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FORMATION OF UNSYMMETRICAL 2-(DIACYLMETHYLENE)-2,3-DIHYDRO-1H-BENZIMIDAZOLES DURING ACIDOLYSIS OF 1-BENZOYL-2-(β-BENZOYLOXY-β-PHENYLVINYL)-1H-BENZIMIDAZOLE

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The reaction of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole with carboxylic acids was investigated. A convenient method was developed for the synthesis of unsymmetrical 2-(diacylmethylene)-2,3-dihydro-1H-benzimidazoles. 2-(4-Pyrazolyl)-1H-benzimidazoles were obtained by the reaction of 2-(benzoylformylmethylene)-2,3-dihydro-1H-benzimidazole with hydrazine.

Keywords: benzimidazoles, pyrazoles, acidolysis, C-acylation.

The acylation of 2-methyl-1H-benzimidazole (**1**) with the Vilsmeier reagent [1] and phthalic anhydride [2] takes place at the methyl group with the formation of symmetrical 2-(diacylmethylene)-2,3-dihydro-1H-benzimidazoles. Acylation with benzoyl chloride in the presence of triethylamine leads with a quantitative yield to the product of N,C,O-tribenzoylation 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (**2**), which when heated with benzoic acid **3a** forms 2-(dibenzoylmethylene)-2,3-dihydro-1H-benzimidazole **4** [3]. The mechanism of the transformation can probably be represented as acidolysis with the intermediate formation of 2-phenacyl-1H-benzimidazole (**4**) and benzoic anhydride **5a**, the reaction of which leads to the formation of the symmetrical diketone **6a**. On the basis of these ideas in the present work we investigated the reaction of compound **2** with carboxylic acids in order to obtain the previously unknown unsymmetrical 2-(diacylmethylene)-2,3-dihydro-1H-benzimidazoles.

We investigated the acidolysis of *p*-nitrobenzoic, phenoxyacetic, acetic, trifluoroacetic, and formic acids **3b-f**. This secured selective acylation of the investigated compound by the mixed anhydrides of benzoic and other employed acids formed intermediately in the reaction. Optimum conditions were found for the formation of the desired compounds **6b-f** (molar ratio of reagents 1:1 or a larger amount of the acid, solvent dioxane or an excess of the acid, temperature 95-105°C, reaction time 1-4 h, yields 59-85%). The choice of reagent ratio can be determined by the solubility of the initial acid, which is important for facilitating the isolation of the final product in the individual state. With the reagents in a molar ratio of 1.1 the reaction is complete in 3-4 h and with an excess of the acid in 1 h.

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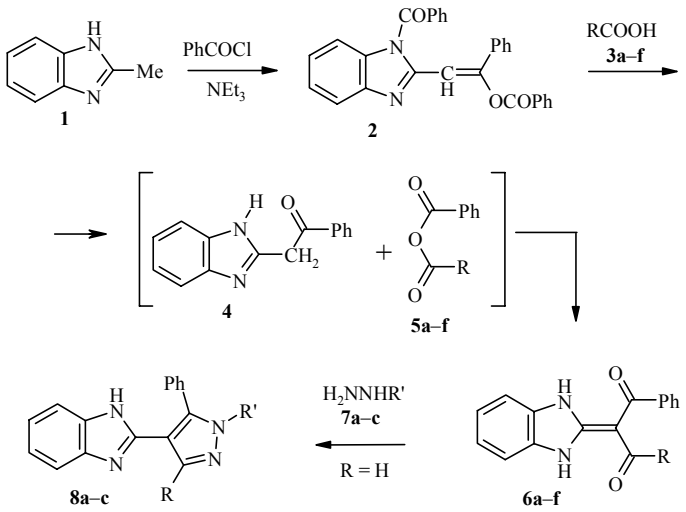
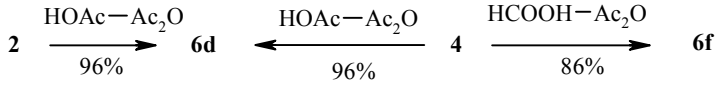


3, **5**, **6 a** R = Ph, **b** *p*-$C_6H_4NO_2$, **c** $PhOCH_2$, **d** Me, **e** CF_3, **f** H;
7, **8 a** R' = H, **b** Ph, **c** *p*-$C_6H_4NO_2$

The yields of the desired compounds can be increased. It was established, for example, that during the acidolysis of compound **2** with acetic acid in the presence of acetic anhydride the yield of the C-acetyl derivative **6d** is increased from 85 to 96%.



