The synthesis of Benzoazines on the base of o-Bromomethylbenzophenone derivatives

Lyudmyla M. Potikha [a], Volodymyr V. Sypchenko[a], Volodymyr O. Kovtunenko[a], Roman I. Zubatyuk[b], Oleg V. Shishkin[b,c]

[a] *Department of Chemistry, Kyiv National Taras Shevchenko University, Kyiv, Ukraine*

[b] *SSI "Institute for Single Crystals" National Academy of Science of Ukraine, Kharkiv, Ukraine*

potikha_l@mail.ru

Convenient and efficient methods for the preparation of novel phthalazine and pyrazino[1,2-b]isoquinoline derivatives are reported that utilized the reaction of [2-(bromomethyl)phenyl](4-chlorophenyl)methanone with 1,2-dinucleophiles. The crystal structure for 11-(4-Chlorophenyl)-1-oxo-1,2-dihydropyrazino[1,2-b]isoquinolin-5-ium bromide is also described.

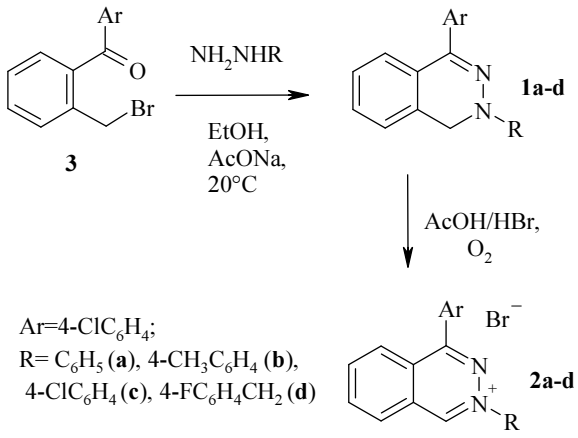
Introduction

A number of natural products and related biologically active compounds contain hetero-aromatic moieties. Thus, the development of strategies for the construction of heteroaromatic compounds is an important subject in organic synthesis and medical chemistry. The [2-(bromomethyl)phenyl](aryl)methanone (*o*-bromomethylbenzophenone) derivatives are specimens of vinylogous series of 2-bromo-1-phenylethanone, and can be use as synthetic equivalents of 1,4-dielectrophylic syntones for synthesis of various heteroaromatic compounds. The using of them in reactions with 1,2-azadinucleophyles leads to benzoazines [1, 2]. We herein describe a facile route to 1-arylphthalazines and pyrazino[1,2-*b*]isoquino-lines which derivatives were shown to selectively and noncompetitively inhibit currents associated activation of AMPA receptor [3], evaluated as potential filaricides [4], CNS-active agents [5], antibiotics [6], antitumor agents [7].

Results and discussion

The main approach to synthesis of 1-arylphthalazines is based on reaction of benzaldehyde acytals derived from benzo-phenones with hydrazines [8]. Now we demonstrated that in this scheme can use *o*-bromomethylbenzophenone derivatives.

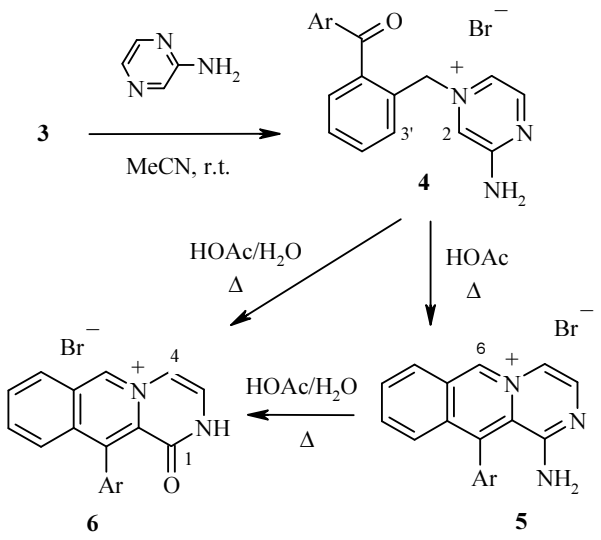
Scheme 1.



The synthesis of 2-R-4-aryl-1,2-dihydrophthalazines (**1, 2**) was performed, according to Scheme 1, via condensation of benzophenone (**3**) with hydrazines, followed by cyclization to provide compounds **1a-d**.

