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TETRAHEDRON

On the methylation of 3-cyano-6-hydroxypyridine-2(1H)-ones

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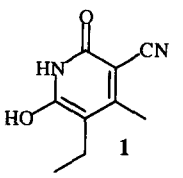
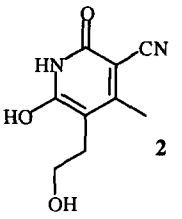
Abstract: In order to prepare new heterocyclic derivatives as building block for compounds with potential biological activities, we were led to study the O-methylation of 3-cyano-6-hydroxypyridine-2(1H)-ones such as **1**. This enabled us to develop a new two steps method to prepare the corresponding 2,6-dimethoxy derivative **5** in 80 % yield. It consisted first in heating **1** in trimethylorthoformate, with or without an acidic catalyst, which gave a mixture of the two mono-methoxy isomers, then a classical methylation of the second hydroxy moiety led almost exclusively to **5**. In this paper we present this "methylation" method and various unexpected results recorded when we attempted to extend it to related derivatives or to other heterocycle containing lactim-lactam functions. An intramolecular transetherification mechanism requiring the simultaneous transfer of a hydrogen and a methyl is suggested. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords : orthoesters, O-alkylation, transetherification

Condensation between β-ketoesters derivatives such as ethyl-2-ethylacetoacetate or 2-acetylbutyrolactone and cyanoacetamide conveniently leads to polysubstituted pyridinediones such as **1** and **2**[1]. Further chemical modifications to give new useful polyfunctionalized intermediates require first the protection of the "1,3-oxo-hydroxy" moieties. Since, in most cases N-alkylation of pyridones leads to stable compounds[2], a bis-O-alkylation of **1** or **2** was deemed necessary to allow further selective chemical transformations.



1



2

Quite expectingly a classical methylation of **1** under basic condition using methyl iodide led to a lot of compounds from which **3**, **4**, and **5** could be identified in 22, 0.7 and 11% yield respectively. Another possible strategy to obtain **5**, successful in a related case[3], required first the bis chlorination of **1**. It failed despite many trials, probably because of a strong steric hindrance.

A different approach, based on the known use of trialkylorthoformate to obtain O-alkyl enols,[4, 5] enabled us to obtain exclusively the mono-O-methyl derivatives **6** and **7**. Indeed, heating compound **1** in trimethylorthoformate in the presence of catalytic amount of montmorillonite K10 (or *para*toluenesulfonic acid) led almost exclusively to compounds **6** and **7**. TLC and NMR monitoring showed the presence of trace amount

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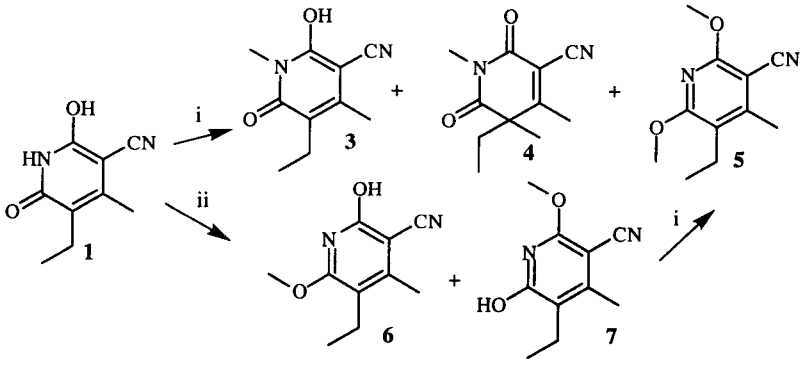
of the dimethoxy derivative **5** and showed an approximate 1 to 5 ratio of unseparable **6** and **7**. From either the purified mixture of isomers or, directly, the dry reaction residue, we then proceeded to a methylation step, using sodium hydride and methyl iodide in DMF. To our surprise this led to an almost quantitative yield (82-85%) of the 2,6-dimethoxyderivative **5**. Probably due to its lesser reactivity towards alkylation, small amount of the mono-methoxy compound **7** was sometimes isolated, enabling us to fully characterise that isomer (i.e. NMR long distance correlation experiments established the methyl position).

