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

Yves Blache,*,† Marie-Eve Sinibaldi-Troin,‡ Aline Voldoire,‡ Olivier Chavignon,§ Jean-Claude Gramain,‡ Jean-Claude Teulade,§ and Jean-Pierre Chapat†

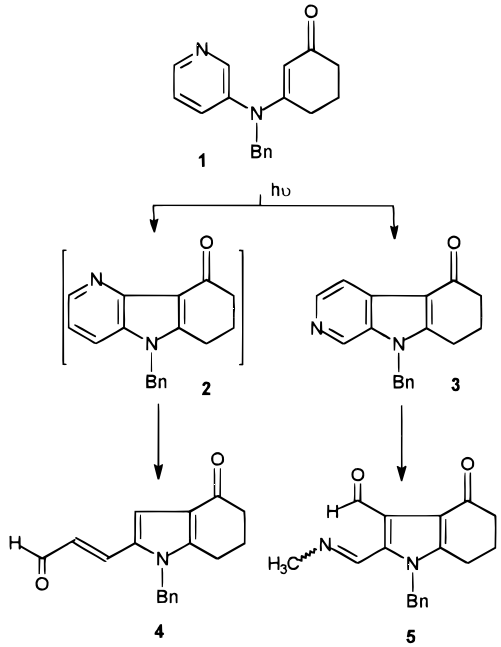
E.A. Pharmacochimie et Biomolécules, Laboratoire de Chimie Organique Pharmaceutique, Université Montpellier I, Faculté de Pharmacie, 15 Avenue Charles Flahault, 34060 Montpellier, France, SEESIB, UMR 6504, 63117 Aubière Cedex, France, and Laboratoire de Chimie Organique Pharmaceutique, Groupe de Recherche en Pharmacochimie, UFR de Pharmacie, 28 Place Henry Dunant, B.P. 38, 63001 Clermont-Ferrand, France

Received April 9, 1997

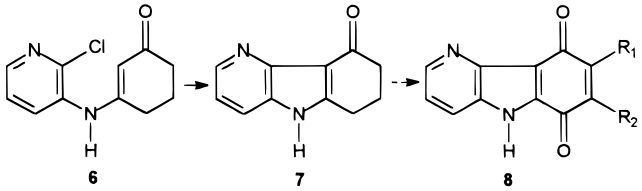
Introduction

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 are implicated in the elaboration of natural compounds related to several classes of indole alkaloids. For example, the synthetic drug ondansetron,[1] a 3-substituted 1,2,3,4-tetrahydro-*1H*-carbazol-4-one, is a potent antagonist of 5-HT_3 receptor. Alosetron,[2] a 3-aza derivative of ondansetron, shows the same activity. In another case, murrayaquinone A, an alkaloid from the root or bark of *Murraya euchrestifolia* HAYATA,[3] which exhibits cardiotonic activity on guinea pig papillary muscle,[4] was synthesized in four steps from 1,2,3,4-tetrahydro-*1H*-carbazol-4-one.[5] As part of our program concerning the elaboration of aza analogs of natural products,[6] we are interested in the chemistry of azacarbazolones that could be used in the synthesis of analogs of murrayaquinones. This class of compounds is related to the pharmacological class of TPBIs.[7] They are of interest for their biological activities as potential anticancer agents.[8] In this context, we have previously reported the photoreaction of enaminone **1**, which led to the two indolones **4** and **5** through an oxidative cleavage of the intermediate 6,7,8,9-tetrahydro-*5H*-pyrido[3,2-*b*]-indol-9-one (**2**) and 6,7,8,9-tetrahydro-*5H*-pyrido[3,4-*b*]-indol-9-one (**3**)[9] (Scheme 1).

Scheme 1



Scheme 2



No regioselectivity of the photocyclization was observed, and we were unable to isolate the regioisomer **2**.

As a continuation of these investigations, we now report the regioselective synthesis of the 6,7,8,9-tetrahydro-*5H*-pyrido[3,2-*b*]indol-9-one system from halogenoarylenaminones by means of a palladium(0)-catalyzed intramolecular cyclization[10] or by a photochemical mediated intramolecular cyclization (Scheme 2).[11]

Results and Discussion

The required *N*-(chloropyridinyl)enaminone **6** was obtained quantitatively by condensation of 3-amino-2-chloropyridine (**9**) with 1,3-cyclohexadione (**10**) in refluxing toluene as already reported.[9] Subsequent alkylation of the nitrogen atom to give the *N*-ethylated enaminone **11** was achieved in 60% yield by use of sodium hydride in refluxing toluene followed by treatment of the resulting sodium salt with a large excess of ethyl iodide (Scheme 3).