Compounds **1** are non-stable in presence of proton donors and easy oxidizes under room temperature leading to salts **2a**-**d**. The structures of the cyclic products **1** and **2** were determined using their ^{1}H NMR and IR spectra.

Scheme 2.



The benzophenone derivatives are also easy-to-use construction blocs for the formation of isoquinoline moiety. In this work, we wish to report a novel approach to annelation of isoquinoline ring system to pyrazine ring, which relies on intramolecular cyclization of 3-amino-1-(2-benzoylbenzyl)pyrazine-1-ium salts (**4**). Compound **4** was prepared by reaction of benzophenone (**3**) with 2-aminopyrazine in MeCN at room temperature for 3 days, according to Scheme 2. 2-Aminopyrazine can give two different products upon alkylation depending on the reaction conditions: one of them is thermodynamically controlled N4 quaternisation product, the other is kinetically controlled product formed by electophilic attack at N1 atom. In our case, a more stable product, *i. e.* quaternary salt **1** was obtained due to prolonged reaction time. Further heating of pyrazinium bromide **1** solution in glacial AcOH led to the cyclisation product – 1-amino-11-(4-chlorophenyl)pyrazino[1,2-*b*]iso-quinolin-5-ium bromide (**5**). When aqueous AcOH was used as the solvent, the cyclization was accompanied by hydrolysis and gave 11-(4-chlorophenyl)-1-oxo-1,2-dihydropyrazino[1,2-*b*]isoquinolin-5-ium bromide (**6**). The mechanism of the formation of **6** *via* hydrolysis of **5** was confirmed by a reference experiment: heating of the amino derivative **5** in aqueous AcOH led to the oxo derivative **6** in high yield. The structures of the cyclization products **5** and **6** were determined using their ^{1}H and ^{13}C NMR spectra, as well as and homo- and heteronuclear correlation experiments with compound **6** (^{1}H-^{1}H COSY, NOESY, HMQC, HMBC), which allowed assignment of signals in routine NMR spectra. A characteristic feature of ^{1}H NMR spectra of **5** and **6** is one-proton singlet at 10.4 – 10.6 p. p. m., which corresponds to proton at C6. Due to low hydrolytic stability of the amino derivative **5**, the signal of the amino group (very broad singlet at 6.50 p. p. m.) was observed only immediately after the solution of **5** in DMSO-d^6 was prepared. After 15 min, the signals of the hydrolisys product **6** appeared in the spectrum of **5**. The upfield shift of signals of protons at C3 and C4 in ^{1}H NMR spectrum of **6** by *ca*. 0.5 p. p. m. comparing to **5** is indicative of re-distribution the electron density in tricyclic ring system. In particular, aromaticity of the pyrazine ring, as well as its and involvement into delocalization of positive charge are

diminiched in **6** as compared to **5**. This fact also affected chemical shifts of the signals in ^{1}H NMR spectra which correspond to the protons of the isoquinoline ring system. The doublet of proton at C-10 was shifted downfield by more than 0.6 p. p. m. in the case of **6** due to influence of the carbonyl group, whereas the signals of protons at C9, and to a lesser extent – at C6 and *p*-chlorophenyl substituent – were observed at higher field. These conclusions were confirmed by ^{13}C NMR spectra of **6**. The signals corresponding to C3 and C4 were observed at 112 – 126 p. p. m., whereas the rest of the resonances – at lower field.

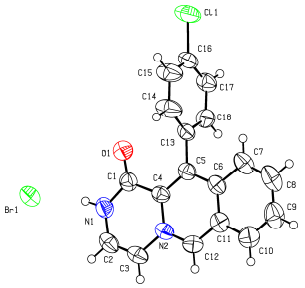


Figure 1. Molecular structure of **6** according to X-Ray diffraction data

Finally, the structure of **6** was unambiquosuly confirmed by X-Ray diffraction study (Figure 1). Analysis of the molecular geometry confirmed the conclusions drawn from NMR data. The length of the N2–C12 bond 1.325(4) Å, which is close to the standard mean value for double bonds 1.29 Å, clearly indicates that the positive charge of organic cation is localized mainly on N2 atom. The conjugation in amide fragment is relatively weak, according to the lengths of the N1–C1 (1.360(4) Å) and C1–O1 (1.206(3) Å) bonds. These values correspond to mean values for isolated N–C and C=O bonds (1.36 Å and 1.21 Å), rather than mean values for amides (1.33 Å and 1.23 Å, respectively). In crystals, the cations of **6** and bromine anions are linked by the N1–H1…Br1 (H…Br 2.46 Å, N-H…Br 168°), C2–H2…Br1^{i} [i: 2-x,-y,1-z] (H…Br 2.72 Å, C–H…Br 165°) and C12–H12…Br1^{ii} [ii: -1+x,y,-1+z] (H…Br 2.78 Å, C-H…Br 140°) intermolecular hydrogen bonds.