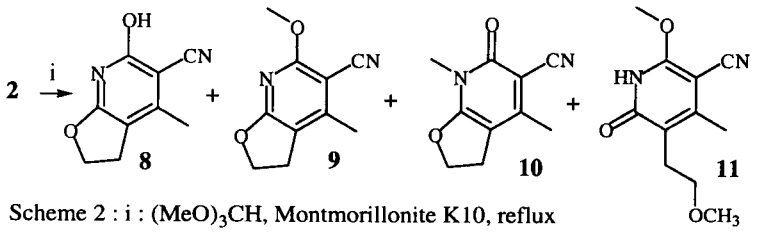


Scheme 1: i: NaH, DMF, MeI; ii: $(MeO)_3CH$, Montmorillonite K10, reflux

Study of the reaction conditions were performed. It turned out that although our studies had been made in the presence of small amount of montmorillonite K10, no acid catalyst was necessary since yields and reaction duration were unchanged in the case of the methylation of **1**. Reaction using triethylorthoformate led to the mono-ethoxy derivatives of **1** in the same manner. Reaction using trimethylorthoacetate led to same result along with sizable amount (10 %) of the dimethoxylated derivative **5**.

Attempts to generalize this method to other heterocycles bearing two "oxo-hydroxy" moieties were performed. The reaction either led to extensive decomposition (pyridine-2,4-dione) or to no reaction at all (uracil, 6-methyluracil and 3,6-dihydroxypyridazine). From 3-cyano-2,6-dihydroxy-4-methylpyridine a highly coloured substance was obtained, reminiscent of reported[6] findings.

Starting from compound **2**, and using the trimethylorthoformate method, we isolated four compounds from the reaction mixture: the known[1] bicyclic derivative **8**, probably arising from an acid-catalysed cyclisation of **2** (10%), its O and N methyl derivatives **9** (7%) and **10** (10%) and the dimethylated compound **11** (12%).

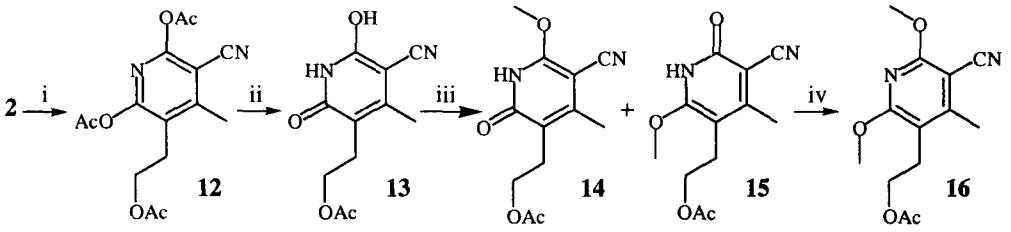


Scheme 2 : i : $(MeO)_3CH$, Montmorillonite K10, reflux

Isolation of the N-methylated compound **10**, clouded a bit an understanding of the reaction process. Moreover, occurrence of the alkylether **11** is resulting from a rare case of transetherification to a primary alcohol.

Treatment of the bicyclic compound **8** with sodium hydride in DMF followed by methyl iodide further established the difference of reactivity between **6** and **8**. Under the same reaction conditions, contrary to **6**, compound **8** led to a 1/5 ratio of the methoxy derivative **9** (13%) and the N-methyl derivative **10** (66%). This last result can probably be explained by steric hindrance considerations (i.e. methoxy of **6** versus 2,3-dihydrofuro[2,3-*b*]pyridine **8**).

In order to suppress the difference of behaviour seen between **1** and **2**, we prepared the acetylated derivative **13** from **2** in two steps. Compound **2** was first triacetylated to give **12** whose treatment with an excess of ethanolic ammonia in dichloromethane resulted in the precipitation of the ammonium salt of **13**. After filtration, the residue was dissolved in water and acidified leading to the precipitation of pure **13**. Reaction of **13** with trimethylorthoformate and montmorillonite K10 led exclusively to the unseparable mixture of the monomethoxy isomers **14** and **15** in close to a 6 to 1 ratio. Methylation of the mixture using a classical method then gave the dimethoxy derivative **16** in 59% yield from **13** along with some unreacted monomethyl derivative **14** (4%) as in the case of the methylation of the mixture of **6** and **7**. The comparatively smaller yield of **16** is likely to be caused by some transesterification taking place in the course of the first step leading to the deacetylated alcohol **2**.



