UNUSUAL REACTION OF 2-(AMINOMETHYL)BENZIMIDAZOLE WITH CHALCONES: SYNTHESIS OF NEW ARYL-SUBSTITUTED PYRROLINES

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The reaction of 2-(aminomethyl)benzimidazole (**1**) with chalcones **2a**–**2e** leads to formation of 3,5-diaryl-2-benzimidazol-2-yl-4,5-dihydropyrroles **3a**–**3e**. The *trans* orientation of benzimidazol-2-yl and 3-aryl substituents in **3a**–**3e** was established by X-ray analysis of **3e**.
Keywords: Nitrogen heterocycles; Nucleophilic addition; Structure elucidation; NMR spectroscopy; Mass spectrometry; X-ray diffraction.

In recent years, α,β-unsaturated ketones have received considerable attention as precursors of many heterocyclic compounds as well as objects for studying a variety of theoretical problems in organic chemistry, such as chemical reactivity. The followed work is a continuation of our research on reactions of nitrogen-containing dinucleophiles with α,β-unsaturated carbonyl compounds as one of the most common synthetic way to nitrogen heterocycles[1,2].

RESULTS AND DISCUSSION

We investigated the reaction of 2-(aminomethyl)benzimidazole (**1**) with chalcones **2a**–**2e** by heating in dimethylformamide. The reaction of amine **1** with non-substituted chalcone **2a** was described[3] but the structure of product **3′** and its evidence, in our opinion, seemed doubtful. We reproduced the experiment; single product was isolated and identified as **3a**, R^1 = R^2 = H. Its melting point and IR data were consistent with those described for **3′**. In the reaction mixture the same compound was indicated by HPLC as a major component. However, its NMR spectra contained signals of

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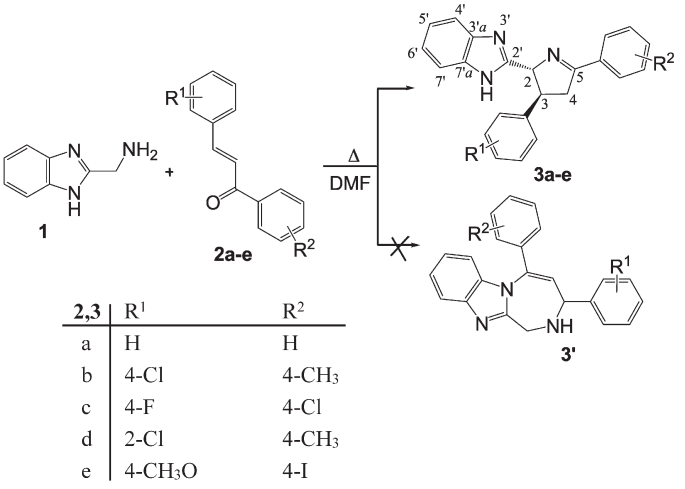
4-spin system in aliphatic region (according to COSY data for **3b**) and in the aromatic region an AA′BB′ system of benzimidazole ring was observed, thus, a symmetrical benzimidazole fragment was present in the molecule, which did not agree with structure **3′**. According to the spectral data we proposed the structure of compound as pyrroline derivative **3a**, and the reaction scheme as follows (Scheme 1). The considered synthetic method allowed synthesis of a range of compounds **3b**–**3e** in a similar way.



2,3	R^1	R^2
a	H	H
b	4-Cl	4-CH_3
c	4-F	4-Cl
d	2-Cl	4-CH_3
e	4-CH_3O	4-I

SCHEME 1

In contrast to the ^{1}H NMR data, the ^{13}C NMR spectra of **3a**, **3b** were not typical of compounds with symmetric benzimidazolyl moiety and showed seven broad signals, which could be explained by its hindered rotation in the molecule (Fig. 1). For **3c**, **3d** only four broad signals for benzimidazole moiety were observed in ^{13}C NMR spectra. The assignment of ^{13}C signals in **3b** (Fig. 1) was made by HSQC and HMBC experiments, for **3a**, **3c**, **3d** by comparison of their ^{13}C chemical shifts with chemical shifts for **3b**. Additionally, the dependence of ^{13}C NMR shifts in substituted toluenes[4] was taken into account.

