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RECYCLIZATION OF 2-(3,6-DIARYL-2,5-DIHYDROPYRIDAZIN-4-YL)-1H-BENZIMIDAZOLES TO 2-[(3,5-DIARYLPYRAZOL-4-YL)METHYL]-1H-BENZIMIDAZOLES

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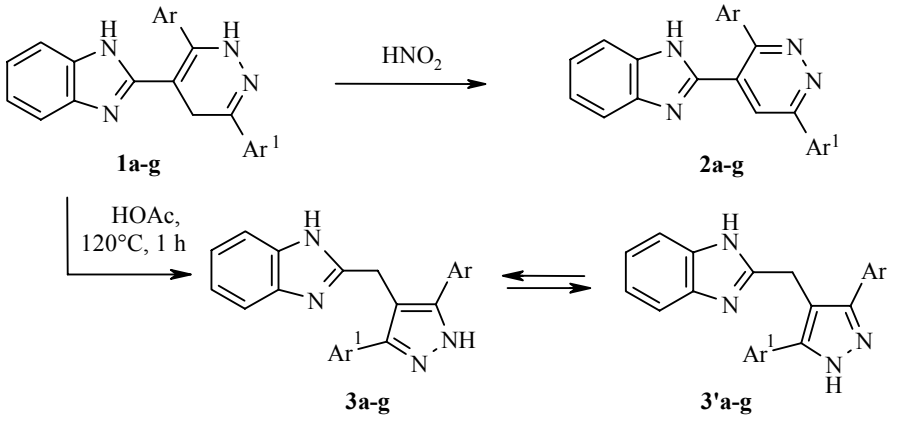
2-(3,6-Diaryl-2,5-dihydropyridazin-4-yl)-1H-benzimidazoles undergo a previously unknown type of recyclization of the pyridazine ring to a pyrazole to give 2-[(3,5-diarylpyrazol-4-yl)methyl]-1H-benzimidazoles. It is suggested that the mechanism of this conversion, which includes formation of a secondary enhydrazine group in the diazine ring and its subsequent contraction, occurs after the intramolecular formation and opening of a cyclopropane ring.

Keywords: benzimidazoles, pyrazoles, pyridazines, recyclization.

We have previously synthesized the 2-(3,6-diaryl-2,5-dihydropyridazin-4-yl)-1H-benzimidazoles **1a-g** which showed a fully expected tendency to oxidative aromatization of the dihydrodiazine ring to a diazine to form the products **2a-g** [1]. In this work we report an unusual reaction of compounds **1a-g** resulting in restructuring of the diazine ring residue.



1–3 a Ar = Ar^1 = Ph; **b** Ar = 4-$MeOC_6H_4$, Ar^1 = Ph; **c** Ar = 3,4,5-$(MeO)_3C_6H_2$, Ar^1 = Ph; **d** Ar = 4-BrC_6H_4, Ar^1 = Ph; **e** Ar = Ph, Ar^1 = 3,4-$(MeO)_2C_6H_3$; **f** Ar = Ph, Ar^1 = 4-ClC_6H_4; **g** Ar = Ph, Ar^1 = 3-$O_2NC_6H_4$

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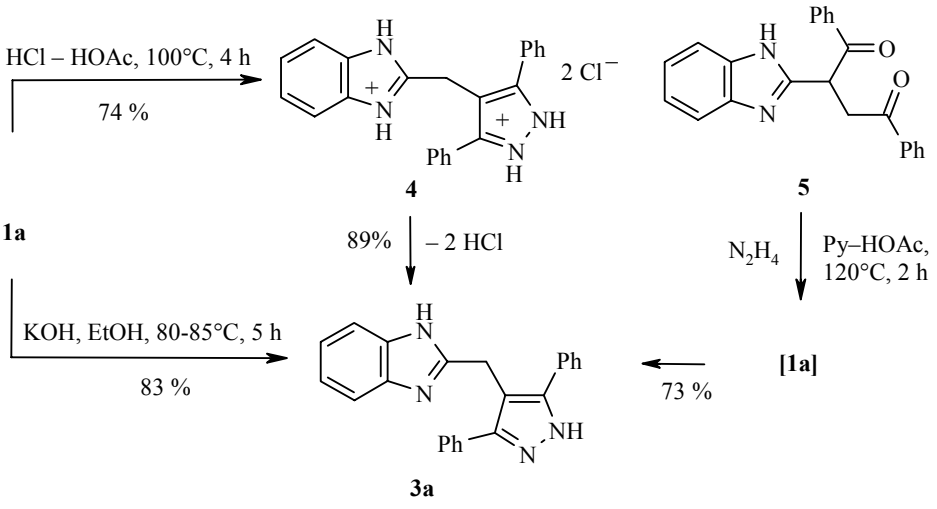
We have found that refluxing compounds **1a-g** in acetic acid (method A) causes ready recyclization to the previously unknown 2-[(3,5-diarylpyrazol-4-yl)methyl]-1H-benzimidazoles **3a-g** which exist in solution in equilibrium with their tautomeric forms **3'a-g**.

