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1,5-ELECTROCYCLIZATION OF 1-ALKYL-3-[(2*Z*)-2,4-DIARYL-4-OXOBUT-2-EN-1-YL]-1H-BENZIMIDAZOL-3-IUM BROMIDES

L. M. Potikha[1]*, A. R. Turelyk[1], and V. A. Kovtunenko[1]

Cyclization of 1-alkyl-3-[(2Z)-2,4-diaryl-4-oxobut-2-en-1-yl]-1H-benzimidazol-3-ium bromides occurs in the presence of MeONa at a reduced temperature of 5–10ºC via a 1,5-electrocyclization mechanism to give 3a,4-dihydro-3H-pyrrolo[1,2-a]benzimidazoles. These are unstable under the reaction conditions and are readily converted to {1-[2-(alkylamino)phenyl]-4-phenyl-1H-pyrrol-3-yl}(phenyl)methanones.

Keywords: benzimidazolium ylide, pyrido[1,2-*a*]benzimidazole, pyrrolo[1,2-*a*]benzimidazole, 1,5-electrocyclization.

Cyclization of imidazolium and benzimidazolium ylides is involved in a number of general methods for design condensed heterocyclic systems with a nodal nitrogen atom and whose mechanism of formation can include the participation of both the cyclic and the acyclic anion center of the ylide molecule [1]. The mechanism of formation under the action of bases of pyrido[1,2-*a*]benzimidazole systems with cyclization of 1-R-3-[(2*Z*)-2,4-diaryl-4-oxobut-2-en-1-yl]-1H-benzimidazol-3-ium bromides (**1**) also included an ylide formation stage [2, 3]. We have found [3] that, depending on the structure of the starting benzimidazolium salt and the reaction conditions, two types of benzimidazolium ylides (**2** or **3**) can be formed and can cyclize to give the 5-R-2,4-diaryl-5H-pyrido[1,2-*a*]benzimidazol-10-ium bromides (**4**). However, formation of the pyridobenzimidazolium salts **4** is not the only possible route for the cyclization of the benzimidazolium quaternary salts **1**.

We have found that the cyclization of the benzimidazolium salts **1** in the presence of the strong base MeONa can occur by two paths depending on the reaction conditions (process temperature) and on the nature of the substituents on the nitrogen atoms. At room temperature or with gentle heating (up to 35ºC) of their solutions in MeOH in the presence of MeONa the main reaction products are the pyridobenzimidazolium bromides **4**. However, in preparative mode this method is only realized in the case of the cyclization of the 1-benzyl- and 1-phenyl-substituted benzimidazolium salts **1c,d**. The products **4c,d** were obtained in comparatively low yields (45 and 57% respectively relatively to their yield (74–89%) when using morpholine or Et_3N [3]) and with a high degree of purity. For the salts **1e–g** the yields of the pyridobenzimidazolium bromides **4e–g** are even lower (< 25%) and the benzimidazolium salts **1a,b** are converted to an inseparable mixture of products. However, if the cyclization of salts **1a,b** is carried out with cooling of their solutions to 5–10ºC, the amount of side products is decreased. The main products then have the {1-[2-(alkylamino)phenyl]-4-phenyl-1H-pyrrol-3-yl}(phenyl)methanone structures **5a,b**.

*To whom correspondence should be addressed; e-mail: potikha_l@mail.ru.

[1] Taras Shevchenko National University, 64 Volodymyrs'ka St., Kyiv 01033, Ukraine.

