CYCLIZATION OF 2-DICYANOMETHYLENE-1,2-DIHYDROPYRIDINE-3-CARBONITRILES WITH HYDROGEN HALIDES: A RE-EXAMINATION ON THE REGIOSELECTIVITY

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Abstract- The cyclization of the title compounds (5a-c) with HCl and HBr has been re-examined. In all cases 5-amino-7-halo-substituted 1,6-naphthyridines (11a-c and 12a-c) were formed independently of the thermal level and the hydrogen halide employed. The structures of 11a-c and 12a-c were unequivocally established by reaction with hydrazine which afforded the corresponding pyrazolo[3,4-h][1,6]naphthyridines (14a-c). The structure of the methoxy derivatives (15a,c and 16a,c) was assigned by two-dimensional nmr studies.

During the past years the research of our group has been mainly focused on the cyclization of 1,5-dinitriles in the presence of anhydrous hydrogen halides as a method for the construction of fused heterocyclic rings.\textsuperscript{1} As a part of this study we have developed a method for the synthesis of 1,2,3,4-tetrahydro-1,6-naphthyridines starting from α,β-unsaturated esters.\textsuperscript{2} Thus, the treatment of the obtained pyridones (1) with malononitrile (2) yielded the corresponding substitution products (3) which underwent cyclization in acid medium (HCl or HBr in dioxane/benzene) to afford the 7-amino-5-halo-8-cyano-1,2,3,4-tetrahydro-1,6-naphthyridin-2-ones (4) (X = Cl, Br)
The direction of the cyclization was found to be independent of the thermal level employed and the nature and position of the substituents R¹ and R².

In connection with this, it is worth pointing out that in 1983 H. Junek et al. reported the synthesis of 7-amino-5-bromo-8-cyano-2,4-dimethyl-1,6-naphthyridine (6a) by cyclization of the 1,5-dinitrile system present in 5a.³ The isomer obtained was assigned on the basis of a positive Nuclear-Overhauser-Effect for the methoxy protons of 7a, obtained by substitution of the bromine atom present in 6a by NaOMe, when the signal of the 4-methyl group was selectively irradiated.

\[
\text{HBr / AcOH} \quad 60^\circ C
\]

5a  

\[
\text{6a} \quad \text{Nu} = \text{Br} \\
\text{7a} \quad \text{Nu} = \text{OMe}
\]

The apparent homogeneity of the results obtained in the cyclization of the tetrahydropyridones (3) and the 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitrile (5a), prompted us to extend this cyclization to the phenyl substituted compounds (5b-c) in order to confirm the general applicability of the method for the synthesis of 5-halo-7-aminonaphthyridines. The present paper covers the unexpected results obtained in this study.

RESULTS AND DISCUSSION

Firstly we obtained the 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitrile (5b) by using the procedure described⁴ by Sharanin et al. in which the corresponding α,β-unsaturated ketone (8b) is treated with 2-amino-1,1,3-tricyanopropene (9) in the presence of ethanolic diethylamine to afford an intermediate salt which is converted to the final product by refluxing in AcOH.⁵

We have also extended this method to the α,β-unsaturated ketones (8a and 8c) to obtain the dicyanomethylene-substituted pyridines (5a and 5c) without isolation of any intermediate salt. The compound (5a) was also synthesized starting from 2,4-pentanedione (10a) according to the procedure described by Junek et al.³ This later procedure failed when it was tested for the synthesis of 5b-c.

Once the starting 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles (5a-c) were obtained, we carried out the cyclization in AcOH with HCl and HBr both at room temperature and at reflux. The spectral data of the products obtained (11a-c when X = Cl and 12a-c when X = Br) showed that the reaction affords the same isomer at room temperature and at reflux. Furthermore, the practical identity of the ir and uv spectra of the compounds formed with HCl and HBr confirmed that the direction of the cyclization is independent of the hydrogen halide and the thermal level employed.

In order to establish the structure of the isomer formed, we treated the bromo and chloro derivatives formed with hydrazine hydrate (80%) in dioxane at reflux. For each set of compounds (X = Cl and X =
Br) the reaction yielded the same intermediate hydrazino-substituted naphthyridines (13a-c), proving the coincidence of the position of the halogen in the chloro and bromo derivatives, which afforded the 7H-pyrazolo[3,4-h] [1,6]naphthyridine-5,9-diamines (14a-c) when heated in EtOH at reflux.

