Reactions of [2-(Bromomethyl)phenyl](4-chlorophenyl)methanone: A New Synthesis of [1,3]Thiazolo[3,2-*b*][2,4]benzodiazepine, Benzimidazo[1,2-*b*][2,4]benzodiazepine and Benzimidazo[1,2-*b*][2]benzazepine Derivatives

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A new approach to the development of a number of azolo-condensed azepines and diazepines has been proposed. The method for the synthesis of [1,3]thiazolo[3,2-*b*][2,4]benzodiazepine, benzimidazo[1,2-*b*][2,4]benzodiazepine and benzimidazo[1,2-*b*][2]benzazepine derivatives involves the reaction of [2-(bromomethyl)phenyl](4-chlorophenyl)methanone with 5-methyl-1,3-thiazol-2-amine, 1*H*-benzimidazol-2-amine and 1,2-dimethyl-1*H*-benzimidazole. The formation of the quaternary salt of the initial diazole has been done under mild conditions in MeCN. The following intramolecular condensation has been realized by heating 2-amino azolium salts in AcOH or in Et₃N as in the case of 2-methyl azolium salt. The structures of these cyclic compounds have been confirmed by mass spectrometry measurements, elemental analysis and NMR spectra.

Introduction

The generally recognized heterocyclization methods suggested by Chichibabin involves the reaction of α -methyl and α -amino pyridines with α -halo ketones. On the basis of the ‘principle of vinylogy’, this pattern was earlier done by using their vinylogs 1-[2-(halogenomethyl)phenyl]methanones in order to produce aryl substituted pyrido[1,2-*b*][2,4]benzodiazepines [1]. Compounds containing the benzodiazepine fragment in their

structures appeared to be quite promising for biological activity tests considering their potential psychological and pharmaceutical effects [2, 3]. The majority of the well known so far medicinal preparations (based on benzodiazepine) are the derivatives of azolo-condensed systems (*Midazolam*, *Chlonazolam*, *Pirazolam*) containing a (het)aryl substituent in the azepine cycle. This very fact made us try to prepare the azolo-condensed benzo(di)azepines on the basis of [2-

(bromomethyl)phenyl](aryl)methanones.

Making use of 2-methyl and 2-amino diazoles in the Chichibabin vinylogous scheme provides the opportunity to produce the derivatives of diazolo[*b*][2,4]benzodiazepine and diazolo[*b*][2]benzazepine systems which have not been extensively studied yet. At the same time, there are some data on the biological activity of the compounds mentioned above. Imidazo[1,2-*b*][2]benzazepines appeared to be quite effective as antiarrhythmic agents [4], for treating diseases and conditions of the central nervous system (CNS) [5,6] and antiviral preparations [7]. Thiazolo[3,2-*b*][2,4]benzodiazepines are useful in treating conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands [8], as inhibitors of platelet aggregation [9,10].

Methods for the synthesis of the derivatives of diazolo[*b*][2,4]benzodiazepines and diazolo[*b*][2]benzazepines, which have been described in literature, are mainly based on the scheme that involves the annulations of the diazole fragment. In a few cases concerning the construction of 2,4-benzodiazepine or 2-benzazepine cycles, phthaloyl chloride [11-13], 2-(bromomethyl)benzoate [14] and *o*-xylylene dibromide [15] have been used to produce the partially hydrogenated derivatives of the above systems. This paper describes a new method of azolo[*b*][2,4]benzodiazepines and azolo[*b*][2]benzazepine syntheses which consists in the interaction of [2-(bromomethyl)phenyl](4-

chlorophenyl)methanone (**1**) with 2-methyl and 2-amino diazoles.

Results and discussion

The reaction of bromoketone **1** with 5-methyl-1,3-thiazol-2-amine and 5-methyl-1,3,4-thiadiazol-2-amine was done on heating the mixture in MeCN (Scheme 1).

Scheme 1. The reactions with 2-aminoazoles.