The reaction is complete after 1 h. The process can be controlled by the decolorization of the reaction mixture since the starting compounds have a yellow color and the final products are colorless. However, freshly prepared reagents **1a-f** should be used since they are of low stability due to the increased tendency of the dihydropyridazine ring to undergo oxidative aromatization.

In the majority of experiments the reaction occurs highly selectively with quite a broad range of variation of the Ar and Ar^1 substituents. The products **3a-f** are obtained in 83-96% yields. However, the reaction is limited by the presence of a nitro group in the starting reagents. Thus the reaction of the nitro-substituted compound **1g** gives a mixture of products according to TLC and the corresponding product **3g** can only be separated in 24% yield together with a 37% yield of the oxidative aromatization product **2g**. In this case the lack of selectivity is evidently due to the known tendency of a nitro group to take part in oxidative-reductive processes.

The recyclization can also occur with catalysis by mineral acid or base. Hence heating compound **1a** with hydrochloric acid gives the bis hydrochloride **4** from which the free base **3a** can be separated after treatment with ammonia (method B). Compound **1a** also isomerises to product **3a** upon refluxing in an alcoholic solution of potassium hydroxide (method C). The product **3a** may also be prepared by treating 2-(benzimidazol-2-yl)-1,4-diphenylbutane-1,4-dione **5** (obtained by method [2]) with hydrazine in a refluxing mixture of pyridine and acetic acid (method D). This method is particularly attractive since the reaction occurs via intermediate formation of the low stability compound **1a** without needing its isolation.



Compound **3a** shows chemical properties in agreement with its structure. It reacts with acetic anhydride or with DMF dimethylacetal at the nitrogen atoms of the benzimidazole and pyrazole rings to give the derivatives **6** and **7** but, in contrast to the starting compound **1a**, is not changed by treatment with nitrous acid in the conditions reported in the study [1].

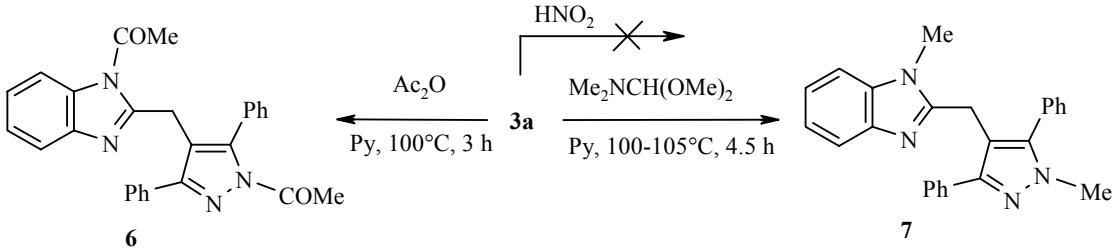


TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formulan	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
3a	$C_{23}H_{18}N_4$	78.69 / 78.83	5.22 / 5.18	15.87 / 15.99	294.5-296	95 (A), 66 (B), 83 (C), 73 (D)
3b	$C_{24}H_{20}N_4O$	75.63 / 75.77	5.37 / 5.30	14.59 / 14.73	272-273.5	94 (A)
3c	$C_{26}H_{24}N_4O_3$	70.64 / 70.89	5.55 / 5.49	12.64 / 12.72	211.5-213	94 (A)
3d	$C_{23}H_{17}BrN_4$	64.23 / 64.35	4.06 / 3.99	12.94 / 13.05	263-265	95 (A)
3e	$C_{25}H_{22}N_4O_2$	73.03 / 73.15	5.34 / 5.40	13.53 / 13.65	255-257	83 (A)
3f	$C_{23}H_{17}ClN_4$	71.64 / 71.78	4.56 / 4.45	14.41 / 14.56	313.5-315	96 (A)
3g	$C_{23}H_{17}N_5O_2$	69.68 / 69.86	4.25 / 4.33	17.59 / 17.71	240-241.5	24 (A)
4	$C_{23}H_{18}N_4 \cdot 2HCl$*	65.12 / 65.26	4.83 / 4.76	13.17 / 13.23	292-293	74
6	$C_{27}H_{22}N_4O_2$	74.52 / 74.64	5.12 / 5.10	12.74 / 12.89	182.5-184	89
7	$C_{25}H_{22}N_4$	79.18 / 79.34	5.94 / 5.86	14.67 / 14.80	191.5-193	88

