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TETRAHEDRON

Heterocyclic Enaminones : Photochemical Synthesis of 6,7,8,9-Tetrahydro-5*H*-pyrido [2,3-*b*]indol-9-ones.

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Abstract: The synthesis of 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-9-ones from arylenaminones is described. Two "routes" have been investigated: a radical process through a photochemical reaction, and a catalytic process through an arylpalladium complex.

keywords: Polycyclic heterocyclic compounds, enaminones, photochemistry.

INTRODUCTION

Interest in the chemistry of tetrahydrocarbazolone derivatives has increased since these structures have been found to represent an interesting class of bioactive heterocyclic compounds, and since they are implicated in the elaboration of natural compounds related to several classes of indole alkaloids. For example, murrayaquinone A, an alkaloid isolated from the root or bark of *Murraya euchrestifolia* HAYATA[1] which exhibits cardiotonic activity on guinea-pig papillary muscle[2], was synthesized in four steps from 1,2,3,4-tetrahydro-1*H*-carbazol-4-one[3]. As part of our program concerning the elaboration of aza-analogs of natural products[4] , we are interested in the synthesis of analogs of murrayaquinones. This class of compounds is related to the pharmacological class of TPBIs[5]. They are of interest for their biological activities as potential anticancer agents[6]. In this context, we are interested in the reactivity of enaminones **1** derived from aminopyridines in view of the synthesis of

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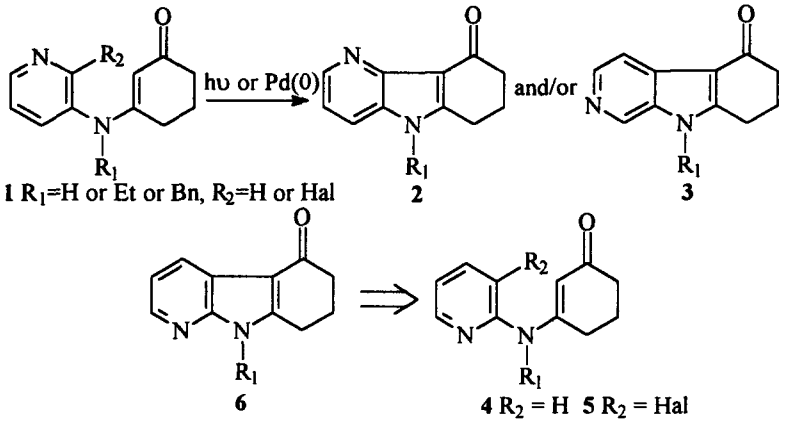
azacarbazolones[7]. Our previous results showed that a palladium (0) catalysed cyclization (Heck reaction)[8] or a photocyclization of *N*-(halogenopyridinyl) enaminones were the most efficient paths for the elaboration of the pyridoindolic framework. The 6,7,8,9-tetrahydro-*5H*-pyrido[3,2-*b*]indol-9-ones **2** were obtained regioselectively, without formation of by-products (scheme 1).

Scheme 1

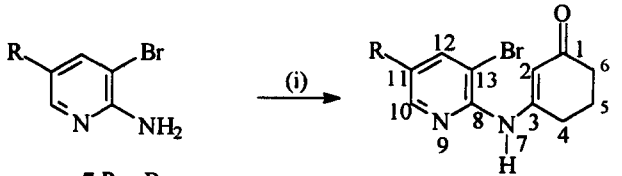


As a continuation of these investigations we now report the application of such methodologies to the study of the reactivity of enaminones derived from 2-aminopyridines **4** or 2-amino-3-halogenopyridines **5**; with a view to the synthesis of 6,7,8,9-tetrahydro-*5H*-pyrido[2,3-*b*]indol-9-ones **6**.

RESULTS AND DISCUSSION

The required enaminones **9,10** were obtained in moderate to excellent yield by condensation of the corresponding pyridines **7,8** with 1,3-cyclohexanedione in refluxing toluene as previously reported[7] (scheme 2).