According to the NMR ¹H studies, the product of the subsequent cyclization 2-amino-3-[2-(4-chlorobenzoyl)benzyl]-5-methyl-1,3-thiazol-3-ium bromide (**2**) is also present in the

reaction mixture as early as at the quaternization stage of the initial amino thiazole. 10-(4-Chlorophenyl)-2-methyl-5H-[1,3]thiazolo[3,2-*b*][2,4]benzodiazepin-4-ium bromide (**3**) was isolated as a pure substance when the quaternization product was crystallized in acetic acid. Unlike thiazolium salt **2**, the quaternary thiadiazolium salt (**4**) appeared to be more inert and it was isolated as a pure substance, and it failed to undergo ring formation. The reason for this was probably a low basicity of the amino group in the case of the more electron-seeking system of 1,3,4-thiadiazole. All attempts to form a ring from salt **4** by the interaction with bases ($\text{Et}_3\text{N}/\text{acetone}$, $\text{K}_2\text{CO}_3/\text{acetone}$) resulted in the destruction of the initial salt. The structure of the alkylation product **4** was proved by NOE experimental data. Exposure to the rays at the frequency given by methylene group at 5.47 ppm, the growth of the intensity of the amino group signal (9.96 ppm) and the doublet of the aromatic proton of the benzene cycle at 7.48 ppm (H-6') was observed which accounted for the formation of 3-benzyl derivative 5-methyl-1,3,4-thiadiazol-2-amine.

The interaction of 1*H*-benzimidazol-2-amine with bromoketone **1** in MeCN leads to the formation of large number by-products that interfere with the purification of the final product of the reaction. The more yielding transformation was done in acetone in the presence of potash at room temperature and resulted in tertiary amine (**5**). Intramolecular condensation of the base was

carried out on heating it in acetic acid, the derivative of 12*H*-benzimidazo[1,2-*b*][2,4]benzodiazepine (**6**) being produced. On heating above 200 °C substance **5**, formed a ring producing **6**, therefore, it made impossible to determine the melting point of starting amine **5**.

Alkylation of 1,2-dimethylbenzimidazole with the help of bromoketone **1** in acetone at room temperature caused the formation of quaternary salt **7** with high yield. Substance **7** appeared to be quite stable to the heating in AcOH, whereas heating it with bases resulted in the intramolecular condensation and production of 7-(4-chlorophenyl)-5-methyl-5*H*,12*H*-benzimidazo[1,2-*b*][2]benzazepin-13-ium bromide (**8**) (Scheme 2).

Scheme 2. The reaction with 1,2-dimethylbenzimidazole.

The structures of the cyclization products **3**, **6**, **8** were confirmed by mass-spectrometry measurements, elemental analysis and by comparing their spectra to those of the earlier prepared salts of 11*H*-pyrido[1,2-*b*][2,4]benzodiazepinium [1] and 5,10-dihydroazepino[2,1-*b*]benzimidazolium [16].

The characteristic features of azolo-condensed diazepines **3**, **6** and azepine **8** are their high rates of the conformational transformations. This was supported by the coalescence and the pronounced widening of the proton signals in the methylene groups in NMR ^1H spectra (at 20 °C) which recorded as highly wide double-proton singlets in the case of substance **3** in the range of 5.4–6.9 ppm.

Conclusions

Consequently, on the basis of ‘principle of vinylogy’ we have proposed a new way of construction of 2,4-benzodiazepine and 2-benzazepine cycles on 1,3-diazoles. The method consists in using *o*-(bromomethyl)benzophenone derivatives in the scheme proposed by Chichibabin. It allows producing aryl substituted derivatives of a series of azolo-condensed hetero systems such as 5*H*-[1,3]thiazolo[3,2-*b*][2,4]benzodiazepine, 12*H*-benzimidazo[1,2-*b*][2,4]benzodiazepine and 5*H*,12*H*-benzimidazo[1,2-*b*][2]benzazepine which have not earlier been affordable.

