]. It is known that the acylation reaction at room temperature usually gives 1-acylbenzimidazoles, while heating predominantly 2-acylbenzimidazoles are formed [13]. 2-Aminobenzimidazole (**2**) is also easily acylated with acid chlorides in a medium of dry inert solvents (benzene, chloroform) in the presence of acid acceptors - triethylamine. Acylation can proceed with the formation of two products simultaneously, which differ in solubility in organic solvents. It should be noted that both isolated isomers in the mass spectrum have the same fragmentation. This is probably due to the migration of the acyl group from the less stable position at N1 to the nitrogen of the amino group (position 2) under the action of electron impact. This phenomenon is also observed when the N1 acyl derivative is heated at 140°C for 1 h [14]. The most difficult reaction is with substituents in the *o*-positions, apparently under the influence of the spatial

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factor. With an increase in the electronegativity of substituents in benzoyl chlorides, the yields of acyl products decrease.

Thus, N-acetylamino-benzimidazoles were obtained mainly by two methods: by acylation of 2-aminobenzimidazole (**2**) with acid chlorides in the presence of triethylamine or by cyclization of *o*-phenylenediamine with acyl cyanamides [9]. Therefore, the purpose of this work is to develop alternative methods for the synthesis of new acetyl derivatives of benzimidazoles, by the reaction of methylbenzimidazol-2-yl carbamate (**1**) with carboxylic acids, to identify factors influencing the course and direction of the reaction, as well as the yield of the resulting isomers.

Experimental

IR spectra were recorded on a System 2000 IR Fourier spectrometer in KBr tablets, ^{1}H NMR spectra - on a Unity-400+ instrument (operating frequency 400 MHz, internal standard TMS, δ scale) solvents - CD_3OD, CD_3COOD, DMSO-d_6. The purity of the products and the progress of the reaction were monitored by TLC on Silufol UV-254 in the system - chloroform: benzene: methanol - 5: 1.5: 1.

High resolution mass spectrum conditions (HR-EI-MS: GCT (Micromass)) are direct sample injection, ionization energy 70 eV and source temperature 250°C. Mass spectra were obtained on a Micromass LCT premier with a LockSpray direct injection source and a Q-TOF (Waters) LC-MS/MS instrument with an ESI source (3 kV, 250°C). In all cases, acetonitrile was used as a solvent.

Hydrolysis of methylbenzimidazol-2-yl carbamate (1): obtaining 2-aminobenzimidazole (2). In a round-bottom flask equipped with a reflux condenser, are placed 100 g (0.52 mol) of methylbenzimidazol-2-yl carbamate (**1**) and 500 ml of water. A solution of 50 g (1.25 mol) NaOH in 150 ml of water is added to the suspension. The reaction mixture is boiled for 2 hours until a homogeneous solution is formed, then 10 g of activated carbon is added, boiled for 30 minutes and hot filtration is carried out. The filtrate is carefully acidified with 40 ml of concentrated hydrochloric acid and cooled to room temperature. The precipitate was filtered off, washed with cold water, dried at 100°C, and 55.7 g (80%) of 2-aminobenzimidazole (**2**) with m.p. 231-233°C.

Synthesis of N-(1H-benzimidazol-2-yl) acetamide (3) (General method). 10 g (0.052 mol) of methylbenzimidazol-2-yl carbamate (**1**) was dissolved in 36 mL of glacial acetic acid (d=1.0498 g/cm^3), the reaction mixture was heated in an oil bath at the boiling point of glacial acetic acid (117°C) for 8 hours. Then the acid was partially (40%) distilled off and the reaction mixture was left overnight at room temperature. The precipitated crystals were filtered off, washed with alcohol, and dried. There was obtained 9.0 g (98%) N-(1H-benzimidazol-2-yl) acetamide (**3**) with m.p. 282-284°C (ethanol), Rf 0.68 (chloroform: benzene: methanol - 5: 1.5: 1). ^{1}H NMR spectrum (400 MHz, CD_3COOD): 11.55 (1H, s, -HN-C=O), 7.56-7.60 (2H, AA`BB`-type, H-4.6) , 7.28-7.32 (2H, AA`BB`-type, H-5.7), 2.27 (3H, s, CH_3). IR spectrum (KBr, cm $^{-1}$): 3150, 3400 (NH, NH_2), 1688 (C=O), 1638 (C=N), 1584 (CN), 1456 (CH_3), 1524 (C=C). MS (70-eV) m/z (%): 175 (14) $[M]^+$, 134 (3.2), 133 (100) $[M\text{-}COCH_2]^+$, 105 (10.4). ESI-HRMS: calculated for $C_9C_9N_3O$: 175.0746, found 175.0755.