The cyclization of the hydrazino group onto the cyano group proved that we have obtained the corresponding 5-amino-7-halo-substituted 1,6-naphthyridines (11a-c and 12a-c) independently of the thermal level (room temperature or reflux) and the hydrogen halide employed (HBr or HCl). That is to say, the isomer formed is always the contrary to that reported by Junek et al. (6a-c), even when the substituents are methyl groups.

In order to clarify the whole matter, our research groups decided to joint their efforts to re-examine both the cyclizations in basic medium and the nmr study of the products obtained. Thus, in one side, we carried out the cyclization of 5a and 5c in NaOMe/MeOH and, on the other side, the substitution of the
halogen atom by methoxide in 11c and 12a. Two different sets of compounds were obtained for which the structures (15a,c and 16a,c) were assigned in accordance with the structures of the haloderivatives used in the nucleophilic substitution.

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Table 1: $^{13}$C Nmr spectral data of naphthyridines (11a-c, 12a-c, 15a,c, and 16a,c)

This result, contrary to the previous assignment carried out on 7a by the NOE experiment led us to reproduce such study. The tests performed indicate that the NOE data seem to be misleading for this group of compounds as they show the tendency to have stacking interactions in different solvents. Such interactions lead not only to concentration dependent chemical shifts but also to NOE enhancements which are caused by the neighborhood and not by intramolecular dipole-dipole interactions. Consequently, we have used long range coupling constants to assign the spectra of 15a,c and 16a,c in an unambiguous way.

To observe the long range proton-carbon couplings, HMBC (Heteronuclear Multiple-Bond Correlation) experiments have been performed. Thereby, two of the compounds, (15a and 15c), can be assigned unambiguously by the fact that the protons of the amino group show a long range coupling to the carbon atom which carries the nitrile group ($\delta = 74$ ppm) (Figure 1). On the other hand, the compound (16c) shows the same kind of coupling, however, according to the structure now the carbon which is
shared by the two ring moieties is influenced (δ = 107.2 ppm). In 16a there is no long range coupling which connects the NH₂ group with the neighbor carbon atoms. This may be due to short T2 relaxation time of these protons, therefore only indirect evidence for the correctness of the structure can be gained from the 2D HMBC spectrum, taking into account that the spectrum of 15a has been assigned unequivocally.

**Figure 1:** Two-dimensional nmr spectrum of 15c showing a long range coupling between the protons of the amino group and the carbon atom which carries the cyano group (δ = 74 ppm)

The results obtained show a high regioselectivity for the cyclization of compounds (5a-c) in front of hydrogen halides affording 5-amino-7-halo-1,6-naphthyridines (11 and 12). The direction of the ring closure was independent of the hydrogen halide used, the thermal level employed and the nature and position of the substituents R¹ and R². As for the cyclization in NaOMe/MeOH, the direction of the cyclization is reversed and the 7-amino-5-methoxy-substituted 1,6-naphthyridines (15) are preferentially formed. However, the dimethyl-substituted 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitrile (5a) was found to be less reactive than the phenyl-substituted compound (5c).

These results agree with our previous findings according to which the cyano group that possesses the highest negative charge density on the nitrogen atom is the first to add the hydrogen halide to give the corresponding imidoyl halide and, consequently, the one that carries the halogen atom in the final product.¹ Thus, in the case of compounds (5), the dicyanomethylene unit is far more reactive than the
cyano group linked to the ring and, consequently, only the 7-halo-substituted derivative is formed. This behavior was already found during the studies on the cyclization of 2-amino-1,1,3-tricyanopropene (9).7

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EXPERIMENTAL

Melting points were taken on a Büchi-Tottoli apparatus and are uncorrected. IR spectra (KBr) were measured on a Perkin-Elmer 683 or on a Bomem Michelson-100 FTIR. 1H and 13C nmr spectra were recorded on a Bruker AC-80, a Varian XL-200/F19, a Varian Gemini-300 and a Bruker AM 360 in DMSO-d6. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as the internal reference standard, coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br s = broad signal. UV spectra were recorded on a Hewlett-Packard 8450 A spectrophotometer. Mass spectra were obtained on a Hewlett-Packard 5995 A spectrometer with an electron beam of 70 eV. Microanalyses were performed on a Carlo-Erba CHNS-O/E 1108 analyzer.

