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SYNTHESIS OF SPIRO 1,4-DIHYDROPYRIDINES BY ACYLATION OF HETEROCYCLIC ENAMINES WITH ISONICOTINOYL CHLORIDE

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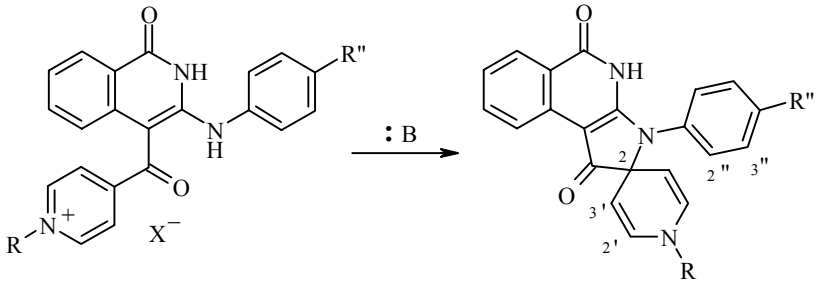
Keywords: 1-alkyl-4-[3'-(4"-arylamino)-1'-oxo-1',2'-dihydro-4'-isoquinolinylcarbonyl]pyridinium halides, 3-arylamino-4-(4-pyridylcarbonyl)-1,2-dihydro-1-isoquinolinones, spiro-1',4'-dihydropyridine[4',2]-(3-aryl-2,3,4,5-tetrahydro-1H-pyrrolo[2,3-*c*]isoquinoline-1,5-diones).

The possibility of obtaining 1,4-dihydropyridine derivatives by addition of enolates to pyridinium salts, described for the first time by Krohnke [1], was used in [2, 3] for synthesis of spiro-annelated 1,4-dihydropyridines. In [4, 6], using as an example the synthesis of complex structures, it was shown to be possible to replace the enolates with the C-ends of the enamine. In [6], attack on the electrophilic center of the pyridinium salt was carried out with both the C-end and the N-end of the enamine, and a mixture of spiro products was obtained. Attack on the electrophilic center with only the N-end of the enamine is described in [7].

We have found that when 1-alkyl-4-[3'-(4"-arylamino)-1'-oxo-1',2'-dihydro-4'-isoquinolinylcarbonyl]-pyridinium halides **1a-d** are treated with bases (triethylamine or pyridine), deprotonation and intramolecular attack by the N-end of the enamine moiety on the γ-position of the pyridinium salt occurs to form 3-aryl-2,3,4,5,1',4'-hexahydrospiro-1H-pyrrolo[2,3-*c*]isoquinoline-2,4'-pyridine-1,5-diones **2a-d**.



1a–d **2a–d**

1, **2** **a** R = Me, R"= Me, **b** R = Et, R"= Me; **c** R = Et, R" = CO_2Et, **d** R = Et, R" = Br;
1 a X = Tos^-, **b–d** X = I^-

The ^1H NMR spectra were taken in DMSO-d_6, operating frequency 400 MHz.

We have shown that 3-arylamino-1-(2H)-isoquinolinones are acylated by isonicotinoyl chloride at the C(4) atom.

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The salts **1a-d** were obtained by quaternization of the isonicotinoyl derivatives using methyl iodide, ethyl iodide, or methyl tosylate.

1'-Methyl-3-(4-methylphenyl)-2,3,4,5,1',4'-hexahydrospiro-1H-pyrrolo[2,3-*c*]isoquinoline-2,4'-pyridine-1,5-dione (2a). A mixture of 4-[3'-(4"-methylphenylamino)-1'-oxo-1',2'-dihydro-4'-isoquinolinyl-carbonyl]-1-methylpyridinium tosylate **1a** (2.7 g, 5 mmol) and pyridine (5 ml) was refluxed for 30 min. The reaction mixture was cooled and diluted with water (50 ml). The precipitate formed was filtered out, washed with water, and recrystallized from DMF. Obtained compound **2a** in 80% yield; mp 270°C. IR spectrum (thin film), ν, cm^{-1}: 3140 (NH), 1570, 1650 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.65 (1H, s, 4-NH); 7.99 (1H, d, *J* = 8.0, 9-H); 7.65 (1H, t, *J* = 8.0, 8-H); 7.23 (1H, t, *J* = 8.0, 7-H); 8.30 (1H, d, *J* = 8.0, 6-H); 6.39 (2H, d, *J* = 7.2, 2',6'-CH); 4.34 (2H, d, *J* = 7.2, 3',5'-CH); 2.90 (3H, s, 1'-NCH_3), 7.09 (2H, d, *J* = 8.8, 2",6"-H); 7.20 (2H, d, *J* = 8.8, 3",5"-H); 2.32 (3H, s, 4"-CH_3). Found, %: C 74.70; H 6.12; N 11.02. $C_{23}H_{19}N_3O_2$. Calculated, %: C 74.78; H 6.01; N 10.90.

