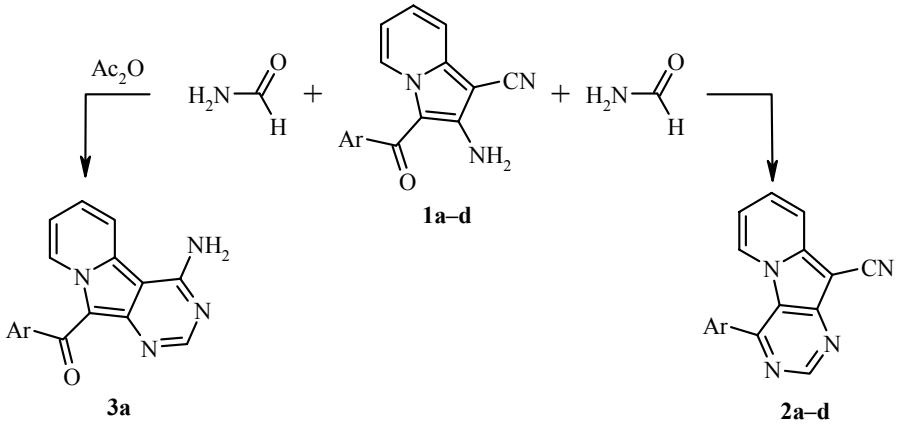
REGIOSELECTIVE REACTION OF 2-AMINO-3-AROYL-1-CYANOINDOLIZINES WITH FORMAMIDE

G. E. Khoroshilov, I. V. Demchak, and M. V. Emelyanova

Keywords: 2-amino-3-aroyl-1-cyanoindolizines, 4-arylpyrimido[4,5-b]indolizine-10-carbonitriles, formamide.

In the course of studying the chemical properties of the 2-amino-3-aroyl-1-cyanoindolizines **1a-d** we found that treatment of the latter with formamide gives the corresponding 4-arylpyrimido[4,5-*b*]indolizine-10-carbonitriles **2a-d**.



1–3 a Ar = Ph; **1,2 b** Ar = 4-ClC_6H_4, **c** Ar = 3,4-$Me_2C_6H_3$, **d** Ar = 4-$BuOC_6H_4$

A similar reaction also occurs upon prolonged heating at the indolizine nitrile and amino groups in the presence of acetic anhydride to give the 4-amino-10-aroylpyrimido[5,4-*a*]indolizine (**3a**) [1]. The reaction products obtained by us are formed by short refluxing of the indolizine in formamide.

^{1}H NMR spectra were recorded on Bruker DRX 500 (500 MHz) and DPX 300 (300 MHz) instruments (compounds **2a-c** and **2d** respectively) using DMSO-d_6 and with TMS as internal standard. IR spectra were recorded using vaseline oil.

The indolizine **1a** were obtained by method [2] and the indolizines **1b-d** by method [3].

Preparation of Compounds 2a-d (General Method). A suspension of the indolizine **1** (2.5 mmol) in formamide (15 ml) was refluxed for 1 h. The solution became homogeneous and turned a green-brown color. Four hours after the completion of refluxing the precipitate was filtered off and washed initially with the mother liquor, then water (1 ml), and then formamide (5 ml) to give compound **2** which was recrystallized from a suitable solvent as needed.

Luhansk Taras Shevchenko National Pedagogical University, Lugansk 91011, Ukraine; e-mail: demchak@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 133-134, January, 2007. Original article submitted July 20, 2006.

 0009-3122/06/4301-0116

4-Phenylpyrimido[4,5-*b*]indolizine-10-carbonitrile (2a). Yield 52%. Mp 198-201°C (methanol). IR spectrum, ν, cm^{-1}: 2216 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.20 (1H, s, H-2); 8.19 (1H, d, *J* = 6.9, H-6); 7.89 (1H, d, *J* = 9.1, H-9); 7.80-7.66 (6H, m, H_{arom}); 7.06 (1H, t, *J* = 7.0, H-7). Mass spectrum, (EI, 70 eV), *m/z* (I_{rel}, %): 269 $[M-1]^+$ (100). Found, %: C 75.51; H 3.71; N 20.69. $C_{17}H_{10}N_4$. Calculated, %: C 75.54; H 3.73; N 20.73.

