3,5-DICYANO-1,4-DIHYDROPYRIDINES AS A SOURCE FOR PREPARATION OF PYRAZOLE AND PYRAZOLO[3,4-*b*]PYRIDINE DERIVATIVES

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Summary: The addition of hydrazine to 3,5-dicyano-1,4-dihydropyridine derivatives proceeds with heterocycle cleavage and leads to 4,4'-methylenebispyrazole or pyrazolo[3,4-*b*]pyridine derivatives.

Introduction

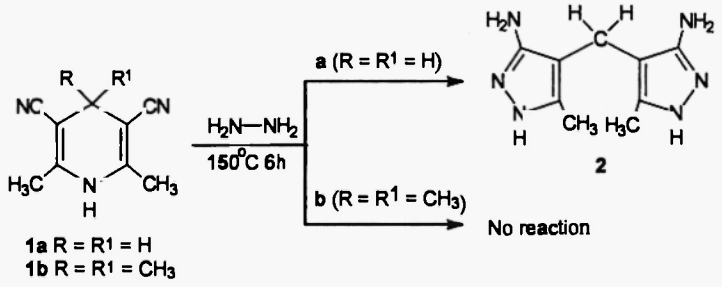
The majority of the synthesized 1,4-dihydropyridines comprises electron-withdrawing substituents in positions 3 and 5, which stabilise dihydropyridines by extending conjugation and transform the usually basic enamine to a weak acid. The typical reactions of the substituents in positions 3, 5 are inhibited. Therefore the ring opening of the majority of 1,4-dihydropyridines is successful only by their treatment with strong bases or acids, leading to cyclohexenone derivatives [1]. Even with hydrazine most of 3,5-alkoxycarbonyl- or 3,5-acetyl-substituted 1,4-dihydropyridines reacted weakly; a long-term heating resulted in bispyrazolylmethane derivatives [2]. Evidently, a secondary intramolecular cycloaddition of hydrazine to C=C double bond of 1,4-dihydropyridines, followed by opening of 1,4-dihydropyridine, proceeds easily and this is not the step determining the reaction rate. Hydrazine incorporation by nucleophilic substitution in position 2 of 1,4-dihydropyridines followed by intramolecular cyclization allows to prepare some condensed heterocyclic compounds, including for example, a pyrazolo[3,4-*b*]pyridine derivative [3], on the basis of an intact cycle of 1,4-dihydropyridine. Various pyrazolopyridines have been widely investigated, and a lot of them possess diverse and remarkable pharmacological activities. For instance an inhibitory action on glycogen synthase kinase-3 beta. These compounds are useful to treat diabetes, neurodegenerative diseases or to be used as immunopotentiators [4].

Our report includes the data on the reaction of 3,5-dicyano-1,4-dihydropyridine derivatives with hydrazine hydrate and the reaction product dependence on 4-substituent of 1,4-dihydropyridines. We propose a different method for preparing some derivatives of pyrazolo[3,4-*b*]pyridine, wherein a cycle cleavage of 3,5-dicyano-1,4-dihydropyridine investigated takes place before the condensed heterocycles are formed.

Results and Discussion

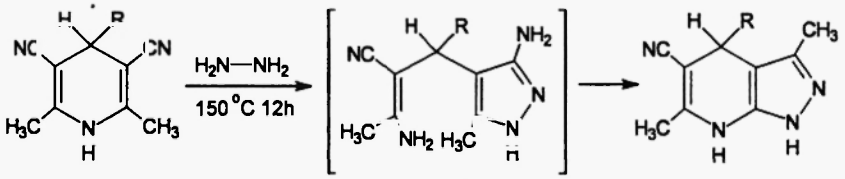
Cyanogroups of 3,5-dicyano-1,4-dihydropyridine derivatives react with hydrazine hydrate slower than 3,5-carbonylsubstituents of the related compounds. The reactions proceed by heating an ethanolic solution of the investigated compounds with an excess of hydrazine monohydrate in autoclave at 150 °C. In spite of a high temperature these reactions proceed unequivocally and, in contrast to a hydrazine reaction with 3,5-dialkoxycarbonyl-1,4-dihydropyridines, no fragmentation of the molecules studied are observed (retro-Michael addition).

Similarly, as in the case with 3,5-carbonylsubstituents [2], 4-nonsubstituted compound **1a** [5] reacted easily (Scheme 1). The reactions did not stop at an amide hydrazone stage, but proceeded until 4,4'-methylenebis(3-amino-5-methylpyrazole) **2** formed. 4,4-Dimethyl-substituted compound **1b** [6] under these conditions remained unchanged.