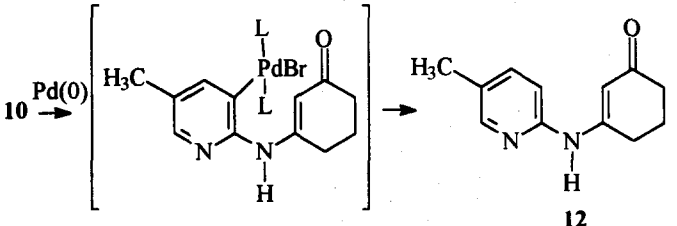
Scheme 2



(i) 1,3-cyclohexanedione/toluene/ Δ/1 hour

Palladium (0) catalyzed reactions: Compounds **9,10** were subjected to an intramolecular Heck reaction (scheme 3). Using a palladium (0) species generated *in situ* (from palladium acetate and triphenylphosphine in dimethylformamide), results were similar to those obtained with 3-aminopyridines: we were unable to isolate any cyclization-product. No reaction occured with **9**, while the dehalogenated enaminone **12** was obtained in the case of the 5-methylated derivative **10**. This indicates that the first step of the reaction occurred (substitution of halogen by the palladium), leading to an intermediary arylpalladium σ-complex **11** which then underwent a reductive cleavage of the C-Pd bond to give **12**. The alternative route which consisted in the use of a preformed species of palladium (0) tetrakis(triphenylphosphine)palladium in hexamethylphosphoramide at 140°C[9] was also not effective in this case.

Scheme 3



11 L=P(Ph)$_3$ **12**

Photochemical reactions: **Irradiation of Compounds 9-10**: We were also interested in the photocyclization of compounds **9,10**. These reactions were conducted under a variety of conditions using a medium pressure mercury UV lamp (400 W), in the presence of triethylamine to scavenge the hydrobromic acid formed. Irradiation of compound **10** was conducted in acetonitrile using a quartz immersion well apparatus, these were the optimal conditions previously described.[7] In this case, 2-methyl-6,7,8,9-tetrahydropyrido[2,3-*b*] indol-9-one **15** was isolated in 15% yield admixed with the dehalogenated enaminone **12** (39%). Change of solvent and wavelength did not improve the result (scheme 4, table 1), while the replacement of the 5-methyl group by a bromine (compound **9**) had dramatic effects, and no reaction occured in this case.

Scheme 4

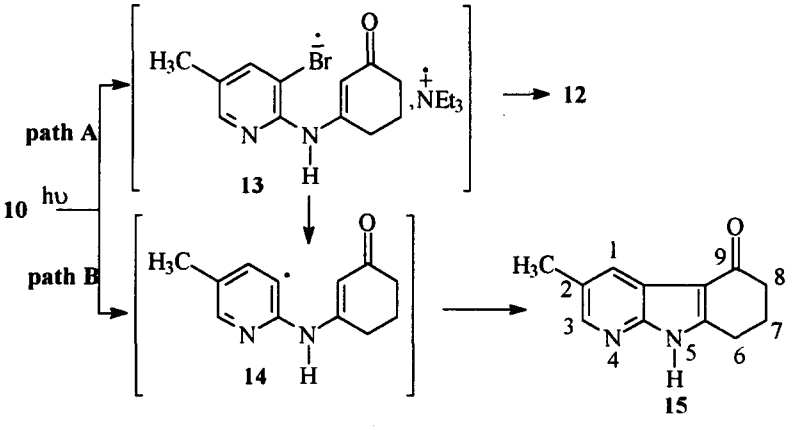


Table 1: irradiation of compound 10

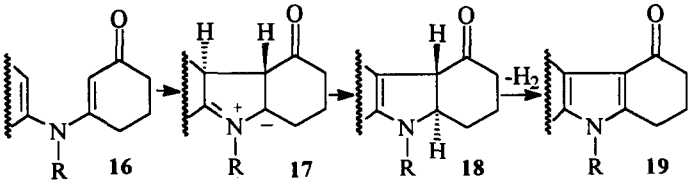
conditions	12	15	recovered starting material 10
CH_3CN/Et_3N/quartz/ 2 hours	39%	8%	20%
C_6H_6/MeOH/Et_3N/Pyrex/ 24 hours	-	-	80%
EtOH/Et_3N/Pyrex/ 2 hours	20%	10%	10%

