STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, LI, 1, 2006

REACTIONS OF THE 3-CYANO-10-METHYL-PYRIDO[3,2-g]QUINOLIN-4-ONE. II*

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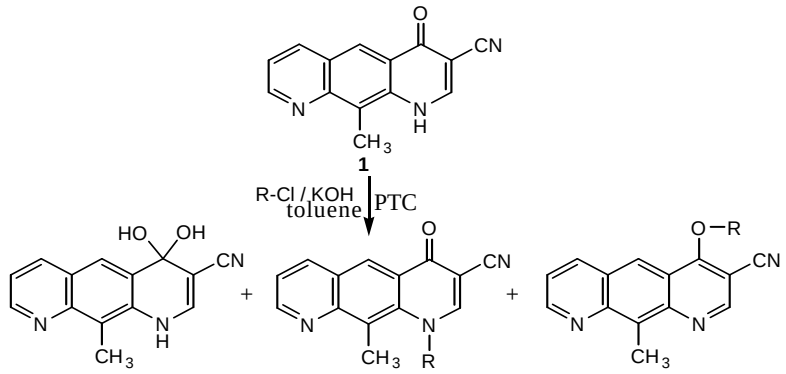
Dedicated to professor Sorin Mager
at his 75th anniversary

ABSTRACT. The synthesis of 4-alkoxy-3-cyano-10-methyl-pyrido[3,2-g]quinoline derivatives is described. The structural assignments were performed by high resolution 2D NMR spectroscopy.

Introduction

The reaction of 3-cyano-10-methyl-pyrido[3,2-g]quinoline-4-one **1** with alkylhalides under PTC conditions, in strong alkaline media was previously described [1]. In the presence of KOH or NaOH, the hydration reaction of the cabonyl bond generates a stable gemminaldiol as the main reaction product and the target alkylation products are minor reaction products under these experimental conditions (scheme 1). The mixture of N-alkyl- and O-alkyl-3-cyano-10-methyl-pyrido[3,2-g]quinoline derivatives contains the two alkylated derivatives in 3:1 ratio.



Scheme 1

* Part I [1]

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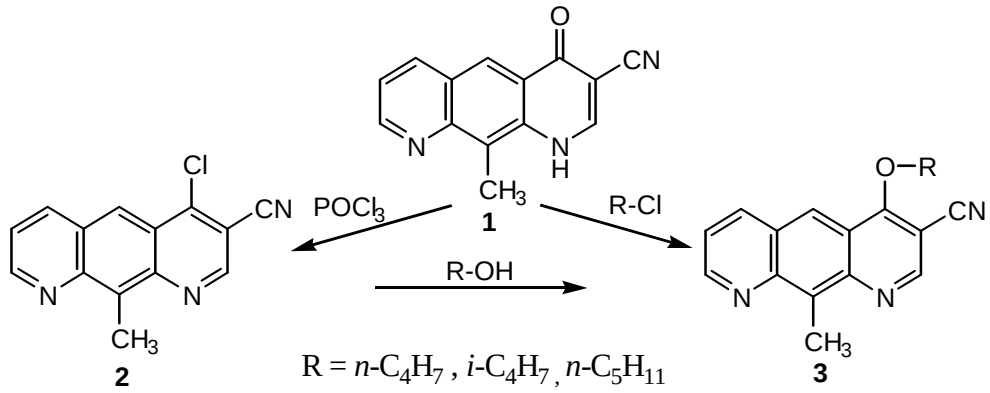
Another reaction strategy is thus required in order to obtain the O-alkyl-3-cyano-10-methyl-pyrido[3,2-g]quinoline derivatives in good yields.

Results and Discussions

The two steps reaction path proposed for the regioselective synthesis of 4-alkoxy-3-cyano-10-methyl-pyrido[3,2-g]quinolines **3** is presented in scheme 2.