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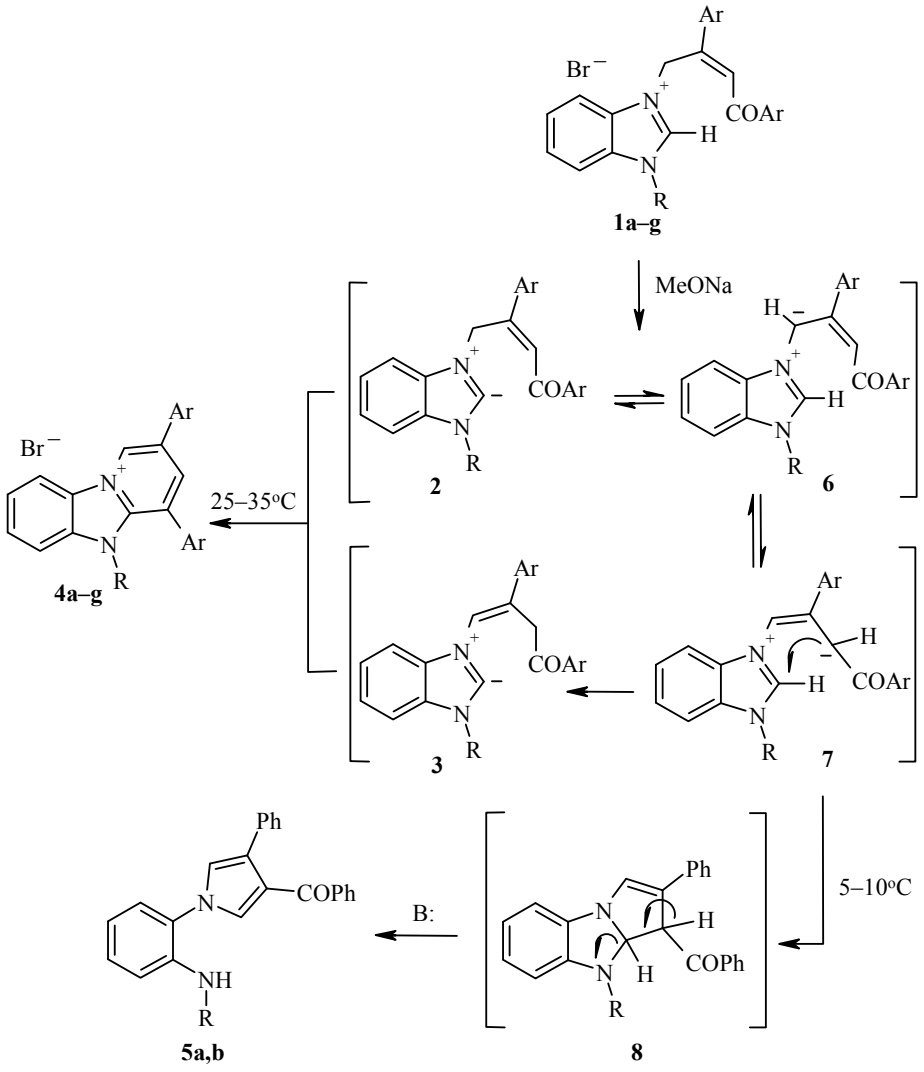
Under these conditions (at 5–10ºC), the results of the reactions of salts **1c–g** are the pyridobenzimidazolium bromides **4c–g** but they are contaminated with a significant amount of the starting salt **1**, even days after addition of the base to its solutions.



1,4 a–d Ar = Ph, **a** R = Me, **b** R = Et, **c** R = Bn, **d** R = Ph;
e–g R = Me, **e** Ar = 4-$MeOC_6H_4$, **f** Ar = 4-ClC_6H_4, **g** Ar = 4-BrC_6H_4; **5 a** R = Me, **b** R = Et

The structure of compounds **5a,b** was proved from their IR and NMR data. The presence in the IR spectrum of a strong band at 1640 cm^{-1} points to the retention of a carbonyl in the reaction product molecule and that of a broad band at 3380–3430 cm^{-1} to the presence of an NH, OH type group. The ^1H NMR spectra primarily show the presence of signals characterizing the NHAlkyl structural fragment as a quartet or triplet (^3J = 5.0–5.5 Hz) which exchanges with D_2O at 5.08 or 4.80 ppm (NH) and a splitting of the signals for the N-methyl (doublet) or N-ethyl group (CH_2 multiplet). Convincing evidence of the structure of the N-arylpyrroles **5a,b** was obtained upon analysis of the COSY, NOESY, and HMBC homo- and heteronuclear correlations in the ethyl derivative **5b** (see Figure 1). Thus, the presence in the compound studied of a benzene ring fragment was indicated by the correlation of the *ortho* protons of one of the phenyl groups at 7.87 with the carbonyl carbon atom at 190.6 ppm. The HMBC spectrum shows strong cross peaks linking the tertiary carbon atoms of the pyrrole fragment (123.9 and 131.6 ppm) and the protons bonded to them at 7.09 and 7.23 ppm and this is only possible in the case where they are mutually distanced by three bonds. These protons also correlate with both of the quaternary ring carbon

atoms at 127.2 and 127.5 ppm. In combination with δC and δH chemical shift values these point to a 3,4-disubstituted pyrrole structure. The presence of the *ortho* phenyl fragment follows from the homonuclear correlations seen in the COSY and NOESY spectra for the group of protons at 7.21–6.66 ppm, which form a single AA'BB' type spin system.