Formation of the by-product **12** suggests that the reaction probably proceeds either through a photoinduced electron transfer (PET)[10] (path A) or directly by a homolytic cleavage of the C-Br bond [11] (path B). Compound **12** could be obtained from the radical anion species **13** with assistance of a hydrogen donating species (triethylamine)[12](path A), while the formation of cyclized compound **15** is assumed from the radical species **14** which is directly obtained from **10** or by the cleavage of the C-Br bond of species **13**. Mechanistic considerations of the preferential formation of **12** and the poor yield observed for the formation of **15** will be discussed further. Optimization of the synthesis of the 6,7,8,9-tetrahydro-*5H*-pyrido[2,3-*b*]indol-9-ones was finally realized by considering the photocyclization of the dehalogenated species **20-21**. According to the studies

of Grellman et al.[13], and Chapman et al.[14], such oxidative cyclizations are known to occur through an electrocyclic ring closure. From an electronic excited state, the carbon-carbon bond is formed leading to a zwitterionic species **17**, which further undergoes a [1,4] hydrogen shift[13d] to give the hexahydro compound **18** and then the expected tetrahydro form **19** (scheme 5).

Scheme 5

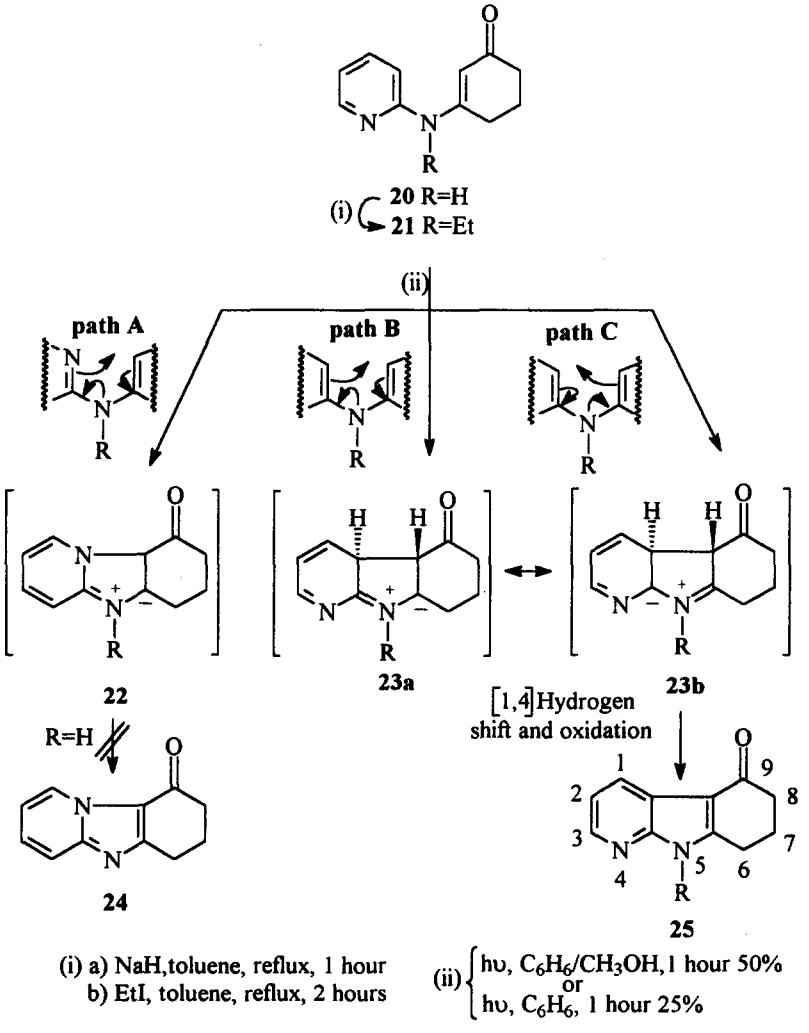
General Pathway for Photocyclization



Irradiation of Compounds 20-21: The secondary enaminone **20** was prepared according to the litterature[7] and its N-ethyl derivative **21** was obtained in 49 % yield by treatment of **20** with sodium hydride in toluene, followed by addition of a large excess of ethyl iodide. Subsequent irradiation of **20-21** using a Pyrex immersion well apparatus and a medium pressure mercury UV lamp (400 W) was investigated in benzene and in a benzene/methanol mixture (50/50). In these conditions, the secondary enaminone **20** did not react (starting material was recovered), while **21** led to the expected 6,7,8,9-tetrahydropyrido[2,3-*b*]indol-9-one **25** in 25% yield and 50% yield respectively (scheme 6). With respect to the general mechanism of cyclization (scheme 5), three pathways can be postulated in this reaction. Paths A and B, which consider a charge migration from the nitrogen into the heterocyclic ring to give the zwitterionic species **22** and **23a**, are consistent with the general reactivity of the pyridines. Path C in which the charge