Chemistry of Heterocyclic Compounds, Vol. 34, No. 12, 1998

LETTERS TO THE EDITOR

UNEXPECTED FORMATION OF PYRIMIDO[4,5-*c*]QUINOLIZINES

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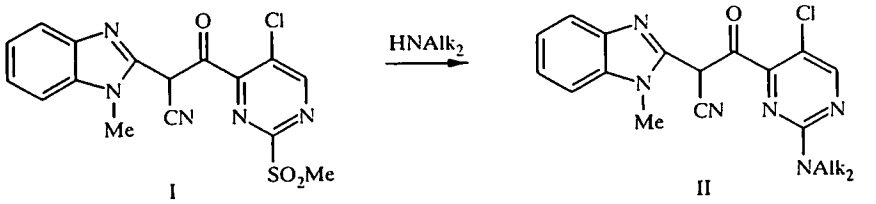
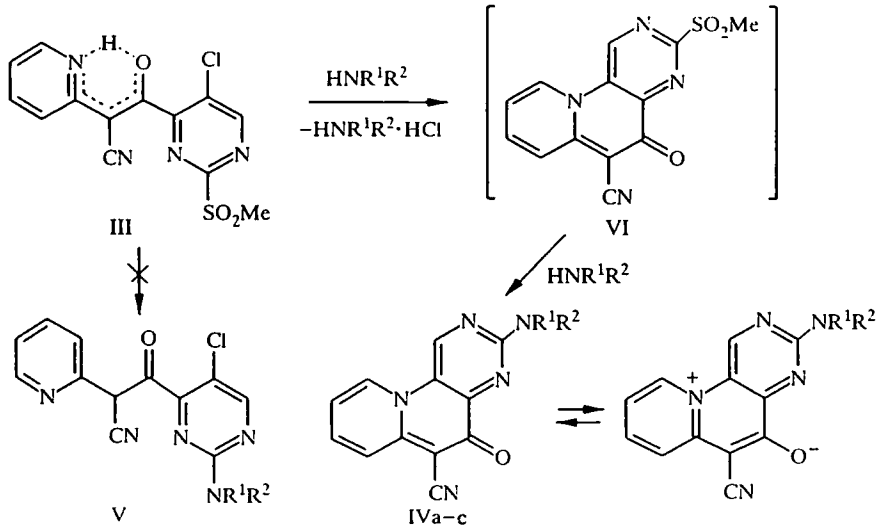
We have previously [1] described the synthesis of 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-heteraryl)ethyl cyanides. It was shown that aliphatic amines reacted regioselectively with compound I with replacement of the methylsulfonyl group to give compound II.



I II

It has been found that 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)ethyl cyanides III react with aliphatic secondary amines to give 3-R^1R^2N-5-oxo-5H-pyrimido-[4,5-*c*]quinolizin-6-yl cyanides IV a-c. All attempts to isolate the uncyclized compounds V, which are structurally similar to compounds II, were unsuccessful.



III VI V IVa–c

Va R^1, R^2 = $-CH_2CH_2-O-CH_2CH_2-$; V b R^1, R^2 = H, CH_2Ph;
V c R^1, R^2 = H, $-(CH_2)_3-OH$

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 0009-31221/98/3412-1442$20.00

No bands characteristic of the methylsulfonyl group were observed in the IR spectra of compounds IV. Elemental analysis results showed that Cl and S were absent and agreed with results expected for the structures of IV. The absence of bands in the region 1750-1640 cm^{-1} allows the conclusion that bipolar structures make a major contribution to the structures of the cyclic molecules IVa-c. The formation of compounds V and their further conversion into IV appears impossible because the chlorine atom at position 5 of the pyrimidine ring is replaced by nucleophiles with considerable difficulty. Similarly, substitution of the strong σ-electron acceptor $-SO_2CH_3$ group by the π-donor $-NAlk_2$ group additionally deactivates position 5. We suggest that the reaction of compound III with amines goes via the formation of a cyclic intermediate VI which cannot be isolated under the given reaction conditions (it was successfully isolated using Et_3N as the base). Evidently the easy cyclization of compound III in comparison with the benzimidazole I derivatives described previously is explained by the decreased steric hindrance in the cyclization stage.

Synthesis of 3-R^1R^2N-5-oxo-5H-pyrimido[4,5-*c*]quinolizin-6-yl Cyanides (IV). The corresponding amine (15 mmol) was added to a solution of 2-[5-chloro-2-(methylsulfonyl)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)ethyl cyanide III (5 mmol) in dry dioxane (25 ml). The reaction mixture was heated at 90-100°C for 4 h. After cooling, the precipitate was filtered off, washed with water, dried, and recrystallized from dimethylformamide. Yield of compounds IV a-c 81-87%.