2-Dicyanomethylene-1,2-dihydropyridine-3-carbonitriles (5a-c). General procedure: A mixture of 0.01 mol of the α,β-unsaturated ketone (8a-c), 1.3 g (0.01 mol) of 2-amino-1,1,3-tricyanopropene (9) and 1.5 g (0.02 mol) of freshly distilled diethylamine in 50 ml of ethanol was stirred at room temperature for 1 h. Then, 0.5 ml of concentrated HCl were added and the mixture was heated for 2 h at 60°C. The solution was concentrated in vacuo and the crude material was heated in AcOH (50 ml) at reflux for 0.5 h. The solid obtained was filtered off to give 5a-c.

2-Dicyanomethylene-1,2-dihydro-4,6-dimethylpyridine-3-carbonitrile (5a). a) Starting from 8a: Yield: 5%, mp 255°C (decomp.) (lit., 255°C (decomp.))8. b) Starting from 10a: A mixture of 0.49 g (0.005 mol) of 2,4-pentanedione (10a) and 0.5 g (0.004 mol) of 2-amino-1,1,3-tricyanopropene (9) in 2 ml of 10% NaOH was stirred at room temperature for 10 min. Then, 80 ml of water were added to the mixture and the solution was acidified with 6M HCl. The solid obtained was filtered off and washed with water to give 0.69 g of 5a. Yield: 93%.

2-Dicyanomethylene-1,2-dihydro-4,6-diphenylpyridine-3-carbonitrile (5b). Yield: 60% (lit., 78%4), mp 250°C (decomp.) (lit., 252°C (decomp.))9.

2-Dicyanomethylene-1,2-dihydro-6-phenylpyridine-3-carbonitrile (5c). Yield: 44%, mp 276°C (decomp.) (lit., 280°C (decomp.))10.

5-Amino-8-cyano-7-halo-1,6-naphthyridines (11a-c, X=Cl) and (12a-c, X=Br). General procedure: A stream of anhydrous hydrogen chloride or hydrogen bromide was bubbled through a suspension of 0.002 mol of the corresponding dihydropyridine (5a-c) in 50 ml of AcOH at the temperature "T" until saturation (1-2 h). The mixture was stirred at room temperature for "t" h in a closed vessel. The solid formed was filtered, washed with water and recrystallized from the solvent "S" to give 11a-c and 12a-c.
5-Amino-7-chloro-8-cyano-2,4-dimethyl-1,6-naphthyridine (11a). a) T = 60°C, t = 15 h, S = DMF, yield: 44%; mp>300°C. IR ν: 3480, 3300 and 3200 (N-H), 2220 (C=O), 1635 (N-H), 1595, 1560 and 1540 (C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.63 (3H, s, Me-C2), 2.85 (3H, s, Me-C4), 7.33 (1H, s, H-3), 8.0 (2H, br s, NH2, deuterated). Ms, m/z (%): 234 (34), 233 (14), 232 (M+, 100), 231 (5), 198 (12), 197 (99), 198 (13), 170 (33), 168 (6), 143 (9), 142 (5). Uv (EtOH): λmax (log e) = 215 (4.26), 255 (4.28), 314 (3.72), 344 (3.80). Anal. Calcd for C14H11N4Cl: C, 56.78; H, 3.90; N, 24.08. Found: C, 56.69; H, 4.08; N, 24.35. b) T = reflux, t = 1 h, S = DMF, yield: 30%. 

5-Amino-7-chloro-8-cyano-2,4-diphenyl-1,6-naphthyridine (11b). a) T = 20°C, t = 120 h, S = ethanol, yield: 47%; mp>300°C. IR ν: 3450, 3280 and 3100 (N-H), 2230 (C=O), 1640 (N-H), 1585, 1550 and 1495 (C=C and C=N), 775 and 690 (Ph). 1H Nmr (DMSO-d6) δ: 7.60 (8H, m, Ph), 8.00 (1H, s, H-3), 8.40 (2H, m, Ph). Ms, m/z (%): 358 (29), 357 (54), 356 (M+, 94), 355 (100), 321 (3), 320 (6), 319 (20), 293 (3), 292 (4), 266 (4), 265 (5). Uv (EtOH): λmax (log e) = 260 (4.38), 294 (4.51), 370 (3.89). Anal. Calcd for C21H13N4Cl: C, 70.69; H, 3.67; N, 15.70. Found: C, 70.65; H, 3.53; N, 15.69. b) T = reflux, t = 0.5 h, S = ethanol, yield: 38%. 