Scheme 3 : i : Ac_2O, H_2SO_4; ii : a) $EtOH/NH_3$ CH_2Cl_2 b) H_3O^+, Cl^- ; iii $(MeO)_3CH$, Montmorillonite K10, reflux; iv : NaH, DMF, MeI

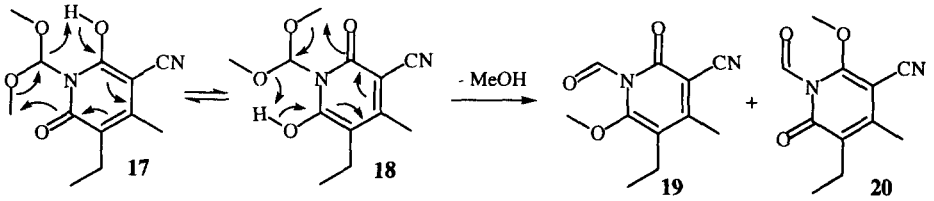
DISCUSSION

Preparation of 3-methoxy-2-cyclohexen-1-one from cyclohexane-1,3-dione has been achieved either using trimethylorthoformate and *para*toluene sulfonic acid[7] or montmorillonite[8] K10, or using methanol and hydrogen chloride[9] or *para*toluene sulfonic acid[10]. Under the latter reaction conditions, no methylation of **1** took place, thus confirming a reactivity difference between these two "1,3-oxo-hydroxy" systems. From a mechanistic point of view, reaction of a ketone, trimethylorthoformate and an acid catalyst was shown to lead to O-methylated enols *via* formation of ketals and subsequent heat-triggered elimination[4].

The N-alkylation of various nitrogen heterocycles[11-13] and amines[14-16] has been reported using trialkylorthoformate. Since the heating of sulfonic acid[17] or sulfuric acid in trimethylorthoformate gives the corresponding methyl esters (see experimental section), acid-catalysed N-alkylation of heterocycles, such as **8** to give **10**, could proceed *via* reaction of such an alkylating species with a nucleophilic center.

On the other hand, we could only find few reports[18-22] mentioning the O-alkylation —either along with N-alkylation or not— of an heterocycle on heating with triethylorthoformate. Moreover, the use of trialkylorthoformate was reported as an O-alkylating agent of phenols[23] and recently as a C-methylating agent[24].

It is unlikely that the exclusive occurrence of methoxy derivatives **6** and **7** or **14** and **15** is due to the formation of an alkylating species since no N-methyl derivative was isolated. Moreover, occurrence of a ketal intermediate as in the case of ketones, followed by an elimination is also unlikely since no reaction took place when boiling compound **1** and an acid catalyst in methanol. Thus another reactive intermediate must be occuring. We suggest in the following scheme a reaction mechanism proceeding *via* the tautomers intermediates **17** and **18** resulting from a nitrogen nucleophilic attack of compound **1** on trimethylorthoformate. Similar compounds have been described[25] in another case and a related intermediate has actually been suggested[21] previously. Then an intramolecular process requiring a simultaneous transfer of a hydrogen and a methyl can take place on either oxygens to give respectively, the N-formyl derivatives **19** and **20**, precursors of **6** or **7**, which might be prone to a fast methanolysis. An alternative is a methyl transfer occuring simultaneously with the departure of methyl formate, *via* the nitrogen protonation of intermediate **17** or **18**, thus avoiding occurrence of the formyl derivatives **19** and **20**.



