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# SYNTHESIS OF 7-AMINO-2-ARYL-4-(N-ARYLCARBAMOYL)-5-PHENYL-3,4-DIHYDROIMIDAZO[1,5-*b*]PYRIDAZINES

**N. N. Kolos and T. V. Berezkina**

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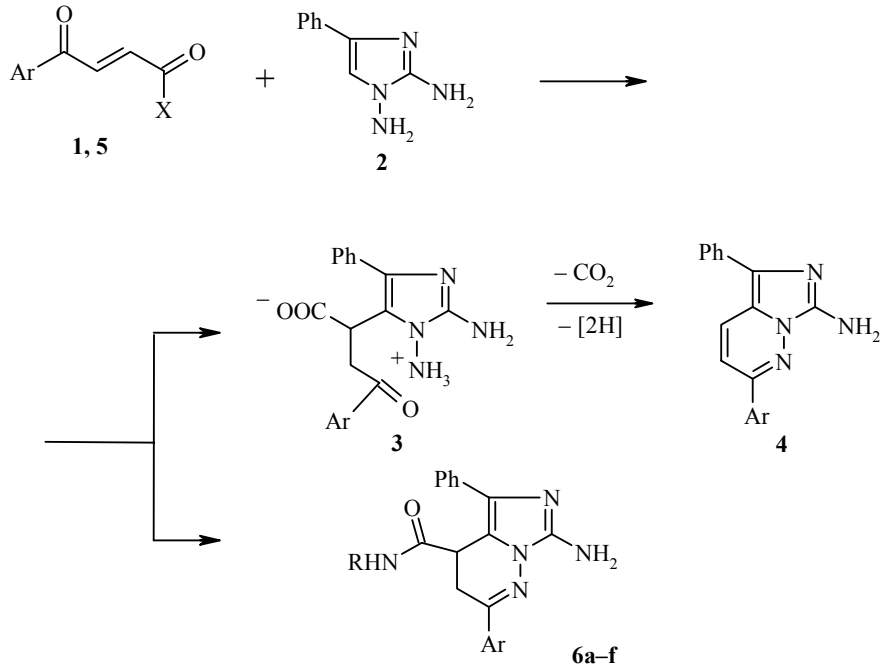
We showed earlier that reaction of β-aroylacrylic acids **1** with 1,2-diamino-4-phenylimidazole (**2**) in alcohols leads to formation of the inner salts **3**. The fact that inner salts are isolated confirms the primacy of hetarylation of enone systems in their reactions with 1,2-diaminoazoles [1]. Cyclization of betaines **3** could be accomplished by boiling in DMF in the presence of catalytic amounts of HCl. However, the reaction is accompanied by decarboxylation and dehydration, leading to formation of exclusively the heteroaromatic derivatives of imidazopyridazine **4** [2].




**1** X = OH, **5** X = NHR; **6 a–d** Ar = Ph, **a** R = Ph, **b** R = *p*-$MeC_6H_4$, **c** R = *p*-$BrC_6H_4$, **d** R = *o*-$ClC_6H_4$; **e**, **f** Ar = *p*-$MeC_6H_4$; **e** R = *p*-$MeC_6H_4$; **f** R = *p*-$BrC_6H_4$

V. N. Karazin Kharkov State University, Kharkov 61077, Ukraine; e-mail: kolos@univer.kharkov.ua.
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We have studied the reactions of N-arylamides of β-aroylacrylic acids **5a-f** with diamine **2**. We have observed that the products of such a reaction, when the starting reagents are boiled in ethanol, are the dihydroimidazo[1,5-*b*]pyridazine derivatives **6a-f**.

In the $^1$H NMR spectra of the synthesized compounds, signals appear from protons of an ABX system for the dihydropyridazine ring: a doublet of doublets and a doublet for the A and B protons of the methylene group, a doublet for the methine proton, and also a one-proton singlet for the amide group in the 9.73-10.51 ppm region, a two-proton singlet for the amino group of the imidazole ring, and multiplets for the aromatic protons, suggesting retention of the aryl rings. Formation of imidazopyridazines **6a-f** also probably includes a step of α-hetarylation of amides **5** by the C-5 atom of the imidazole ring followed by cyclocondensation, although we could not isolate any addition products. Dihydroimidazopyridazines **6a-f** are rather stable and do not undergo dehydration when stored in air or when boiled in protic solvents.

The $^1$H NMR spectra were taken on a Varian Mercury VX-200 (200 MHz) spectrometer in DMSO-$d_6$, internal standard TMS. The IR spectra were obtained on a Specord IR-75 in KBr.

**7-Amino-2,5-diphenyl-4-(N-phenylcarbamoyl)-3,4-dihydroimidazo[1,5-*b*]pyridazine (6a).** A mixture of β-benzoylacrylic acid N-phenylamide **5a** (0.5 g, 2 mmol), 0.35 g (2 mmol) of diamine **2** in 20 ml ethanol was boiled until the starting amide disappeared (~1 h 30 min). After cooling down to room temperature, the precipitate was filtered out and recrystallized from ethanol. Obtained: 0.65 g (80%) of compound **6a** with mp 217-218°C. IR spectrum, ν, cm$^{-1}$: 1630 (C=N), 1687 (C=O), 3290, 3427 (NH, $NH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.09 (1H, dd, $J_{3a3b}$ = 18.0, $J_{3a4}$ = 8.0, H-3a); 3.41 (1H, d, $J_{3a3b}$ = 18.0, H-3b); 4.56 (1H, d, $J_{3a4}$ = 8.0, H-4); 6.09 (2H, br. s, $NH_2$); 7.02-8.00 (15H, m, Ar); 10.37 (1H, br. s, NH). Found, %: N 17.21. $C_{25}H_{21}N_5O$. Calculated, %: N 17.18.