Scheme 1

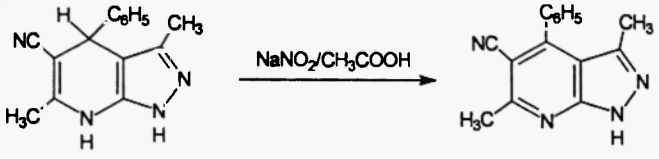
4-Monosubstituted compounds **3a–c** [5, 7, 8] reacted with hydrazine hydrate slower than compound **1a**. In this case hydrazine reacted only with one cyano group. After formation of a pyrazole cycle and cleavage of 1,4-dihydropyridine, recyclization and formation of pyrazolo[3,4-*b*]pyridine derivative **5a–c** took place by condensing 3-amino-2-methyl-4-pyrazolyl- and aminovinyl moieties of intermediate **4a–c** (Scheme 2). The supposed intermediate has not been isolated.



Scheme 2

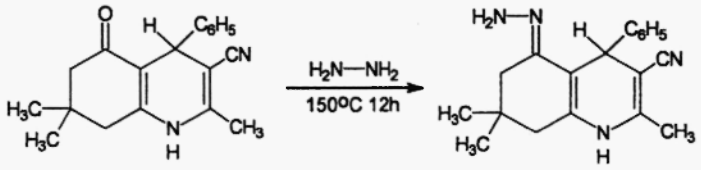
The presence or lack of substitutuents in position 4 of investigated 1,4-dihydropyridines determined the reaction course with hydrazine. The substituent in position 4 of 1,4-dihydropyridines hindered the reaction and prevented from hydrazine addition to the second cyano group. Evidently, after pyrazole was formed and 1,4-dihydropyridine cleaved, the second cyano group, conjugated with vinylamino group, fails to react with hydrazine. At the same time, intramolecular addition of an aminopyrazole part to the polar cyanovinylamine moiety proceeds easily.

The synthesized partially hydrogenated 4,7-dihydro-1H-pyrazolo[3,4-*b*]pyridine derivatives **5a–c** can be easily oxidized, for example, by nitrous acid, similarly to many 1,4-dihydropyridines (Scheme 3).



Scheme 3

In an attempt to apply the hydrazine reaction to compound 7 [9], a bicyclic substance relative to dihydropyridine **3b**, only hydrazone **8** was obtained (Scheme 4).



7 **8**

Scheme 4

Experimental

Melting points were determined on a HMR microscope. Elemental analyses (C, H, N) were within ±0.4% of theoretical values. UV spectra were recorded on a Hitachi 557 spectrophotometer; peak positions λ_{max} are expressed in nm; lg ε values are presented in parentheses. IR spectra were recorded on a Perkin Elmer 580B spectrometer in Nujol; peak positions ν_{max} are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker WH-90 spectrometer and chemical shifts are reported as δ values (ppm) relative to tetramethylsilane.

4,4'-Methylenebis(3-amino-5-methylpyrazole) (2). A mixture of 10 g (0.063 mol) of **1a** and 20 ml (0.41 mol) of hydrazine monohydrate in 60 ml of ethanol was heated in autoclave at 150 °C for 6 h and evaporated. The white crystalline residue was dissolved in hot ethanol and recrystallized by adding ethyl acetate and hexane. Yield of **2** is 10.3 g (79%), m.p. 247–249 °C. UV (C_2H_5OH): 202 (3.92), 229 (3.99); IR: 3415, 3335, 3200, 3180, 3090, 1622, 1602, 1590, 1495. ^{1}H-NMR (DMSO-d_6): 1.94 (6H, s, 5,5'-CH_3), 3.11 (2H, s, CH_2), 4.27 (4H, br.s., 3,3'-NH_2), 10.4–11.3 (2H, band, 1,1'-NH). Calculated for $C_9H_{14}N_6$: C 52.41, H 6.84, N 40.75. Found: C 52.46, H 6.96, N 40.85.

3,4,6-Trimethyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (5a). A mixture of 0.33 g (1.90 mmol) of **3a** and 1.2 ml (24.7 mmol) of hydrazine monohydrate in 2.5 ml of ethanol was heated in a thick-walled glass pressure vessel (5 ml volume) at 150 °C for 12 h. After cooling a white precipitate was filtered off. Yield of **5a** 0.11 g (31%), after crystallization from DMFA + water m.p. 291–293 °C (subl.). UV (C_2H_5OH): 203 (3.94), 220 (3.97), 298 (4.01); IR: 3260, 3200, 3135, 3065, 2179, 1607, 1558, 1515. ^{1}H-NMR (DMSO-d_6): 1.22 (3H, d, J = 7 Hz, 4-CH_3), 2.00 (3H, s, 3-CH_3), 2.10 (3H, s, 6-CH_3), 3.63 (1H, q, J = 7 Hz, 4-H), 9.36 (1H, s, 7-NH), 11.72 (1H, br.s., 1-NH). Calculated for $C_{10}H_{12}N_4$: C 63.81, H 6.43, N 29.76. Found: C 63.75, H 6.44, N 29.73.