X-ray structural analysis of **3e** finally confirmed the proposed structure for compounds **3a**–**3e** (Fig. 2) and allowed to establish the *trans* configuration of benzimidazolyl and 3-aryl substituents. In the crystal phase compound **3e** exists as a solvate with benzene in the 2:1 ratio. The solvent molecule is located in the partial position in the center of symmetry.

The dihydropyrrole ring adopts an envelope conformation. The deviation of the C(11) atom from the mean plane of the remaining atoms of the ring

is 0.43 Å. The benzimidazolyl substituent has pseudoequatorial orientation and is turned relatively to the N(3)–C(8) bond of the dihydropyrrole ring (the C(9)–N(3)–C(8)–C(7) and N(2)–C(7)–C(8)–N(3) torsion angles are –140.3(3) and 72.8(4)°, respectively). Such orientation of this substituent leads to shortening of the H(11)···N(2) distance (2.62 Å compared with the van der Waals radii sum[5] 2.67 Å), which cannot be considered a hydrogen

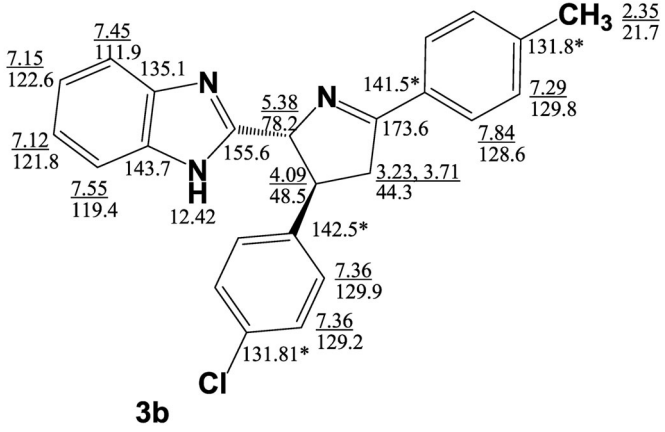


FIG. 1
The ^{1}H and ^{13}C NMR data for **3b** (δ, ppm)

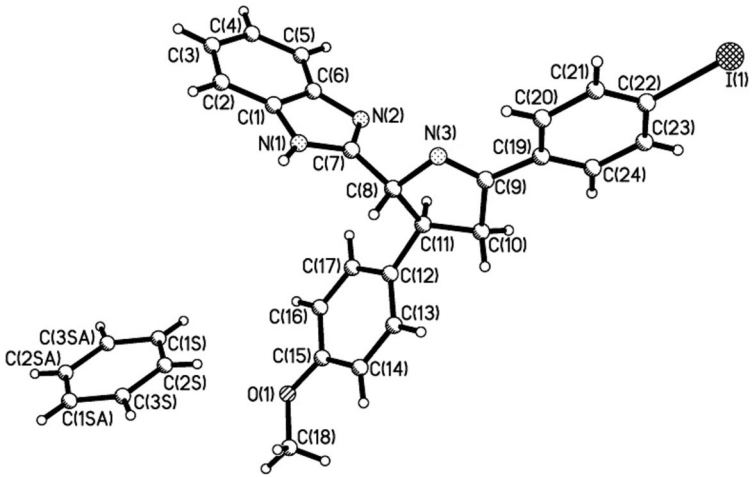


FIG. 2
The molecular structure of compound **3e** with the numbering of non-hydrogen atoms