N-(1H-Benzimidazol-2-yl) butyramide (4). The reaction was carried out similarly to the above method, 10 g (0.052 mol) of methylbenzimidazol-2-yl carbamate (**1**) was dissolved in 40 ml of butyric acid (d=0.9563 g/cm^3), the reaction mixture was heated at the boiling point of the acid (163.5°C) within 8 hours. The reaction mixture was left overnight at room temperature. The precipitated crystals were filtered off, washed, dried, and 7.13 g (61.2%) of the product (**4**) is obtained with m.p. 250-252°C (ethanol), Rf=0.86 (chloroform: benzene: methanol - 5: 1.5: 1). ^{1}H NMR spectrum (400 MHz, DMSO-d_6): 7.38 (2H, br.s, H-4.7), 7.02 (2H, AA`BB`-type, H-5,6), 2.37 (2H, t, J=7.35, O=C-CH_2), 1.56-1.65 (2H, m, $CH_2CH_2CH_3$), 0.88 (3H, t, J=7.34, $CH_2CH_2CH_3$). IR spectrum (KBr, cm^{-1}): 3361 (NH), 1683 (C=O), 1630 (C=N), 1564 (CN), 2878, 2962 (CH_2, CH_3), 1513 (C=C). MS (70 eV) m/z (%): 226 (100) $[M]^+$, 212 (3.8) ESI-HRMS: calculated for $C_{11}C_{13}N_3O$: 226.0956, found 226.0956.

N-(1H-Benzimidazol-2-yl) isobutyramide (5). Similarly to the above-described method, 10 g (0.052 mol) of methylbenzimidazol-2-yl carbamate (**1**) was dissolved in 40 ml of isobutyric acid (d=0.965 g/cm^3). The reaction mixture was heated in an oil bath at the reflux temperature of butyric acid (155°C) for 8 hours. The reaction mixture was left overnight at room temperature. The precipitated crystals were filtered off, washed, dried, and 8 g (86.8%) of product (**5**) with m.p. 176-178°C (DMF), Rf=0.28 (chloroform: benzene: methanol - 5: 1.5: 1). ^{1}H NMR spectrum (400 MHz, CD_3OD): 7.22 (2H, AA`BB`-type, H-4,7), 7.07 (2H, AA`BB`-type, H-5,6), 2.05 (1H, m, $CH(CH_3)_2$), 0.9 (6H, d, J=6.4, $CH(CH_3)_2$). IR spectrum (KBr, cm^{-1}): 3360 (NH), 1683 (C=O), 1630 (C=N), 1564 (CN), 2862, 2963 (CH, CH_3), 1513 (C=C).

Interaction of methylbenzimidazol-2-yl carbamate (1) with benzoic acid. Preparation of N-(1H-benzimidazol-2-yl) benzamide (6) and 2-amino-1*H*-benzo[d]imidazole-3-benzoate (7). The reaction was carried out similarly to the above method, 5 g (0.026 mol) of methylbenzimidazol-2-yl carbamate (**1**) was dissolved in 5 ml of DMF, 4 g