**Compounds 6b-f** were obtained similarly, where the boiling time was varied from 30 min (compound **6c**) to 2 h (compound **6f**).

**7-Amino-2,5-diphenyl-4-[N-(*p*-methylphenyl)carbamoyl]-3,4-dihydroimidazo[1,5-*b*]pyridazine (6b).** Yield 75%; mp 218-219°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1627 (C=N), 1680 (C=O), 3276, 3403 (NH, $NH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, $CH_3$), 3.07 (1H, dd, $J_{3a3b}$ = 17.4, $J_{3a4}$ = 7.2, H-3a); 3.43 (1H, d, $J_{3a3b}$ = 17.4, H-3b); 4.53 (1H, d, $J_{3a4}$ = 7.2, H-4); 6.08 (2H, br. s, $NH_2$), 7.01-7.51 (11H, m, Ar); 7.68 (2H, d, *J* = 8.0, *o*-Ar); 8.00 (2H, d, *J* = 8.0, *o*-Ar); 10.26 (1H, br. s, NH). Found, %: N 16.66. $C_{26}H_{23}N_5O$. Calculated, %: N 16.62.

**7-Amino-2,5-diphenyl-4-[N-(*p*-bromophenyl)carbamoyl]-3,4-dihydroimidazo[1,5-*b*]pyridazine (6c).** Yield 80%; mp 242°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1625 (C=N), 1669 (C=O), 3330, 3430 (NH, $NH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.06 (1H, dd, $J_{3a3b}$ = 17.5, $J_{3a4}$ = 7.7, H-3a); 3.43 (1H, d, $J_{3a3b}$ = 17.5, H-3b); 4.53 (1H, d, $J_{3a4}$ = 7.7, H-4); 6.10 (2H, br. s, $NH_2$); 7.15-7.51 (11H, m, Ar); 7.67 (2H, d, *J* = 8.0, *o*-Ar); 8.00 (2H, d, *J* = 8.0, *o*-Ar); 10.51 (1H, br. s, NH). Found, %: N 14.45. $C_{25}H_{20}BrN_5O$. Calculated, %: N 14.40.

**7-Amino-2,5-diphenyl-4-[N-(*o*-chlorophenyl)carbamoyl]-3,4-dihydroimidazo[1,5-*b*]pyridazine (6d).** Yield 78%; mp 212-213°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1640 (C=N), 1693 (C=O), 3283, 3343, 3423 (NH, $NH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.07 (1H, dd, $J_{3a3b}$ = 17.4, $J_{3a4}$ = 8.0, H-3a); 3.43 (1H, d, $J_{3a3b}$ = 17.4, H-3b); 4.76 (1H, d, $J_{3a4}$ = 8.0, H-4); 6.11 (2H, br. s, $NH_2$); 7.15-7.51 (11H, m, Ar); 7.74 (2H, d, *J* = 8.0, *o*-Ar); 8.02 (2H, d, *J* = 8.0, *o*-Ar); 9.73 (1H, br. s, NH). Found, %: N 15.81. $C_{25}H_{20}ClN_5O$. Calculated, %: N 15.85.

**7-Amino-2-(*p*-methylphenyl)-4-[N-(*p*-methylphenyl)carbamoyl]-5-phenyl-3,4-dihydroimidazo-[1,5-*b*]pyridazine (6e).** Yield 75%; mp 235-236°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1627 (C=N), 1666 (C=O), 3303, 3336, 3433 (NH, $NH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, $CH_3$), 2.34 (3H, s, $CH_3$), 3.03 (1H, dd, $J_{3a3b}$ = 16.7, $J_{3a4}$ = 6.9, H-3a); 3.27 (1H, d, $J_{3a3b}$ = 16.7, H-3b); 4.51 (1H, d, $J_{3a4}$ = 6.9, H-4); 6.04 (2H, br. s, $NH_2$), 7.04 (2H, d, *J* = 8.0, *o*-Ar), 7.16 (2H, *d*, *J* = 8.0, *o*-Ar), 7.23-7.39 (5H, m, $C_6H_5$); 7.67 (2H, d, *J* = 8.0, *o*-Ar); 7.90 (2H, d, *J* = 8.0, *o*-Ar); 10.23 (1H, br. s, NH). Found, %: N 16.12. $C_{27}H_{25}N_5O$. Calculated, %: N 16.08.

**7-Amino-2-(*p*-methylphenyl)-4-[N-(*p*-bromophenyl)carbamoyl]-5-phenyl-3,4-dihydroimidazo[1,5-*b*]-pyridazine (6f).** Yield 71%; mp 240-241°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1629 (C=N), 1689 (C=O), 3300, 3370, 3423 (NH, $NH_2$). $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, $CH_3$), 3.05 (1H, dd, $J_{3a3b}$ = 17.6, $J_{3a4}$ = 7.8, H-3a); 3.33 (1H, d, $J_{3a3b}$ = 17.6, H-3b); 4.51 (1H, d, $J_{3a4}$ = 7.8, H-4); 6.06 (2H, br. s, $NH_2$), 7.04 (2H, d, *J* = 8.0, *o*-Ar), 7.16-7.45 (9H, m, Ar), 7.65 (2H, d, *J* = 8.0, *o*-Ar), 7.90 (2H, d, *J* = 8.0, *o*-Ar), 10.49 (1H, br. s, NH). Found, %: N 14.06. $C_{26}H_{22}BrN_5O$. Calculated, %: N 14.00.

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