3,6-Dimethyl-4-phenyl-4,7-dihydro-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5b). A mixture of 10 g (0.043 mol) of **3b** and 20 ml (0.41 mol) of hydrazine monohydrate in 50 ml of ethanol was heated in autoclave at 150 °C for 12 h. After cooling a white precipitate was filtered off, washed with water and ethanol and crystallized from DMFA + water. Yield of **5b** 5.55 g (52%), m.p. 306–307 °C (subl.). UV (C_2H_5OH): 205 (4.16), 228 (3.99), 306 (4.04). IR: 3240, 3195, 3130, 3060, 2180, 2178, 1627, 1605, 1555, 1515. ^{1}H-NMR (DMSO-d_6): 1.73 (3H, s, 3-CH_3), 2.07 (3H, s, 6-CH_3), 4.72 (1H, s, 4-H), 6.90–7.45 (5H, m, 4-C_6H_5), 9.60 (1H, br.s., 7-NH), 11.13–12.20 (1H, band, 1-NH). Calculated for $C_{15}H_{14}N_4$: C 71.98, H 5.64, N 22.38. Found: C 71.76, H 5.68, N 22.33.

3,6-Dimethyl-4-(3-pyridyl)-4,7-dihydro-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5c). A mixture of 0.33 g (1.4 mmol) of **3c** and 1.2 ml (24.7 mmol) of hydrazine monohydrate in 2.5 ml of ethanol was heated in a pressure vessel at 150 °C for 12 h, evaporated and recrystallized from DMFA + water. Yield of white crystalline monohydrate **5c** 0.13 g (35%), m.p. 252–253 °C. UV (C_2H_5OH): 205(4.04), plato 218–232 (3.88), 265 (3.78), 312 (3.91). IR (anhydrous sample): 3240, 3200, 3135, 3070, 2182, 2179, 1625, 1610, 1590, 1575, 1555, 1515. ^{1}H-NMR (DMSO-d_6): 1.75 (3H, s, 3-CH_3), 2.08 (3H, s, 6-CH_3), 4.85 (1H, s, 4-H), 7.25–7.80 (2H, m, 4-Py-4',5'-H), 8.35–8.65 (2H, m, 4-Py-2',6'-H), 9.72 (1H, br.s., 7-NH), 11.60–12.30 (1H, band, 1-NH). Calculated for $C_{14}H_{13}N_5 \cdot H_2O$: C 62.44, H 5.61, N 26.01. Found: C 62.37, H 5.60, N 25.97.

3,6-Dimethyl-4-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (6). 1.0 g (4.24 mmol) of **5b** was dissolved in 50 ml of hot acetic acid. 1.0 g (14.50 mmol) of sodium nitrite in small portions was added to the hot solution. The mixture was boiled for 2 min, cooled and mixed with 100 ml of water. A white precipitate was recrystallized from ethanol + water. Yield of **6** 0.62 g (62%), m.p. 192–194 °C. UV (C_2H_5OH): 205 (4.21), 242 (4.38), 313 (3.81). IR: 3190, 3130, 2220, 1595, 1585, 1570, 1500. ^{1}H-NMR ($CDCl_3$): 2.10 (3H, s, 3-CH_3), 2.97 (3H, s, 6-CH_3), 7.35–7.70 (5H, m, 4-C_6H_5), 7.00–8.60 (1H, band, 1-NH). Calculated for $C_{15}H_{12}N_4$: C 72.56, H 4.87, N 22.54. Found: C 72.26, H 4.85, N 22. 55.

5-Hydrazono-4-phenyl-2,7,7-trimethyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (8). A mixture of 0.33 g (1.13 mmol) of **7** and 1.2 ml (24.7 mmol) of hydrazine monohydrate in 2 ml of ethanol was heated in a pressure vessel at 150 °C for 12 h. After cooling a yellowish precipitate was filtered off and washed with water and ethanol. Yield of **8** 0.29 g (84%); after crystallization from DMFA + water, m.p. 233–236 °C. UV (C_2H_5OH): 205 (4.10), 228 (4.25), 306 (3.83). IR : 3400, 3190, 3190, 2180, 1658, 1630, 1625, 1600, 1565, 1512. ^{1}H-NMR (DMSO-d_6): 0.87 and 1.02 (2×3H, 2×s, 7-$C(CH_3)_2$), 1.75–2.35 (4H, m, 6-CH_2 and 8-CH_2), 1.97 (3H, s, 2-CH_3), 4.52 (1H, s, 4-H), 5.65 (2H, br.s., 5-N–NH_2), 6.95–7.35 (5H, m, 4-C_6H_5), 8.66 (1H, br.s., 1-NH). Calculated for $C_{19}H_{22}N_4$: C 74.48, H 7.24, N 18.28. Found: C 74.25, H 7.24, N 17.90.

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