* Found, %: Cl 16.78. Calculated, %: Cl 16.75.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	4.17 (2H, s, CH_2); 7.11 (2H, m, H-5,6); 7.33 (1H, m, H-7); 7.39 (6H, m, 6H_{Ph}-*m*,-*p*); 7.51 (1H, m, H-4); 7.55 (4H, d, *J* = 7.0, 4H_{Ph}-*o*); 12.19 (1H, s, H-1*); 13.33 (1H, s, H-1'*)
3b	3.72 (3H, s, H_3CO); 4.14 (2H, s, CH_2); 6.95 (2H, m, 2H_{Ar}-*m*); 7.11 (2H, m, H-5,6); 7.34 (3H, m, 3H_{Ph}-*m*,-*p*); 7.40 (1H, m, H-7); 7.47 (2H, d, *J* = 8.0, 2H_{Ar}-*o*); 7.51 (1H, m, H-4); 7.54 (2H, d, *J* = 7.0, 2H_{Ph}-*o*); 12.18 (1H, s, H-1); 13.20 (1H, s, H-1')
3c	3.52 (6H, s, 2H_3CO-*m*); 3.62 (3H, s, H_3CO-*o*); 4.14 (2H, s, CH_2); 6.84 (2H, s, Ar); 7.12 (2H, m, H-5,6); 7.34 (1H, m, H-7); 7.42 (3H, m, 3H_{Ph}-*m*,-*p*); 7.52 (1H, m, H-4); 7.59 (2H, d, *J* = 7.5, 2H_{Ph}-*o*); 12.29 (1H, s, H-1); 13.25 (1H, s, H-1')
3d	4.16 (2H, s, CH_2); 7.10 (2H, m, H-5,6); 7.35 (1H, m, H-7); 7.38 (3H, m, 3H_{Ph}-*m*,-*p*); 7.52 (6H, m, 2 H_{Ph}-*o* + 4 H_{Ar}); 7.60 (1H, m, H-4); 12.20 (1H, s, H-1); 13.39 (1H, s, H-1')
3e	3.31 and 3.72 (3H and 3H, s, 2H_3CO); 4.13 (2H, s, CH_2); 6.97 (1H, m, H_{Ar}-5); 7.06 (1H, d, *J* = 7.5, H_{Ar}-6); 7.11-7.15 (3H, m, H-5,6 + H_{Ar}-2); 7.28 (1H, m, H-7); 7.35 (1H, m, H-7); 7.40–7.42 (3H, m, 3H_{Ph}-*m*,-*p*); 7.52 (1H, m, H-4); 7.57 (2H, d, *J* = 7.0, 2H_{Ph}-*o*); 12.23 (1H, s, H-1); 13.20 (1H, s, H-1')
3f	4.17 (2H, s, CH_2); 7.11 (2H, m, H-5,6); 7.26-7.53 (9H, m, 5H_{Ph} + H-4,7 + 2 H_{Ar}-*m*); 7.59 (2H, d, *J* = 7.0, 2H_{Ar}-*o*); 12.21 (1H, s, H-1); 13.40 (1H, s, H-1')
3g	4.22 (2H, s, CH_2); 7.10 (2H, m, H-5,6); 7.29–7.50 (4H, m, 3H_{Ph}-*m*,-*p* + H-7); 7.57 (3H, d, *J* = 7.0, 2H_{Ph}-*o* + H-4); 7. 62 and 7.72 (0.8 + 0.2H, two t, *J* = 7.0, 1H_{Ar}-5); 8.02 and 8.04 (0.2 + 0.8H, two d, *J* = 7.0, H_{Ar}-6); 8.10 and 8.18 (0.8 + 0.2H, two d, *J* = 7.0, H_{Ar}-4); 8.43 and 8.47 (0.8 + 0.2H, two s, H_{Ar}-2); 12.27 (1H, s, H-1); 13.56 and 13.60 (0.8 + 0.2H, two s, H-1')
4	4.70 (2H, s, CH_2); 7.28 (2H, t, *J* = 7.5, 2H_{Ph}-*p*); 7.36 (4H, t, *J* = 7.5, 4H_{Ph}-*m*); 7.40 (2H, m, H-5,6); 7.55 (4H, d, *J* = 7.5, 4H_{Ph}-*o*); 7.57 (2H, m, H-4,7)
6	2.72 and 2.73 (3H and 3H, two s, 2H_3CCO); 4.22 (2H, s, CH_2); 7.29-7.33 (7H, 5$H_{5\text{-}Ph}$ + + H-5,6); 7.34-7.39 (3H, m, 3$H_{3\text{-}Ph}$-*m*,-*p*); 7.60-7.64 (3H, m, 2$H_{3\text{-}Ph}$-*o* + H-4); 7.81 (1H, d, *J* = 8.0, H-7)
7	3.58 and 3.79 (3H and 3H, two s, 2H_3C); 3.40 (2H, s, CH_2); 7.12 (1H, t, *J* = 7.0, H-5); 7.18 (2H, t, *J* = 7.0, H-6); 7.25 (1H, m, $H_{3\text{-}Ph}$-*p*); 7.31 (2H, m, 2$H_{3\text{-}Ph}$-*m*); 7.39-7.43 (6H, m, 5$H_{5\text{-}Ph}$ + H-7); 7.52 (1H, d, *J* = 7.0, H-4); 7.55 (2H, d, *J* = 7.0, 2$H_{3\text{-}Ph}$-*o*)

