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SYNTHESIS OF PYRIMIDO[4,5-*b*]INDOLIZINES BY REACTION OF 2-AMINO-3-AROYL-1-R-INDOLIZINES WITH FORMAMIDE

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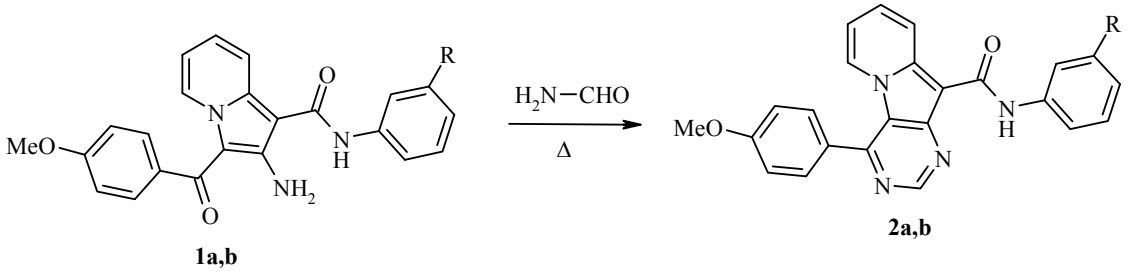
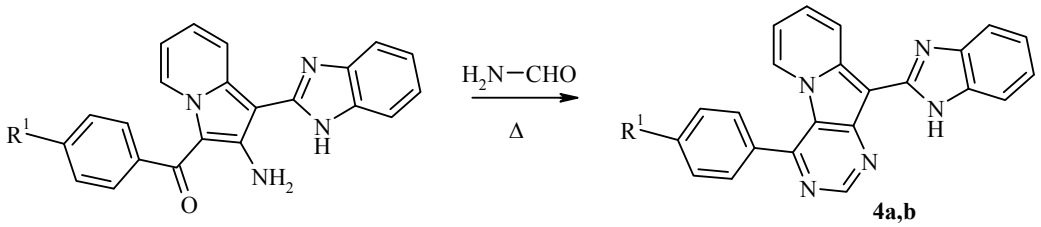
Continuing our studies of the chemical properties of 2-amino-3-aroyl-1-R-indolizines [1] we have examined the reaction of the indolizines **1a**,**b** and **3a**,**b** when refluxed for a short time with formamide to give the corresponding pyrimido[4,5-*b*]indolizines **2a**,**b** and **4a**,**b**.



1a,b **2a,b**

a R = Me, **b** R = CF_3



3a,b **4a,b**

a R^1 = H, **b** R^1 = OMe

Only one of the two possible reaction routes is realized and this involves the amino and carbonyl groups. Hence, in the IR spectra of compounds **2** and **4**, signals for the amino and carbonyl groups are lost and signals appear which are typical of a secondary amide group and an imidazole NH group [2]. The mass spectrum of compound **2a** shows a signal of relative intensity 3.1% which corresponds to the molecular weight.

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The base peak (intensity 100%, *m/z* 302) is due to the loss of *m*-toluidine from compound **2a** and is typical of similar systems [2, 3]. On this basis we conclude that compounds **2a**,**b** are formed regioselectively.

IR spectra were taken on an IRS-40 spectrophotometer using vaseline oil and ^{1}H NMR spectra on a Varian VRX-200 instrument (200 MHz) using DMSO-d_6 with TMS as internal standard. Mass spectra (EI, 70 eV) were obtained on a Varian 1200L instrument.

The indolizines **1a**,**b** and **3a**,**b** were prepared by a known method [4, 5].

4-Phenyl-10-R-pyrimido[4,5-*b*]indolizines 2a,**b and 4a**,**b (General Method)**. The corresponding indolizine **1** or **3** (2.5 mmol) was refluxed in formamide (15 ml) for 1 h. The solution became homogeneous and green-brown in color. After 4 h the precipitate formed was filtered off, washed with the mother liquor, then with water (1 ml) and formamide (5 ml), and recrystallized from ethanol.