5-Amino-7-chloro-8-cyano-2-phenyl-1,6-naphthyridine (11c). a) T = 20°C, t = 48 h, S = ethanol, yield: 77%; mp>300°C. IR ν: 3400, 3350 and 3150 (N-H), 2230 (C=O), 1655 (N-H), 1600, 1585, 1575 and 1545 (C=C and C=N), 765 and 700 (Ph). 1H Nmr (DMSO-d6) δ: 7.55 (3H, m, m- and p-Ph), 8.24 (1H, d, J = 8.8 Hz, H-3), 8.33 (2H, m, o-Ph), 8.63 (2H, br s, NH2, deuterated), 8.78 (1H, d, J = 8.8 Hz, H-4). Ms, m/z (%): 283 (6), 282 (34), 281 (19), 280 (M+, 100), 246 (11), 245 (60), 218 (16), 191 (12), 164 (7). Uv (EtOH): λmax (log e) = 259 (4.37), 288 (4.54), 367 (3.96). Anal. Calcd for C15H10N4Br: C, 64.18; H, 3.23; N, 19.96. Found: C, 64.40; H, 3.30; N, 19.67. b) T = reflux, t = 0.5 h, S = ethanol, yield: 89%. 

5-Amino-7-bromo-8-cyano-2,4-dimethyl-1,6-naphthyridine (12a). a) T = 20°C, t = 15 h, S = DMF, yield: 67%; mp>300°C. IR ν: 3490, 3310 and 3210 (N-H), 2220 (C=O), 1635 (N-H), 1595, 1560 and 1540 (C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.62 (3H, s, Me-C2), 2.84 (3H, s, Me-C4), 7.34 (1H, s, H-3), 8.0 (2H, br s, NH2, deuterated). Ms, m/z (%): 279 (13), 278 (91), 277 (15), 276 (M+, 100), 198 (10), 197 (80), 171 (5), 170 (33), 143 (8). Uv (EtOH): λmax (log e) = 217 (4.24), 256 (4.34), 316 (3.78), 342 (3.85). Anal. Calcd for C14H9N4Br: C, 47.67; H, 3.27; N, 20.22. Found: C, 47.43; H, 3.22; N, 20.05. b) T = 60°C, t = 15 h, S = DMF, yield: 83%. c) T = reflux, t = 0.5 h, S = DMF, yield: 64%. 

5-Amino-7-bromo-8-cyano-2,4-diphenyl-1,6-naphthyridine (12b). a) T = 20°C, t = 96 h, S = ethanol, yield: 51%; mp>300°C. IR ν: 3460, 3270 and 3080 (N-H), 2220 (C=O), 1630 (N-H), 1570, 1540 and 1490 (C=C and C=N), 770 and 685 (Ph). 1H Nmr (DMSO-d6) δ: 5.4 (2H, br s, NH2, deuterated), 7.63 (8H, m, Ph), 8.03 (1H, s, H-3), 8.41 (2H, m, Ph). Ms, m/z (%): 402 (100), 401 (100), 400 (M+, 99), 399 (100), 321 (14), 320 (13), 319 (34), 294 (4), 293 (7), 292 (8), 267 (7), 266 (11), 265 (11), 240 (8). Uv (EtOH): λmax (log e) = 260 (4.31), 294 (4.49), 375 (3.81). Anal. Calcd for C21H13N4Br: C, 62.86; H, 3.27; N, 13.96. Found: C, 62.66; H, 3.21; N, 13.80. b) T = reflux, t = 0.5 h, S = ethanol, yield: 40%. c) T = reflux, t = 12 h, S = ethanol, yield: 50%. 