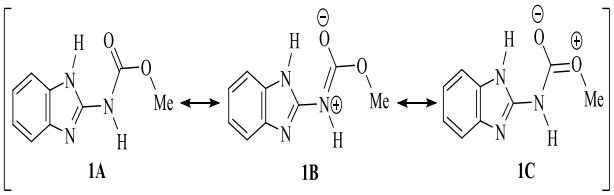
(0.032 mol) of benzoic acid were added, and the mixture was heated in an oil bath at the boiling point of DMF (153°C) within 5 hours. The reaction mixture was left overnight at room temperature. The precipitated crystals were filtered off, washed with alcohol, and dried. Obtained 3.2 g (51.6%) of N-(1H-benzimidazol-2-yl) benzamide (**6**), m.p. 225-227°C, Rf=0.75 (chloroform: benzene: methanol - 5:1.5:1). The filtrate was distilled off to dryness, the residue was recrystallized from alcohol, and 0.8 g (12.9%) of the salt - 2-amino-1*H*-benzo[d]imidazole-3-benzoate (**7**) is obtained with m.p. 242-243°C, Rf=0.81 (chloroform: benzene: methanol - 5: 1.5: 1).

^{1}H NMR spectrum (400 MHz, DMSO-d_6): 8.8 (2H, dd, J=2.8, J=6.98, H-2`, 6`), 7.55 (1H, tt, J=2.5, J=7.4, H-4`), 7.47 (2H, tt, J=2.15, J=7.6, H-3`,5`), 7.38-7.43 (2H, AA`BB`-type, H-4.7), 7.06-7.10 (2H, AA`BB`-type, H-5,6). IR spectrum (KBr, cm $^{-1}$): 3437 (NH), 1658 (C=O), 1631 (C=N), 1566 (C-N), 1516 (C=C). MS (70 eV) m / z (%) (Compound **6**): 237 (13) $[M]^+$, 209 (11.7), 105 (100), 77 (34). ESI-HRMS: calculated for $C_{14}C_{11}N_3O$: 237.0902, found 237.0902. (Compound **7** - salt): 237 (40) $[M]^+$, 236 (11.7), 209 (11.7), 105 (100), 77 (34). ESI-HRMS: calculated for $C_{14}C_{11}N_3O$: 237.0902, found 237.0901.

Results and discussion

The object of this work is methylbenzimidazol-2-ylcarbamate (1), which is the active ingredient of the drug carbendazim (bavistin, derozol, olgin, MBC), which has been used until now as a systemic fungicide from the benzimidazole class. It is obtained by the reaction of 2-aminobenzimidazole (**2**) with methyl chlorocarbonic acid in pyridine in good (70%) yield.

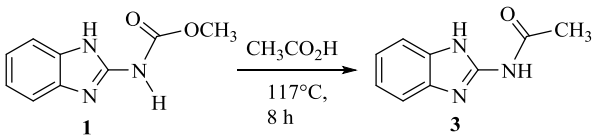
One of the important features of the organic carbamates is their existence in three possible resonance forms (**1A, 1B, 1C**), as a result of which carbamates are highly stable [15-18]:



The structure shows that carbamates are very similar in structure to amides. In addition, the carbamate (amidoesteric) fragment plays an important role from the point of view of medicinal chemistry; they are often found not only in drugs, but also in prodrug molecules [19].

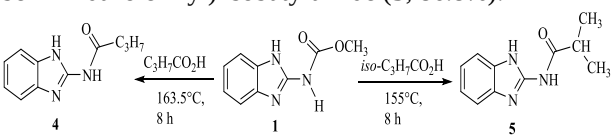
In order to synthesize of new acetylamino-benzimidazoles with potential anthelmintic activity, we studied the reaction of methylbenzimidazol-2-yl carbamate (**1**) with aliphatic and aromatic carboxylic acids under various conditions (temperature, reaction duration). To reveal the influence of the nature of substituents on the reactivity, acetic, butyric, isobutyric and benzoic acids were used as carboxylic acids [20-25].