This mechanism accounts for most of our results. The outcome of the methyl transfer would only depend on the equilibrium between **19** and **20**, steric hindrance or electronic effect being factors in this equilibrium. The occurrence of the alkylether **11**, which is a rare case of alkyl transetherification[26], might even take place *via* an alternate transfer of the methyl on the alcohol moiety—on a Dreiding model, the geometry allowing such transfer does not appear that unfavourable. The isolation of this ether is probably the strongest evidence in favour of such mechanism. Indeed it is unlikely that this transetherification could proceed in an intermolecular fashion. Other effects are taking place in the case of the trials with uracil or 6-methyluracil, possibly by preventing the first step of this mechanism.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Varian multi-400 spectrometers. Unless otherwise stated, $CDCl_3$ was the solvent used. Shifts are given in ppm (δ) with respect to the TMS signal and coupling constants (J) are given in Hertz. Signals attribution was sometimes confirmed by two dimentional NMR experiments (COSY, NOESY, HMQC, HMBCR). Column chromatography was performed on Merck silica gel 60 (0.060 - 0.200 mm). When necessary, solvents were dried using activated 3 Å or 4 Å molecular sieves. Activation of the molecular sieves was done by using a plastic-free domestic microwave oven (irradiation in a quartz beaker of 100-200 g of new molecular sieve until partial melting, i.e. from 1 to 8 min by periods of 1 min alternated with cooling). **CAUTION**: due to residual traces of solvents, microwave irradiation of molecular sieve previously used can result in a serious explosion.

The preparation of compound **2** was made according to the reported procedure[1]. For compound **1**, the reaction time was increased up to 14 days and followed by the same treatment as **2** thus giving 55% of **1**.

3-cyano-2,6-dihydroxy-5-ethyl-4-methylpyridine **1** : M.p. = 233°C. ^1H (DMSO): 0.96 (t, 3H, J = 7.3, CH_3); 2.26 (s, 3H, CH_3), 2.45 (q, 2H, J = 7.3, CH_2). ^{13}C : 13.3 (CH_3); 17.1 (CH_3); 19.4 (CH_2); 84.2 (C-3); 114.4 (C-5); 116.9 (CN); 151.9 (C-4); 161.9 (C-2 and C-6). Anal. ($C_9H_{10}N_2O_2$): Calc: C: 60.66, H: 5.66, N: 15.72; found, C: 60.76, H: 5.73, N: 15.81.

3-cyano-2,6-dihydroxy-5-(2-hydroxyethyl)-4-methylpyridine **2** : M.p. > 240°C (dec.) lit.[1] > 250°C (dec.). ^1H (DMSO): 2.49 (s, 3H, CH_3); 2.57 (t, 2H, J = 7.0, CH_2); 3.41 (t, 2H, J = 7.0, CH_2). ^{13}C : 18.0 (CH_3); 29.1 (CH_2); 59.1 (CH_2); 84.7 (C-3); 109.7 (CN); 117.1 (C-5); 153.8 (C-4); 162.0 and 162.2 (C-2 and C-6).

Methylation of **1**: Compound **1** (17,8 g, 0,1 mol.) was dissolved in dry DMF (200 ml). The solution was cooled to 0°C and 95 % sodium hydride (5,8 g, 0,23 mol.) was added portion-wise. After stirring the suspension under an inert atmosphere for 30 mn, methyl iodide (13,7 ml, 0,22 mol.) was added and the solution stirred for 24 hours allowing the temperature to rise back to 25 °C. The solution was then concentrated to dryness, the residue was dissolved in ether, the organic phase extracted with water. The aqueous phase was acidified the precipitate was filtered, washed with water to yield **3** (4.2 g, 22%, recristallised from toluene, non optimised). The organic phase was dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographied over silica eluting with a mixture of heptane and ethylacetate (proportion slowly varing from 3-1 to 2-1) to give (in order of polarity) compounds **5** (2.3 g, 11%; distilled in a bulb to bulb apparatus at 0,8 torr) and **4** (which had to be further purified *via* a chromatography over alumina (neutral, 4.7% water) eluting with heptane-ethylacetate 3-1 to give 0.14 g, 0.7%; recristallized from heptane).

3-cyano-1,4-dimethyl-5-ethyl-6-hydroxypyridin-2-one **3** : M.p. = 198°C. ^1H (DMSO): 0.93 (t, 3H, J = 6.4, CH_3); 2.19 (s, 3H, CH_3); 2.40 (q, 2H, J = 6.4, CH_2); 3.27 (s, 3H, CH_3). ^{13}C : 13.4 (CH_3); 17.4 (CH_3); 19.2 (CH_2); 28.2 (NCH_3); 81.4 (C-3); 113.9 (CN); 117.9 (C-5); 148.6 (C-4); 159.9 (C-2 and C-6). Anal. ($C_{10}H_{12}N_2O_2$): Calc: C: 62.49, H: 6.29, N: 14.57; found, C: 62.52, H: 6.27, N: 14.29.