bond owing to a very small value of the C–H···N angle (107°). The substituent at the C(11) atom has pseudoequatorial orientation and it is turned relatively to the C(10)–C(11) bond (the C(9)–C(10)–C(11)–C(12) and C(10)–C(11)–C(12)–C(13) torsion angles are –148.5(3) and 29.0(6)°, respectively), which is probably caused by repulsion between atoms of the aromatic and dihydropyrrole rings (the shortened distances H(10b)···C(13) 2.75 Å (2.87 Å), H(10b)···H(13) 2.20 Å (2.34 Å), H(13)···C(10) 2.82 Å (2.87 Å)). The methoxy group of this substituent is coplanar to the plane of the aromatic ring (the C(18)–O(1)–C(15)–C(14) torsion angle is –1.6(7)°) in spite of a significant repulsion between methyl group and the benzene ring (the shortened distances H(14)···C(18) 2.54 Å (2.87 Å), H(14)···H(18a) 2.25 Å (2.34 Å), H(18a)···C(14) 2.70 Å (2.87 Å), H(18b)···C(14) 2.84 Å (2.87 Å)). The substituent at the C(9) atom is slightly turned relatively to the N(3)–C(9) endocyclic double bond (the N(3)–C(9)–C(19)–C(20) torsion angle is 19.1(6)°) owing to the presence of the shortened intramolecular distances (H(10a)···H(24) 2.30 Å (2.34 Å), H(20)···N(3) 2.56 Å (2.67 Å) and H(24)···C(10) 2.79 Å (2.87 Å)).

In the crystalline phase the molecules **3e** form infinite chains along the [001] axis due to formation of the N(1)–H(1N)···N(2)′ (x, $-0.5 - y$, $-0.5 + z$) intermolecular hydrogen bond (H···N 2.00 Å, N–H···N 164°) (Fig. 3). Also the C(17)–H(17)···I(1)′ ($-x$, $-0.5 + y$, $0.5 - z$) hydrogen bond (H···I 3.17 Å, C–H···I 142°) is observed in the crystals.

Compounds **3a**, **3b** appeared to be easily reduced into pyrrolidine derivatives **4a**, **4b** by the action of sodium borohydride in methanol (Scheme 2).

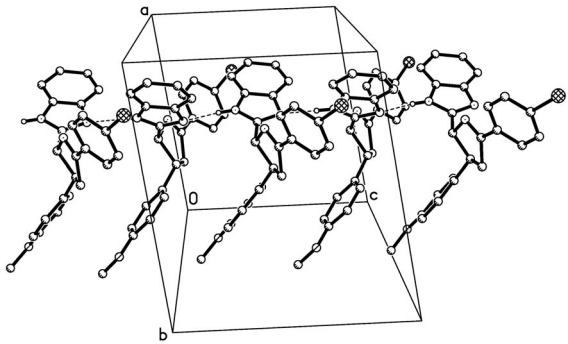
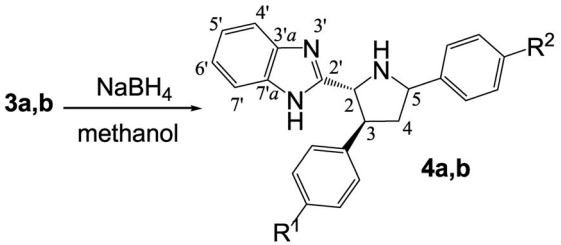


FIG. 3
The infinite chains of the molecules **3e** along the [001] crystallographic direction in crystal phase. The hydrogen bonds are shown by dashed lines



4	R^1	R^2
a	H	H
b	4-Cl	4-CH_3

SCHEME 2

The ^{1}H NMR spectra of **4a**, **4b** contained signals of a five-spin proton system in aliphatic region and broad singlet of NH at ~3.45 ppm (which disappeared by addition of deuterated methanol), the barely resolved multiplet of aromatic protons and singlet of benzimidazole NH at low fields. The ^{13}C NMR spectra of **4a**, **4b** showed six broad signals for the benzimidazole moiety which could be easily assigned by comparison with those for corresponding **3a**, **3b**, which showed the hindered rotation in **4a**, **4b**, similar to **3a**, **3b**.