4-(4-Methoxyphenyl)-N-(*m*-tolyl)pyrimido[4,5-*b*]indolizine-10-carboxamide (2a). Yield 46%; mp 208-209ºC, IR spectrum, ν, cm^{-1}: 3418, 1652, 1559. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.04 (1H, s, NH); 9.21 (1H, s, H-2); 8.69 (1H, d, *J* = 9.1, H-9); 8.21 (1H, d, *J* = 7.1, H-6); 7.85-7.52 (5H, m, H arom); 7.35-7.13 (3H, m, H arom); 7.01 (1H, t, *J* = 6.9, H-7); 6.90 (1H, d, *J* = 7.1, H arom); 3.89 (3H, s, OCH_3); 2.33 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 408 $[M]^+$ (3.1), 304 (3.0), 303 (17.4), 302 (100), 287 (8.2), 259 (6.0), 258 (29.4), 257 (5.4), 233 (2.4), 232 (2.6), 231 (8.4), 230 (7.0), 205 (2.1), 204 (3.8), 203 (4.3), 202 (2.1), 107 (10.3), 106 (4.4), 104 (3.2), 91 (3.5), 80 (2.1). Found, %: C 73.58; H 4.88; N 13.67. $C_{25}H_{20}N_4O_2$. Calculated, %: C 73.51; H 4.94; N 13.72.

4-(4-Methoxyphenyl)-N-[3-(trifluoromethyl)phenyl]pyrimido[4,5-*b*]indolizine-10-carboxamide (2b). Yield 59%; mp 206-207.5ºC. IR spectrum, ν, cm^{-1}: 3436, 1653, 1559. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.25 (1H, s, NH); 9.14 (1H, s, H-2); 8.78 (1H, d, *J* = 9.0, H-9); 8.44 (1H, d, *J* = 7.1, H-6); 8.29 (1H, s, H arom); 7.91 (1H, d, *J* = 9.0, H arom); 7.74-7.60 (3H, m, H arom); 7.54 (1H, t, *J* = 7.6, H-8); 7.34 (1H, d, *J* = 8.1, H arom); 7.17 (2H, d, *J* = 8.7, H arom); 6.94 (1H, t, *J* = 6.4, H-7); 3.94 (3H, s, OCH_3). Found, %: C 64.87; H 3.76; N 12.17. $C_{25}H_{17}N_4F_3O_2$. Calculated, %: C 64.93; H 3.71; N 12.12.

10-(1H-Benzimidazol-2-yl)-4-phenylpyrimido[4,5-*b*]indolizine (4a). Yield 68%; mp 224ºC. IR spectrum, ν, cm^{-1}: 3488. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.30 (1H, s, NH); 9.23 (1H, s, H-2); 9.13 (1H, d, *J* = 9.2, H-9); 8.21 (1H, d, *J* = 6.9, H-6); 7.77-7.58 (8H, m, H arom); 7.16-7.12 (2H, m, H arom); 6.82 (1H, t, *J* = 6.9, H-7). Found, %: C 76.51; H 4.09; N 19.43. $C_{23}H_{15}N_5$. Calculated, %: C 76.44; H 4.18; N 19.38.

10-(1H-Benzimidazol-2-yl)-4-(4-methoxyphenyl)pyrimido[4,5-*b*]indolizine (4b). Yield 83%; mp 258-260ºC. IR spectrum, ν, cm^{-1}: 3466. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.32 (1H, s, NH); 9.26 (1H, s, H-2); 9.04 (1H, d, *J* = 10.0, H-9); 8.36 (1H, d, *J* = 8.0, H-6); 7.97-7.52 (7H, m, H arom); 7.20-7.14 (2H, m, H arom); 7.03 (1H, t, *J* = 8.0, H-7); 3.90 (3H, s, OCH_3). Found, %: C 73.70; H 4.31; N 17.95. $C_{24}H_{17}N_5O$. Calculated, %: C 73.64; H 4.38; N 17.89.

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