Claisen Condensation of *N*-Methylpyrrolidinone and α-Chloronicotinic esters

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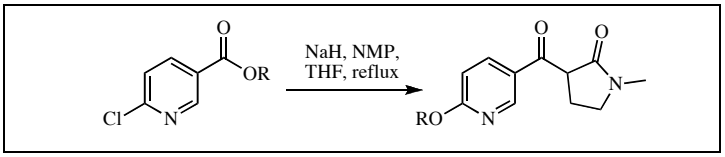

Reaction between α-halo-nicotinic esters and a nucleophilic source such as the *N*-methylpyrrolidin-2-one (NMP) gave unexpected results. The presence of the halide on the pyridine gave a very interesting migration reaction. Extension to 6-methylnicotinic ester derivatives lead to an unexpected carbanion condensation.

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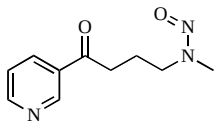
INTRODUCTION

N-Alkyl-3-nicotinoyl-pyrrolidin-2-ones are very interesting intermediates for the synthesis of 4-(*N*-methylnitrosamine)-1-(3pyridinyl)-1-butanone derivatives (NNK, Scheme I). NNK is a nitrosamine present in tobacco smoke, which is a procarcinogen. It is activated by CYP2A6 [1a] and acts as a biomarker of exposure to cigarette smoke and smoking addiction.

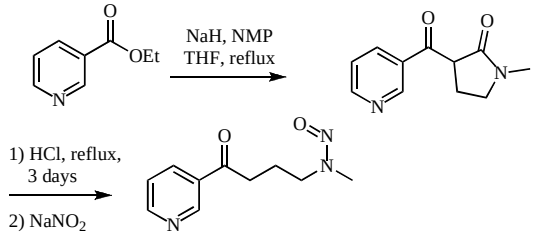
Scheme I



NNK

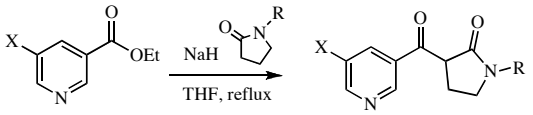
Synthesis of these NNK derivatives has been described starting from ethylnicotinate, which reacts with NMP to give *N*-methyl-3-nicotinoyl-pyrrolidin-2-one. The resulting lactam was opened under strong acidic conditions. Nitrosation of the secondary amine afforded NNK in good yield [1] (Scheme II).

Scheme II



Related literature describes the synthesis of NNK derivatives starting from different nicotinic esters [2] or by varying the pyrrolidinone N-alkyl side chain [3] (Scheme III).

Scheme III

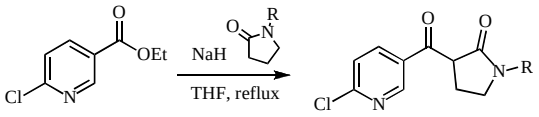


X = H, F, Cl, Br, I

R = Me, Et,

In order to extend this type of precursors for immunological tests, our objective was the synthesis of 3-[(6-chloro-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone derivatives **(8)**, by applying the same method to 6-chloronicotinates **(4b)** (Scheme IV).

Scheme IV



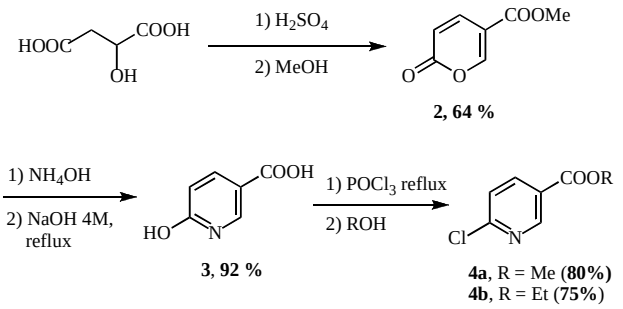
4b **8**

RESULTS AND DISCUSSION

First we synthesized the 6-hydroxynicotinic acid **(2)** by a modification of the method described by Von Pechmann [4,5,6]. Coumalic acid **(1)** previously prepared by using fuming sulfuric acid, was synthesized in concentrated sulfuric acid (2 mL/g of malic acid). The reaction was slower, but yield was similar and the acidic waste was lowered in this manner. 6-Hydroxynicotinic acid **(3)** was obtained from methyl coumalate **(2)** and transformed to 6-

chloronicotinate esters **(4a, 4b)** using phosphorus oxychloride and either methyl or ethyl alcohol [7] with satisfactory yield (Scheme V).