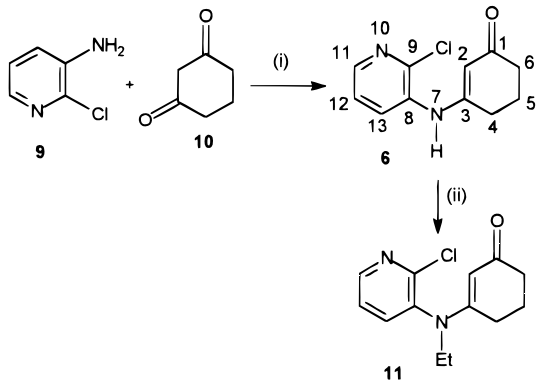
Photochemical Cyclization. The reactions were conducted under a variety of conditions using a medium-pressure mercury UV lamp (400 W) in the presence of triethylamine to scavenge the hydrochloric acid formed. Irradiation of 3-[(2-chloro-3-pyridinyl)amino]cyclohex-2-en-1-one (**6**) in a benzene/methanol solution (50/50) for

* To whom correspondence should be addressed. Fax: (33) 04 67 53 30. E-mail: yblache@pharma.univ-montp1.fr.
† Université Montpellier I.
‡ SEESIB.
§ UFR de Pharmacie.

(1) Clark, D. R.; Miller, B. A.; Berger, J.; Repbe, B. D.; Weinhardt, K. K.; Kowalczyk, A. B.; Eglen, M. R.; Bonhaus, W. D.; Lee, C.; Michel, D. A.; Smith, L. W.; Wong, H. F. E. *J. Med. Chem.* **1993**, *36*, 2645.
(2) Knaggs, R. A.; Cable, M. K.; Cannell, J. P. R.; Sidebottom, J. P.; Wells, N. G.; Sutherland, R. D. *Tetrahedron Lett.* **1995**, *36*, 477.
(3) Wu, T-S.; Ohta, T.; Furukawa, H.; Kuoh, C.-S. *Heterocycles* **1983**, *20*, 1267. Furukawa, H.; Wu, T.-S.; Ohta, T.; Kuoh, C.-S.. *Chem. Pharm. Bull.* **1985**, *33*, 4132.
(4) Takeya, K.; Itoigawa, M.; Furukawa, H. *Eur. J. Pharmacol.* **1989**, *169*, 137.
(5) Matsuo, K.; Ishida, S. *Chem. Pharm. Bull.* **1994**, *42*, 1325.
(6) Blache, Y.; Hichour, M.; Chavignon, O.; Gueiffier, A.; Teulade, J.-C.; Dauphin, G.; Chapat, J.-P. *Heterocycles* **1997**, *45*, 57. Chavignon, O.; Teulade, J.-C.; Roche, D.; Madesclaire, M.; Blache, Y.; Gueiffier, A.; Chabard, J.-L.; Dauphin, G. *J. Org. Chem.* **1994**, *59*, 6413. Blache, Y.; Gueiffier, A.; Chavignon, O.; Teulade, J.-C.; Dauphin, G.; Chapat, J.-P. *Heterocycl. Commun.* **1996**, *2*, 331.
(7) Skibo, B. E.; Islam, I.; Heileman, M. JH.; Schulz, W. G. *J. Med. Chem.* **1994**, *37*, 78.
(8) Skibo, B. E.; Schulz, W. G. *J. Med. Chem.* **1993**, *36*, 3050.
(9) Blache, Y.; Chavignon, O.; Sinibaldi-Troin, M.-E.; Gueiffier, A.; Teulade, J.-C.; Troin, Y.; Gramain, J.-C. *Heterocycles* **1994**, *38*, 1241.
(10) Akermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365. Grigg, R. *J. Heterocycl. Chem.* **1994**, *31*, 631.
(11) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074.