3-cyano-1,4,5-trimethyl-5-ethylpyridin-2,6-dione **4** : M.p. = 123.5 °C. ^1H: 0.66 (t, 3H, J = 7.5, CH_3); 1.47 (s, 3H, CH_3); 1.75 (m, 1H, 1/2 CH_2); 2.15 (m, 1H, 1/2 CH_2); 2.3 (s, 3H, CH_3); 3.24 (s, 3H, NCH_3). ^{13}C : 9.3 (CH_3-4); 18.2 (CH_3-5); 25.2 (CH_3 ethyl); 26.7 (N-CH_3); 32.9 (CH_2); 51.2 (C-3); 108.9 (C-5); 112.7 (CN); 159.5 (C-6); 172.0 (C-4); 174.2 (C-2). Anal. ($C_{11}H_{14}N_2O_2$): Calc: C: 64.06, H: 6.84, N: 13.58; found, C: 63.96, H: 6.59, N: 13.61.

3-cyano-2,6-dimethoxy-5-ethyl-4-methylpyridine **5** : M.p. < 50°C. ^{1}H: 1.02 (t, 3H, J = 7.5, CH_3); 2.39 (s, 3H, CH_3); 2.52 (q, 2H, J = 7.5; CH_2); 3.94 and 3.97 (2s, 2x3H, 2 OCH_3). ^{13}C : 13.1 (CH_3); 17.1 (CH_3); 18.6 (CH_2); 54.0 (2 OCH_3); 88.0 (C-3); 116.2 (CN); 117.0 (C-5); 153.6 (C-4); 161.5 and 162.8 (C-2 and C-6). Anal. ($C_{11}H_{14}N_2O_2$): Calc: C: 64.06, H: 6.84, N: 13.58; found, C: 64.07, H: 6.92, N: 13.62.

General procedure for the monomethylation of **1**, **2** or **13** : The suspension of the 2,6-dihydroxypyrimidine (0,05 mol.) and montmorillonite K10 (0.04 g) was heated to reflux in trimethylorthoformate (100 ml., 0.9 mol.) for 3 hours in the case of **13**, 24 hours in the case of **1** and 48 hours in the case of **2**. The solution obtained was then concentrated to dryness. The residue obtained was either treated directly in cold DMF with sodium hydride followed by methyl iodide (case of **1** or **13**) or in the case of **2** chromatographied over silica gel eluting with a mixture of heptane and ethylacetate (proportion from 2-1 to 1-2) to give compounds (in order of polarity) **9** (7 %), **11** (14 %), **8** (10 %) and **10** (10 %).

6-hydroxy-4-methyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile **8** : M.p. > 260°C (dec.). lit.[1] > 250°C (dec.). ^{1}H (DMSO): 2.26 (s, 3H, CH_3); 3.07 (t, 2H, J = 8.6, CH_2); 4.67 (t, 2H, J = 8.6, CH_2). ^{13}C : compound not soluble enough.

6-methoxy-4-methyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile **9** : M.p. = 155°C (heptane) lit.[27] = 155-156°C. ^{1}H: 2.35 (s, 3H, CH_3); 3.12 (t, 2H, J = 8.2, CH_2); 3.96 (s, 3H, OCH_3); 4.70 (t, 2H, J = 8.2, CH_2). ^{13}C : 17.8 (CH_3); 26.2 (CH_2); 54.7 (OCH_3); 70.6 (CH_2); 87.8 (C-5); 110.5 (C-3a); 115.6 (CN); 150.1 (C-4); 166.6 and 169.2 (C-6 and C-7a).