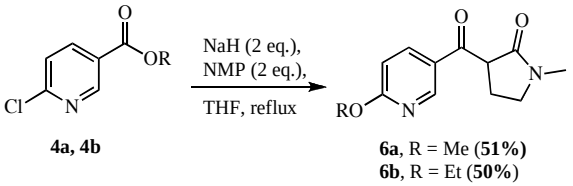
Scheme V



We applied the method described for the synthesis of the 1-methyl-3-nicotinoyl-pyrrolidinone to the synthesis of the 3-[(6-chloro-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone, starting from the previously prepared ethyl 6-chloronicotinate **(4b)**.

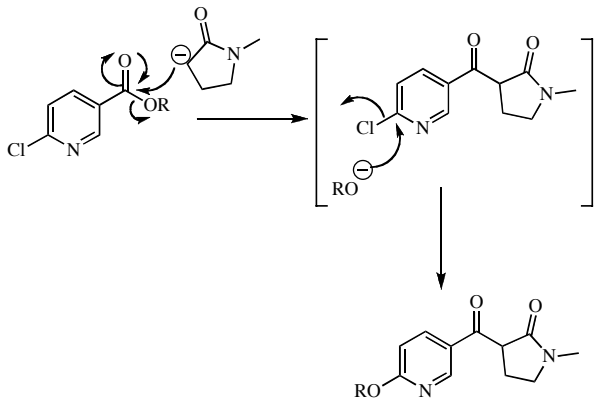
By monitoring the reaction by TLC, formation of a product different from the starting material was observed. The presence of a 1,3-diketone was confirmed when dark blue spot appears by developing TLC plate with ethanolic $FeCl_3$ solution. After work up of the reaction and analysis of the product by mass spectrometry, we noticed that the chlorine atom was missing. Presence of a sp3 CH was confirmed by ^1H NMR experiment. In fact, signals of the lactam were very complex to explain due to the asymmetric carbon, making the two CH_2 of the NMP diastereotopic. Moreover new ethoxy group signals were detected at 4.43 ppm (CH_2) and 1.39 ppm (CH_3), different from the ethoxy group from the starting material (4.3 ppm (CH_2) and 1.24 ppm (CH_3)). The ^{13}C NMR experiment shows that the carbon was linked to chlorine at 155.6 ppm has disappeared but is still quaternary. These results lead us to the following conclusion: the chlorine atom has been substituted by the ethoxy group from the starting ester (Scheme VI).

Scheme VI



To explain this reaction, we propose the following mechanism (Scheme VII).

Scheme VII



Claisen condensation between the ester and the carbanion formed by reaction of NMP with sodium hydride released an ethoxy group, which made a nucleophilic substitution of the α-chlorine on the pyridine ring. This type of reaction has been well described in literature [8].

To extend the study, we applied the same conditions to different esters available from commercial 2-chloro-nicotinic acid [9] (Table 1). These esters were reacted in the Claisen condensation (Scheme VIII), and afforded generally the condensation-substitution product along with the starting material. Substitution varied with chain length and alcohol type. In this way, tertiary alcohol did not give the substitution product certainly due to steric hindrance (Table 1, entry 7).

Scheme VIII

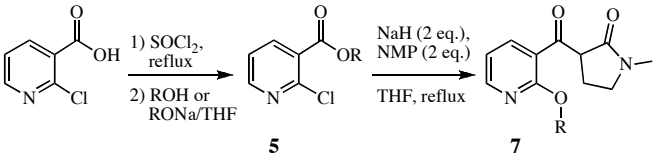
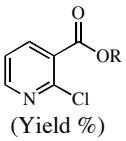
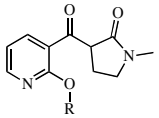