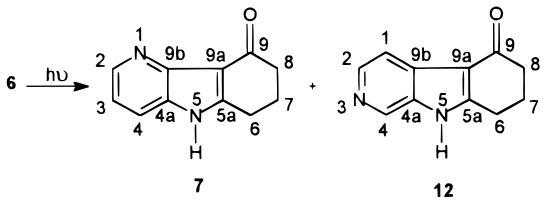
S0022-3263(97)00637-3 CCC: $14.00

Scheme 3[a]



[a] Reagents and conditions: (i) toluene, *p*-toluenesulfonic acid, reflux 3 h; (ii) NaH, toluene, reflux, then C_2H_5I.

Scheme 4



Scheme 5

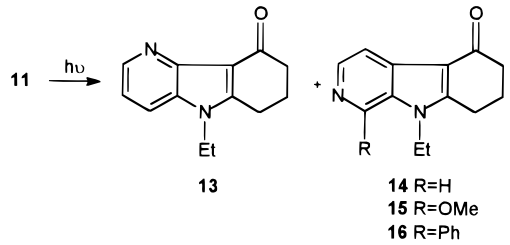


Table 1. Photocyclization of Enaminone 6

condns	yield (%) of compd 7	12
$C_6H_6/CH_3OH/N(Et)_3$/Pyrex/45min	33	6
$CH_3OH/N(Et)_3$/quartz/30min		22
$CH_3CN/N(Et)_3$/Pyrex/35Min	39	
$CH_3CN/N(Et)_3$/quartz/25min	20	

45 min afforded a mixture of the two regioisomers **7** and **12**. The reaction was optimized by change of solvents and of the wavelength of irradiation by using a Pyrex or quartz immersion well apparatus. Optimal conditions for obtaining **7** included using acetonitrile in a Pyrex reactor. Surprisingly, the regioselectivity of the cyclization was reversed by using methanol in a quartz reactor, and compound **12** was isolated in moderate yield (Scheme 4, Table 1).

In order to optimize the yields of the cyclization step, the photochemistry of the *N*-ethylated derivative **11** was investigated under the same conditions. The results were quite different: as well as obtaining the two regioisomers **13** and **14**, the two derivatives of 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*b*]indol-9-ones substituted on the 4-position **15** and **16** were isolated (Scheme 5, Table 2).

Formation of the byproducts **12**, **14**, **15**, and **16** suggests that the reaction probably proceeds through either a photoinduced electron transfer[12] (path 1 or 2) followed by the cleavage of the C−Cl bond to give the intermediate enaminones **19**−**21** or directly by homolytic

Table 2. Photoclization of Enaminone 11

condns	yield (%) of compd 13	14	15	16
$C_6H_6/CH_3OH/N(Et)_3$/Pyrex/60 min	30	19	13	6
$CH_3OH/N(Et)_3$/quartz/35min	31	27	13	
$CH_3CN/N(Et)_3$/Pyrex/45min	31	17		
$CH_3CN/N(Et)_3$/quartz/20min	42	7		

