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SHORT COMMUNICATIONS

1,4-Diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole—A New Heterocyclic System. Synthesis and Properties

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Abstract—The first representative of a new heterocyclic system, 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]-benzimidazole, has been synthesized by condensation of ethyl (2-benzoyl-1*H*-benzimidazol-1-yl)acetate with hydrazine hydrate, followed by thermal heterocyclization of intermediate bis-hydrazone.

Keywords: 5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole, synthesis, thermal heterocyclization, hydrazine hydrate, ethyl (2-benzoyl-1*H*-benzimidazol-1-yl)acetate.

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Seven-membered nitrogen-containing heterocycles, as well as benzimidazole derivatives, exhibit a broad spectrum of pharmacological activity [1–4]. These heterocycles are structural units of a number of commercial drugs such as phenazepam, tofisopam, omeprazole, esomeprazole, mebendazole, etc. The concept of combining pharmacophoric groups in a single molecule underlies an important line in the design of new medicinal agents. For example, fused benzimidazo-1,4-diazepin-2-ones [5] are considered to be potential antitumor agents, while 4,5-dihydro[1,2,4]triazepino-[3,5-*a*]benzimidazole derivatives possess bacteriostatic and fungicidal properties [6].

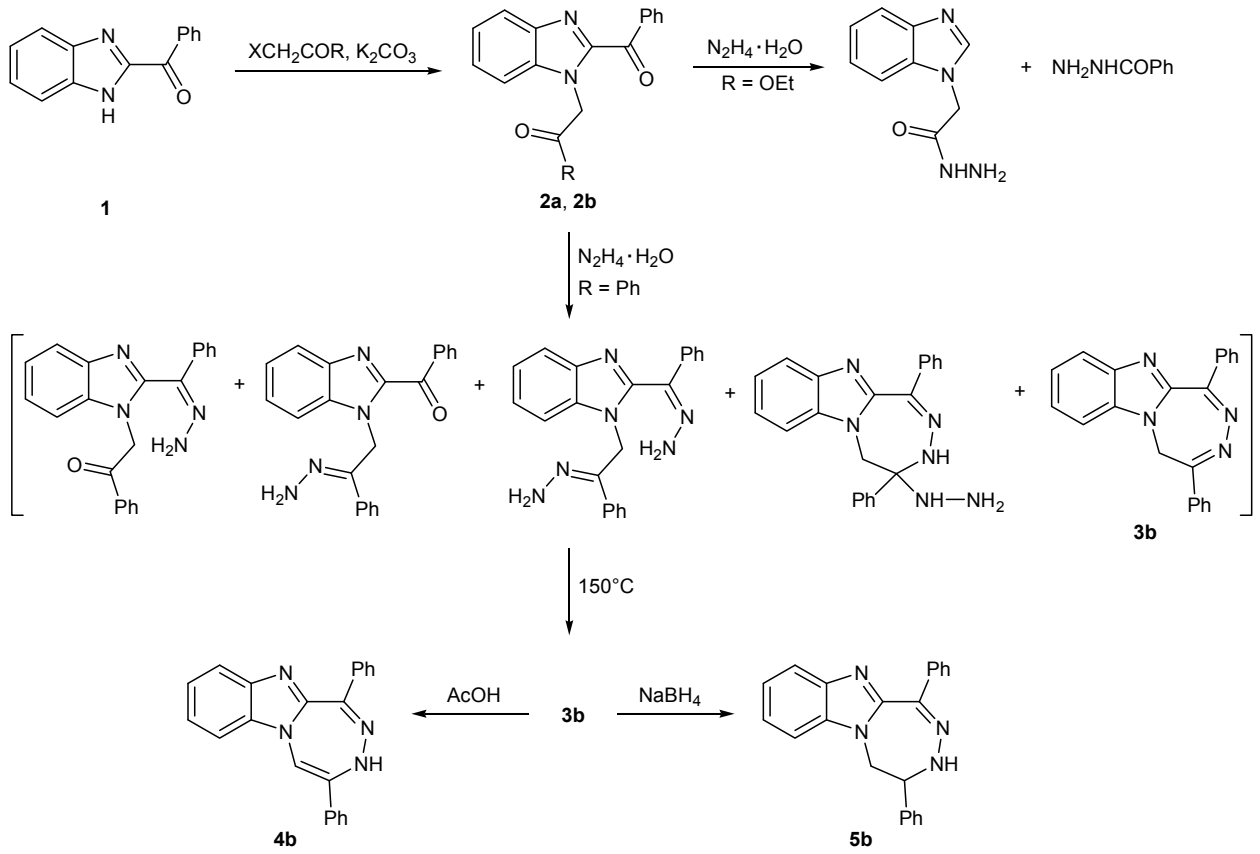
On the other hand, triazepinobenzimidazoles belong to a poorly explored heterocyclic system. Several examples of synthesis of 1,2,4- [6–8] and 1,3,5-triazepinobenzimidazoles have been reported [9], whereas no published data are available on 1,2,5-triazepinobenzimidazoles.