Experimental part

^1H NMR were recorded on the Varian VXR-400, internal standard was TMS. IR spectra were recorded on the PerkinElmer Spectrum BX. Elemental analyses were made on the universal analyzer vario MikroCube, for the determination of halogens the Sheninger method is used. Melting points were determined on a Tile heating instrument. A check on the purity of the obtained compounds was affected by the GLC mass

spectrometric method on an Agilent 1100 Series instrument, with an Agilent LC/MSD SL selective detector (samples were introduced in a matrix of $\text{CF}_3\text{CO}_2\text{H}$, ionization by EI). [2-(Bromomethyl)phenyl](4-chlorophenyl)methanone **1** was prepared as reported [17]. All other chemicals and solvents are commercially available and were used without further purification.

*10-(4-Chlorophenyl)-2-methyl-5H-[1,3]thiazolo[3,2-*b*][2,4]benzodiazepin-4-ium bromide 3.*

The mixture of 1 g (3.2 mmol) of [2-(bromomethyl)phenyl](4-chlorophenyl)methanone **1** and 1.08 g (3.5 mmol) of 5-methyl-1,3-thiazol-2-amine in 10 mL of anhydrous MeCN was heated for 8 h at 60 °C, allowed to stand over 24 h at room temperature. The precipitate was filtered off, washed with acetone, and presented a mixture of 2-amino-3-[2-(4-chlorobenzoyl)benzyl]-5-methyl-1,3-thiazol-3-ium bromide **2** and 10-(4-chlorophenyl)-2-methyl-5*H*-[1,3]thiazolo[3,2-*b*][2,4]benzodiazepin-4-ium bromide **3** (1:1). The resulting mixture was dissolved in 10 ml of AcOH and boiled for 3 hours. The solvent was evaporated and 10 ml of acetone was added to the residue. The precipitate was filtered off, washed with acetone, recrystallized from MeOH to afford colorless solid of **3**.

Yield: 0.62 g, 48%; mp > 300 °C (MeOH); ^1H NMR (400 MHz, DMSO- d_6 , J Hz): δ 8.16 (1H, s, H-3), 7.92 (2H, d, 3J = 8.5, H-2',

H-6'), 7.88 (1H, d, $^3J = 8.0$, H-7), 7.75 (1H, d, $^3J = 8.0$, H-6), 7.70 (2H, d, $^3J = 8.5$, H-3', H-5'), 7.64 (1H, t, $^3J = 8.0$, H-8), 7.49 (1H, d, $^3J = 8.0$, H-9), 6.85 (1H, broad. s, C(5)H_AH_B), 5.50 (1H, broad. s, C(5)H_AH_B), 2.58 (3H, s, CH₃) ppm; MS (CI): $m/z = 325.8$ ([M-Br]⁺, 100%), 327.7 (28%); Analysis (calcd, found)%: C (53.28, 53.34); H (3.48, 3.50); N (6.90, 6.92); S (7.90, 7.92).

2-Amino-3-[2-(4-chlorobenzoyl)benzyl]-5-methyl-1,3-thiazol-3-ium bromide 2 (50% in mixture). IR (KBr): ν 3136 (NH₂), 1651 (C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, J Hz): δ 9.70 (2H, broad. s, NH₂), 7.87 (1H, d, $^3J = 8.0$, H-6'), 7.77 (2H, d, $^3J = 8.5$, H-2'', H-6''), 7.58 (2H, d, $^3J = 8.5$, H-3'', H-5''), 7.51 (2H, m, H-4', H-5'), 7.18 (1H, d, $^3J = 8.0$, H-3'), 7.07 (1H, s, H-4), 5.45 (2H, s, CH₂), 2.21 (3H, s, CH₃).

2-Amino-3-[2-(4-chlorobenzoyl)benzyl]-5-methyl-1,3,4-thiadiazol-3-ium bromide 4.

The mixture of 1.08 g (3.2 mmol) of methanone **1** and 0.40 g (3.5 mmol) of 5-methyl-1,3,4-thiadiazol-2-amine in 10 mL of anhydrous MeCN was heated for 8 h at 60 °C, allowed to stand over 24 h at room temperature. The precipitate was filtered off, washed with acetone, recrystallized from MeNO₂ to afford colorless solid of **4**.