In our opinion, acidic catalysis of the cyclization can be explained by considering the reaction mechanism as electrophilic aromatic substitution. The reaction is activated by a donor substituent at γ position of the azine ring, with the assistance of protonated carbonyl group of **4**.

Conclusions

In conclusions, the reactions of *o*-bromomethylbenzophenone with 1,2-azadinucleophyles are examined, and a novel approach to synthesis of 2-R-4-aryl-1,2-dihydrophthalazines is proposed, which is based on the reaction of *o*-bromomethylbenzophenone derivatives with hydrazines. A novel approach to synthesis of pyrazino[1,2-*b*]isoquinolinium salts is based on intramolecular cyclization of 3-amino-1-benzylpirazinium salts derived from *o*-bromomethylbenzophenone. The method allows for the preparation of previously inaccessible 1-amino- and 1-oxo-pyrazino[1,2-*b*]isoquinoline derivatives.

Experimental part

4-(4-Chlorophenyl)-2-phenyl-1,2-dihydrophthalazine (**1a**). To the solution of compound **3** (0.5 g, 1.6 mmol) in 10 mL of

ethanole under inert atmosphere with intensive stirring was added phenylhydrazine (0.19 g, 1.8 mmol) and AcONa (0.4 g). The reaction mixture was allowed for 1 d. at the r.t. and the formed precipitate was filtered and washed with water. Yield: 0.35 g (69%). M.p. 98–99˚C (*i*-PrOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (2H, d, ^3J = 8.4 Hz, H-2'', H-6''), 7.57-7.32 (9H, m, Ar-H), 7.25 (1H, d, ^3J = 7.6 Hz, H-8), 6.99 (1H, t, ^3J = 7.2 Hz, H-4'), 4.84 (2H, s, CH_2) ppm; IR (KBr): ν 3028, 1597, 1491, 1305, 1130, 1085, 747 cm^{-1}; Anal. calcd. for $C_{20}H_{15}ClN_2$: C 75.35, H 4.74, N 8.79. Found: C 75.18, H 4.77, N 8.71.

Compounds **1b-d** were obtained under same procedure for **1a**.

4-(4-Chlorophenyl)-2-phenyl-phthal-azin-2-ium bromide (**2a**). To the mixture of compound **1a** (0.32 g, 1.0 mmol) in 10 mL AcOH and 10 mL EtOH was added 0.5 mL 6N HBr and the mixture was allowed to stand at r.t. for 3 d. The solvent was evaporated in vacuum and 10 mL Et_2O was added to residue. The formed precipitate of **2a** was filtered. Yield 0.28 g (70%). M.p. 228–230˚C (*i*-PrOH-Hexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (1H, s, H-1), 8.90 (1H, d, ^3J = 8.0 Hz, Ar-H), 8.53 (2H, m, Ar-H), 8.42 (1H, d, ^3J = 8.0 Hz, Ar-H), 8.22 (2H, m, Ar-H), 8.03 (1H, d, ^3J = 9.2 Hz, Ar-H), 7.97 (2H, d, ^3J = 8.4 Hz, H-2'', H-6''), 7.81 (4H, m, Ar-H) ppm; IR (KBr): ν 3023, 2904, 1594, 1491, 1374, 1086, 822, 768 cm^{-1}; Anal. calcd. for $C_{20}H_{14}BrClN_2$: C 60.40, H 3.55, N 7.04. Found: C 60.56, H 3.51, N 7.05.

Compounds **2b-d** were obtained under same procedure for **2a**.