We carried out the reaction of methylbenzimidazol-2-yl carbamate (**1**) with glacial acetic acid at the boiling point of the acid (117°C) for 8 hours. Acid is taken in excess - as a reagent and solvent:



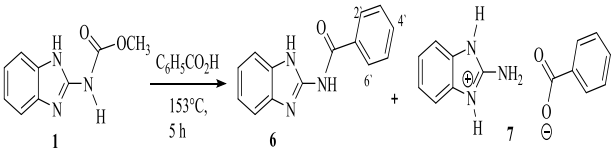
As a result of the reaction, the product, N-(1H-benzimidazol-2-yl) acetamide (**3**), was synthesized in almost quantitative yield (98%); the formation of the isomeric N3-acetyl derivative was not detected.

Continuing similar studies, the interaction of the initial carbamate (**1**) with butyric and isobutyric acids was studied and acylation products were obtained only at exocyclic amino groups - N-(1H-benzimidazol-2-yl) butyramide (**4**, 61.2%) and N-(1H-benzimidazole-2-yl) isobutyramide (**5**, 86.8%):



The reactions in butyric (bp 163.5°C) and isobutyric acids (bp 155°C) were carried out analogously to the above method - by boiling for 8 hours. The results show that with an increase in the reaction temperature (in the case of butyric acid), the yield of the acyl product sharply decreases, apparently due to the decomposition of the resulting product (**4**).

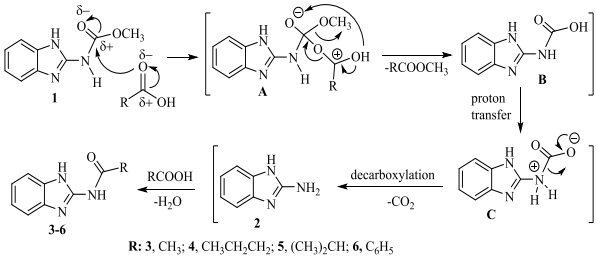
We were interested in studying the interaction of methylbenzimidazol-2-ylcarbamate (**1**) with benzoic acid (BA). The reaction was carried out by boiling a mixture of equimolar amounts of reagents **1**: BA in dimethylformamide (bp 153°C) for 5 hours. As a result of the reaction, N-(1H-benzimidazol-2-yl) benzamide (**6**, 51.6%) and a relatively low yield salt of the intermediate 2-aminobenzimidazole (**2**) with benzoic acid - 2-amino-1H-benzo[d]imidazole -3-yl benzoate (**7**, 12.9%):



It was found that in the case of benzoic acid, the reaction products are formed in relatively low yields. This can be explained by steric factors. The synthesis of analogous salts of 2-aminobenzimidazole with 3-phenylpropic and 2-octinic acids was carried out recently, and their structures in crystals were studied [26].

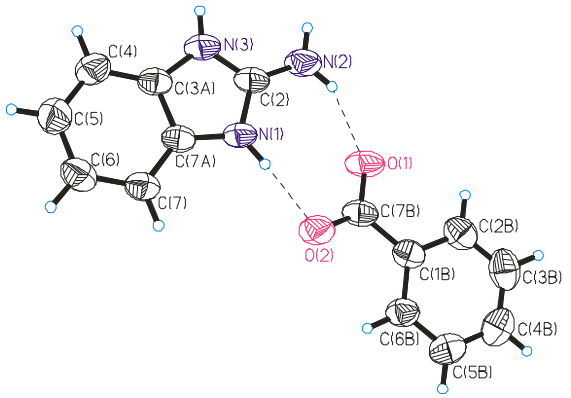
Thus, it was revealed that as a result of the reaction from the initial carbamate (**1**) with aliphatic carboxylic acids of *normal* and *iso*-structure, as well as benzoic acid, 2-acetamides are formed (**3-6**).