migration occurs into the cyclohexene ring is consistent with the reactivity of enaminone systems[15], and should give the zwitterionic species **23b**, (mesomeric form of **23a**). No evidence was shown for path A. Effectively, if this mechanistic route could occur, we should be able to isolate the known pyridobenzimidazolone **24** [16] when subjecting the secondary enaminone **20** (R = H) to irradiation. Since the formation of the zwitterionic species **23a** is a necessary intermediate state for the isolation of **25**, both paths B and C can be considered.

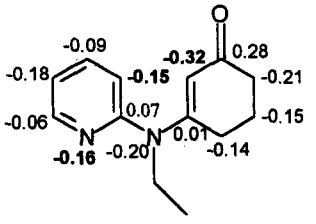
Scheme 6

Proposed Reaction Scheme for the Synthesis of 25

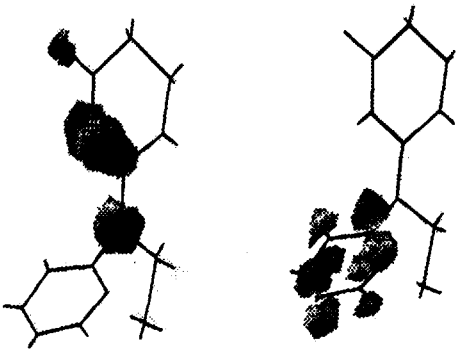


The latter pathway was finally supported by the results of semi-empirical molecular orbital calculations AM1 calculation within MOPAC 6.0 (PRECISE option)[17]. Considering charge and orbital control of the reaction as outlined in the frontier molecular concept from a $HOMO_{C\text{-}2\ enaminone}/LUMO_{C\text{-}13\ pyridine}$ controlled process as well as from net atomic charge estimations, it is likely that the reaction took place according to path C (figure 1).

figure 1



Net atomic charges calculation on AM1optimized structure of compound **21**



A **B**

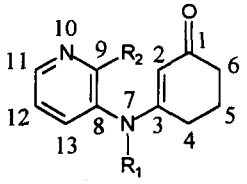
frontier molecular orbitals for compound **21** calculated from an AM1 optimized structure of **21** A (HOMO), B (LUMO)

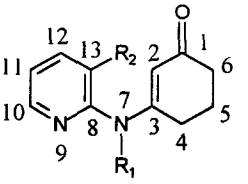
Moreover, these mechanistic considerations are consistent with the results obtained from the cyclizations of the halogenated derivative **10**. Effectively, when this reaction was conducted in a benzene/methanol mixture which favours a six Π electron mechanism for the oxidative cyclization rather than a photoinduced electron transfer[7], starting material was recovered, and no N-insertion was found. In addition, the poor yields obtained for **15** can be explained as follows. The use of acetonitrile which favours a PET mechanism, leads preferentially to the dehalogenated enaminone **12** (through **13**), and does not undergo an oxidative cyclization through a six Π electron mechanism under these conditions.

CONCLUSIONS

We have described the reactivity of enaminones derived from 2-aminopyridines in view of the obtention of tetrahydropyrido[2,3-*b*]indol-9-ones.[7] Recapitulative reactivity of the 2-amino and 3-amino derivatives is summarized in table 2.