CONCLUSION

We have investigated the reaction of 2-(aminomethyl)benzimidazole (**1**) with chalcones **2a**–**2e** which led to the formation of *trans*-3,5-diaryl-2-benzimidazol-2-yl-4,5-dihydropyrroles **3a**–**3e**. The structure of **3a**–**3e** was established by NMR methods and X-ray analysis. Reduction of **3a**, **3b** with sodium borohydride gave corresponding 3,5-diaryl-2-benzimidazol-2-yl-pyrrolidines **4a**, **4b**.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus. The yields of **3a**–**3e** and **4a**, **4b** are given after their crystallization. The ^{1}H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were recorded in DMSO-d_6 at 200 MHz for ^{1}H and 50 MHz for ^{13}C on a Varian Mercury VX-200 spectrometer, internal standard was $Si(CH_3)_4$. The EI mass spectra were obtained on a Varian 1200L spectrometer with electron energy 70 eV.

X-ray Diffraction Study

The colorless crystals of **3e** ($C_{24}H_{20}IN_3O{\cdot}0.5C_6H_6$) are monoclinic. At 293 K, a = 10.4401(6) Å, b = 25.097(1) Å, c = 9.4927(5) Å, β = 97.480(5)°, V = 2466.1(2) Å^3, M_r = 532.38, Z = 4, space

group $P2_1/c$, d_{calc} = 1.434 g/C m^3, μ(MoKα) = 1.321 mm^{-1}, $F(000)$ = 1068. Intensities of 20431 reflections (5668 independent, R_{int} = 0.038) were measured on a Xcalibur-3 diffractometer (graphite monochromatized MoKα radiation, CCD detector, ω-scaning, $2\theta_{max}$ = 55°). The structure was solved by direct method using a SHELXTL package[6]. The absorption correction was performed by multiscan method (T_{min} = 0.476, T_{max} = 0.831). Positions of the hydrogen atoms were located from electron density difference maps and refined within the "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl group and 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 5620 reflections was converged to wR_2 = 0.188 (R_1 = 0.061 for 3701 reflections with $F > 4\sigma(F)$, S = 1.161). CCDC 721897 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

3,5-Diaryl-2-benzimidazol-2-yl-4,5-dihydropyrroles (**3a**–**3e**). General Procedure

A solution of 0.33 g (2.5 mmol) of 2-(aminomethyl)benzimidazole (**1**) and 2 mmol of corresponding chalcone in 0.3 ml of dimethylformamide was refluxed for 2 h. Compound **3a** (from unsubstituted chalcone), which precipitated during reflux, was filtered off and recrystallized from ethanol. In case of **3b**–**3e**, the reaction mixture after reflux was kept at room temperature for several days and, after beginning of crystallization, put into refrigerator. The precipitate obtained was recrystallized from ethanol (**3e** from benzene).

3,5-Diphenyl-2-benzimidazol-2-yl-4,5-dihydropyrrole (**3a**). M.p. 243 °C (lit.[3] 243 °C). Yield 27%. For $C_{23}H_{19}N_3$ (337.42) calculated: 12.45% N; found: 12.12% N. ^{1}H NMR: 3.27 (1 H, m), 3.79 (1 H, m), 4.11 (1 H, m), 5.44 (1 H, m), 7.05–7.65 (12 H, m), 7.85–8.05 (2 H, m), 12.44 (1 H, br s). ^{13}C NMR: 44.5 (C-4), 49.1 (C-3), 78.5 (C-2), 112.0 (broad, C-4 of benzimidazole), 119.4 (broad, C-7 of benzimidazole), 121.8 (broad, C-6 of benzimidazole), 122.7 (broad, C-5 of benzimidazole), 127.2 (*p*-C_{Ar}), 128.0, 128.6, 129.25, 129.32 (four signals for *o*-,*m*-C_{Ar}), 131.7, 134.4 (two signals for *i*-C_{Ar}), 135.1 (broad, C-3*a* of benzimidazole), 143.6 (C-7*a* of benzimidazole), 155.7 (C-2 of benzimidazole), 173.9 (C-5). EI MS, *m/z* (%): 337 (57), 233 (100), 219 (16), 119 (19), 103 (46).

3-(4-Chlorophenyl)-5-(4-methylphenyl)-2-benzimidazol-2-yl-4,5-dihydropyrrole (**3b**). M.p. 203–206 °C. Yield 24%. For $C_{24}H_{20}ClN_3$ (385.89) calculated: 10.89% N; found: 10.87% N. ^{1}H and ^{13}C NMR data are shown in Fig. 1. EI MS, *m/z* (%): 385 (15), 350 (39), 267 (36), 246 (100), 138 (22), 130 (20), 118 (20), 103 (62).