* Undergoes deuterium exchange.

The composition and structure of the synthesized compounds were confirmed by their elemental analytical data (Table 1) and ^{1}H NMR spectra (Table 2). The structure of compounds **3a** and **3g** also agree with chromato-mass analytical data and the diacetyl derivative **6** with the IR spectrum. Moreover the structure of compound **3a** was unambiguously established by an X-ray structural study (see Fig. 1). In the molecule the

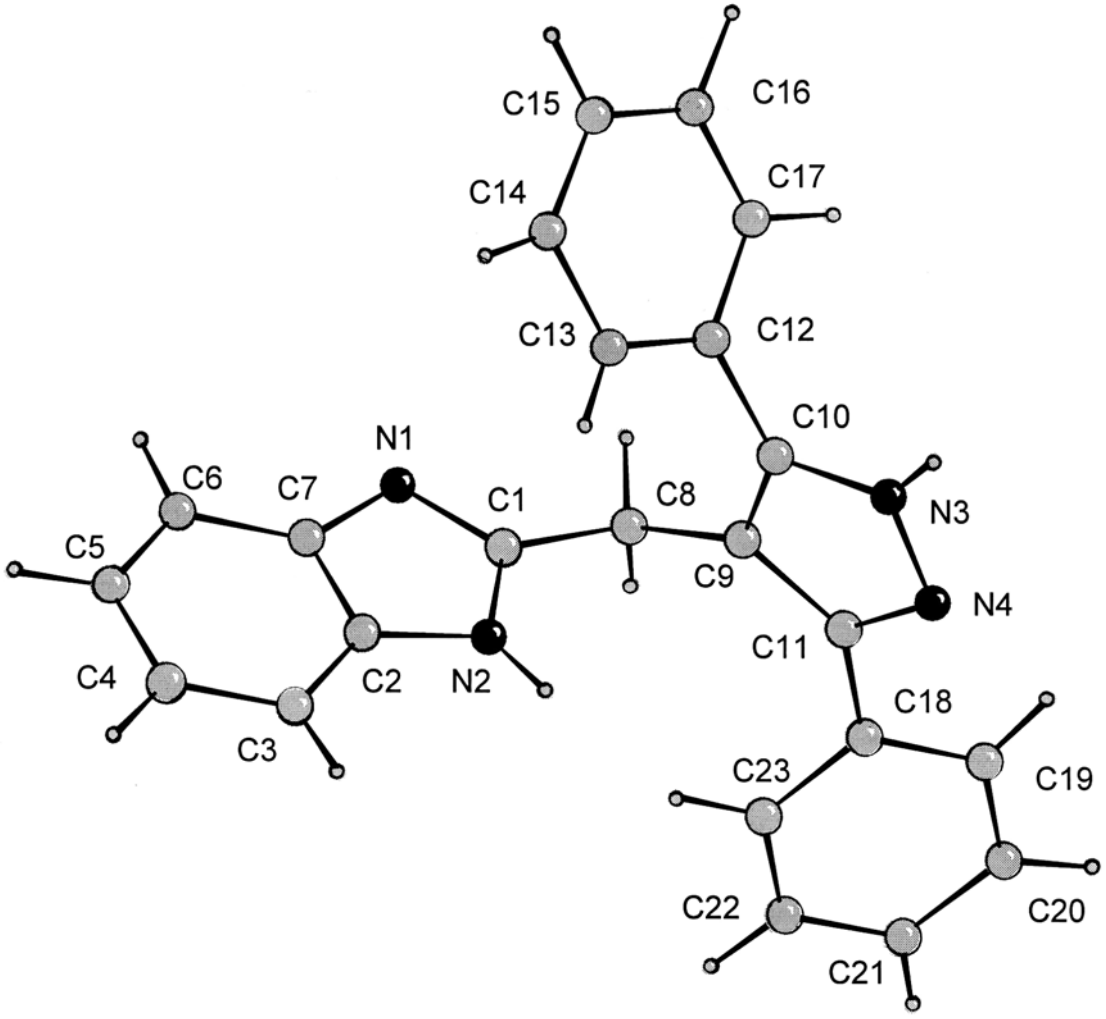


Figure 1. General view of the compound **3a** molecule from X-ray analysis.

system N(1)N(2)C(1-7) is almost planar, the deviation from the plane not exceeding 0.027 Å. The benzene rings are twisted from the N(3)N(4)C(9-11) plane by 78.4 and 40.1º. All of the bond lengths and angles in the molecule are close to the corresponding parameters in a series of related compounds [5, 6]. In the solid state the molecules of compound **3a** are associated by N(2)–H···N(4) intermolecular hydrogen bonds as centrosymmetric dimers which, in turn are linked in a 2D network by N(3)–H···N(1) hydrogen bonds (Fig. 2).

The ^{1}H NMR spectra point to an inhibition of migration of protons between the ring nitrogen atoms in the benzimidazole fragment of compounds **3a-g**. As a result the H-1 signal is a rather broad singlet at 12.18-12.29 ppm and the signals for H-4 and H-7 appear separately at 7.51-7.60 and 7.28-7.40 