Yield: 0.48 g, 35%; mp 231–233 °C (MeNO₂); IR (KBr): ν 3095 (NH₂), 3013 (NH₂), 2899, 1664 (C=O), 1628, 1579, 1550, 1264, 1090, 923, 737 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, J Hz): δ 7.69–7.60 (5H, m, H-3', H-

5', H-6', H-2'', H-6''), 7.52 (1H, t, $^3J = 8.0$, H-4'), 7.46 (2H, d, $^3J = 8.5$, H-3'', H-5''), 9.96 (2H, broad. s, NH₂), 5.47 (2H, s, CH₂), 2.29 (3H, s, CH₃) ppm; MS (CI): $m/z = 344.9$ ([M-Br]⁺, 100%), 346.7 (30%); Analysis (calcd, found)%: C (48.07, 48.10); H (3.56, 3.60); N (9.89, 9.86); S (7.55, 7.58).

{2-[(2-Amino-1H-benzimidazol-1-yl)methyl]phenyl}(4-chlorophenyl)methanone 5.

To a solution of 1.08 g (3.2 mmol) of methanone **1** in 20 mL of anhydrous acetone was added 0.6 g of K₂CO₃ and stirred the mixture for 3 hours at room temperature. The solvent was evaporated in vacuo, the residue was washed with water. Solid recrystallized from *i*-PrOH to afford colorless solid of **5**.

Yield: 0.86 g, 74%; mp > 210 °C (decomp., *i*-PrOH); IR (KBr): ν 3369 (NH₂), 3328 (NH₂), 3059, 1669 (C=O), 1649, 1587, 1555, 1460, 1295, 1269, 1243, 1091, 930, 739 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, J Hz): δ 7.77 (2H, d, $^3J = 8.5$, H-2'', H-6''), 7.46 (2H, m, H-4, H-6), 7.38 (1H, t, $^3J = 8.0$, H-5), 7.12 (1H, d, $^3J = 8.0$, H-4'), 6.92 (1H, t, $^3J = 8.0$, H-6''), 6.85–6.75 (3H, m, H-3, H-5'', H-7''), 6.47 (2H, broad. s, NH₂), 5.36 (2H, s, CH₂) ppm; ¹³C NMR (100.7 MHz, DMSO-d₆): δ 196.5 (C=O), 155.9 (C-2), 143.6, 136.4, 134.8, 132.5, 132.4 (2C), 132.1 (2C), 130.4, 129.4 (4C), 127.4 (2C), 121.3, 118.8, 115.5, 108.3, 43.7 (CH₂) ppm; MS (CI): $m/z = 362.7$ ([M+H]⁺, 100%), 364.7 (29%);

Analysis (calcd, found)%: C (69.71, 69.45); H (4.46, 4.50); Cl (9.80, 9.82); N (11.61, 11.57).

7-(4-Chlorophenyl)-12H-benzimidazo[1,2-b][2,4]benzodiazepine 6.

A solution of 0.72 g (2.0 mmol) of {2-[(2-amino-1H-benzimidazol-1-yl)methyl]phenyl}(4-chlorophenyl)methanone **5** in 20 ml of AcOH was boiled for 3 hours. The solvent was evaporated and 10 mL of acetone was added to the residue. The precipitate was filtered, washed with a small amount of acetone, recrystallized from MeOH to afford yellow solid of **6**.

Yield: 0.35 g, 51%; mp 293–295 °C (decomp., MeOH); IR (KBr): ν 3059, 1581, 1556, 1408, 1091, 747, 729 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6 , J Hz): δ 7.86 (2H, d, $^3J = 8.5$, H-2', H-6'), 7.83 (1H, t, $^3J = 8.0$, H-10), 7.75 (1H, d, $^3J = 8.0$, H-11), 7.64 (3H, m, H-4, H-3', H-5'), 7.55 (1H, d, $^3J = 8.0$, H-1), 7.45 (1H, d, $^3J = 8.0$, H-9), 7.34 (1H, d, $^3J = 8.0$, H-8), 7.24 (1H, t, $^3J = 8.0$, H-3), 7.17 (1H, t, $^3J = 8.0$, H-2), 5.42 (2H, broad. s, CH_2) ppm; MS (CI): $m/z = 344.7$ ($[\text{M}+\text{H}]^+$, 100%), 346.8 (30%); Analysis (calcd, found)%: C (73.36, 73.40); H (4.10, 4.08); Cl (10.31, 10.33); N (12.22, 12.20).