Compound **6d** is formed with a 96% yield during the C-acetylation of compound **4** [obtained by the morpholinolysis of compound **2** [3]] with a mixture of acetic acid and its anhydride. The C-formyl derivative **6f** was obtained similarly with an 86% yield from compound **4** and a mixture of formic acid and acetic anhydride.

The obtained results partly confirm the presented acidolysis scheme, but the two-stage mechanism must be considered over-simplified. The sequence of the acidolysis of the nonequivalent O- and N-acyl bonds has not been explained. Besides, the reaction details are not significant enough for a final result. The motivating force for the transformations of the initial and intermediate compounds with labile O- and N-acyl bonds is probably the formation of thermodynamically compounds containing stronger carbon-acyl bonds.

2-Cyanomethyl-1H-benzimidazole is acylated by acid anhydrides at the methylene group [4], and the discussed C-acylation of compound **4** is therefore a normal phenomenon. However, the advantage of our method is the fact that more readily available initial substances are used in place of compound **4** and the anhydrides. A limitation of the reaction is that it only makes it possible to introduce a benzoyl or more electrophilic acyl group. The obtained products (β-carbonyl compounds) can provide a source of previously unobtainable heteroarylbenzimidazoles. We found that compound **6f** reacts with the hydrazines **7a-c** to form 2-(4-pyrazolyl)-1H-benzimidazoles **8a-c**.

The obtained new compounds **6b-f** and **8a-c** are stable crystalline substances. Compound **6b** like its dibenzoyl analog **6a** is yellow. Compounds **6d**,**f** are pale-yellow, and **6c**,**e** and **8a-c** are colorless substances. Compounds **6b-d**,**f** are poorly soluble in organic solvents, and their trifluoromethyl analog **6e** reacts with boiling 2-propanol to form a homogeneous solution. The pyrazole **8a** is readily soluble in alcohols, and its derivatives **8b**,**c** are less soluble compounds.

The structure of the synthesized new compounds was confirmed by the data from IR and ^{1}H NMR spectroscopy (see the experimental section and Table 1). The extremely informative proton spectra, which make it possible to reveal the stereochemical details, are examined in greater detail. Thus, the spectral characteristics of the unsymmetrical β-dicarbonyl compounds **6b-f** and their symmetrical dibenzoyl structural analog **6a** [3] have common features. In the new diketones the symmetry of distribution of electron density in the benzimidazole ring is retained. The narrow multiplet signal of 5- and 6-H appears at 7.24-7.31 ppm, and that of 4- and 7-H at 7.67-7.75 ppm; the protons at positions 1 and 3 are equivalent and resonate in the form of a common singlet at 12.94-13.20 ppm. This confirms the enaminocarbonyl structure of the compounds stabilized by two intramolecular hydrogen bonds.

The phenyl rings in the acetyl and formyl derivatives **6d**,**f** appear as a narrow multiplet at 7.47 and 7.48 ppm (as in toluene [5]), i.e., they are turned from the plane of the molecule so much that they hardly make any contact with the adjacent carbonyl group. In these compounds the substituents CH_3 and H at the second carbonyl group are probably in the field of the screening effect of the phenyl ring and resonate at 1.64 and 9.31 ppm, i.e., upfield from the position expected for the methyl ketone and aldehyde (2.10 and 9.96 ppm [5]). On the other hand in the dibenzoyl compound **6a** and its *p*-nitrobenzoyl, phenoxybenzoyl, and trifluoroacetyl analogs **6b**,**c**,**e** the phenyl rings appear in a broad region with resolution of the individual multiplet signals for the protons at the *ortho*, *meta*, and *para* positions. In these compounds between the substituents at the carbonyl groups there is probably mutual repulsion, due to unfavorable overlap of the orbitals of the aromatic rings and the electronegative atoms. This removes the dicarbonylmethylenebenzimidazole fragment of the molecule from the coplanar state and secures partial conjugation of the phenyl ring with the adjacent C=O group.

