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An Efficient Synthesis of 3-Cyanoquinoline Derivatives

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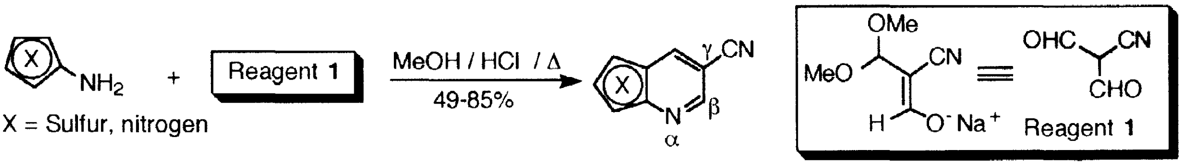
Abstract: A short and efficient method is reported for the preparation of 3-cyanoquinoline derivatives. Reaction of 3,3-dimethoxy-2-formyl-propanenitrile sodium salt **1** with various anilines **2** afforded (E) enamines **3** which were subsequently isomerized into (Z) enamines **4** and cyclized in a one pot procedure to give 3-cyanoquinolines **5** in good yields.

As part of a project aimed at obtaining precursors of quinoline based models of NADH,[1] we have been interested in the synthesis of quinoline derivatives substituted at C-3 by a carboxylic acid or related fonctionality. Classical methods for the construction of the quinoline ring involve the cyclization of substituted benzene derivatives. Such reactions include the Skraup, Friedländer, Doebner-von Miller and Combes syntheses.[2] Of the different methods available in the literature for the synthesis of the quinoline ring, only few can be applied efficiently to the preparation of 3-substituted quinoline derivatives.[3] We recently reported an efficient synthesis of various γ-cyano fused pyridines by a [3+3] approach related to the Combes methodology, involving an heteroarylamine and 3,3-dimethoxy-2-formyl-propanenitrile sodium salt **1** (Scheme 1).[4] In this approach, the fused pyridine ring is built by direct condensation of reagent **1** (chemical equivalent of a 1,3-diformyl derivative) with amino derivatives of various electron-rich heterocycles to afford in a one-pot procedure pyridines fused to another heteroaromatic ring.



Scheme 1

In this paper we wish to report an expansion of this efficient methodology to the synthesis of 3-cyanoquinoline compounds, by reacting various aniline derivatives with the readily available masked 1,3-diformyl derivative **1** (Scheme 2). In a first attempt, *m*-anisidine **2a** was reacted with **1** under the same conditions used with heteroamines *i.e.* in refluxing methanol in the presence of HCl. Under these conditions (Z) enamine **3a** was isolated as the sole product of the reaction in almost quantitative yield (Scheme 2). In contrast to heteroamines previously reported, the ring closure did not take place. This result may be explained partly by the lower reactivity of the phenyl ring towards electrophilic attacks compared to that of heteroamines owing to the strong electron donating effect of pyrrole and thiophene rings. In addition, the failure in the cyclization stage which requires the formation of the (E) isomer **4a** as intermediate may be ascribed in part to the exclusive formation of the (Z) isomer **3a** under the reaction conditions used.

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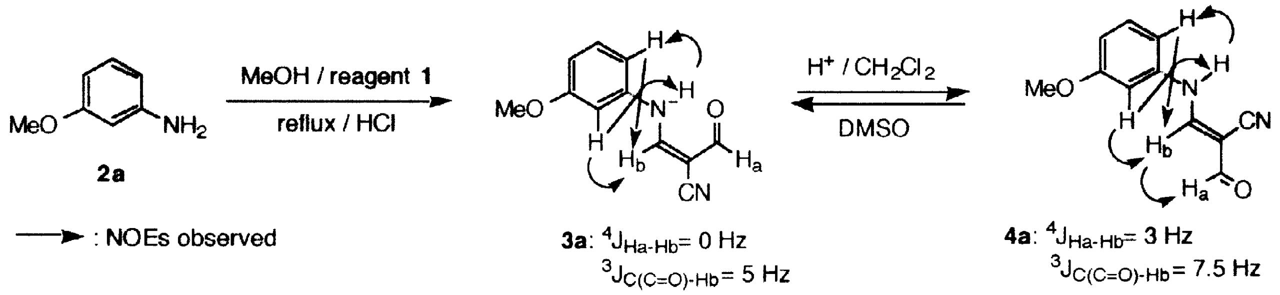
In the course of this study, we found out that the use of $TiCl_4$, $BF_3.Et_2O$ or CF_3COOH in CH_2Cl_2 at room temperature promoted isomerisation of **3a** to give the corresponding (Z) isomer **4a** in a quantitative yield. It is interesting to note that the (Z) isomer **4a** was in turn converted to the (E) isomer **3a** within a few hours at room temperature in DMSO (Scheme 2). Both isomers were assigned by comparing $^3J_{C(C=O)\text{-}Hb}$ and $^4J_{Ha\text{-}Hb}$ coupling constants. Further information on the conformation adopted by isomers **3a** and **4a** could be obtained by a NOESY experiment. The main results of this NMR study are shown on scheme 2. As can be seen interconversion between the two isomers (E) and (Z) proceeds rather easily. This phenomenon is well known in the case of "push-pull" alkenes.[5]