3-Amino-1-[2-(4-chlorobenzoyl)benzyl]pyrazin-1-ium bromide (**4**). The mixture of benzophenone **3** (3.10 g, 10.0 mmol) and 2-aminopyrazine (1.04 g, 11.0 mmol) in MeCN (10 mL) allowed to stand at r.t. for 3 d. The precipitate formed was filtered and washed with acetone to give **4**. Yield 1.21 g (30%). White crystals: mp 221–223 ^{o}C (MeCN–DMF, 1 : 1 v/v). ^{1}H NMR (400 MHz, DMSO-d^6), δ 8.63 (1H, d, J = 2.5 Hz, 6-H), 8.07 (1H, d, J = 2.5 Hz, 5-H), 8.02 (1H, s, 2-H), 7.97 (2H, br.s, NH_2), 7.78–7.63 (7H, m, 4',5',6'-H, 2",3",5",6"-H), 7.58 (1H, d, J = 8.0 Hz, 3'-H), 5.82 (2H, s, CH_2) ppm; IR (KBr): ν 3368 (NH), 3284 (NH), 3130, 2951, 1646 (C=O), 1588, 1542, 1519, 1270, 925, 747 cm^{-1}; Anal. calcd. for $C_{18}H_{15}BrClN_3O$: C 53.42, H 3.74, Br 19.74, Cl 8.76, N 10.38. Found: C 53.40, H 3.71, Br 19.75, Cl 8.73, N 10.40.

1-Amino-11-(4-chlorophenyl)pyrazino-[1,2-b]isoquinolin-5-ium bromide (**5**). A solution of pyrazinium bromide **4** (0.503 g, 1.24 mmol) in of glacial acetic acid (10 mL) was refluxed for 5 h and then cooled. The precipitate formed was filtered and washed with acetone to give **5**. Yield 0.36 g (75%). Yellow crystals: mp > 300 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (1H, s, 6-H), 8.58 (1H, d, J = 8.0 Hz, 7-H), 8.52 (1H, br.d, J = 4.5 Hz, 4-H), 8.19–8.08 (2H, m, 8,9-H), 8.05 (1H, d, J = 4.5 Hz, 3-H), 7.87 (2H, d, J = 8.0 Hz, 2',6'-H), 7.67 (2H, d, J = 8.0 Hz, 3',5'-H), 7.53 (1H, d, J = 8.0 Hz, 10-

H), 6.50 (2H, br.s, NH_2) ppm; IR (KBr): ν 3473 (NH), 3431 (NH), 3101, 3049, 2971, 1620 (C=N), 1605, 1501, 1491, 1473, 1437, 1385, 1086, 768 cm^{-1}; Anal. calcd. for $C_{18}H_{13}BrClN_3$: C 55.91, H 3.39, Br 20.66, Cl 9.17, N 10.87. Found: C 55.88, H 3.37, Br 20.67, Cl 9.15, N 10.90.

11-(4-Chlorophenyl)-1-oxo-1,2-dihydro-pyrazino[1,2-b]isoquinolin-5-ium bromide (**6**). A solution of pyrazinium bromide **4** (0.501 g, 1.24 mmol) in a mixture of AcOH–H_2O (9 : 1 v/v) (10 mL) was heated for 15 h and then cooled. The precipitate formed was filtered and washed with acetone to give **6**. Yield 0.35 g (72%). Orange crystals: mp > 300 ^oC (H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 11.96 (1H, br d, *J* = 5.0 Hz, NH), 10.41 (1H, s, 6-H), 8.60 (1H, d, *J* = 7.0 Hz, 7-H), 8.18 (2H, m, 8,10-H), 7.97 (1H, d, *J* = 6.0 Hz, 4-H), 7.62 (3H, m, 3,2',6'-H), 7.56 (1H, d, *J* = 8.0 Hz, 9-H), 7.33 (2H, d, *J* = 8.0 Hz, 3',5'-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.4 (1-C), 144.0 (6-C), 140.8 (4'-C), 137.3 (8-C), 136.8 (6a-C), 134.8 (11-C), 133.6 (2C, 10,1'-C), 131.0 (2C, 3',5'-C), 130.6 (7-C), 129.8 (11a-C), 128.9 (2C, 2',6'-C), 128.0 (10a-C), 127.6 (9-C), 125.6 (3-C), 112.6 (4-C) ppm; IR (KBr): ν 3400 (NH), 3014, 2846, 1703 (C=O), 1667 ($C=N^+$), 1614, 1385, 1197, 1085, 802, 769, 727, 515 cm^{-1}; Anal. calcd. for $C_{18}H_{12}BrClN_2O$: C 55.77, H 3.12, Br 20.61, Cl 9.15, N 7.23. Found: C 55.75, H 3.13, Br 20.60, Cl 9.13, N 7.25. Crystal data were deposited to Cambridge Crystallographic Data Centre, deposition number CCDC 887989.

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