Table 1

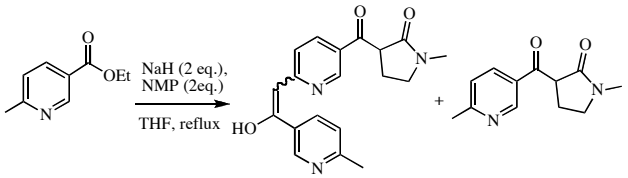
Entry	ROH	 (Yield %)	 (Yield %)
1	CH_3OH	**5a** (87[a])	**7a** (47)
2	CH_3CH_2OH	**5b** (80[a])	**7b** (46)
3	$CH_3CH_2CH_2OH$	**5c** (51[a])	**7c** (61)
4	$(CH_3)_2CHOH$	**5d** (55[a])	**7d** (55)
5	$CH_3CH_2CH_2CH_2OH$	**5e** (81[b])	**7e** (43)
6	$CH_3CH(OH)CH_2CH_3$	**5f** (68[a])	**7f** (54)
7	$(CH_3)_3COH$	**5g** (59[b])	**7g** (-)
8	$(CH_3)_2CHCH_2CH_2OH$	**5h** (70[b])	**7h** (48)

Esters were prepared according to Method A (a) or B (b) described in experimental part

By studying this reaction, we have shown that migration of an alkoxy group formed *in situ* was possible. Steric hindrance was the only limitation of the method.

The same reaction was performed starting from ethyl 6-methylnicotinate [10]. In fact, from the condensation we could isolate a second compound in 45 % yield along with the desired compound. This structure was identified as shown in Scheme IX. In fact, the product was formed through deprotonation of the methyl group and condensation on the ester of a second molecule (Scheme X). This was unexpected as normally deprotonation of methyl pyridine occurs with stronger bases such as phenyl lithium [11], LDA [12] or different sodium or potassium bases [13].

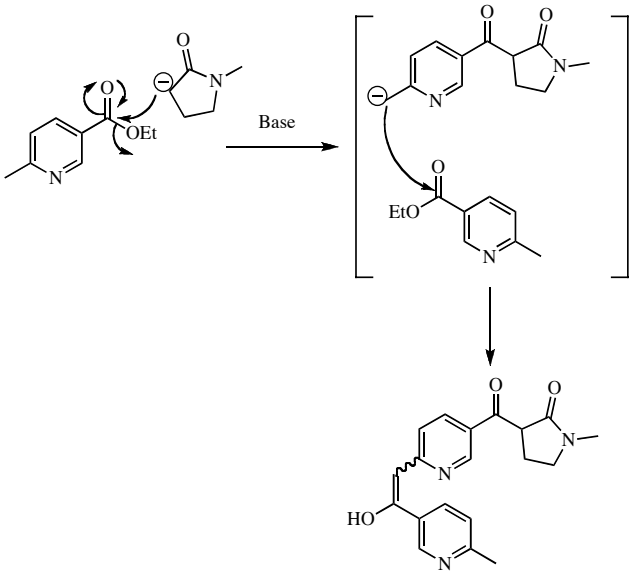
Scheme IX



9, 45 %

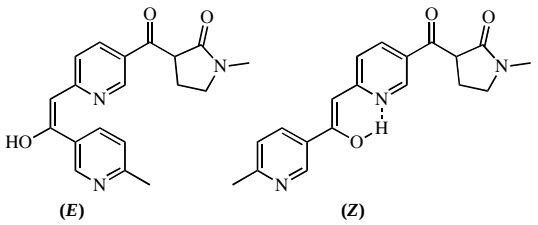
To explain the reaction we propose the following mechanism (Scheme X), involving reactivity similar to scheme VII.

Scheme X



The NMP carbanion reacts with the nicotinic ester, releasing an ethoxy group into the media. The acidity of the methyl group, enhanced by the diketone in the *para* position, was then deprotonated to react with another ester, to give the ketone detected as its enol form (Scheme X).

Scheme XI



(*E*) **(*Z*)**

Stereochemistry (*Z* or *E*) could be determined by analogy with the study on (*Z*)-2-(2-hydroxy-2-phenyl-vinyl)pyridine [14]. According to the literature, the tautomer ratio due to hydrogen bonding depends on solvent [15], temperature [16] and substitutions [16,17]. NMR analysis in our case shows only an enol form, which has been assigned to the *Z*-isomer (Scheme XI).