The present communication reports a synthetic approach to the first representative of a new heterocyclic system, 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole, starting from 1*H*-benzimidazol-2-yl(phenyl)methanone (**1**). The alkylation of **1** with ethyl iodoacetate in DMF in the presence of potassium carbonate gave ethyl (2-benzoyl-1*H*-benzimidazol-1-yl)acetate (**2a**) in a good yield. Compound **1** failed to react with ethyl chloroacetate. By analogy with the data of [10, 11], treatment of **2a** with hydrazine hydrate was expected to produce the corresponding hydrazone. However, the reaction of **2a** with hydrazine hydrate in boiling methanol involved elimination of the benzoyl group with the formation of 2-(1*H*-benzimidazol-1-yl)acetohydrazide and benzohydrazide.

The alkylation of **1** with α-bromoacetophenone under similar conditions afforded 2-(2-benzoyl-1*H*-benzimidazol-1-yl)-1-phenylethanone (**2b**). Compound **2b** reacted with hydrazine hydrate in methanol to give a mixture of several products (according to the ^{1}H NMR data), one of which was 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (**3b**); the fraction of **3b** in the product mixture did not exceed 5–7%. After heating the product mixture for 2 h at 150°C, triazepinobenzimidazole **3b** was isolated in 50% yield.

Compound **3b** underwent prototropic isomerization to 1,4-diphenyl-3*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (**4b**) on heating in boiling acetic acid. The reduction of **3b** with sodium tetrahydridoborate afforded (4*RS*)-1,4-diphenyl-4,5-dihydro-3*H*-[1,2,5]triazepino-[5,4-*a*]benzimidazole (**5b**). Attempted oxidation of **3b** with selenium dioxide in acetic acid led to the formation of initial compound **2b**. A similar result was obtained previously [12] in the oxidation of 4-methyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine with selenium dioxide in dioxane.

Ethyl (2-benzoyl-1*H*-benzimidazol-1-yl)acetate (2a) and 2-(2-benzoyl-1*H*-benzimidazol-1-yl)-1-phenylethanone (2b) (*general procedure***).** Compound



X = I, R = OEt (**a**); X = Br, R = Ph (**b**).

1, 15.95 g (71.85 mmol), was dissolved in 160 mL of DMF, 107.8 mmol of ethyl iodoacetate (in the synthesis of **2a**) or α-bromoacetophenone (in the synthesis of **2b**) and 39.66 g (278.4 mmol) of finely powdered potassium carbonate were added, and the resulting suspension was stirred for 4 h on heating on a boiling water bath. The mixture was poured into 600 mL of water, and the precipitate was filtered off, dried, and recrystallized from methanol.

Compound **2a**. Yield 75%, white crystals, mp 68–69°C. ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, CH_3, J = 7.2 Hz), 4.21 q (2H, CH_2, J = 7.2 Hz), 5.44 s (2H, CH_2), 7.38 t (1H, H_{arom}, J = 7.6 Hz), 7.46 t (1H, H_{arom}, J = 7.6 Hz), 7.57 t (2H, H_{arom}, J = 7.2 Hz), 7.66–7.74 m (2H, H_{arom}), 7.86 d (1H, H_{arom}, J = 8.0 Hz), 8.40 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.0 (CH_3), 48.5 (CH_2), 63.0 (CH_2), 113.0, 123.4, 125.4, 127.6, 129.9, 133.0, 135.1, 138.0, 138.1, 143.2, 147.8, 169.7 (C=O), 187.1 (C=O). Found, %: C 70.11; H 5.25; N 9.08. $C_{18}H_{16}N_2O_3$. Calculated, %: C 70.12; H 5.23; N 9.09.

Compound **2b**. Yield 83%, white crystals, mp 186–187°C. IR spectrum, ν, cm^{-1}: 1680 s (C=O), 1640 s (C=O), 1600 s (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 6.27 s (2H, CH_2), 7.35–7.47 m (2H, H_{arom}), 7.53–7.63 m (4H, H_{arom}), 7.65–7.77 m (3H, H_{arom}), 7.88 d (1H, H_{arom}, J = 8.0 Hz), 8.14 d (2H, H_{arom}, J = 7.6 Hz), 8.37 d (2H, H_{arom}, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 53.6 (CH_2), 113.2, 123.3, 125.2, 127.4, 129.8, 130.2, 130.6, 133.0, 135.1, 135.6, 136.5, 138.2, 138.4, 143.4, 148.2, 187.2 (C=O), 194.3 (C=O). Found, %: C 77.62; H 4.76; N 8.21. $C_{22}H_{16}N_2O_2$. Calculated, %: C 77.63; H 4.74; N 8.23.