1-[2-(4-Chlorobenzoyl)benzyl]-2,3-dimethyl-3H-benzimidazol-1-ium bromide 7.

To a solution of 0.8 g (5.5 mmol) of 1,2-dimethyl-1H-benzimidazole in 10 mL of anhydrous acetone was added 1.55 g (5.0 mmol)

of methanone **1** and allowed to stand over 72 h at room temperature. The formed precipitate was filtered off, washed with acetone, recrystallized from MeNO₂ to afford colorless solid of **7**.

Yield: 1.44 g, 63%; mp 261–262 °C (MeNO₂); IR (KBr): ν 3008, 2868, 1656 (C=O), 1583, 1474, 1278, 1091, 926, 775, 752 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6 , J Hz): δ 7.93 (1H, d, $^3J = 8.0$, H-6), 7.65–7.53 (10H, m, H-3–H-5, H-4'–H-5', H-2'–H-6''), 7.25 (1H, d, $^3J = 8.0$, H-6'), 5.92 (2H, s, CH_2), 3.96 (3H, s, NCH_3), 2.84 (3H, s, CCH_3) ppm; ^{13}C NMR (100.7 MHz, DMSO- d_6): δ 196.3 (C=O), 153.5 (C-2), 139.4, 136.8, 135.5, 134.0, 132.3 (3C), 132.2, 131.4, 130.4, 129.4 (3C), 128.7, 126.9, 126.8, 113.7, 113.5, 47.3 (CH_2), 32.6 (N- CH_3), 11.5 (2- CH_3) ppm; MS (CI): $m/z = 375.9$ ($[\text{M}-\text{Br}]^+$, 100%), 377.8 (28%); Analysis (calcd, found)%: C (60.61, 60.66); H (4.42, 4.39); N (6.15, 6.14).

7-(4-Chlorophenyl)-5-methyl-5H,12H-benzimidazo[1,2-b][2]benzazepin-13-ium bromide 8.

To a solution of 0.46 g (1.0 mmol) of bromide **7** in 20 mL of *i*-PrOH was added 0.5 mL of Et₃N. The reaction mixture was boiled for 3 hours, the precipitate was filtered off, washed with acetone to afford colorless solid of **8**.

Yield: 0.34 g, 77%; mp > 300 °C (MeOH); IR (KBr): ν 3008, 1597, 1566, 1482, 1091, 775 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6 , J Hz): δ 8.49 (1H, d, $^3J = 8.0$, H-1), 8.01 (1H, d, $^3J = 8.0$, H-4), 7.95 (1H, d, $^3J = 8.0$, H-11), 7.75–

7.63 (8H, m, H-2, H-3, H-6, H-10, H-2'-H-6'), 7.45 (1H, t, $^3J = 8.0$, H-9), 7.11 (1H, d, $^3J = 8.0$, H-8), 5.71 (2H, broad. s, CH₂), 4.16 (3H, s, CH₃) ppm; ¹³C NMR (100.7 MHz, DMSO-d₆): δ 155.5 (C-5a), 146.8, 139.9, 136.8, 136.4, 135.6, 133.4, 132.3, 132.2 (2C), 131.7, 130.8, 129.8, 129.6, 129.5 (2C), 127.3, 127.1, 113.8, 113.5, 111.3, 47.9 (CH₂), 32.8 (CH₃) ppm; MS (CI): m/z = 357.9 ([M-Br]⁺, 100%), 359.8 (30%); Analysis (calcd, found)%: C (63.10, 63.15); H (4.14, 4.17); N (6.40, 6.42).

Conclusions

The conclusions section should come in this section at the end of the article, before the acknowledgements. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance.

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