ppm. Tautomerism arising from migration of a proton between the pyrazole ring nitrogen atoms in the series of compounds **3a-f** causes a broadening of the aromatic substituent protons signals and also H-1' (singlet at

13.20-13.40 ppm). It should be noted that both phenyl groups in compound **2a** are chemically equivalent and their signals coincide: the *o*-protons appear as a doublet at 7.55 ppm and the *m* and *p*-protons as a broadened multiplet at 7.39 ppm. On the other hand, in compound **3g** the electronic nature of the aromatic substituents differ more significantly (Ar = Ph, Ar^1 = 3-$O_2NC_6H_4$), broadening is not observed, and doubling of the signals for the nitrophenyl group and H-1' is observed which corresponds to the appearance of the individual tautomers. According to the integrated intensities of these signals the tautomer form **3g** content is ~ 80%. Its increased stability is likely due to the fact that the electron donor effect of the nitrogen atom in the pyrazole ring is transmitted to the 3-nitrophenyl substituent by the shortest conjugated chain. In form **3'g** the conjugated chain is two bonds longer and hence it is energetically less favored. We have previously observed similar prototropic effects in the ^{1}H NMR spectra of structural analogs of compounds **3a-g** – 2-(pyrazol-4-yl)-1H-benzi-midazoles which are substituted in the pyrazole ring by one or two aryl groups [3, 4].

