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CONVENIENT METHOD FOR THE ANNELATION OF A PYRIDINE RING TO AZAHETEROCYCLIC SYSTEMS

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Keywords: 3-methyl-1-oxo-1H-benzo[*c*]quinolizine-4-carbonitrile, 3-(4-bromophenyl)-7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile, 3-methyl-1-oxo-1H-pyrido[2,1-*b*]benzothiazole-4-carbonitrile, 7-methyl-5-oxo-2-phenyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyridine-8-carbonitrile, 5-methyl-5-oxo-1-phenyl-5H-1,3,4-triazolo[1,5-*a*]pyridine-8-carbonitrile, 2-methyl-4-oxo-4H-quinolizine-1-carbonitrile, 3-(4-chlorophenyl)-7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile, annelation.

The reaction of 4-phenyl-2-cyanomethylthiazole with ethyl acetoacetate at 180°C gives 7-methyl-5-oxo-3-(4-phenyl)-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile (**1a**) in only 34% yield [1]. Carrying out the analogous reaction with 2-cyanomethylbenzimidazole in the presence of ammonium acetate gave tricyclic 3-methyl-1-oxo-1H,5H-pyrido[1,2-*a*]benzimidazole-4-carbonitrile in 98% yield [2]. We have studied the scope of this reaction relative to cyanomethyl derivatives of other aza heterocycles. This method proved general. 2-Cyanomethylazoles such as 4-(*p*-chlorophenyl)thiazole, 4-(*p*-bromophenyl)thiazole, benzothiazole, 5-phenyl-1,3,4-thiadiazole, and 1-phenyl-1,3,4-triazole as well as 2-cyanomethylazines such as pyridine and quinoline react with equivalents of ethyl acetoacetate and two equivalent amounts of ammonium acetate at 150°C over 30-45 min. Subsequent treatment of the reaction mixture with water readily leads to di- or tricyclic systems **1-6**, in which the pyridine ring is annelated to the corresponding azaheterocycles. We should note that the yields of compounds **1b** and **1c**, which are similar to the product **1a**, reach 94-95% when the reaction is carried out under such conditions (Scheme 1).

The ^{1}H NMR spectra were taken in DMSO-d_6 on a Varian Mercury 400 spectrometer at 400 MHz. The IR spectra were taken on a Pye Unicam SP-300 spectrometer.

3-(4-Chlorophenyl)-7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile (1b) was obtained in 95% yield; mp 236°C (DMF). IR spectrum, ν, cm^{-1}: 2210 (C≡N), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.377 (3H, s, CH_3); 6.067 (1H, s, 6-H); 7.369 (4H, s, *p*-Cl–C_6H_4); 7.443 (1H, s, 2-H). Found, %: Cl 11.82; N 9.27; S 10.81. $C_{15}H_9ClN_2OS$. Calculated, %: Cl 11.79; N 9.31; S 10.66.

3-(4-Bromophenyl)-7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyridine- 8-carbonitrile (1c) was obtained in 94% yield; mp 237°C (DMF). IR spectrum, ν, cm^{-1}: 2205 (C≡N), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.380 (3H, s, CH_3); 6.067 (1H, s, 6-H); 7.293 (2H, d, 2'- and 6'-H); 7.442 (1H, s, 2-H); 7.522 (2H, d, 3'- and 5'-H). Found, %: Br 22.96; N 8.38; S 9.48. $C_{15}H_9BrN_2OS$. Calculated, %: Br 23.15; N 8.12; S 9.29.

3-Methyl-1-oxo-1H-pyrido[2,1-*b*]benzothiazole-4-carbonitrile (2) was obtained in 97% yield; mp 239°C (DMF). IR spectrum, ν, cm^{-1}: 2200 (C≡N), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.412 (3H, s, CH_3); 6.333 (1H, s, 2-H); 7.591 (2H, m, 7- and 8-H); 8.089 (1H, dd, 6-H); 9.060 (1H, dd, 9-H). Found, %: N 12.24; S 14.17. $C_{12}H_8N_2OS$. Calculated, %: N 12.27; S 14.05.