According to data from the ^{1}H NMR spectra, the pyrazole **8a** is characterized by tautomerism due to proton migration between the nitrogen atoms of the pyrazole ring. This agrees with previously obtained data on the tautomerism of 2-(4-pyrazolyl)benzimidazoles [6]. We note that in the hydrochloride of the compound the tautomeric interconversions are accelerated so much that the tautomeric forms do not appear individually. In the base, however, the singlet signals of the protons of the amino groups and also of the pyrazole ring are doubled. The ratio of the integral intensities is 1:1, demonstrating the energy equivalence of the tautomeric forms. At first sight this conclusion contradicts data on the tautomerism of 3(5)-methyl-5(3)-phenylpyrazole, which indicate that the proton of the N–H bond is removed preferentially from the phenyl ring [7, 8]. Substitution of the methyl group by the hydrogen atom having less steric hindrances should probably demonstrate even more strongly the energy nonequivalence of the tautomeric forms, but the benzimidazole ring probably has a substantial effect on the tautomerism of compound **8a**. As acceptor it must enter into conjugation with the electron-donating pyrazole ring. Thus, there is a tendency to bring both heterocycles into one plane. As a result the phenyl ring experiences disturbances on the part of the benzimidazole and is forced to turn away from the plane of the pyrazole ring, losing here the electronic influence on the whole molecule and the steric influence on the nearest environment, thereby securing the equivalence of the pyrazole nitrogen atoms. The phenyl ring retains its conjugation with the adjacent π-electron-deficient carbon atom of the pyrazole ring, and its *ortho*, *meta*, and *para* protons appear separately in the spectrum.

In pyrazoles **8b**,**c** the C-phenyl ring experiences hindrances on the part of the benzimidazolyl and N-aryl substituent and is turned fully away from the plane of the pyrazole ring, appearing in the ^{1}H NMR spectrum in the form of a narrow multiplet at 7.36 and 7.45 ppm respectively (like the phenyl group of toluene). It is thus confirmed that the 5-phenyl-substituted pyrazoles and not the 3-phenyl-substituted isomers are obtained. Thus, previously unknown unsymmetrical 2-(diacylmethylene)-2,3-dihydro-1H-benzimidazoles, which are prospective reagents for the synthesis of 2-heterylbenzimidazoles, can be obtained by a simple procedure from readily obtainable reagents, 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole, and carboxylic acids.

TABLE 1. The Characteristics of the ^{1}H NMR Spectra of Compounds **6a-f** and **8a-c**

Com-pound	δ, ppm (DMSO-d_6), *J* (Hz)
6a	7.04 (6H, m, *p*- + *m*-C_6H_5); 7.27 (6H, m, *o*-C_6H_5 + 5-, 6-H); 7.70 (2H, m, 4-, 7-H); 13.09 (2H, s, NH)
6b	7.07 (3H, m, *p*- + *m*-C_6H_5); 7.32 (4H, m, *o*-C_6H_5 + 5-, 6-H); 7.50 (2H, m, *m*-$C_6H_4NO_2$, *J* = 8.7); 7.75 (2H, m, 4-, 7-H); 7.88 (2H, m, *o*-$C_6H_4NO_2$, *J* = 8.7); 13.10 (2H, s, NH)
6c	4.17 (2H, s, CH_2); 6.60 (2H, d, *o*-OC_6H_5); 6.83 (1H, m, *p*-OC_6H_5); 7.16 (2H, m, *m*-OC_6H_5); 7.27 (2H, m, 5-, 6-H); 7.46 (3H, m, *p*- + *m*-C_6H_5); 7.63 (2H, d, *o*-C_6H_5, *J* = 7.7); 13.07 (2H, s, NH)
6d	1.64 (3H, s, CH_3); 7.24 (2H, m, 5-, 6-H); 7.47 (5H, m, C_6H_5); 7.67 (2H, m, 4, 7-H); 13.09 (2H, s, NH)
6e	7.31 (2H, m, 5-, 6-H); 7.49 (2H, m, *m*-C_6H_5); 7.59 (1H, m, *p*-C_6H_5); 7.67 (2H, m, 4-, 7-H); 7.73 (2H, m, *o*-C_6H_5, *J* = 7.4); 12.94 (2H, s, NH)
6f	7.30 (2H, m, 5-, 6-H); 7.48 (5H, m, C_6H_5); 7.74 (2H, m, 4-, 7-H); 9.31 (1H, s, CHO); 13.20 (2H, s, NH)
8a	7.15 (2H, m, 5-, 6-H); 7.38 (2H, m, *m*-C_6H_5); 7.46 (2H, m, 4-, 7-H); 7.56 (1H, m, *p*-C_6H_5); 7.86 (2H, d, *o*-C_6H_5, *J* = 7.5); 8.07 and 8.30 (1H, 2s, 3'-H); 12.33 and 12.38 (1H, 2s, 1-H); 13.34 and 13.50 (1H, 2s, 1'-H); hydrochloride: 7.50 (3H, m, *p*- + *m*-C_6H_5); 7.54 (2H, m, 5-, 6-H); 7.62 (2H, m, *o*-C_6H_5); 7.75 (2H, m, 4-, 7-H); 8.57 (1H, s, 3'-H); NH not appears
8b	7.13 (2H, m, 5-, 6-H); 7.25 (2H, m, *o*-C_6H_5N); 7.37 (8H, m, *p*- + *m*-C_6H_5N+C_6H_5); 7.48 (2H, m, 4-, 7-H); 8.35 (1H, s, 3'-H); 12.40 (1H, s, 1-H)
8c	7.14 (2H, m, 5-, 6-H); 7.45 (7H, m, 4-, 7-H + C_6H_5); 7.49 (2H, d, *o*-$C_6H_4NO_2$, *J* = 9.8); 8.23 (2H, d, *m*-$C_6H_4NO_2$, *J* = 9.8); 8.47 (1H, s, 3'-H); 12.46 (1H, s, 1-H)