Scheme 2

As previously described, the chlorination of 3-cyano-10-methyl-pyrido[3,2-g]quinolin-4-one **1** with phosphorous oxychloride generated 4-chloro-3-cyano-10-methyl-pyrido[3,2-g]quinoline **2** in good yields [2]. The chlorine substituent in position *4* of the quinoline ring can be easily replaced by nucleophilic aromatic substitution. The reactivity of **2** is enhanced by the electron withdrawing effect of the nitrile group situated in position *3* of the heterocycle. For these reasons **2** was considered as an efficient intermediate for the synthesis of 4-alkoxy-3-cyano-10-methyl-pyrido[3,2-g]quinolines **3**.

The reaction of **2** with several alkoxides in the corresponding alcohols (such as *n*-butanol, *i*-butanol, amyl alcohol) were performed. The reaction conditions were summarized in table 1.

Table 1.
The reaction conditions for the alkylation of **2** with alkoxides.

Alkoxide	Reaction conditions Temperature [^{o}C]	Time [h]	Yield [%]
Sodium *n*-butoxide	110	2	42%
Sodium *i*-butoxide	110	2	48%
Sodium *n*-pentoxide	130	2	30%

The structures of the reaction products **3** were assigned by high resolution NMR experiments. 2D-NMR spectra were used for the complete structural assignments, as follows:

- The ^{1}H-^{1}H homocorrelations that generate the splitting pattern of the protons in the structure **3** were observed by the proton 2D COSY with gradients experiment (parameter set COSY 45gs-BBI). Figure 1 presents a detail of this 400 MHz 2D COSY spectrum, showing the cross peaks determined by the homogenous spin-spin couplings in the aromatic region and the corresponding structural assignments.

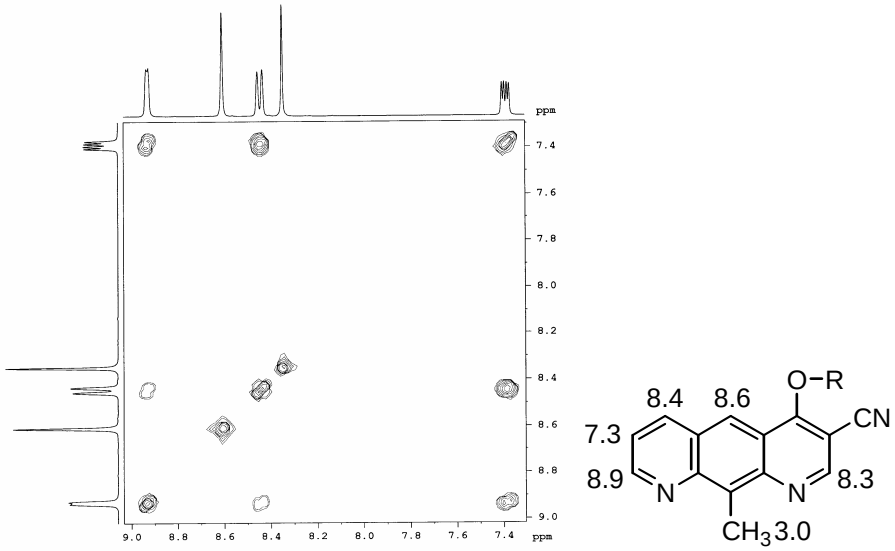


Fig 1.
400 MHz 2D NMR COSY spectrum of 3 (detail of the aromatic region) and the corresponding structural assignments

The tertiary carbon atoms of the heterocycle **3** were assigned according to the inverse ^{1}H-^{13}C correlation with z-gradients experiment (parameter set: HMQCgs-BBI). Figure 2 presents the 400 MHz 2D ^{1}H-^{13}C hetercorrelation spectrum, and the corresponding structural assignments.