The formation of the N-arylpyrroles **5a,b** when the imidazolium salts **1a,b** are cyclized can be explained in the following way. Under the action of base, the N-alkyl-substituted quaternary benzimidazolium salts form two types of ylides with localization of the negative charge on the endo- (C(2)) or the exocyclic carbon atom. In our case (N-(2,4-diaryl-4-oxo-2-butenyl)benzimidazolium salts) four ylide structures are formed, as indicated previously [3]. Two of these have the negative charge localized on the *endo* carbon (**2** or **3**) and two – localized on the *exo* carbon of the butenyl fragment (**6** or **7**). Reaction of ylide **7** can be achieved by separation of the proton at the C(2) atom to give ylide **3** with further cyclization to the pyrido[1,2-*a*]benzimidazole system or *via* addition of the anion center to the electron-deficient C(2) atom to give the pyrrolo[1,2-*a*]benzimidazole system **8**. The low stability of 3a,4-dihydro-3H-pyrrolo[1,2-*a*]benzimidazole derivatives with acceptor substituents in the pyrrole ring in the presence of base has been noted previously [4, 5]. In the case of the intermediate compound **8** the base initiates the cleavage of the N(4)–C(3a) bond to give the N-arylpyrroles **5a,b**. A similar 1,5-electrocyclization mechanism involving an ylide of type **7** also explains the reaction of 1-[(2*Z*)-4-oxo-2,4-diphenylbut-2-en-1-yl]pyridinium salts to indolizines under the action of base [6, 7].

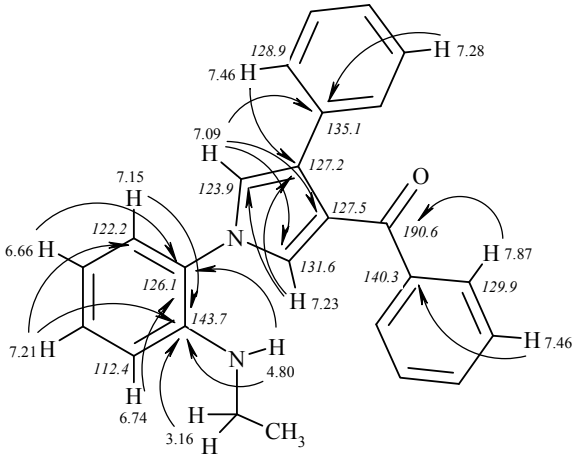


Fig. 1. Structurally significant HMBC correlations for compound **5b.**

Differences in the behavior of salts **1a,b** and **1c–g** are mainly a result of the effect of the nature of the substituent on the nitrogen atoms in the imidazolium salts **1** on the mobility of the proton at position 2. More acceptor substituents at the N(1) atom (**1c,d**, R = Bn, Ph) or donor substituents in the benzene rings of the butenyl fragment (**1e**) enable the cleavage of the H-2 proton, transition to ylide **2**, and then to the pyrido-[1,2-*a*]benzimidazole. The presence of acceptor substituents in the benzene rings of the butenyl fragment (**1f,g**) on one hand facilitates the transition **2** → **6** → **7** but also increases the acceptor effect of the substituent at atom N(3) in the type **7** structure which leads to ylide **3** and then to the pyrido[1,2-*a*]benzimidazoles. Evidently the optimal combination of structural factors for the realization of the conversion **1** →**7** →**5** is only observed for salts **1a,b**. A type **7** structure is thermodynamically less stable than **3** with a smaller separation of charges. Hence the likelihood of the transition **7** → **8** → **5** is only increased at lower temperature.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument for KBr tablets. ^{1}H NMR spectra and ^{1}H and ^{13}C NMR 2D correlation spectroscopic experiments were carried out on a Varian Mercury 400

instrument (400 and 100 MHz respectively) using DMSO-d_6 with TMS as internal standard. Melting points were determined on a Boetius heating block. Monitoring of the purity of compounds prepared was carried out by HPLC mass spectrometry using an Agilent 1100 Series instrument with an Agilent LC/MSD SL detector (sample introduced in a CF_3COOH matrix, EI ionization).

The 1-R-3-[(2*Z*)-2,4-diaryl-4-oxobut-2-en-1-yl]-1H-benzimidazol-3-ium bromides **1a–g** were prepared by the method reported in [2, 3]. Melting points and ^{1}H NMR spectroscopic data for compounds **4c,d** agreed with the literature [3].