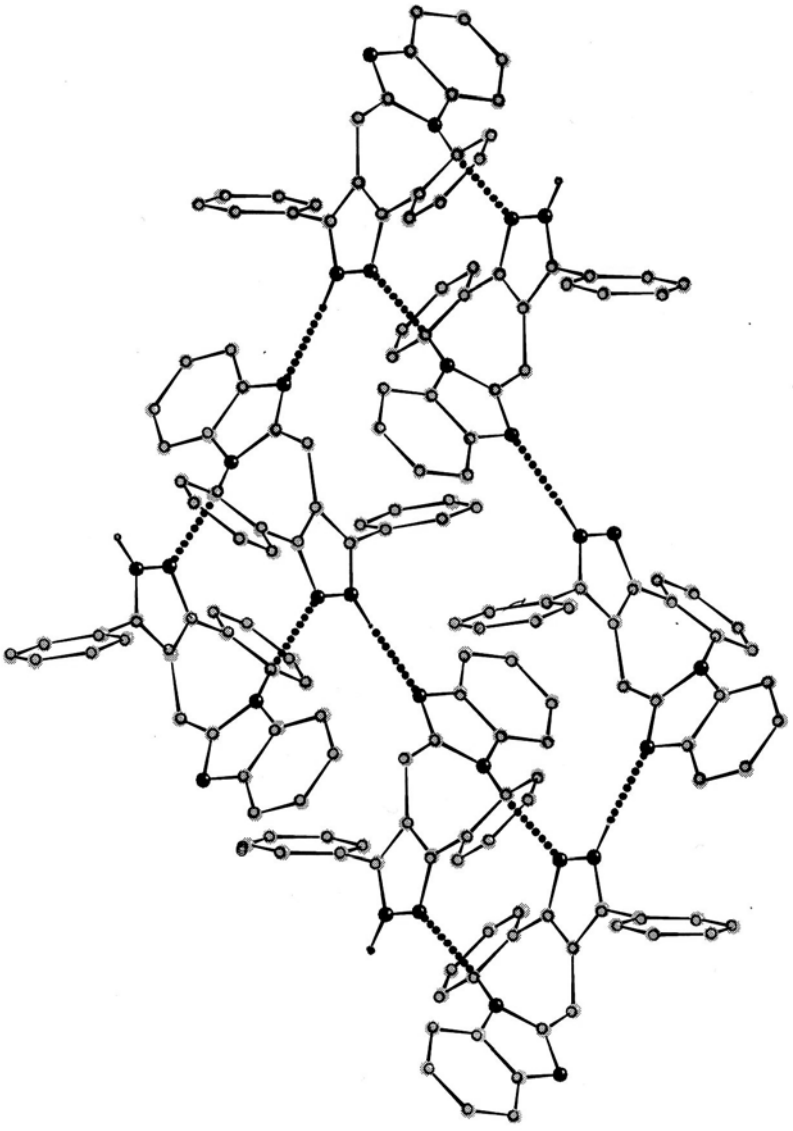


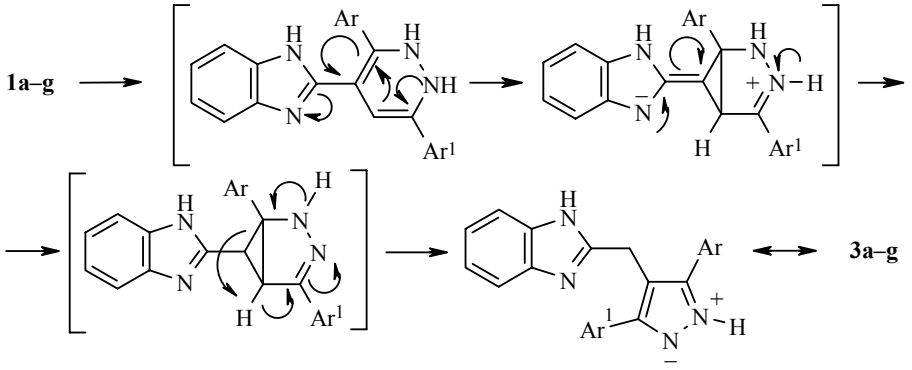
Figure 2. Crystal packing of compound **3a.**

The ^{1}H NMR spectrum of salt **4** shows a phenylene fragment typical of benzimidazole salts (a symmetrical picture for the H-5,6 resonance signals and for H-4,7 at lower field, see [2]). The appearance of the phenyl ring is similar to those above mentioned for the base **3a** but with separately observed *o*-, *m*-, and *p*-protons in successive order from low to higher field.

The ^{1}H NMR spectrum of the diacetyl derivative has a number of features. The acetyl group on the benzimidazole fragment nitrogen atom has a deshielding effect on the adjacent phenyl fragment H-7 proton which thus appears to low field at 7.81 ppm (in compounds **3a-f** the H-7 signal occurs at 7.28-7.40 ppm). The second acetyl group (on the pyrazole fragment nitrogen atom) is sterically hindered by the nearby phenyl substituent and it appears to be placed orthogonally to the plane of the heterocycle, thus appearing as a narrow multiplet at 7.29 ppm. In the spectrum of the dimethyl derivative **7** this effect appears in part (the multiplet for the 5-phenyl group is somewhat broadened at 7.39-7.43 ppm) because the methyl group (in contrast to an acetyl) does not possess magnetic anisotropic properties and shows less steric hindrance.