5-Amino-7-bromo-8-cyano-2-phenyl-1,6-naphthyridine (12c). a) T = 20°C, t = 148 h, S = ethanol, yield: 62%; mp>300°C. IR ν: 3380, 3320 and 3160 (N-H), 2230 (C=O), 1650 (N-H), 1600, 1585, 1565 and 1540 (C=C and C=N), 760 and 700 (Ph). 1H Nmr (DMSO-d6) δ: 7.57 (3H, m, m- and p-Ph), 8.32 (1H, d, J = 8.8 Hz, H-3), 8.36
5-Amino-8-cyano-7-hydrazino-1,6-naphthyridines (13a-c). General procedure: A mixture of 0.0003 mol of the corresponding 7-halonaphthyridine (11a-c or 12a-c), 0.5 ml (8.2 mmol) of 80% hydrazine hydrate and 50 ml of dioxane was heated at reflux for 3 h. The solution was concentrated in vacuo to give a solid, which was suspended in water, filtered off and recrystallized from ethanol to give 13a-c.

5-Amino-8-cyano-7-hydrazino-2,4-diphenyl-1,6-naphthyridine (13a). a) Starting from 11a. Yield: 66%, mp>300 °C. Ir ν: 3500, 3350, 3280 and 3220 (N-H), 1620, 1590, 1575 and 1555 (N-H, C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.47 (3H, s, Me-C2), 2.72 (3H, s, Me-C4), 4.5 (2H, br s, NH2, deuterable). 6.82 (1H, s, H-3), 7.20 (2H, br s, NH2, deuterable), 7.95 (1H, br s, NH, deuterable). 13C Nmr (DMSO-d6): 22.6 (Me-C4), 24.4 (Me-C2), 70.5 (C-8), 105.5 (C-4a), 118.0 (CN), 120.5 (C-3), 146.0 (C-4), 156.3 (C-8a), 159.8 (C-5), 160.7 (C-7), 162.5 (C-2).

Ms, m/z (%): 229 (13), 228 (M+-100), 227 (41), 213 (21), 212 (17), 198 (14), 197 (27), 172 (12), 171 (13), 170 (13). Uv (EtOH): λ max (log ε) 215 (4.17), 254 (4.36), 307 (3.86), 364 (3.68). b) Starting from 12a. Yield: 80%.

5-Amino-8-cyano-7-hydrazino-2,4-diphenyl-1,6-naphthyridine (13b). a) Starting from 11b. Yield: 81%, mp 265 °C. Ir ν: 3470, 3300 and 3190 (N-H), 2220 (C=N), 1640 (N-H), 1600, 1585, 1560 and 1520 (C=C and C=N), 780 and 700 (Ph). Ms, m/z (%): 353 (24), 352 (M+-100), 351 (66), 337 (23), 336 (26), 321 (12). Uv (EtOH): λ max (log ε) 256 (4.33), 292 (4.46), 367 (3.67). b) Starting from 12b. Yield: 91%.

5-Amino-8-cyano-7-hydrazino-2,4-diphenyl-1,6-naphthyridine (13c). a) Starting from 11c. Yield: 68%, mp>300°C.

5,9-Diamino-2,4-dimethyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (14a). A mixture of 0.0002 mol of 12a, 0.5 ml (8.2 mmol) of 80% hydrazine hydrate and 30 ml of dioxane was heated at reflux for 3 h and the solid obtained was filtered off and heated in ethanol at reflux for 6 h to give 14a. Yield: 72%, mp>300°C (ethanol). Ir ν: 3520, 3420, 3350 and 3300 (N-H), 1610 and 1575 (N-H, C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.60 (3H, s, Me-C2), 2.87 (3H, s, Me-C4), 5.44 (2H, br s, NH2, deuterable), 6.49 (2H, br s, NH2, deuterable), 7.04 (1H, s, H-3), 11.5 (1H, br s, NH, deuterable). 13C Nmr (DMSO-d6): 23.4 (Me-C4), 24.4 (Me-C2), 92.4 (C-9a), 109.0 (C-4a), 121.1 (C-3), 146.2 (C-4), 149.6 (C-10), 150.6 and 150.7 (C5 and C9), 158.7 (C6a), 160.6 (C2). Ms, m/z (%): 229 (16), 228 (M+-100), 227 (42), 213 (16), 212 (13), 197 (9), 172 (8), 170 (8). Uv (EtOH): λ max (log ε) 228 (4.48), 281 (4.25), 349 (3.77). Anal. Calcd for C11H12N6: C, 57.88; H, 5.30; N, 36.82. Found: C, 58.25; H, 5.52; N, 37.17.