5-R-2,4-Diaryl-5H-pyrido[1,2-*a*]benzimidazol-10-ium Bromides 4c,d (General Method). Na (0.25 g, 11.0 mmol) was dissolved in MeOH (15 ml). The salt **1c,d** (2.5 mmol) was added with stirring to the MeONa solution. Stirring was continued at 25–30ºC for 1.5 h. The precipitate formed on cooling was filtered off and washed with 2-propanol to give the pyrido[1,2-*a*]benzimidazolium bromides in 45% (**4c**) or 57% (**4d**) yield.

{1-[2-(Alkylamino)phenyl]-4-phenyl-1H-pyrrol-3-yl}(phenyl)methanones 5a,b (General Method). Na (0.25 g, 11.0 mmol) was dissolved in MeOH (15 ml) and cooled to 0–5ºC. The salt **1a,b** (1.15 mmol) was added with stirring. The mixture was held at 5–10ºC for a further 1.5 h. The precipitate was filtered off and washed with 2-propanol.

Compound 5a. Yield 0.17 g (42%); mp 178–179ºC (MeCN). IR spectrum, ν, cm^{-1}: 3430 (NH), 1640 (C=O), 1600, 1530, 1330, 1280, 900, 790, 700. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.86 (2H, d, ^3J = 8.0, H-2',6'); 7.52 (1H, t, ^3J = 8.0, H-4'); 7.44 (4H, m, H-3',5',2",6"); 7.29–7.20 (4H, m, H-3"-H-5", H-4"′); 7.19 (1H, d, ^4J = 2.0, H-2); 7.14 (1H, d, ^3J = 7.5, H-6"′); 7.07 (1H, d, ^4J = 2.0, H-5); 6.70–6.44 (2H, m, H-3"′,5"′); 5.08 (1H, q, ^3J = 5.0, NH); 2.75 (3H, d, ^3J = 5.0, NCH_3). ^{13}C NMR spectrum, δ, ppm: 190.3 (C=O), 144.3 (C-2"′); 140.3 (C-1′); 135.0 (C-1"); 132.1 (C-4′); 131.3 (C-2); 130.3 (C-4"′); 129.8 (C-2′,6′); 129.0 (C-3′,5′); 128.6 (C-2",6"); 128.3 (C-3",5"); 127.5 (C-3); 127.3 (C-4); 126.5 (C-4"); 126.2 (C-1"′); 123.7 (C-5); 122.4 (C-6"′); 116.9 (C-5"′); 112.2 (C-3"′), 30.9 (CH_3). Found, %: C 81.71; H 5.69; N 7.98. $C_{24}H_{20}N_2O$. Calculated, %: C 81.79; H 5.72; N 7.95.

Compound 5b. Yield 0.19 g (44%); mp 124–125ºC (2-propanol). IR spectrum, ν, cm^{-1}: 3380 (NH), 1640 (C=O), 1600, 1520, 1450, 1280, 790. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.87 (2H, d, ^3J = 8.0, H-2′,6′); 7.53 (1H, t, ^3J = 8.0, H-4′); 7.46 (4H, m, H-3′,5′,2",6"); 7.28 (2H, t, ^3J = 8.0, H-3",5"); 7.23 (1H, d, ^4J = 2.0, H-2); 7.21 (2H, m, H-4",4"'); 7.15 (1H, d, ^3J = 7.5, H-6"′); 7.09 (1H, d, ^4J = 2.0, H-5); 6.74 (1H, d, ^3J = 7.5, H-3"′); 6.66 (1H, t, ^3J = 7.5, H-5"′); 4.80 (1H, t, ^3J = 5.5, NH); 3.16 (2H, m, NCH_2); 1.21 (3H, t, ^3J = 7.0, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.6 (C=O); 143.7 (C-2"′); 140.3 (C-1′); 135.1 (C-1"); 132.6 (C-4′); 131.6 (C-2); 130.0 (C-4"′); 129.9 (C-2′,6′); 129.1 (C-3′,5′); 128.9 (C-2",6"); 128.5 (C-3",5"); 127.5 (C-3); 127.2 (C-4); 126.7 (C-4"); 126.1 (C-1"′); 123.9 (C-5); 122.2 (C-6"′); 116.6 (C-5"′), 112.4 (C-3"′); 38.0 (NCH_2); 14.9 (CH_3). Found, %: C 81.89; H 6.10; N 7.63. $C_{25}H_{22}N_2O$. Calculated, %: C 81.94; H 6.05; N 7.64.

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