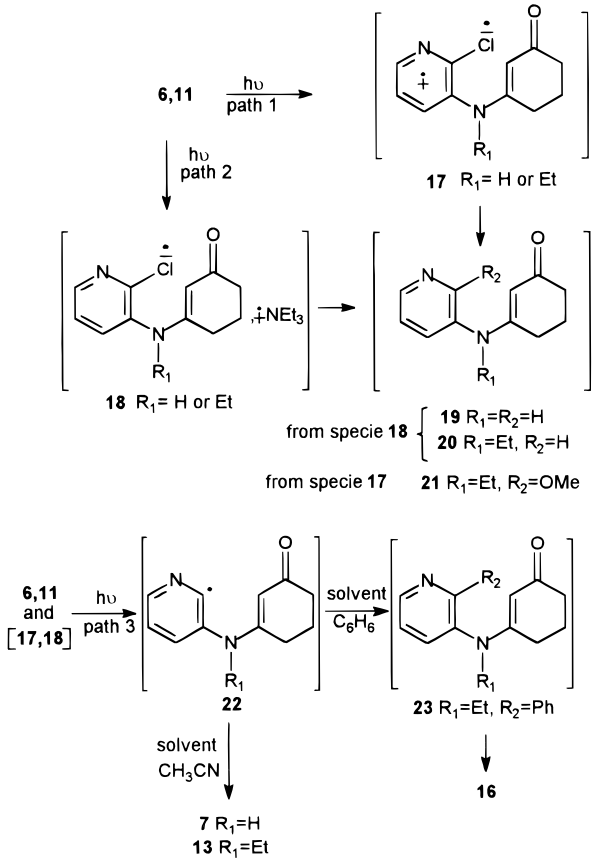
cleavage of the C−Cl bond[13] (path 3) to give the intermediate enaminone **23**, which could not be isolated (only **21** is obtained in 17% yield using MeOH as solvent in a quartz reactor). In our case, the acceptor species is the anti-bonding σ C−Cl orbital, and the electron donor species could be either the π system of the pyridine ring (path 1), leading to a zwitterionic biradical, or the lone pair/nonbonding orbital of the triethylamine giving a radical anion (path 2).[14] Formation of **19** and **20** could be obtained from the radical anion species **18** with assistance of a hydrogen-donating species (triethylamine),[15] further dehydrogenative photocyclization by a six-center mechanism[16] on the C-9 or C-13 position would give **7**, **12**, **13**, and **14**. Regarding the enaminone **21** and the pyridoindole **15**, the substitution by a methoxy group implicates the formation of the zwitterionic biradical **17**, which can then react with a nucleophilic solvent such as methanol.[17] For compound **16**, its synthesis probably results from the reaction of a phenyl radical formed by irradiation of the solvent with the radical species **22** to give the enaminone **23**, which can then form **16**. Furthermore, from this hypothesis, change of solvent could greatly influence the path of the reaction by elimination of side reactions. This is well supported by using acetonitrile, which is non-nucleophilic and does not give any radical species. In this case, the reaction gives the preferential formation of **7** and **13**, with total regioselectivity concerning the secondary enaminone **6** (Scheme 6).

Finally, two mechanisms can be postulated for these cyclizations: (1) homolytic cleavage of the C−Cl bond leading to the regioselective formation of **7** and **13**, when the reaction is carried out in an appropriate solvent, and (2) a photoinduced electron transfer and *via* the dehalogenated enaminones leading to the loss of regioselectivity and yielding the byproducts **12** and **14**−**16**.

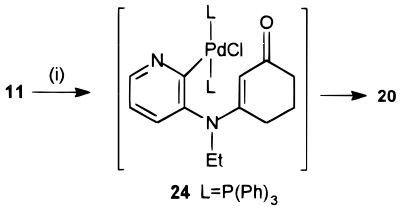
Palladium-Catalyzed Cyclization. The synthesis of heterocycles using Pd(0) and bromo derivatives[18] or iodo derivatives[19] has been extensively studied, but the reactivity of chloro derivatives has been poorly investigated.[10] The reaction proceeds *via* an arylpalladium σ-complex formed by oxidative addition of the aryl halide on palladium(0). This mechanism, related to palladium-

(12) Grounwater, W. P.; Hughes, D.; Hursthouse, B. M.; Lewis, R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 669.
(13) Iida, H.; Yuasa, Y.; Kibayashi, *J. Org. Chem.* **1979**, *44*, 1236.
(14) Fox, A. M. *Adv. Photochem.* **1986**, *13*, 237.
(15) Beecroft, R. A.; Davidson, R. R.; Goodwin, D. *Tetrahedron Lett.* **1983**, *24*, 5673.
(16) Baron, U.; Bartelt, G.; Eychmüller, A.; Grellmann, K. H.; Schmidt, U.; Tauer, E.; Weller, H. *J. Photochem.* **1985**, *28*, 187. Grellmann, K. H.; Sherman, G. M.; Linschitz, H. *J. Am. Chem. Soc.* **1963**, *85*, 1181.
(17) Ishibe, N.; Yutaka, S.; Masui, J.; Ishida, Y. *J. Chem. Soc., Chem. Commun.* **1975**, 241. Ullrich, J. W.; Chiu, F.-T.; Tiner-Harding, T.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 220. Heijer, J. D. H.; Shadid, O. B.; Cornelisse, J.; Havinga, E. *Tetrahedron* **1977**, *33*, 779. Carrona, T.; Marrochi, S.; Vittimberga, B. M. *J. Heterocycl. Chem.* **1980**, *17*, 399.
(18) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938.
(19) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297.