The resonances of the CH_2 groups of the synthesized compound are in the order 4.13-4.22 (**3a-g**), 4.70 (**4**), 4.22 (**5**), and 3.40 ppm (**7**) and are shifted to low field with the occurrence of structural factors which lower the electron density on the heterocycles.

Based on the structure of the starting and formed compounds the recyclization occurs as the result of a restructuring of the carbon-carbon bonds. Its mechanism likely includes an initial 1,3-proton shift step in the diazine ring from the methylene group to the nitrogen atom. The secondary enhydrazine group formed in this way can react intramolecularly with the already present carbon-carbon bond to give closure of a cyclopropane ring and contraction of the six to a five membered heterocycle. This increases the electrophilicity of the pyridazine ring C-3 atom, promoted because of the electron acceptor effect of the benzimidazole fragment. Subsequent opening of the three membered ring at another carbon-carbon bond with a 1,2-proton shift possibly occurs spontaneously. This assists the electronic effect of both nitrogen atoms of the 4,5-dihydropyrazole ring (donor for one and acceptor for the other) and also simultaneously the aromatization of the pyrazole ring to give the final products **3a-g**.



The recyclization of certain pyridazine compounds to pyrazoles has been reported previously [7-11] but they differ from that given above by one overall feature which is a result of the opening of an existing and formation of a new nitrogen-carbon bond. We have not found any evidence for the restructuring of a pyridazine ring to a pyrazole via formation of a new and fission of an existing carbon-carbon bond. It should also be noted that there have also been reported four representatives of 2-(4-pyrazolyl)-1H-benzimidazoles substituted in the pyrazole ring by an aryl (position 1) and two methyl groups (positions 3 and 5) which were synthesized by a classical method (cyclocondensation of arylhydrazines with 3-[(1H-benzimidazol-2-yl)methyl]pentane-2,4-dione) and they possess clear bactericidal and fungicidal activity [12].

Hence in the case of the reaction of 2-(3,6-diaryl-2,5-dihydropyridazin-4-yl)-1H-benzimidazoles to 2-[(3,5-diarylpyrazol-4-yl)methyl]-1H-benzimidazoles we have revealed a novel type of recyclization of a

pyridazine ring to a pyrazole, differing in the fact that it involves restructuring of carbon–carbon bonds. The reaction likely has a wider general character and can find its place in organic synthetic practice.

EXPERIMENTAL

Monitoring of the reaction course and purity of the synthesized compounds was carried out by TLC on Silufol UV-254 plates in the solvent system benzene – ethanol (9: 1) and revealed using UV light. The ^{1}H NMR spectra of the compounds were recorded on a Bruker Avance DRX 500 (500 MHz) spectrometer using DMSO-d_6 with TMS as standard. The IR spectrum of compound **6** was recorded on a UR-20 instrument for a KBr tablet. Chromato-mass analysis for compounds **3a** and **3g** was carried out on an Agilent 1100 Series high resolution liquid chromatograph fitted with an Agilent LC/MSD SL mass detector. Compounds were dried for 4 h at 125ºC before elemental analysis and spectroscopic investigation.

X-ray Investigation of a Single Crystal of Compound 3a was performed at room temperature on a Bruker Apex II automatic diffractometer (MoKα radiation, λ = 0.71073 Å, θ_{max} = 26.5º, $-26 \le h \le 30$, $12 \le k \le 13$, $-16 \le l \le 18$). Unit cell parameters for the crystal: a = 24.694(2), b = 10.5061(9), c = 15.1393(12) Å, β = 112.228(6)º, space group $C2/c$. 11706 reflections were collected, the structure was refined in full matrix anisotropic approximation, and all of the H atoms were revealed in electron density difference synthesis with R = 0.037 and R_w = 0.039, GOF = 1.195 (3716 independent reflections with R_{int} = 0.019). The full set of X-ray structural data for compound **3a** has been placed in the Cambridge structural database (reference CCDC 651222).