5,9-Diamino-2,4-dimethyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (14b). A mixture of 0.003 mol of 11b, 0.5 ml (8.2 mmol) of 80% hydrazine hydrate and 50 ml of dioxane was heated at reflux for 24 h. The solution was concentrated in vacuo and the solid obtained was heated in ethanol at reflux for 35 h to give 14b. Yield: 67%, mp>300°C (ethanol). Ir ν: 3490, 3320 and 3220 (N-H), 1620, 1605, 1570, 1550 and 1500 (N-H, C=C and C=N),
780 and 710 (Ph). Ms, m/z (%): 353 (22), 352 (M⁺, 100), 351 (71), 337 (66), 336 (70), 323 (9), 322 (29), 321 (46) Uv (EtOH): λmax (log ε): 248 (4.42), 289 (4.43), 383 (3.80).

5,9-Diamino-2-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridine (14c). A mixture of 0.0003 mol of 12c, 0.5 ml (8.2 mmol) of 80% hydrazine hydrate and 50 ml of dioxane was heated at reflux for 2 h. The solution was concentrated in vacuo and the solid obtained was heated in ethanol at reflux for 7 h to give 14c. Yield: 88%, mp >300°C (ethanol). Ir ν: 3450, 3360 and 3200 (N-H), 1650, 1620, 1610, 1575 and 1560 (N-H, C=C and C=N), 775 and 695 (Ph). Ms, m/z (%): 277 (18), 276 (M⁺, 100), 247 (14), 220 (8), 193 (5), 166 (6). Uv (EtOH): λmax (log ε): 249 (4.33), 284 (4.45), 385 (3.81).

5-Amino-4-cyano-7-methoxy-2-phenyl-1,6-naphthyridine (3.86). Reflux for 24 h. The solution was kept in a refrigerator overnight and the solid obtained was filtered off (0.4 g, yield: 17%) and recrystallized from methanol to give pure 15a. mp 250°C. Ir ν: 3440, 3320 and 3210 (N-H), 1640 (N-H), 1580 and 1560 (C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.49 (3H, s, Me-C2), 2.58 (3H, s, Me-C4). 3.99 (3H, s, OMe), 6.89 (1H, s, H-3). 7.10 (2H, br s, NH₂, deuterable). Ms, m/z (%): 229 (14), 228 (M⁺, 100), 227 (5), 212 (21), 200 (16), 199 (48), 197 (13), 171 (7), 132 (13). Uv (EtOH): λmax (log ε): 245 (4.58), 283 (3.93), 292 (3.85), 361 (3.75).

7-Amino-8-cyano-2,4-dimethyl-5-methoxy-1,6-naphthyridine (15a). A mixture of 2 g (0.01 mol) of 5a and 0.7 g (0.03 mol) of sodium in 30 ml of methanol was heated at reflux for 48 h. The solution was kept in a refrigerator overnight and the solid obtained was filtered off (0.4 g, yield: 17%) and recrystallized from methanol to give pure 15a. mp 250°C. Ir ν: 3440, 3320 and 3210 (N-H), 1640 (N-H), 1580 and 1560 (C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.49 (3H, s, Me-C2), 2.58 (3H, s, Me-C4). 3.99 (3H, s, OMe), 6.89 (1H, s, H-3), 7.10 (2H, br s, NH₂, deuterable). Ms, m/z (%): 229 (14), 228 (M⁺, 100), 227 (5), 212 (21), 200 (16), 199 (48), 197 (13), 171 (7), 132 (13). Uv (EtOH): λmax (log ε): 245 (4.58), 283 (3.93), 292 (3.85), 361 (3.75).