5-(4-Chlorophenyl)-3-(4-fluorophenyl)-2-benzimidazol-2-yl-4,5-dihydropyrrole (**3c**). M.p. 207–209 °C. Yield 28%. For $C_{23}H_{17}ClFN_3$ (389.85) calculated: 10.78% N; found: 10.82% N. ^{1}H NMR: 3.25 (1 H, m), 3.74 (1 H, m), 4.11 (1 H, m), 5.41 (1 H, m), 6.91–7.24 (4 H, m), 7.27–7.45 (2 H, m), 7.45–7.73 (4 H, m), 7.80–8.13 (2 H, m), 12.43 (1 H, br s). ^{13}C NMR: 44.5 (C-4), 48.5 (C-3), 78.4 (C-2), 116.0 (d, $^2J(^{13}C^{19}F)$ = 21.2, *m*-C_{Ar} of C_6H_4F-4), 115.7 (broad, C-4 and C-7 of benzimidazole), 122.3 (broad, C-5 and C-6 of benzimidazole), 129.34 (*o*-C_{Ar} of C_6H_4Cl-4), 129.9 (d, $^3J(^{13}C^{19}F)$ = 8.2, *o*-C_{Ar} of C_6H_4F-4), 130.41 (*m*-C_{Ar} of C_6H_4Cl-4), 133.2, 136.5 (two signals for *i*-C_{Ar} and *p*-C_{Ar} of C_6H_4Cl-4), 139.4 (d, $^4J(^{13}C^{19}F)$ = 3.1, *i*-C_{Ar} of C_6H_4F-4), ~139.0 (broad, C-3*a* and C-7*a* of benzimidazole), 155.4 (C-2 of benzimidazole), 161.68 (d, $^1J(^{13}C\text{-}^{19}F)$ = 242, *p*-C_{Ar} of C_6H_4F-4), 173.0 (C-5). EI MS, *m/z* (%): 389 (6), 267 (57), 130 (16), 122 (91), 103 (100).

3-(2-Chlorophenyl)-5-(4-methylphenyl)-2-benzimidazol-2-yl-4,5-dihydropyrrole (**3d**). M.p. 205–209 °C. Yield 7%. For $C_{24}H_{20}ClN_3$ (385.89) calculated: 10.89% N; found: 10.82% N. ^{1}H NMR: 2.35 (3 H, s), 3.23 (1 H, m), 3.79 (1 H, m), 4.43 (1 H, m), 5.58 (1 H, m), 6.95–7.65 (10 H, m), 7.68–8.00 (2 H, m), 12.45 (1 H, br s). ^{13}C NMR: 21.8 (CH_3), 43.9 (C-4), 46.0 (C-3), 77.1 (C-2), 115.7 (broad, C-4 and C-7 of benzimidazole), 122.2 (C-5 and C-6 of benzimidazole), 128.45, 128.69 (*o*-C_{Ar} of $C_6H_4CH_3$-4), 129.04, 129.30, 129.82 (*m*-C_{Ar} of $C_6H_4CH_3$-4), 130.3, 131.6, 133.6, ~140.5 (broad, C-3*a* and C-7*a* of benzimidazole), 140.8, 141.6, 155.6 (C-2 of benzimidazole), 173.5 (C-5). EI MS, *m/z* (%): 386 (14), 350 (100), 267 (12), 247 (90), 130 (68), 118 (59), 103 (97).

5-(4-Iodophenyl)-3-(4-methoxyphenyl)-2-benzimidazol-2-yl-4,5-dihydropyrrole (**3e**). Isolated as a solvate with benzene, m.p. 125–128 °C. Yield 34%. For $C_{24}H_{20}IN_3O$ (493.34) calculated: 8.52% N; found: 8.49% N. ^{1}H NMR: 3.20 (1 H, m), 3.69 (3 H, s), 3.71 (1 H, m), 4.04 (1 H, m), 5.34 (1 H, m), 6.68–6.98 (2 H, m), 7.00–7.35 (4 H, m), 7.35–7.65 (2 H, m), 7.65–7.80 (2 H, m), 7.80–8.08 (2 H, m), 12.42 (1 H, br). EI MS, *m/z* (%): 493 (25), 375 (89), 359 (62), 119 (12), 103 (100).