3-(1'-Ethyl-4-methylphenyl)-2,3,4,5,1',4'-hexahydrospiro-1H-pyrrolo[2,3-*c*]isoquinoline-2,4'-pyridine-1,5-dione (2b) was obtained similarly as for compound **2a**. Yield 82%; mp 331°C. IR spectrum (thin film), ν, cm^{-1}: 3140 (NH), 1575, 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 11.51 (1H, s, 4-NH); 7.99 (1H, d, *J* = 8.0, 9-H); 7.58 (1H, t, *J* = 8.0, 8-H); 7.18 (1H, t, *J* = 8.0, 7-H); 8.30 (1H, d, *J* = 8.0, 6-H); 6.39 (2H, d, *J* = 7.6, 2',6'-CH); 4.34 (2H, d, *J* = 7.6, 3',5'-CH); 3.20 (2H, q, 1'-NCH_2CH_3); 0.94 (3H, t, 1'-NCH_2CH_3); 7.05 (2H, d, *J* = 9.0, 2",6"-H); 7.19 (2H, d, *J* = 9.0, 3",5"-H); 2.35 (3H, s, 4"-CH_3). Found, %: C 75.11; H 5.48; N 10.91. $C_{24}H_{21}N_3O_2$. Calculated, %: C 75.18; H 5.52; N 10.96.

4-(Carbethoxyphenyl)-1'-ethyl-2,3,4,5,1',4'-hexahydrospiro-1H-pyrrolo[2,3-*c*]isoquinoline-2,4'-pyridine-1,5-dione (2c) was obtained similarly as for compound **2a**. Yield 79%; mp 238°C. IR spectrum, (thin layer), ν, cm^{-1}: 3140 (NH), 1580, 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 11.84 (1H, s, 4-NH); 8.01 (1H, d, *J* = 8.0, 9-H); 7.60 (1H, t, *J* = 8.0, 8-H); 7.22 (1H, t, *J* = 8.0, 7-H); 8.32 (1H, d, *J* = 8.0, 6-H); 6.45 (2H, d, *J* = 5.6, 2',6'-CH); 3.25 (2H, d, *J* = 5.6, 3',5'-CH); 4.34 (2H, q, 1'-NCH_2CH_3); 1.027 (3H, t, 1'-NCH_2CH_3); 7.29 (2H, d, *J* = 7.6, 2",6"-H); 7.90 (2H, d, *J* = 7.6, 3",5"-H); 4.34 (2H, q, 4"-OCH_2CH_3); 1.37 (3H, t, 4"-OCH_2CH_3). Found, %: C 70.70; H 5.21; N 9.47. $C_{26}H_{23}N_3O_4$. Calculated, %: C 70.73; H 5.25; N 9.52.

3-(4-Bromophenyl)-1'-ethyl-2,3,4,5,1',4'-hexahydrospiro-1H-pyrrolo[2,3-*c*]isoquinoline-2,4'-pyridine-1,5-dione (2d) was obtained similarly as for compound **2a**. Yield 85%; mp 291°C. IR spectrum (thin film), ν, cm^{-1}: 3140 (NH), 1570, 1640 (C=O). ^{1}H NMR spectrum, δ, ppm: 11.74 (1H, s, 4-NH); 8.01 (1H, d, *J* = 8.0, 9-H); 7.60 (1H, t, *J* = 8.0, 8-H); 7.20 (1H, t, *J* = 8.0, 7-H); 8.29 (1H, d, *J* = 8.0, 6-H); 6.44 (2H, d, *J* = 7.2, 2',6'-CH); 4.28 (2H, d, *J* = 7.2, 3',5'-CH); 4.38 (2H, q, 1'-NCH_2CH_3); 1.42 (3H, t, 1'-NCH_2CH_3); 7.10 (2H, d, *J* = 8.8, 2",6"-H); 7.48 (2H, d, *J* = 8.8, 3",5"-H). Found, %: C 61.59; H 4.01; Br 17.80; N 9.32. $C_{23}H_{18}BrN_3O_2$. Calculated, %: C 61.62; H 4.05; Br 17.82; N 9.37.

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