Table 2: recapitulative reactivity of enaminones derived from 2- and 3-aminopyridines





Photochemical reactions	
R_1 = Et or Bn, R_2 = H -6 Π electrons mecanism -no regioselectivity of the C-insertion on the C-9 or C-13 position of the pyridinic ring, -oxydative cleavage	**R_1 = Et, R_2 = H** -6 Π electrons mecanism -C-insertion on the C-13 position of the pyridinic ring, no N-insertion -no oxydative clivage
R_2 = Hal -PET + 6 Π electrons mecanisms -C-insertion on the C-9 or C-13 position -orientation of the regioselectivity by change of wavelength and solvent	**R_2 = Hal** -PET -C-insertion on the C-13 position with low yields
Palladium (0)catalysed reactions	
R_2 = Hal, Pd(0) generated *in situ* **-R_1 = H,** degradation **-R_1 = Et,** reductive clivage of the C-Pd bond	**R_2 = Hal, R1 = H,** Pd(0) generated *in situ* -reductive cleavage of the C-Pd bond
R_2 = Hal, R_1 = H or Et, preformed species of Pd(0) -regioselective C-insertion on the C-9 position of the pyridinic ring	**R_2 = Hal, R1 = H,** -reductive cleavage of the C-Pd bond

Finally, the use of halogenated enaminones as starting materials in the intramolecular Heck reaction or photocyclization was shown to be the best way for the synthesis of 6,7,8,9-tetrahydropyrido[3,2-*b*] and [3,4-*b*]indol-9-ones. In contrast, the synthesis of 6,7,8,9-tetrahydropyridodo[2,3-*b*]indol-9-one is better accomplished by photocyclization of simple enaminones derived from 2-aminopyridine.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis was perfomed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-NMR spectra were taken on Brüker AC 100 or WM 360 or EM 400WB; ^{13}C-NMR spectra were obtained at 26°C with proton noise decoupling at 25 MHz with a Brüker AC 100 instrument. Chemical shifts are

expressed relative to residual chloroform. Mass spectra were recorded on a LKB 2091 spectrometer at 15eV [θ(source)=180°C]. Dichloromethane was dried over activated alumina and distilled from calcium hydride.

3-[(3,5-dibromo-2-pyridinyl)amino]cyclohex-2-en-1-one (9) A solution of 2-amino-5-bromopyridine (7) (3 g, 12 mmol), 1,3-cyclohexanedione (1.8 g, 15 mmol), and *p*-toluenesulfonic acid monohydrate (70 mg, 0.39 mmol) in 265 ml of anhydrous toluene was refluxed with a Dean-Stark for 3 hours. After cooling, the solution is basified and extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *in vacuo*. Recrystallization from ethanol gave **9** (95%); mp 132-134°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 2.06 (m, 2H), 2.33 (t, 2H, J = 5.9 Hz), 2.60 (t, 2H, J = 5.9 Hz), 7.00 (br.s, 2H), 7.89 (d, 1H, J = 2.1 Hz), 8.23 (d, 1H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ: 21.6, 20.9, 36.4, 108.2, 108.5, 111.7, 142.1, 146.9, 148.6, 155.6, 199.3; Anal. Calcd for $C_{11}H_{10}Br_2N_2O$: C, 38.18; H, 2.93; N, 8.14. Found: C, 38.32; H, 2.85; N, 8.10.

3-[(3-bromo-5-methyl-2-pyridinyl)amino]cyclohex-2-en-1-one (10). This compound was obtained according to the procedure used for (**9**). Purification was made by chromatography on silica gel eluted with dichloromethane (65 %); mp 145-147°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 1.95 (m, 2H), 2.22 (s, 3H), 2.28 (t, 2H, J = 5.7 Hz), 2.51 (t, 2H, J = 5.9 Hz), 6.65 (s, 1H), 6.93 (br.s, 1H), 7.54 (d, 1H, J = 1.4 Hz), 7.95 (d, 1H, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ: 14.6, 21.2, 29.3, 36.0, 105.7, 108.3, 128.2, 140.6, 145.7, 147.1, 156.7, 198.7; Anal. Calcd for $C_{12}H_{13}BrN_2O$: C, 50.26; H, 4.66; N, 9.96. Found: C, 50.14; H, 4.49; N, 10.12.