4-(4-Chlorophenyl)pyrimido[4,5-*b*]indolizine-10-carbonitrile (2b). Yield 43%. Mp 317-318°C (ethanol). IR spectrum, ν, cm^{-1}: 2214 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.18 (1H, s, H-2); 8.26 (1H, d, *J* =7.9, H_6); 7.98 (1H, d, *J* = 10.0, H-9); 7.82 (2H, d, *J* = 7.2, $H_{3'\text{-arom}}$, $H_{5'\text{-arom}}$); 7.76 (1H, t, *J* = 8.4, H-8); 7.73 (2H, d, *J* = 7.2, $H_{2'\text{-arom}}$, $H_{6'\text{-arom}}$); 7.10 (1H, t, *J* = 11.5, H_7). Found, %: C 67.05; H 2.94; N 18.32. $C_{17}H_9ClN_4$. Calculated, %: C 67.00; H 2.98; N 18.39.

4-(3,4-Dimethylphenyl)pyrimido[4,5-*b*]indolizine-10-carbonitrile (2c). Yield 46%. Mp 283-285°C (ethanol). IR spectrum, ν, cm^{-1}: 2216 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.15 (1H, s, H-2); 8.31 (1H, d, *J* = 7.2, H-6); 7.96 (1H, d, *J* = 9.4, H-9); 7.75 (1H, t, *J* = 7.8, H-8); 7.55 (1H, s, $H_{2'\text{-arom}}$); 7.48 (1H, d, *J* = 7.4, $H_{5'\text{-arom}}$); 7.42 (1H, d, $H_{6'\text{-arom}}$); 7.07 (1H, t, J = 8.0, H-7); 2.39 (3H, s, CH-3); 2.35 (3H, s, CH-3). Found, %: C 76.43; H 4.75; N 18.75. $C_{19}H_{14}N_4$. Calculated, %: C 76.49; H 4.73; N 18.78.

4-(4-Butoxyphenyl)pyrimido[4,5-*b*]indolizine-10-carbonitrile (2d). Yield 46%. Mp 283-285 C. IR spectrum, ν, cm^{-1}: 2218 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 9.12 (1H, s, H-2); 8.48 (1H, d, *J* = 8.7, H-6); 7.97 (1H, d, *J* = 9.16, H-9); 7.74 (3H, m, H_{arom}); 7.18 (2H, d, J = 8.1, $H_{2'\text{-arom}}$); 7.08 (1H, t, *J* = 8.15, H-7); 4.12 (2H, t, J = 8.4, OCH_2); 1.78 (2H, m, $C\underline{H_2}CH_2CH_3$); 1.49 (2H, m, $CH_2C\underline{H_2}CH_3$); 0.95 (3H, t, J = 9.0, CH-3). Found, %: C 73.64; H 5.26; N 16.37. $C_{21}H_{18}N_4O$. Calculated, %: C 73.67; H 5.30; N 16.36.

The IR spectra of the final products clearly show the signal of a cyano group conjugated to the aromatic ring while the signals for the amino and keto groups are not seen. The broad singlet for the amino group is not seen in the ^1H NMR spectra. Mass spectroscopic data for **2a** and elemental analysis for compounds **2a-d** also point to the occurrence of a reaction at the amino and carbonyl groups of the starting indolizine.

A more detailed investigation of this regioselective reaction of formamide with multifunctional compounds will be the subject of a separate report.

REFERENCES

1. O. I. Abd El-Salam, *Monatsh. Chem.*, **131**, 959 (2000).
2. H. Pauls and F. Kröhnke, *Chem. Ber.*, **110**, 1294 (1977).
3. G. E. Khoroshilov, *Khim. Geterotsikl. Soedin.*, 1245 (2001). [*Chem. Heterocycl. Comp.*, **37**, 1141 (2001)].