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument for tablets with potassium bromide. The ^{1}H NMR spectra were obtained on a Varian VXR-300 spectrometer at 300 MHz with DMSO-d_6 as solvent and TMS as internal standard. The reactions and the individuality of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the 9:1 benzene–ethanol solvent system (development in UV light).

2-(Benzoyl-*p*-nitrobenzoylmethylene)-2,3-dihydro-1H-benzimidazole (6b). A mixture of compound **2** (8.88 g, 20 mmol) and acid **3b** (3.34 g, 20 mmol) in anhydrous dioxane (10 ml) was boiled for 4 h. After cooling the mixture was mixed with water (50 ml). The aqueous layer was decanted. The residue was boiled with 2-propanol (30 ml) until crystallization began. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 6.51 g (84%); mp 248.5-250°C (*n*-butanol–DMF, 3:1). IR spectrum, ν, cm^{-1}: 1350, 1540 (NO_2), 1595, 1615 (C=C and C=O), 3275 (NH). Found, %: C 68.7; H 4.0; N 10.8. $C_{22}H_{15}N_3O_4$. Calculated, %: C 68.6; H 3.9; N 10.9.

2-(Benzoylphenoxyacetylmethylene)-2,3-dihydro-1H-benzimidazole (6c). A mixture of compound **2** (0.44 g, 1 mmol), acid **3c** (0.23 g, 1.5 mmol), and anhydrous dioxane (1 ml) was boiled for 3 h. To the boiling solution we added water (0.5 ml). After cooling the precipitate was filtered off and washed with 2-propanol. Yield 0.22 g (59%); mp 216.5-218°C (aqueous dioxane, 1:2). IR spectrum, ν, cm^{-1}: 1595, 1615 (C=C and C=O), 3255 (NH). Found, %: C 74.7; H 4.8; N 7.6. $C_{22}H_{15}N_3O_4$. Calculated, %: C 74.6; H 4.9; N 7.6.

2-(Acetylbenzoylmethylene)-2,3-dihydro-1H-benzimidazole (6d). A. A mixture of compound **2** (2.22 g, 5 mmol) and acid **3d** (4.2 ml, 70 mmol) was kept at 95-100°C for 45 min. After cooling the mixture was stirred with 2-propanol (4.0 ml). The precipitate was filtered off and washed with 2-propanol. Yield 1.18 g (85%); mp 273.5-275°C (*o*-xylene). IR spectrum, ν, cm^{-1}: 1600, 1615 (C=C and C=O), 3215 (NH). Found, %: C 73.5; H 5.1; N 10.0. $C_{22}H_{15}N_3O_4$. Calculated, %: C 73.4; H 5.1; N 10.0.

B. A mixture of compound **2** (1.11 g, 2.5 mmol), acetic anhydride (1.89 ml, 20 mmol), and acid **3d** (1.8 ml, 30 mmol) was boiled for 20 min. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 0.67 g (96%).

C. A mixture of compound **6** (1.18 g, 5 mmol), acetic anhydride (1.89 g, 20 mmol), and acid **3d** (1.8 ml, 30 mmol) was kept at 95-100°C for 1 h. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 1.33 (96%).

A mixed melting test with samples obtained by methods A-C did not give a melting point depression.