3-[(5-methyl-2-pyridinyl)amino]cyclohex-2-en-1-one (12). To a stirred solution of palladium acetate (6 mg, 0.03 mmol), triphenylphosphine (15 mg, 0.06 mmol), sodium hydrogencarbonate (235 mg, 2.79 mmol) in dry dimethylformamide (21 ml), were added 350 mg (1.4 mmol) of **10** under nitrogen. The resulting mixture was refluxed for 15 hours, and then filtered through celite after being cooled. The filtrate was washed with a saturated solution of sodium hydrogencarbonate and extracted with dichloromethane. The organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica gel using an ether/methanol mixture as eluent (85/15) gave **12** as a brown paste; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (m, 2H), 2.25 (s, 3H), 2.34 (t, 2H, J = 5.8 Hz), 2.55 (t, 2H, J = 6.0 Hz), 6.32 (s, 1H), 6.98 (d, 1H,

J = 8.4 Hz), 7.37 (dd, 1H, J = 8.4 and 2.4 Hz), 8.04 (d, 1H, 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.6, 21.7, 29.6, 36.5, 103.0, 114.2, 128.0, 138.6, 148.0, 150.6, 159.7, 199.3. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.98; N, 13.86. Found: C, 71.39; H, 6.73; N, 13.59.

2-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-one (15). A solution of enaminone (**10**) (280 mg, 1.0 mmol) in the appropriate solvent (150 ml) was irradiated for the time indicated in table 1. The solvents were then evaporated under reduced pressure. Compound (**15**) was purified by flash chromatography on silica gel using a CH_2Cl_2/MeOH mixture as eluent (95/5) to give (**15**) as a brown paste; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.26 (m, 2H), 2.41 (s, 3H), 2.65 (t, 2H, J = 5.9 Hz), 3.05 (t, 2H, J = 5.9 Hz), 7.33 (d, 1H, J = 1.4 Hz), 7.57 (d, 1H, J = 1.4 Hz), 9.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:18.4, 23.7, 25.4, 38.3, 116.0, 124.5, 127.4, 132.3, 146.8, 152.6, 160.0, 188.1. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.78; H, 6.23; N, 13.69.

3-[(2-pyridinyl)ethylamino]cyclohex-2-en-1-one (21). Compound **20**[7] (2.95 g, 15.7 mmol) was added to a suspension of sodium hydride (2.87 g, 70.7 mmol, 60% in mineral oil) in anhydrous toluene (350 ml). The mixture was refluxed for 2 hours and cooled to room temperature. Ethyl iodide (15 ml, 188 mmol) was then slowly added and the mixture was refluxed for 7 hours. Solvent was removed and the residue washed with water. After extraction with dichloromethane, the organic layers were dried over sodium sulfate and evaporated *in vacuo*. The crude product was chromatographed on silica gel using an ether/methanol mixture as eluent (85/15) to give **21** as a yellow oil (49%); ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 1.00 (t, 3H, J = 6.8 Hz), 1.71 (m, 4H), 2.14 (t, 2H, J = 5.7 Hz),), 3.62 (q, 2H, J = 6.8 Hz), 5.25 (s, 1H), 7.03 (m, 2H), 7.59 (td, 1H, J = 7.7 and 1.2 Hz), 8.30 (dd, 1H, J = 4.8 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ: 12.2, 22.6, 28.7, 46.0, 102.3, 121.3, 121.7, 138.2, 149.2, 155.7, 163.4, 198.0. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.18; H, 7.46; N, 12.96. Found: C, 71.99; H, 7.59; N, 12.81.

6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-one (25). A solution of enaminone **21** (215 mg, 1.0 mmol) in the appropriate solvent (150 ml) was irradiated for 1 hour. The solvents were then evaporated under reduced

pressure. Compound **25** was purified by flash chromatography on silica gel using a CH_2Cl_2/MeOH mixture as eluent (95/5) to give **25** as a brown paste; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, 3H, J = 7.1 Hz), 2.25 (m, 2H), 2.51 (t, 2H, J = 5.6 Hz), 2.95 (t, 2H, J = 5.9 Hz), 4.30 (q, 2H, J = 7.1 Hz), 7.20 (dd, 1H, J = 7.8 and 4.8 Hz), 8.33 (dd, 1H, J = 4.8 and 1.5 Hz), 8.47 (dd, 1H, J = 7.8 and 1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.3, 22.05, 23.2, 37.1, 37.8, 111.0, 117.5, 118.4, 129.5, 143.5, 148.1, 151.8, 193.6. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08. Found: C, 72.99; H, 6.71; N, 12.89.

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