In summary, we have shown that a Claisen condensation on 2 or 6-chloronicotinates or methyl-nicotinates must be run carefully in order to avoid unexpected side reactions.

EXPERIMENTAL

Purification by column chromatography was performed by using silica gel 60A (0.07-0.200mm). Melting points were determined on a Stuart Scientific SMP3 Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6 as solvent. Elemental Analyses were done in a LECO CHNS 932 equipment. Mass spectra were performed on a MS/GC using Varian GC 3800 fitted with a Saturn 2000 MS and a Maldi-ToF MS Bruker Reflex.

Coumalic acid (1). In a 2 L flask, 200 g (1.19 mol) of malic acid were slowly added portionwise to 400 mL of concentrated sulfuric acid (Caution: gloves and safety glasses have to be worn). The solution was heated on a water bath until the evolution of gas stopped. The reaction mixture was then cooled and poured slowly onto 800 g of crushed ice. After standing 24 hours, the acid was filtered on a Büchner funnel, washed with three 50 mL portions of ice cold water and dried, yielding 67% of a pale yellow solid. Mp= 203-205°C, Mp_{lit}= 205-208 [18]. ^{1}H NMR (250 MHz, DMSO d_6): δ 8.60 (s, 1H), 7.81 (d, J = 12 Hz, 1H), 6.62 (t, J = 12 Hz, 1H). ^{13}C NMR (250 MHz, DMSO d_6): δ 166.3, 160.2, 159.1, 142.8, 114.9, 112.2.

6-Hydroxynicotinic acid (3). From the above described coumalic acid **(1)**, access to 6-hydroxynicotinic acid was achieved by the described procedure (using methyl coumalate **(2)** as intermediate) [4,5,6].

Preparation of alkyl 6-chloronicotinates was described in the literature. Methyl 6-chloronicotinate (4a) [7b, 21]**, ethyl 6-chloronicotinate (4b)** [7].

Preparation of 2-chloronicotinoyl chloride hydro-chloride. 0.3 Mol of $SOCl_2$ was added carefully to 0.1 mol of 2-chloronicotinic acid; the mixture was stirred and

refluxed overnight. Excess of $SOCl_2$ was removed under vacuum to dryness. The crude product was directly used in the following steps.

Procedure for the preparation of 2-chloronicotinic esters (4).

Method A. 0.05 mol of 2-chloronicotinoyl chloride hydrochloride was mixed with an excess of the appropriate alcohol and refluxed overnight. Excess of alcohol was removed under vacuum to dryness. The remaining product was then poured carefully onto ice water and basified with solid $NaHCO_3$ until the pH was alkaline. The crude was extracted with ethyl acetate, organic layers were dried over magnesium sulfate and evaporated. Purification by column chromatography (Petroleum ether-Ethyl acetate, 3/1) yields a yellow oil.

Method B. To 1.1 molar equivalents of the appropriate alcohol in THF, are added 1.1 equivalents of sodium hydride (60% in oil). The mixture was heated 1 hour at 60°C. Then, 1 equivalent of 2-chloronicotinoyl chloride hydrochloride was added, and the mixture was refluxed overnight. Solvent was removed, and the remaining product was poured onto water, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated to dryness, product was purified by column chromatography (ethyl acetate).

Methyl 2-chloronicotinate (5a) [22]**, Ethyl 2-chloronicotinate (5b)** [23]**, *tert*-Butyl 2-chloronicotinate (5g)** [24].

Propyl 2-chloronicotinate (5c). This compound was obtained as a yellow oil (51%).^{1}H NMR (250 MHz, $CDCl_3$): δ 8.34 (d, J = 12 Hz, 1H), 8.03 (d, J = 12 Hz, 1H), 7.20 (t, J = 12 Hz, 1H), 4.19 (t, 2H), 1.66 (m, 2H), 0.88 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 164.4, 151.6, 149.6, 140.4, 127.0, 122.1, 67.5, 21.9, 10.4. MS (EI): m/z (%) = 158 (100), 199 (2.1, [M$^+$]). *Anal.* Calcd. for $C_9H_{10}ClN_2O$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.21; H, 5.11; N, 6.99.