The quaternary carbon atoms were assigned according to the ^{1}H-^{13}C inverse long range heterocorrelation with z-gradients experiment (parameter set: HMBCgs-BBI). In figure 3, the cross peaks in the HMBC spectrum show the ^{1}H-^{13}C heterocorrelations through two and three covalent bonds that enabled the structural assignments.

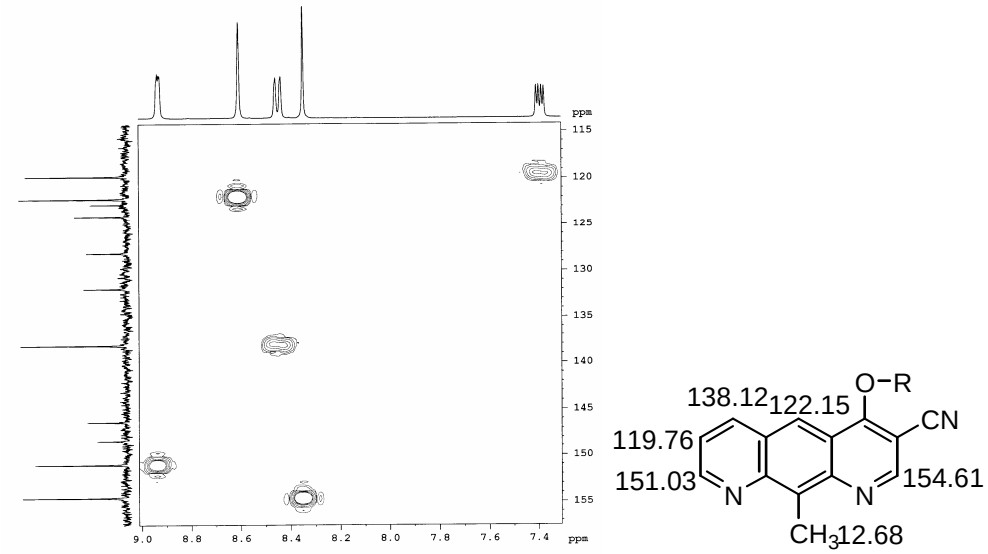


Fig 2.
400 MHz 2D NMR HMQC spectrum of 3 (detail of the aromatic region) and the corresponding structural assignments

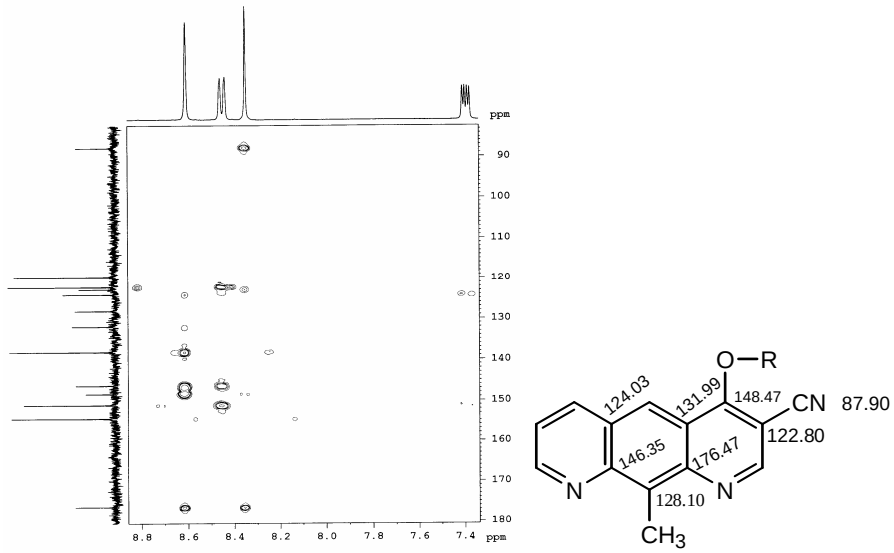


Fig.3.
400 MHz 2D NMR HMBC spectrum of 3 (detail of the aromatic region) and the corresponding structural assignments.