1,4-Diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (3b). A mixture of 5.8 g (17.06 mmol) of compound **2a**, 70 mL of methanol, and 1.11 mL (22.18 mmol) of hydrazine hydrate was refluxed for 7 h. The solution was cooled to room temperature and poured into 500 mL of brine. The precipitate was filtered off, dried, and heated for 2 h at 150°C. The melt was cooled to room temperature, 10 mL of methanol was added, and the mixture was stirred until complete dissolution, maintaining it slightly boiling. The solution was cooled to room temperature, and the precipitate was filtered off and washed with methanol. Yield 2.85 g (50%), bright yellow crystals, mp 221–

222°C. IR spectrum, ν, cm^{-1}: 1620 m (C=C_{arom}), 1450 s (C=N–N=C). ^1H NMR spectrum, δ, ppm: 4.74 d and 6.22 d (1H each, CH_2, J = 14.0 Hz), 7.31 t (1H, H_{arom}, J = 7.6 Hz), 7.42 t (1H, H_{arom}, J = 8.0 Hz), 7.46–7.54 m (6H, H_{arom}), 7.77 d (1H, H_{arom}, J = 8.0 Hz), 8.09 d (2H, H_{arom}, J = 6.8 Hz), 8.13 d (2H, H_{arom}, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 42.5 (CH_2), 112.4, 122.4, 124.9, 126.0, 129.3, 130.0, 130.7, 131.0, 132.5, 132.6, 134.5, 135.4, 137.2, 144.7, 145.5, 149.2, 154.3. Found, %: C 78.54; H 4.81; N 16.64. $C_{22}H_{16}N_4$. Calculated, %: C 78.55; H 4.79; N 16.65.

1,4-Diphenyl-3*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (4b). A mixture of 0.4 g (1.19 mmol) of compound **3b** and 5 mL of glacial acetic acid was refluxed for 10 h. After cooling, the precipitate was filtered off and washed with methanol. Yield 0.12 g (30%), dark yellow needles, mp 223–224°C. ^1H NMR spectrum, δ, ppm: 7.38 t (1H, H_{arom}, J = 6.8 Hz), 7.45–7.66 m (8H, H_{arom},), 7.98 d (1H, H_{arom}, J = 8.0 Hz), 8.29 d (2H, H_{arom}, J = 7.6 Hz), 8.52 d (1H, H_{arom}, J = 8.4 Hz), 9.06 d (2H, H_{arom}, J = 7.6 Hz), 9.63 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 115.7, 117.1, 121.3, 125.3, 127.9, 129.7, 130.2, 130.3, 130.5, 130.7, 131.4, 132.5, 137.4, 137.9, 138.7, 140.4, 143.4, 149.2. Found, %: C 78.54; H 4.81; N 16.64; $C_{22}H_{16}N_4$. Calculated, %: C 78.55; H 4.79; N 16.65.

(4*RS*)-1,4-Diphenyl-4,5-dihydro-3*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (5b). Sodium tetrahydridoborate, 0.45 g (11.9 mmol), was added to a mixture of 0.4 g (1.19 mmol) of compound **3b** and 7 mL of anhydrous dioxane, and the resulting suspension was refluxed for 1.5 h with stirring. Methanol, 10 mL, was added, and the mixture was refluxed for an additional 1 h with stirring. The solution was cooled to room temperature, and the precipitate was filtered off. The organic phase was poured into 100 mL of water, and the oily material was separated and dissolved in 1 mL of methanol on heating. The resulting solution was diluted with 5 mL of diethyl ether, and the precipitate was filtered off and washed with diethyl ether. Yield 0.1 g (25%), white crystals, mp 176–177°C. IR spectrum, ν, cm^{-1}: 3360 m (NH), 1600 s (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 4.52–4.78 m (3H, CH_2, CH), 7.10–7.17 m (2H, H_{arom},), 7.23–7.31 m (5H, H_{arom}), 7.39 t (2H, H_{arom}, J = 7.6 Hz), 7.49 d (1H, H_{arom}, J = 7.2 Hz), 7.62 d (2H, H_{arom}, J = 7.2 Hz), 8.67 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 53.3 (CH_2), 64.6 (CH), 111.7, 121.5, 124.0, 124.6, 128.6, 128.9, 129.1, 129.9, 130.5, 131.4, 134.0, 137.7, 139.7, 142.3, 144.2, 149.1. Found, %: C 78.06; H 5.37; N 16.57. $C_{22}H_{18}N_4$. Calculated, %: C 78.08; H 5.36; N 16.56.

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The IR spectra were recorded in KBr on a Specord IR-75 spectrometer. The melting points were measured on a Boetius type melting point apparatus and are uncorrected. The elemental analyses were obtained with a Vario EL Cube Elementar analyzer.

CONFLICT OF INTERESTS

The author declares the absence of conflict of interests.

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