4,7-dimethyl-6-oxo-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile **10** : M.p. = 232°C (heptane) lit.[27] = 229-230°C. ^{1}H : 2.28 (s, 3H, CH_3); 3.12 (t, 2H, J = 8.8, CH_2); 3.40 (s, 3H, NCH_3); 4.84 (t, 2H, J = 8.8, CH_2). ^{13}C : compound not soluble enough. m/z (C.I.) = 191. Anal. ($C_{10}H_{10}N_2O_2$): Calc: C: 59.45, H: 6.35, N: 12.60; found, C: 59.21, H: 6.41, N: 12.57.

3-cyano-2-methoxy-5-(2-methoxyethyl)-4-methylpyridin-6-one **11** : M.p. = 149°C (heptane). ^{1}H: 2.42 (s, 3H, CH_3); 2.82 (t, 2H, J = 5.7, CH_2); 3.37 (s, 3H, OCH_3); 3.58 (t, 2H, J = 5.7, OCH_2); 3.95 (s, 3H, OCH_3). ^{13}C : 18.1 (CH_3); 26.2 (CH_2); 54.4 (OCH_3-2); 59.0 (OCH_3); 72.3 (OCH_2); 89.4 (C-3); 111.3 (C-5); 115.8 (CN); 154.6 (C-4); 161.8 (C-6); 162.9 (C-2). m/z (C.I.) = 223. Anal. ($C_{11}H_{14}N_2O_3$): Calc: C: 63.05, H: 5.30, N: 14.73; found, C: 62.86, H: 5.26, N: 14.89.

Methylation of the mixture **6** and **7** or the mixture of **14** and **15** : The dry crude mixture (0,05 mol of the preceeding step) was dissolved in 200 ml of dry DMF. The solution was cooled to 0°C and 95 % sodium hydride (1,4 g, 0,055 mol.) was added portion-wise. After stirring the suspension for 30 mn. under an inert atmosphere, methyl iodide (3,4 ml, 0,055 mol.) was added and the solution stirred for 24 hours allowing the temperature to rise back to 25 °C. The solution was then concentrated to dryness, the residue was chromatographied over silica eluting with a mixture of heptane and ethylacetate 3-1 to give either compound **5** (82 %, purified as described before) and **7** (3,7 %) or compounds **16** (59 %) and **14** (4 %).

3-cyano-5-ethyl-2-methoxy-6-hydroxy-4-methylpyridine **7** : M.p. = 159 °C (heptane). ^{1}H: 1.07 (t, 3H, J = 7.0, CH_3); 2.41 (s, 3H, CH_3); 2.52 (q, 2H, J = 7.0, CH_2); 3.92 (s, 3H, OCH_3). ^{13}C : 12.8 (CH_3); 17.2 (CH_3); 18.8 (CH_2); 54.6 (OCH_3); 88.5 (C-3); 115.5 (CN); 116.2 (C-5); 153.7 (C-4); 161.6 (C-6); 162.4 (C-6). Anal. ($C_{10}H_{12}N_2O_2$): Calc: C: 62.49, H: 6.29, N: 14.57; found, C: 62.33, H: 6.49, N: 14.41.

5-(2-acetyloxyethyl)-3-cyano-2,6-dimethoxy-4-methylpyridine **16** : M.p. = 71°C (heptane). ^{1}H: 1.98 (s, 3H, CH_3); 2.42 (s, 3H, CH_3); 2.85 (t, 2H, J = 6.9, CH_2); 3.95 and 3.97 (2s, 6H, 2 OCH_3); 4.11 (t, 2H, J = 6.9,

CH_2). ^{13}C : 17.6 (CH_3); 20.9 ($COCH_3$); 25.0 (CH_2); 54.1 and 54.2 (2 OCH_3); 62.7 (OCH_2); 88.5 (C-3); 110.9 (C-5); 115.9 (CN); 153.6 (C-4); 163.1 and 163.6 (C-2 and C-6); 170.9 ($COCH_3$). Anal. ($C_{13}H_{16}N_2O_4$): Calc: C: 59.08, H: 6.1, N: 10.6; found, C: 59.21, H: 6.01, N: 10.46.