3-Morpholino-5-oxo-5H-pyrimido[4,5-*c*]quinolizin-6-yl Cyanide (IVa). M.p. >300°C (dec). IR spectrum (KBr, cm^{-1}): 2200 (CN). ^1H NMR spectrum (100 MHz, DMSO-D_6) δ: 9.80 (1 H, s, 1-H), 9.33 (1 H, d, J = 7.2 Hz, 10-H), 7.87 (1 H, dd, J = 8.8, 6.5 Hz, 8-H), 7.54 (1 H, dd, J =8.8, 1.1 Hz, 7-H), 7.23 (1 H, ddd, J = 7.2, 6.5, 1.1 Hz, 9-H), 3.8 (8 H, m, morpholino). UV spectrum (DMF): λ_{max} = 284, 328 nm. Found, %: C 62.64, H 4.21, N 22.27. Calc. for $C_{16}H_{13}N_5O_2$, %: C 62.53, H 4.26, N 22.79.

3-Benzylamino-5-oxo-5H-pyrimido[4,5-*c*]quinolizin-6-yl Cyanide (IV b). M.p. 317°C (dec). IR Spectrum (KBr, cm^{-1}): 3300 (NH), 2195 (CN). ^1H NMR spectrum (100 MHz, DMSO-D_6) δ: 9.70 (1 H, s, 1-H), 9.30 (1 H, d, J = 7.2 Hz, 10-H), 8.62, (1 h, br.s, NH), 7.85 (1 H, dd, J = 8.8, 6.5 Hz, 8-H), 7.62 (1 H, dd, J = 8.8, 1.1 Hz, 7-H), 7.4-7.1 (6 H, m, 9-H + Ph), 4.66 (2 H, d, J = 6.8 Hz, $NHCH_2Ph$). UV spectrum (DMF), λ_{max} = 282, 324 nm. Found, %: C 69.84, H 3.91, N 21.41. Calc. for $C_{19}H_{13}N_5O$, %: C 69.72, H 4.00, N 21.39.

3-[(3-Hydroxypropyl)amino]-5-oxo-5H-pyrimido[4,5-*c*]quinolizin-6-yl Cyanide (IVc). M.p. 287-288°C (dec). IR spectrum (KBr, cm^{-1}): 3400 (NH), 2195 (CN). ^1H NMR spectrum (100 MHz, DMSO-D_6) δ: 9.70 (1 H, s, 1-H), 9.30 (1 H, d, J = 7.2 Hz, 10-H), 8.07 (1 H, br.s, NH), 7.85 (1 H, dd, J = 8.8, 6.5 Hz, 8-H), 7.62 (1 H, dd, J = 8.8, 1.1 Hz, 7-H), 7.21 (1 H, ddd, J = 7.2, 6.5, 1.1 Hz, 9-H), 4.5 (1 H, br.s, OH), 3.48 (4 H, m, $NHCH_2CH_2CH_2OH$), 1.74 (2 H, q, $NHCH_2CH_2CH_2OH$). UV spectrum (DMF), λ_{max} = 282, 324 nm. Found, %: C 61.05, H 4.52, N 23.70. Calc. for $C_{15}H_{13}N_5O_2$, %: C 61.01, H 4.44, N 23.72.

3-Methylsulfonyl-5-oxo-5H-pyrimido[4,5-*c*]quinolizin-6-yl Cyanide (VI). M.p. >330°C. IR spectrum (KBr, cm^{-1}): 2205 (CN), 1310, 1130 (SO_2). ^1H NMR spectrum (100 MHz, DMSO-D_6) δ: 10.49 (1 H, s, 1-H), 9.58 (1 H, d, J = 7.2 Hz, 10-H), 8.05 (1 H, dd, J = 8.8, 6.5 Hz, 8-H), 7.8 (1 H, dd, J = 8.8, 1.1 Hz, 7-H), 7.38 (1 H, ddd, J = 7.2, 6.5, 1.1 Hz, 9-H), 3.55 (3 H, s, SO_2CH_3) UV spectrum (DMFA), λ_{max} = 282 nm. Found, %: N 18.74, S 10.61. Calc. for $C_{13}H_8N_4O_3S$, %: N 18.66, S 10.68.

REFERENCE

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