2-[(3,5-Diphenylpyrazol-4-yl)methyl]-1H-benzimidazole (3a). A. A mixture of compound **1a** (0.25 g) and glacial acetic acid (1.25 ml) was held for 1 h at 120ºC. The reaction mixture was diluted with acetone (1.25 ml), water (2 ml) and 20% aqueous ammonia solution (2 ml) and refluxed with stirring to full crystallization of the oil produced. After cooling, the precipitate was filtered off, washed with water, and dried to give analytically pure product (0.237 g) (100% pure by chromato mass analysis). Found, M+1 = 351. $C_{23}H_{18}N_4$. Calculated, M = 350.

Products 3b-f were prepared similarly from compounds **1b-f** (the **3d-f** products were recrystallized from a mixture of pyridine and ethanol (1:3)).

B. A mixture of the bis hydrochloride **4** (0.2 g), pyridine (1.5 ml), and 20% aqueous ammonia (0.5 ml) was heated to reflux with stirring and diluted dropwise with water (4 ml). After cooling, the precipitate was filtered off, washed with water, and dried to give the pure compound **3a** (0.149 g).

C. A mixture of compound **1a** (0.175 g, 0.5 mmol), potassium hydroxide (0.084 g, 1.5 mmol), and ethanol (1.5 ml) was refluxed for 6 h. The hot reaction solution was diluted with water (1.5 ml), heated with stirring to reflux, and left to cool slowly. The precipitate formed was filtered off, washed with 2-propanol, dried, and recrystallized from chlorobenzene to give the pure compound **3a** (0.145 g).

D. A mixture of compound **5** (0.172 g, 0.5 mmol), 80% hydrazine hydrate (0.2 ml), pyridine (2 ml), and glacial acetic acid (0.5 ml) was refluxed for 3 h. Water (1 ml) was added with stirring to the hot reaction solution. After cooling, the precipitate was filtered off and washed with water to give the pure compound **3a** (0.128 g).

Samples of the compound **3a** prepared by the methods A to D were identical by TLC and mixed sample melting points.

2-{[(3-Nitrophenyl)-5-phenyl-1H-pyrazol-4-yl]methyl}-1H-benzimidazole (3g). A mixture of compound **1g** (0.395 g, 1 mmol) and glacial acetic acid (2 ml) was held for 1 h at 120ºC. After cooling, the precipitate was filtered off (after it was crystallized from a mixture of acetic acid and water (1:1) to give compound **2g** (0.148 g), identical in TLC data and mixed sample melting point to a sample prepared according the method [1]). The filtrate was basified with 20% aqueous ammonia solution (4 ml) and heated to reflux. After cooling, the aqueous layer was poured off and the residue refluxed with acetonitrile (2 ml) to complete crystallization. After cooling, the precipitate was filtered off, recrystallized from a mixture of pyridine and

water (2: 1) and then ethanol and water (1:1) to give the product **3g** (0.096 g) which was 99.77% pure from chromato-mass analysis. Found, M+1 = 396. $C_{23}H_{17}N_5O_2$. Calculated, M = 395.

2-[(3,5-Diphenyl-1H-pyrazol-2-io-4-yl)methyl]-3H-benzimidazol-1-ium Dichloride (4). A mixture of compound **1a** (0.35 g, 1 mmol), glacial acetic acid (1.5 ml), water (1 ml), and concentrated hydrochloric acid (0.3 ml, 3 mmol) was heated for 4 h at 100-105ºC. After cooling, the precipitate was filtered off and washed with 2-propanol to give analytically pure product (0.314 g).

1-Acetyl-2-[(1-acetyl-3,5-diphenyl-1H-pyrazol-4-yl)methyl]-1H-benzimidazole (6). A mixture of compound **3a** (0.35 g, 1 mmol), acetic anhydride (0.284 ml, 3 mmol), and anhydrous pyridine (1 ml) was held for 3 h at 100-105ºC. 2-Propanol (1 ml) and water (1 ml) were added and stirred. After cooling, the precipitate was filtered off and washed with 2-propanol to give analytically pure product (0.387 g). IR spectrum: 1270 cm^{-1} (C=O).

1-Methyl-2-[(1-methyl-3,5-diphenyl-1H-pyrazol-4-yl)methyl]-1H-benzimidazole (7). A mixture of compound **3a** (0.175 g, 0.5 mmol), DMF dimethylacetal (0.5 ml), and anhydrous pyridine (0.5 ml) was held for 4.5 h at 100-105ºC. 2-Propanol (1 ml) and water (1 ml) were added and the product was refluxed with stirring to the beginning of crystallization. After cooling, the precipitate was filtered off, washed with a mixture of 2-propanol and water (1:1), and dried to give analytically pure product (0.168 g).

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