Conclusions

The reaction path proposed for the regioselective O-alkylation of 3-cyano-10-methyl-pyrido[3,2-g]quinoline-4-one afforded 4-alkoxy-3-cyano-10-methyl-pyrido[3,2-g] quinolines **3** in moderate yields.

Experimental

General procedure for 4-alkoxy-3-cyano-10-methyl-pyrido [3,2-g]quinolines preparations.

7 mL anhydrous alcohol was placed in a round bottom flask, treated with 0.04 g clean sodium (2 mmol) and warmed gently until all the sodium has reacted. 4-Chloro-3-cyano-10-methyl-pyrido[3,2-g] quinoline 0,25 g (1 mmol) were added and the solution was refluxed for 2 hours. The solution was cooled, then filtered. The filtrate was poured in water. The precipitate thus formed was filtrate and the solution was extracted with ether and then the solvent was evaporated. The product, a yellow powder, was recrystallised from ethanol.

4-(1-butoxy)-3-cyano-10-methyl-pyrido[3,2-g]quinoline

IR [cm^{-1}] 2850, 2900 (C-H stretching vibration), 2220 (C≡N stretching vibration), 1603, 1500 (aromatic C=C stretching vibration), 1220 (C-O stretching vibration).

^{1}H-RMN (400 MHz): δ_H (DMSO-d_6 solution): 8.93 (dd, 1H, J = 4Hz, J = 1.2 Hz, H_8) 8.60 (s, 1H, H_5), 8.44 (dd, 1H, J = 8.4 Hz, J = 1,2 Hz, H_6), 8.34 (s, 1H, H_2), 7.38 (dd, 1H, J = 8.4 Hz, J = 4 Hz, H_7), 4.40 (t, 2H), 3.44 (m, 4H), 3.02 (s, 3H), 1.06 (t, 3H).

^{13} C-RMN δ_C 176.45, 154.57, 151. 03, 148.37, 146.35, 138.13, 131.92, 128.07, 124.03, 122. 76, 122.17, 119.77, 87.92 (CN), 56.54, 19.06, 12.67.

4-(2-methyl-1-propoxy)-3-cyano-10-methyl-pyrido[3,2-g]quinoline

IR [cm^{-1}] 2215 (C≡N stretching vibration), 1603, 1565 (aromatic C=C stretching vibration), 1276, 1047 (C-O stretching vibration).

^{1}H-RMN (400 MHz): δ_H (DMSO-d_6 solution): 8.93 (dd, 1H, J = 4Hz, J = 1.2 Hz, H_8) 8.60 (s, 1H, H_5), 8.44 (dd, 1H, J = 8.4 Hz, J = 1,2 Hz, H_6), 8.34 (s, 1H, H_2), 7.38 (dd, 1H, J = 8.4 Hz, J = 4 Hz, H_7), 4.39 (d, 2H), 3.43 (m, 1H), 3.02 (s, 3H), 1.07 (d, 6H).

^{13} C-RMN δ_C 176.47, 154.61, 151.02, 148.47, 146.35, 138.12, 131.99, 128.10, 124.03, 122.80, 122.15, 119.76, 87.90 (CN), 56.54, 19.05, 12.69.

4-(1-pentoxy)-3-cyano-10-methyl-pyrido[3,2-g]quinoline

^{1}H-RMN (400 MHz): δ_H (DMSO-d_6 solution): 8.91 (dd, 1H, H_8) 8.58 (s, 1H, H_5), 8.42 (dd, 1H, H_6), 8.34 (s, 1H, H_2), 7.38 (dd, 1H, H_7), 4.2 (t, 2H), 3.5 (m, 2H), 3.02 (s, 3H), 1.07 (m, 5H).

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2. C. Moldovan , C. Cristea , I. A. Silberg , A. Mahamoud , C. Deleanu and J. Barbe, *Heterocyclic Communications,* **2004**, *10 (1)***,** 19-24.