2-(Benzoyltrifluoroacetylmethylene)-2,3-dihydro-1H-benzimidazole (6e). A mixture of compound **2** (4.44 g, 10 mmol), anhydrous dioxane (5 ml), and acid **3e** (1.53 ml, 20 mmol) was boiled for 1 h. Dioxane was evaporated under the vacuum of a water-jet pump at 95-100°C. The residue was dissolved in boiling toluene (10 ml). The solution was cooled with running water and left at 15-20°C for 1.5 h. The precipitate was filtered off and washed with toluene. Yield 2.47 g (74%); mp 207.5-209°C (toluene). IR spectrum, ν, cm^{-1}: 1605, 1625 (C=C and C=O), 3250 (NH). Found, %: C 61.8; H 3.5; N 8.7. $C_{17}H_{11}F_3N_2O_2$. Calculated, %: C 61.5; H 3.3; N 8.4.

2-(Benzoylformylmethylene)-2,3-dihydro-1H-benzimidazole (6e). A. A mixture of compound **2** (4.44 g, 10 mmol), anhydrous dioxane (10 ml), and 90% acid **3f** (0.85 ml, 20 mmol) was boiled for 1 h. To the hot mixture while stirring we added water (5 ml). After cooling the precipitate was filtered off and washed with 2-propanol. Yield 2.02 g (77%); mp 283.5-285.5°C (aqueous acetic acid, 1:4). IR spectrum, ν, cm^{-1}: 1615, 1630 (C=C and C=O), 3240 (NH). Found, %: C 72.6; H 4.5; N 10.5. $C_{16}H_{12}N_2O_2$. Calculated, %: C 72.7; H 4.6; N 10.6.

B. To a mixture of compound **4** (4.72 g, 20 mmol) and anhydrous dioxane (20 ml) we added a mixture of 90% acid **3f** (1.68 ml, 40 mmol) and acetic anhydride (8 ml, 80 mmol). The mixture was heated to boiling. At the end of the exothermic reaction the mixture was boiled for 5 min, and water (30 ml) was then cautiously added drop by drop over 3 min with shaking. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 4.43 g (84%). A mixed melting test with a sample obtained by method A did not give a melting point depression.

2-[3(5)-Phenyl-4-pyrazolyl]-1H-benzimidazole (8a). A mixture of compound **6f** (3.0 g, 11.4 mmol) and hydrazine (3.0 ml, 60 mmol) hydrate in ethanol (15 ml) was boiled with a reflux condenser for 3 h. The solution was evaporated under the vacuum of a water-jet pump at 95-100°C. The residue was mixed with water (30 ml) and concentrated hydrochloric acid (3 ml) and heated to boiling. After cooling the precipitate was filtered off, washed with iced water and with acetone, and dried at 95-100°C. We obtained 2.60 g of hydrochloride of compound **8a** (0.6 g of the sample was recrystallized from water for the ^1H NMR spectrum). A mixture of the obtained salt (2.0 g), acetone (10 ml), and 20% ammonia (2.0 ml) was boiled for 1 min and was then diluted with water (20 ml). The boiling was continued with evaporation of the acetone until the product had fully crystallized. The precipitate was filtered off and washed with water. Yield 1.43 g (63%); mp 188-189.5°C (aqueous 2-propanol, 1:2). Found, %: C 73.7; H 4.6; N 21.5. $C_{16}H_{12}N_4$. Calculated, %: C 73.8; H 4.7; N 21.5.

2-(1,5-Diphenyl-4-pyrazolyl)-1H-benzimidazole (8b). A mixture of compound **6f** (0.26 g, 1 mmol), phenylhydrazine (0.15 ml, 1.5 mmol), and DMF (1.5 ml) was boiled for 3 h. Water was added cautiously drop by drop with stirring until crystallization began. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 0.16 g (48%); mp 291-292°C (aqueous pyridine, 1:4). Found, %: C 78.7; H 4.6; N 16.6. $C_{22}H_{16}N_4$. Calculated, %: C 78.5; H 4.8; N 16.7.

2-[1-(4-Nitrophenyl)-5-phenyl-4-pyrazolyl]-1H-benzimidazole (8b). A mixture of compound **6f** (0.26 g, 1 mmol), *p*-nitrophenylhydrazine (0.18 g, 1.2 mmol), DMF (2.5 ml), and concentrated hydrochloric acid (0.12 ml, 1.2 mmol) was boiled for 2 h. After cooling 20% ammonia (0.24 ml) was added, and the mixture was heated to boiling with stirring. Water was added cautiously drop by drop with stirring until crystallization began. After cooling the precipitate was filtered off and washed with 2-propanol. Yield 0.23 g (60%); mp 259-260.5°C (aqueous DMF, 1:3). Found, %: C 69.4; H 4.2; N 18.5. $C_{22}H_{15}N_5O_2$. Calculated, %: C 69.3; H 4.0; N 18.4.

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