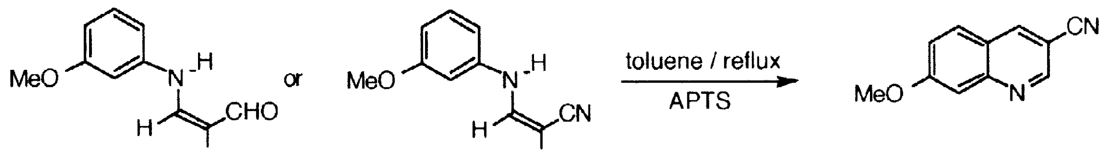


3a: $^4J_{Ha\text{-}Hb}$= 0 Hz
$^3J_{C(C=O)\text{-}Hb}$= 5 Hz

4a: $^4J_{Ha\text{-}Hb}$= 3 Hz
$^3J_{C(C=O)\text{-}Hb}$= 7.5 Hz

Scheme 2

Enamine **3a** was then treated with Lewis and Brönsted acids under various conditions with a view to promote both isomerisation and cyclization steps. In the presence of PCl_3 in refluxing heptane,[6] the starting enamine **3a** was recovered quantitatively. The use of $AlCl_3$ afforded enamine **4a**. Attempts to react enamine **3a** with CF_3COOH at reflux promoted its isomerisation as well, along with the formation of some trace of the desired quinoline **5a**. Treatment of enamine **4a** in refluxing toluene in the presence of 1 eq. of *p*-toluene sulfonic acid gave the best results, affording the desired quinoline **5a** in 65% yield (Scheme 3). Alternatively, under these conditions both isomerisation and cyclization steps could be performed in a one-pot procedure affording quinoline **5a** in 65% overall yield from the (Z) isomer **3a** (Scheme 3). Only one regioisomer was obtained resulting from the high preference of the methoxy substituent to orient electrophilic attacks of carbonyl group at para position. This preferencial orientation is well known in similar electrophilic cyclizations and can be exemplified by the Skraup synthesis of 7-methoxyquinoline from *m*-anisidine and glycerol.[7]



3a **4a** **5a**:Yield=65%

Scheme 3

To evaluate the scope of the method, we have engaged various substituted anilines with 3,3-dimethoxy-2-formyl-propanenitrile sodium salt **1**. As described above, anilines **2b-j** were treated in refluxing methanol in the presence of HCl with reagent **1**, affording enamines **3b-j** in good yields excepted with 3,5-dimethoxyaniline **2d**. In the latter case, 5,7-dimethoxy-3-cyanoquinoline **5d** was obtained directly in good yield without isolation of the intermediate enamine **3d** (Entry 4). This result is probably a consequence of the high electron-donating effect exerted by both methoxy groups ideally located for the electrophilic cyclization. As reported above, no trace of the (Z) isomer in the crude products was detected by ^1H NMR. The so-obtained enamines derivatives **3** were subjected to isomerisation and ring-closure steps, under the best conditions selected *i.e.* in refluxing toluene in the presence of *p*-toluene sulfonic acid.

From the results outlined in table 1, it appears cleary that the outcome of the cyclization step is highly dependent on the nature of the substituents. Only phenyl rings bearing a strongly activating group (*i.e.* a methoxy group) properly located, promoted the cyclization step of enamines **4** giving rise to the desired quinolines **5** in 60% to 68% yield (Entries 1, 2, 4, 5, 6). In the absence of such an activating group, only isomerisation of enamines **3** into their (E) isomer **4** was observed along with the formation of tarry materials (Entries 3, 7, 8, 9, 10). As previously evoked, when the cyclization could give two regioisomers, only the less hindered one was obtained, resulting from the electrophilic attack of the aldehyde at the para position of the methoxy group (Entry 2). However, when this position is blocked an ortho-cyclization took place to give the corresponding quinoline **5e** (Entry 5).

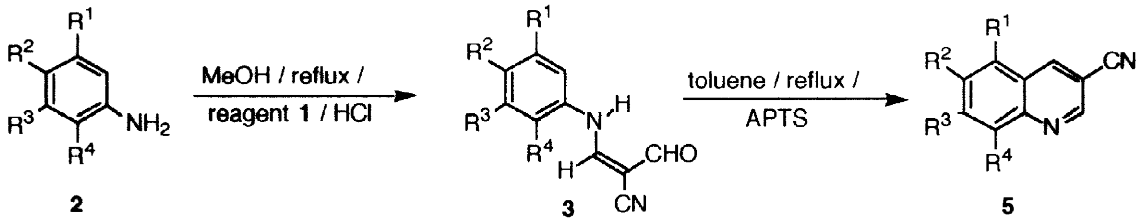


Table **1**: Reactions of **1** with Various Anilines **2**. Cyclization of Intermediate Enamines **3**