3,5-Diaryl-2-benzimidazol-2-ylpyrrolidines (**4a**, **4b**). General Procedure

$NaBH_4$ (0.19 g, 5 mmol) was added in small portions to a stirred warm solution of 0.19 g (0.5 mmol) of corresponding 3,5-diaryl-2-benzimidazol-2-yl-4,5-dihydropyrrole (compound **3a**, **3b**) in 15 ml of methanol during 1.5 h. After stirring for 0.5 h crude product was precipitated by addition of 40 ml of water. After standing at room temperature overnight, it was filtered off, dried and recrystallized from chloroform to give 3,5-diaryl-2-benzimidazol-2-ylpyrrolidines **4a**, **4b**.

2-Benzimidazol-2-yl-3,5-diphenylpyrrolidine (**4a**). M.p. 194–198 °C. Yield 28%. For $C_{23}H_{21}N_3$ (339.17) calculated: 12.38% N; found: 12.20% N. ^{1}H NMR: 1.93 (1 H, m), 2.72 (1 H, m), 3.46 (1 H, br s), 3.86 (1 H, m), 4.57 (1 H, m), 4.61 (1 H, m), 6.63–8.07 (14 H, m), 12.28 (1 H, s). ^{13}C NMR: 46.0, 52.6, 62.5, 64.3, 111.9 (broad, C-4 of benzimidazole), 119.1 (broad, C-7 of benzimidazole), 121.8 (broad, C-5 and C-6 of benzimidazole), 127.00, 127.40 (*p*-C_{Ar}), 127.29, 128.11, 128.89, 129.08 (*o*-,*m*-C_{Ar}), 135.0 (broad, C-3*a* of benzimidazole), 143.5, 145.0 (*i*-C_{Ar}), 143.8 (broad, C-7*a* of benzimidazole), 158.1 (C-2 of benzimidazole). EI MS, *m/z* (%): 339 (5), 235 (52), 219 (45), 119 (100), 104 (13).

3-(4-Chlorophenyl)-5-(4-methylphenyl)-2-benzimidazol-2-ylpyrrolidine (**4b**). M.p. 108–112 °C. Yield 30%. For $C_{24}H_{22}ClN_3$ (387.90) calculated: 10.83% N; found: 10.80% N. ^{1}H NMR: 1.88 (1 H, m), 2.27 (3 H, s), 2.65 (1 H, m), 3.45 (1 H, br s), 3.80 (1 H, m), 4.49 (1 H, m), 4.55 (1 H, m), 6.45–8.00 (12 H, m), 12.23 (1 H, s). ^{13}C NMR: 21.4 (CH_3), 45.9 and 51.9 (C-3 and C-4 of pyrrolidine), 62.3 and 64.3 (C-2 and C-5 of pyrrolidine), 111.9 (broad, C-4 of benzimidazole), 119.0 (broad, C-7 of benzimidazole), 122.0 (broad, C-5 and C-6 of benzimidazole), 127.2, 129.0 (*o*-,*m*-C_{Ar} of $C_6H_4CH_3$-4), 129.5, 130.0 (*m*-,*o*-C_{Ar} of C_6H_4Cl-4), 131.6 (*p*-C_{Ar} of C_6H_4Cl-4), 135.0 (broad, C-3*a* of benzimidazole), 136.4, 141.7, 142.6 (*i*-,*p*-C_{Ar} of $C_6H_4CH_3$-4 and *i*-C_{Ar} of C_6H_4Cl-4), 143.8 (broad, C-7*a* of benzimidazole), 157.9 (C-2 of benzimidazole). EI MS, *m/z* (%): 387 (2), 255 (31), 249 (100), 233 (83), 138 (16), 118 (14), 103 (63).

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