5-(2-acetyloxyethyl)-3-cyano-6-hydroxy-2-methoxy-4-methylpyridine **14** : M.p. = 139°C (heptane). ^1H: 2.00 (s, 3H, CH_3); 2.45 (s, 3H, $COCH_3$); 2.88 (t, 2H, J = 6.9, CH_2); 3.93 (s, 3H, OCH_3); 4.17 (t, 2H, J = 6.9, CH_2). ^{13}C : 12.7 (CH_3); 20.9 ($COCH_3$); 25.3 (CH_2); 54.8 (OCH_3); 62.6 (OCH_2); 88.6 (C-3); 110.1 (C-5); 115.4 (CN); 155.2 (C-4); 161.1 (C-6); 163.1 (C-2); 171.2 (CO). Anal. ($C_{12}H_{14}N_2O_4$): Calc: C: 57.59, H: 5.64, N: 11.19; found, C: 57.51, H: 5.51, N: 10.92.

Preparation of compound **12** : Compound **2** (12 g, 0.062 mol.) was dispersed in acetic anhydride (100 ml, 1.06 mol.). Two drop of sulfuric acid were added and the suspension was stirred overnight. The solution obtained was concentrated to dryness and the residu dispersed in water. The white precipitate obtained was filtered, washed with water and dried yielding compound **12** (18.8 g, 95%).

5-(2-acetyloxyethyl)-3-cyano-2,6-diacetyloxy-4-methylpyridine **12** : M.p. = 98°C. ^1H: 1.98 (s, 3H, $COCH_3$); 2.37 and 2.40 (2s, 2x3H, 2 $COCH_3$); 2.62 (s, 3H, CH_3); 2.96 (t, 2H, J = 6.6, CH_2); 4.13 (t, 2H, J = 6.6, CH_2); ^{13}C : 18.4 (CH_3); 20.8, 20.8 and 20.9 (3 $COCH_3$); 26.1 (CH_2); 61.8 (OCH_2); 103.2 (C-3); 113.2 (CN); 123.1 (C-5); 156.7 (C-4); 157.1 and 157.8 (C-2 and C-6); 167.5, 167.8 and 170.7 (3 $COCH_3$). Anal. ($C_{15}H_{16}N_2O_6$): Calc: C: 56.25, H: 5.04, N: 8.75; found, C: 55.91, H: 4.98, N: 8.41.

Preparation of compound **13** : To a solution of **12** (18.8 g, 0.058 mol.) in dichloromethane (700 ml) was added an excess of methanolic ammonia. A precipitate quickly occurred and the completion of the reaction was monitored by TLC. The precipitate was filtered, washed with dichloromethane and dried. This was dissolved in warm water (600 ml), the solution was made acid using 35% hydrochloric acid and cooled. The precipitate was filtered, washed with water and dried yielding **13** (13.1 g, 93.8 %).

5-(2-acetyloxyethyl)-3-cyano-2,6-dihydroxy-4-methylpyridine **13** : M.p. = 140°C (dec.). ^1H (DMSO) : 1.97 (s, 3H, CH_3); 2.02 (s, 3H, CH_3); 2.53 (t, 2H, J = 8.0, CH_2); 3.88 (t, 2H, J = 8.0, CH_2); 9.60 (s, 1H, NH). ^{13}C : 18.2 (CH_3); 20.8 ($COCH_3$); 25.0 (CH_2); 62.6 (OCH_2); 83.9 (C-3); 109.3 (C-5); 116.6 (CN); 150.4 (C-4); 161.0 (C-2 and C-6); 170.8 ($COCH_3$). Anal. ($C_{11}H_{12}N_2O_4$, H_2O): Calc: C: 51.97, H: 5.55, N: 11.02; found, C: 51.97, H: 5.41, N: 10.83.

Preparation of dimethyl sulfate from sulfuric acid and trimethylorthoformate : **CAUTION** : This reaction may proceed quickly with evolution of a low boiling liquid (methyl formate, Eb. = 32°C) which can cause projection of sulfuric acid. To a cold (0°C) solution of trimethylorthoformate (86 ml, 0.78 mol.) was slowly added concentrated sulfuric acid (10 ml, 0.187 mol.). The solution was stirred for 2 hours and gently heated overnight. The black solution obtained was distilled first at ambient pressure and then under vacuum (13 mm) to yield dimethyl sulfate identical with a commercially available sample (2.15 g, 10 % non optimised).

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