Isopropyl 2-chloronicotinate (5d). This compound was obtained as a yellow oil (55%).^{1}H NMR (250 MHz, CDCl3): δ 8.39 (d, J = 12 Hz, 1H), 8.03 (d, J = 12 Hz, 1H), 7.20 (t, J = 12 Hz, 1H), 5.13 (m, 1H), 1.21 (m, 6H). ^{13}C NMR (250 MHz, CDCl3): δ 163.9, 151.4, 149.7, 139.8, 127.5, 122.1, 69.8, 21.6. MS (EI): m/z (%) = 140 (100), 199 (12.4, [M$^+$]). *Anal.* Calcd. for $C_9H_{10}ClN_2O$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.25; H, 4.96; N, 7.11.

Butyl 2-chloronicotinate (5e). This compound was obtained as a yellow oil (81%).^{1}H NMR (250 MHz, $CDCl_3$): δ 8.42 (d, J = 12 Hz, 1H), 8.09 (d, J = 12 Hz, 1H), 7.28 (t, J = 12 Hz, 1H), 4.29 (t, J = 13 Hz, 2H), 1.70 (m, 2H), 1.40 (m, 2H), 0.91 (t, J = 14 Hz, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 164.6, 151.7, 149.8, 140.2, 127.2, 122.2, 65.9, 30.5, 19.2, 13.6. MS (EI): m/z (%) = 158 (100), 213 (1.0, [M$^+$]). *Anal.* Calcd. for $C_{10}H_{12}ClN_2O$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.29; H, 5.57; N, 6.62.

***sec*-Butyl 2-chloronicotinate (5f).** This compound was obtained as a yellow oil (68%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.44 (d, J = 12 Hz, 1H), 8.07 (d, J = 12 Hz, 1H), 7.27 (t, J = 12 Hz, 1H), 5.10 (m, 1H), 1.96 (m, 2H), 1.36 (d, 3H), 0.88 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 164.2, 151.7, 149.6, 140.1, 127.6, 122.1, 74.5, 28.6, 19.4, 9.9. MS (EI): m/z (%) = 140 (100), 213 (0.6, [M$^+$]). *Anal.* Calcd. for $C_{10}H_{12}ClN_2O$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.25; H, 5.58; N, 6.61.

Isopentyl 2-chloronicotinate (5h). This compound was obtained as a yellow oil (70%).^{1}H NMR (250 MHz, $CDCl_3$): δ 8.42 (d, J = 12 Hz, 1H), 8.08 (d, J = 12 Hz, 1H), 7.28 (t, J = 12 Hz, 1H), 4.30 (t, 2H), 1.67 (m, 1H), 1.56 (m, 2H), 0.97 (d, 6H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 164.5, 151.6, 149.7, 140.2, 127.1, 122.1, 64.6, 37.1, 24.9, 22.3. MS (EI): m/z (%) = 158 (100), 228 (17,0, [M+H]). *Anal.* Calcd. for $C_{11}H_{14}ClN_2O$: C, 58.03; H, 6.20; N, 6.15. Found: C, 58.19; H, 6.17; N, 6.07.

Typical procedure for Claisen condensation. In a round bottom flask under argon fitted with a refrigerant, are placed 2 equivalents of sodium hydride (60% in oil) and anhydrous THF (100 mL/g NaH). Two equivalents of NMP in THF (10 mL/g NMP) were added dropwise, and stirred 30 minutes. One equivalent of the appropriate ester in THF (10 mL/g ester) is dropped and the mixture was refluxed overnight. THF was removed under vacuum, and the crude was poured onto a solution of 6 *M* HCl. The aqueous layer was extracted with ethyl acetate, and neutralized with solid $NaHCO_3$. Then, the aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (EtOAc) affords the final product.

3-[(6-Methoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (6a). This compound was obtained as a yellow solid (51%). Mp= 89-90°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.30 (d, 1H, J = 10 Hz), 6.81 (d, 1H, J = 9 Hz), 4.34 (m, 1H), 4.01 (s, 3H), 3.60-3.39 (m, 2H), 2.86 (s, 3H), 2.70-2.25 (m, 2H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 193.7, 169.8, 166.9, 150.9, 139.3, 125.7, 125.9, 110.8, 54.1, 50.5, 48.1, 30.0 21.1. MS (EI): m/z (%) = 98(57), 136 (100), 191 (27), 234 (28, [M$^+$]). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.55; H, 6.11; N, 11.89.