Entry	Aniline 2[a]	R^1	R^2	R^3	R^4	3 / Yield	5 / Yield
1	**2a**	H	H	OCH_3	H	**3a**: 90%	**5a**: 65%
2	**2b**	H	OCH_3	OCH_3	H	**3b**: 95%	**5b**: 66%
3	**2c**	H	OCH_3	H	CH_3	**3c**: 90%	b
4	**2d**	OCH_3	H	OCH_3	H	**3d**: non isolated	**5d**: 68%
5	**2e**	OCH_3	H	H	CH_3	**3e**: 91%	**5e**: 63%
6	**2f**	H	H	OCH_3	CH_3	**3f**: 96%	**5f**: 60%
7	**2g**	H	H	H	OCH_3	**3g**: 97%	b
8	**2h**	CH_3	H	CH_3	H	**3h**: 90%	b
9	**2i**	H	H	F	H	**3i**: 94%	b
10	**2j**	H	CH_3	CH_3	H	**3j**: 97%	b

a: Compound **2f** was prepared according to literature methods by ortho-lithiation of the pivaloylaniline issued from **2a**, followed by methylation of the resulting lithiated species: See Ref 8. All other anilines **2** were commercially available. b: ^1H NMR spectra showed the formation of enamines **4** together with tarry materials

Although this methodology suffers from the range of aniline derivatives able to undergo electrophilic cyclization, we have developed a new and straightforward method for constructing 3-cyanoquinolines based on the condensation of aniline derivatives with the readily available reagent **1**.

Typical Procedure: To a solution of **2b** (1.53 g, 10 mmol) in methanol (40 mL) was added 3,3-dimethoxy-2-formyl-propanenitrile sodium salt **1** (2.06 g, 12.5 mmol) and 12N HCl (2.5 mL, 30 mmol). The resulting mixture was refluxed for two hours. After cooling, the precipitate was filtered off, washed with cooled methanol, and dried under vacuum for at least 3 hours to afford 1.02 g (95%) of the desired enamine **3b** as a yellow solid. The crude enamine **3b** was used without further purification in the next step. ^1H NMR (DMSO-d_6 at 200 MHz) δ 10.97 (d, 1H, J= 13.3 Hz), 9.28 (s, 1H), 8.63 (d, 1H, J = 13.3 Hz), 7.05 (m, 3H), 3.77 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6 at 50 MHz) δ 186.92, 157.33, 149.36, 146.60, 133.02, 114.91, 112.29, 109.94, 103.15, 87.84, 55.83, 55.78.

To a suspension of enamine **3b** (1.16 g, 5 mmol) in toluene (40 mL), *p*-toluene sulfonic acid (0.95 g, 5 mmol) was added and the resulting mixture was stirred at reflux for 16 hours. The reaction mixture was cooled to room temperature before adding 10% aq. Na_2CO_3 (20 mL). After phases separation, the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated affording a brown solid. Flash chromatography on alumina with cyclohexane/CH_2Cl_2 (1/4) as eluent yielded 707 mg (66%) of quinoline **5b**. ^1H NMR ($CDCl_3$ at 200 MHz) δ 8.87 (d, 1H, *J*= 2.0 Hz), 8.33 (d, 1H, *J*= 2.0 Hz), 7.46 (s, 1H), 7.08 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$ at 50 MHz) δ 155.97, 152.10, 149.00, 147.49, 139.39, 122.98, 118.43, 108.78, 105.60, 105.03, 56.76, 56.60. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.15; H, 4.56; N, 12.97. Other ^1H NMR data: Quinoline **5a** ($CDCl_3$ at 200 MHz) δ 8.96 (d, 1H, *J*= 2.0 Hz), 8.43 (d, 1H, *J*= 2.0 Hz), 7.79-7.27 (m, 3H), 4.00 (s, 3H). Quinoline **5d** ($CDCl_3$ at 200 MHz) δ 8.92 (d, 1H, *J*= 2.0 Hz), 8.74 (d, 1H, *J*= 2.0 Hz), 7.03 (d, 1H, *J*= 2.0 Hz), 6.58 (d, 1H, *J*= 2.0 Hz), 3.99 (s, 3H), 3.97 (s, 3H). Quinoline **5e** ($CDCl_3$ at 200 MHz) δ 9.03 (d, 1H, *J*= 2.0 Hz), 8.92 (d, 1H, *J*= 2.0 Hz), 7.61 (d, 1H, *J*= 8.0 Hz), 6.87 (d, 1H, *J*= 8.0 Hz), 4.02 (s, 3H), 2.70 (s, 3H). Quinoline **5f** ($CDCl_3$ at 200 MHz) δ 9.00 (d, 1H, *J*= 2.0 Hz), 8.43 (d, 1H, *J*= 2.0 Hz), 7.75 (d, 1H, *J*= 9.0 Hz), 7.44 (d, 1H, *J*= 9.0 Hz), 4.04 (s, 3H), 2.66 (s, 3H).

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