7-Amino-8-cyano-2,4-dimethyl-5-methoxy-1,6-naphthyridine (15c). A mixture of 2.4 g (0.01 mol) of 5c and 0.7 g (0.03 mol) of sodium in 30 ml of methanol was heated at reflux for 24 h. The solution was concentrated in vacuo and the solid obtained was washed with water and dried to give 2.1 g (yield: 75%) of 15c. mp 240-241°C. Ir ν: 3450, 3350 and 3250 (N-H), 2220 (C=C=N), 1650 (N-H), 1610, 1590, 1560 and 1510 (C=C and C=N), 770 and 700 (Ph). 1H Nmr (DMSO-d6) δ: 4.04 (3H, s, OMe), 7.40 (2H, br s, NH₂, deuterable), 7.53 (3H, m, m and p-Ph), 7.80 (1H, d, J = 8.5 Hz, H-3), 8.25 (2H, m, o-Ph), 8.28 (1H, d, J = 8.5 Hz, H-4) (It is worth noting that the chemical shifts show a strong concentration dependence). Ms, m/z (%): 277 (19), 276 (M⁺, 100), 275 (11), 248 (11), 247 (37), 220 (5), 219 (5), 180 (5), 164 (5). Uv (EtOH): λmax (log ε): 222 (4.34), 278 (4.61), 384 (3.84).

5-Amino-8-cyano-2,4-dimethyl-7-methoxy-1,6-naphthyridine (16a). A mixture of 0.55 g (0.002 mol) of 12a and 0.46 g (0.02 mol) of sodium in 100 ml of methanol was heated at reflux for 20 h. The mixture was kept in a refrigerator overnight and the solid obtained was filtered off (0.32 g, yield: 70%) and recrystallized from methanol to give pure 16a. mp 273°C. Ir ν: 3500, 3340 and 3225 (N-H), 2220 (C=C=N), 1630 (N-H), 1600, 1580 and 1560 (C=C and C=N). 1H Nmr (DMSO-d6) δ: 2.51 (3H, s, Me-C2), 2.76 (3H, s, Me-C4), 3.97 (3H, s, OMe), 7.02 (1H, s, H-3), 7.61 (2H, br s, NH₂, deuterable). Ms, m/z (%): 229 (14), 228 (M⁺, 100), 227 (13), 213 (35), 210 (10), 199 (24), 198 (9), 197 (10), 196 (15), 171 (12), 157 (14), 131 (9), 104 (8). Uv (EtOH): λmax (log ε): 248 (4.40), 303 (3.70), 363 (3.86).

5-Amino-8-cyano-7-methoxy-2-phenyl-1,6-naphthyridine (16c). A mixture of 0.16 g (0.0006 mol) of 11c and 0.13 g (0.006 mol) of sodium in 75 ml of methanol was heated at reflux for 24 h. The solid obtained was filtered off and washed with methanol to give 0.11 g (yield: 70%) of 16c. mp 280°C (d). Ir ν: 3400, 3330 and 3230 (N-H), 2230 (C=C=N), 1645 (N-H), 1600, 1580, 1545 and 1495 (C=C and C=N), 770 and 700 (Ph). 1H Nmr (DMSO-d6) δ: 4.08 (3H, s, OMe), 7.62 (3H, m, m- and p-Ph), 8.05 (1H, d, J = 8.7 Hz, H-3), 8.37 (2H, m, o-Ph), 8.40 (2H, br s,
NH$_2$, deuterable), 8.75 (1H, d, $J = 8.7$ Hz, H-4). Ms, m/z (%): 277 (19), 276 (M$^+$, 100), 275 (23), 248 (7), 247 (31), 244 (7), 206 (8), 179 (7). UV (EtOH): $\lambda_{max}$ (log $e$): 284 (4.42), 383 (3.75).

REFERENCES AND NOTES


5. During the synthesis of 5b we obtained the intermediate salt (17b) as it was stated in the procedure described by Sharanin et al., such kind of salt was not formed when we used this method to obtain 5a,c. On the other hand, when we tried to scale-up the synthesis of 5b by using 20 g (0.1 mol) of 8b, the 2-dicyanomethyl-4,6-diphenyl-1,4-dihydropyridine-3-carbonitrile (18b) was obtained as by-product in 12.4% yield., mp 166-7°C. \textit{IR} $v$: 3370, 3340, and 3030 (NH), 2230 (CN), 1665, 1595, and 1495 (C=C), 760, 700 cm$^{-1}$. \textit{H Nmr} (DMSO-d$_6$) $\delta$: 4.20 (1H, s, CH(CN)$_2$), 4.15 (1H, d, $J = 6$ Hz, H-4), 5.75 (1H, d, $J = 6$ Hz, H-5), 7.0-7.8 (11H, m, Ph and NH). Ms, m/z (%): 323 (24), 322 (M$^+$, 100), 321 (28), 295 (17), 294 (15), 245 (12), 218 (16), 206 (74).


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