3-[(6-Ethoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (6b). This compound was obtained as a yellow solid (50%). Mp: 103-105°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.32 (d, 1H, J = 10 Hz), 6.82 (d, 1H, J = 9 Hz), 4.53 (q, 2H), 4.34 (m, 1H), 3.64-3.36 (m, 2H), 2.85 (s, 3H), 2.75-2.16 (m, 2H), 1.39 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 193.7, 169.8, 166.7, 150.9, 139.6, 125.7, 126.9, 110.9, 62.6, 50.4, 47.9, 29.5, 21.2, 14.5. MS (EI): m/z (%) = 122 (100), 150 (76), 205 (50), 248 (25, [M$^+$]). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.91; H, 6.55; N, 11.21.

3-[(2-Methoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (7a). This compound was obtained as a yellow oil (47%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.99 (d, J = 10 Hz, 1H), 6.92 (t, J = 9 Hz, 1H), 4.56 (m, 1H), 3.89 (s, 3H), 3.38-3.27 (m, 2H), 2.75 (s, 3H), 2.40-2.20 (m, 2H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 197.6, 170.5, 161.5, 150.7, 140.1, 121.2, 116.9, 53.6, 53.2, 47.5, 29.2, 21.6. MS (EI): m/z (%) = 136 (100), 234 (19.6, [M+]). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.56; H, 5.95; N, 12.01.

3-[(2-Ethoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (7b). This compound was obtained as a yellow oil (46%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.28 (d, J = 8 Hz, 1H), 8.03 (d, J = 10 Hz, 1H), 6.96 (t, J = 9 Hz, 1H), 4.67 (m, 1H), 4.38 (q, 2H), 3.54-3.32 (m, 2H), 2.90 (s, 3H), 2.57-2.25 (m, 2H), 1.35 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.3, 171.1, 161.6, 151.1, 140.3, 121.5, 117.1, 62.6, 53.8, 47.9, 29.8, 22.3, 14.6. MS (EI): m/z (%) = 150 (100), 248 (39.9, [M$^+$]). *Anal.* Calcd. for

$C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.94; H, 6.47; N, 11.21.

1-Methyl-3-[(2-propoxy-3-pyridinyl)carbonyl]-2-pyrrolidinone (7c). This compound was obtained as a yellow oil (61%-). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.26 (d, J = 8 Hz, 1H), 7.83 (d, J = 10 Hz, 1H), 6.77 (t, J = 9 Hz, 1H), 4.52 (m, 1H), 4.21 (t, 2H), 3.33-3.14 (m, 2H), 2.64 (s, 3H), 2.28-2.11 (m, 2H), 1.59 (m, 2H), 0.86 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.1, 170.7, 161.5, 150.8, 139.9, 121.3, 116.8, 68.1, 53.5, 29.5, 22.3, 10.4. MS (EI): m/z (%) = 122 (100), 262 (12.6, [M+]). *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.19; H, 6.88; N, 10.61.

3-[(2-Isopropoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (7d). This compound was obtained as a yellow oil (55%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.26 (d, J = 8 Hz, 1H), 8.02 (d, J = 10 Hz, 1H), 6.88 (t, J = 9 Hz, 1H), 5.41 (m, 1H), 4.58 (m, 1H), 3.52-3.30 (m, 2H), 2.59 (s, 3H), 2.59 (m, 2H), 1.32 (m, 6H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.6, 171.2, 161.1, 151.1, 140.3, 121.6, 116.7, 69.2, 53.8, 47.8, 29.7, 22.6, 22.0. MS (EI): m/z (%) = 122 (100), 262 (17.6, [M$^+$]). *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.16; H, 6.85; N, 10.74.