The probable reaction mechanism is shown below: the reaction begins with a nucleophilic attack of the carboxylic acid on the starting carbamate with the formation of a salt-like intermediate **A**, which, after cleavage of the methyl ester of the used carboxylic acid, is easily converted to (1H-benzimidazol-2-yl) carbamic acid (**B**). It is known, that carbamic acids are readily decomposed through the transfer of a proton of the carboxyl group with the formation of an ionic salt (**C**) of the amino acid type, which, after decarboxylation, is converted to 2-aminobenzimidazole (**2**):



Further, the resulting intermediate amine (**2**) is acylated at the exocyclic amino group to form the corresponding 2-acetamides (**3-6**).

X-ray diffraction analysis of crystals of compound **7** confirmed that it is indeed a salt of 2-amino-1,3-dihydro-2*H*-benzimidazole with benzoic acid. The spatial structure and numbering of atoms of the 1,3-dihydro-2*H*-benzimidazol-2-iminium benzoate molecule are shown in Figure 1.



In the crystal structure of 2-amino-1,3-dihydro-2*H*-benzimidazole, the (N1-N3/C2/C3A/C4-C7/C7A) part of the molecule is flat with an accuracy of ±0.0123 Å. The dihedral angles between the planar benzene ring (with an accuracy of ±0.0065) and the carbonyl fragment (C7B/O1/O2) in the benzoate ion is 17.4 (4)°. This arrangement of two fragments is observed in analogous structures like 2-amino-1*H*-benzimidazolium 3-phenylpropynoate and 2-amino-1*H*-benzimidazolium oct-2-ynoate [26]. As follows from the figure 1, 2-amino-1,3-dihydro-2*H*-benzimidazole and benzoate fragments are observed intermolecular hydrogen bonds of the type N1—H1A…O2 and N2—H2B…O1. The parameters of this hydrogen bond are as follows: distances N1…O2 2.778(3), H…O2 1.92 Å, angle N1—H… O2 174º (*x*, *y*, *z*); distances N2…O1 2.808(3), H2B… O1 2.02 Å, angle N2 — H…O 152º (*x*, *y*, *z*).

X-ray structural study. Crystals of 1,3-dihydro-2*H*-benzimidazol-2-iminium benzoate (**7**) were grown from ethanol by slow evaporation of the solvent at room temperature. The unit cell parameters were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα radiation (T= 290 K). Monoclinic system, space group $P2_1/c$, a=9.792 (2), b=10.877 (2), c=12.353 (3) Å; β=105.86(3)°, V=1265.6(5) Å^3, M=255.27, Z=4, $d_{calc.}$ = 1.340 g/cm^3, μ = 0.757, scan area $4.69 \leq \theta \leq 76.08^o$, crystal dimensions 0.53 x 0.30 x 0.25 mm. A three-dimensional set of 4529 reflections (2541 independent) was obtained. The absorption correction was introduced using the SADABS program [27].

The structure was solved by direct methods using the SHELXS-97 software package [28], the structure refinement calculations were performed using the SHELXL-2014/8 program [29]. All non-hydrogen atoms were refined by the method of least squares in F^2 in the full-matrix anisotropic approximation to R 0.0483, R_W 0.1052 using 1519 reflections (S 1.023). The positions of hydrogen atoms were established geometrically and refined with fixed parameters of isotropic displacement $U_{iso}=nU_{eq}$, where n=1.2 for methylene groups and an aromatic ring (U_{eq} is the equivalent isotropic displacement parameter of the corresponding carbon atoms).

The results of the single crystal X-ray diffraction analysis have been deposited with the Cambridge Structural Database as a CIF-file (CCDC 2049631).

Conclusions

It was revealed for the first time that the reaction of methylbenzimidazol-2-ylcarbamate (**1**) with aliphatic carboxylic acids of *normal* and *iso*-structure, as well as benzoic acid, proceeds by reacylation; thus, new 2-acetamides are formed. It was shown that with an increase in the size of the alkyl group and the reaction temperature (in the case of butyric acid), due to the possible thermal decomposition of the reaction product forming the reaction, the yield of the target acyl products sharply decreases. A possible mechanism of reacylation is presented.

Conflicts of interest

There are no conflicts to declare.

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