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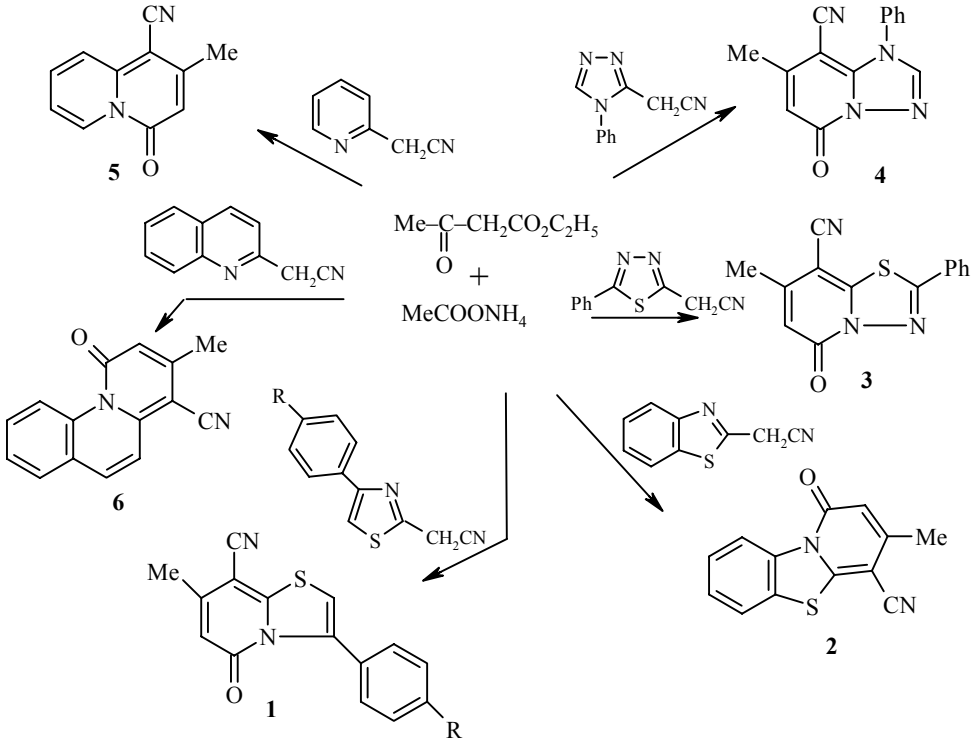
Scheme 1



1 a R = H, **b** R = Cl, **c** R = Br

7-Methyl-5-oxo-2-phenyl-5H-1,3,4-thiadiazolo[3,2-*a*]pyridine-8-carbonitrile (3) was obtained in 96% yield; mp 249°C (DMF). IR spectrum, ν, cm^{-1}: 2210 (C≡N), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.409 (3H, s, CH_3); 6.362 (1H, s, 6-H); 7.645 (3H, m, 3'-, 4'-, 5'-H_{Ph}); 8.018 (2H, d, 2'-, 6'-H_{Ph}). Found, %: N 15.94; S 11.62. $C_{14}H_9N_3OS$. Calculated, %: N 15.72; S 11.99.

7-Methyl-5-oxo-1-phenyl-5H-1,3,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (4) was obtained in 46% yield; mp 233°C (ethanol). IR spectrum, ν, cm^{-1}: 2210 (C≡N), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.318 (3H, s, CH_3); 6.040 (1H, s, 6-H); 7.626 (3H, d, 3', 4'-, 5'-H_{Ph}); 7.676 (2H, d, 2'-, 6'-H_{Ph}); 9.065 (1H, s, 2-H). Found, %: N 22.16. $C_{14}H_{10}N_4O$. Calculated, %: N 22.39.

2-Methyl-4-oxo-4H-quinolizine-1-carbonitrile (5) was obtained in 67% yield; mp 224°C (DMF). IR spectrum, ν, cm^{-1}: 2205 (C≡N), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.491 (3H, s, CH_3); 6.371 (1H, s, 3-H); 7.374 (1H, t, 8-H); 7.913 (2H, dist. t, 7- and 9-H); 9.079 (1H, d, 6-H). Found, %: N 15.46. $C_{11}H_8N_2O$. Calculated, %: N 15.21.

3-Methyl-1-oxo-1H-benzo[*c*]quinolizine-4-carbonitrile (6) was obtained in 40% yield; mp 224°C (DMF). IR spectrum, ν, cm^{-1}: 2200 (C≡N), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.384 (3H, s, CH_3); 6.550 (1H, s, 2-H); 7.625 (1H, m, 8- and 5-H); 7.689 (1H, t, 9-H); 7.919 (1H, d, 7-H); 8.015 (1H, d); 9.626 (1H, d, 10-H). Found, %: N 11.83. $C_{15}H_{10}N_2O$. Calculated, %: N 11.96.

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