3-[(2-Butoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (7e). This compound was obtained as a yellow oil (43%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.15 (d, J = 8 Hz, 1H), 7.91 (d, J = 10 Hz, 1H), 6.81 (t, J = 9 Hz, 1H), 4.54 (m, 1H), 4.22 (t, 2H), 3.40-3.19 (m, 2H), 2.71 (s, 3H), 2.27 (m), 2.36-2.19 (m, 2H), 1.40 (m, 2H), 1.31, (m, 2H), 0.86 (t, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.3, 170.8, 161.2, 150.8, 139.9, 121.5, 116.5, 73.5, 53.6, 47.5, 29.4, 28.7, 22.4, 19.1, 9.7. MS (EI): m/z (%) = 122 (100), 276 (11.9, [M$^+$]). *Anal.* Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.29; H, 7.26; N, 10.20.

3-[(2-sec-Butoxy-3-pyridinyl)carbonyl]-1-methyl-2-pyrrolidinone (7f). This compound was obtained as a yellow oil (54%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.19 (d, J = 8 Hz, 1H), 7.95 (d, J = 10 Hz, 1H), 6.86 (t, J = 9 Hz, 1H), 5.13 (m, 1H), 4.59 (m, 1H), 3.45-3.24 (m, 2H), 2.77 (s, 3H), 2.27 (m, 2H), 1.76-1.60 (m, 2H), 1.29 (m, 3H), 0.86 (m, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.3, 170.8, 161.2, 150.8, 139.9, 121.5, 116.5, 73.5, 53.6, 47.5, 29.4, 28.7, 22.4, 19.1, 9.7. MS (EI): m/z (%) = 122 (100), 276 (8.7, [M$^+$]). *Anal.* Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.23; H, 7.27; N, 10.21.

3-{[2-(Isopentyloxy)-3-pyridinyl]carbonyl}-1-methyl-2-pyrrolidinone (7h). This compound was obtained as a yellow oil (48%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.93 (d, J = 10 Hz, 1H), 6.84 (t, J = 9 Hz, 1H), 4.57 (m, 1H), 4.30 (t, 2H), 3.45-3.26 (m, 2H), 2.76 (s, 3H), 2.28-2.18 (m, 2H), 1.59 (m, 3H), 0.86 (d, 6H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 198.2, 170.9, 161.6, 150.9, 147.9, 140.1, 138.6, 121.4, 116.9, 65.3, 53.6, 47.7, 37.7, 29.7, 25.1, 22.5, 22.4. MS (EI): m/z (%) = 122 (100), 221 (24.3), 290 (3, [M$^+$]). *Anal.* Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.27; H, 7.55; N, 9.58.

Typical procedure for synthesis of 3-({6-[(Z)-2-hydroxy-2-(6-methyl-3-pyridinyl)ethenyl]-3-pyridinyl-}carbonyl)-1-methyl-2-pyrrolidinone (9). In a round bottom flask under argon fitted with a refrigerant, were stirred 2 equivalents of sodium hydride (60% in oil) in anhydrous THF (100 mL/g NaH). Two equivalents of NMP (10 mmol; 1 g) in THF (10 mL /g NMP) was added dropwise, and the reaction mixture was stirred 30 minutes at room temperature. One equivalent of ethyl 6-methylnicotinate (5 mmol; 0.895 g) dissolved in THF (10 mL/g ester) were added dropwise and the mixture heated at reflux overnight. THF was removed, and the residue was poured onto a solution of 6 *M* HCl. The aqueous layer was extracted with ethyl acetate, and then neutralized with 4 *M* NaOH. Aqueous layer was extracted with ethyl acetate; and the organic layer was dried over magnesium sulfate and evaporated. Product was suspended in ether, stirred 15 minutes and filtered, affording 45% of an orange solid. Mp= 165-167°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 15.59 (s, 1H), 8.84 (s, 1H), 8.80 (s, 1H), 8.10 (d, J = 9 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.13 (d, J = 8 Hz, 1H), 6.96 (d, J = 9Hz, 1H), 6.00 (s, 1H), 4.20 (m, 1H), 3.50-3.25 (m, 2H), 2.81 (s, 3H), 2.81-2.15 (m, 2H), 2.45 (s, 3H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 192.1, 170.5, 169.4, 159.1, 146.7, 145.5, 136.7, 134.0, 129.7, 125.3, 123.2, 120.9, 93.1, 50.6, 47.9, 29.9, 24.2, 20.7. Calcd. for $C_{19}H_{19}N_3O_3$ m/z = 338.149 (M+H). Found m/z = 338.157 (M+H).

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