Scheme 6



Scheme 7[a]



[a] Key: (i) $Pd(OAc)_2/P(Ph)_3/DMF/NaHCO_3$/reflux.

catalyzed aromatic substitution (the Heck reaction[20]), should induce complete regioselectivity for the cyclization of compounds **6** and **11**. We first investigated the way that consists of generating the palldium(0) species *in situ* from palladium acetate and triphenylphosphine in refluxing dimethylformamide. Under these conditions, compound **6** did not react. In the case of the *N*-ethylated derivative **11** the arylpalladium σ-complex is formed, but the cyclization did not occur, and the intermediate **24** leads to the dehalogenated enaminone **20** (Scheme 7).

An alternative route to the catalytic cyclization of **6** and **11** was to use a preformed species of palladium(0). The available tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) was employed in hexamethylphosphoric triamide (HMPA) in the presence of sodium hydrogencarbonate at 140 °C.[21] Under these conditions, the two enaminones **6** and **11** cyclized to give the corresponding 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*a*]indol-9-ones **7** and **13** in 39% and 42% yield, respectively. The reaction occurred without the formation of byproducts.

In conclusion, we have described two convenient methods for the synthesis of 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*a*]indol-9-ones from halogeno enaminones. The advantage of the photochemical approach is the control of the regioselectivity of the photocyclization toward the C-2 or C-4 position of the pyridine ring by changing the solvent and the wavelength of irradiation. The second way, using palladium(0) reagents, is the first example of the use of these reagents with chloro enaminones. Further work on related systems is under way.

Experimental Section[22]

3-[(2-Chloro-3-pyridinyl)amino]cyclohex-2-en-1-one (6). A solution of 3-amino-2-chloropyridine (**9**) (5 g, 38.9 mmol), 1,3-cyclohexadione (**10**) (5.66 g, 50.5 mmol), and *p*-toluenesulfonic acid monohydrate (70 mg, 0.39 mmol) in 265 mL of anhydrous toluene was refluxed in a Dean−Stark apparatus for 3 h. After cooling, the solution was basified and extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *in vacuo*. This compound, obtained in 99% yield, was used without further purification. An analytical sample was obtained by recrystallization from ethanol: mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.03 (m, 2 H), 2.32 (t, 2 H, J = 5.6 Hz), 2.52 (t, 2 H, J = 5.8 Hz), 5.44 (s, 1 H), 6.61 (br s, 1 H), 7.19 (dd, 1 H, J = 7.8, 4.5 Hz), 7.68 (dd, 1 H, J = 7.8, 1.7 Hz), 8.10 (dd, 1 H, J = 4.5, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 21.4, 28.8, 36.2, 100.0, 122.8, 132.3, 134.7, 145.8, 162.5, 198.4. Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.98. Found: C, 59.42; H, 4.91; N, 12.75.

3-[(2-Chloro-3-pyridinyl)ethylamino]cyclohex-2-en-1-one (11). Compound **6** (3.5 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 h and cooled to room temperature. Ethyl iodide (15 mL, 188 mmol) was then slowly added and the mixture was refluxed for 7 h. 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 **11** as a yellow oil: 60% yield; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.00 (t, 3 H, J = 7.2 Hz), 1.68−2.23 (m, 6 H), 3.42 (br s, 2 H), 5.09 (s, 1 H), 7.23 (dd, 1 H, J = 7.7, 4.6 Hz), 7.48 (dd, 1 H, J = 7.7, 1.9 Hz), 8.24 (dd, 1 H, J = 4.6, 1.9 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 11.8, 21.5, 27.0, 35.4, 45.8, 100.1, 123.1, 136.7, 139.1, 148.2, 150.0, 163.0. Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.43; H, 6.11; N, 11.04.

Photocyclization of Enaminone 6. General Method. A solution of enaminone **6** (250 mg, 1.12 mmol) in the appropriate solvent (150 mL) was irradiated with an immersion well apparatus under nitrogen for the time indicated in Table 1. The solvents were then evaporated under reduced pressure. All compounds were purified by flash chromatography on silica gel eluted using a $CHCl_3$/MeOH mixture as eluent (93/7, then 90/10).

6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*b*]indol-9-one (7): mp 272−274 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (m, 2 H), 2.45 (t, 2 H, J = 6.2 Hz), 2.95 (t, 2 H, J = 6.1 Hz), 3.80 (br s, 1 H), 7.02 (dd, 1 H, J = 4.8, 8.2 Hz), 7.63 (dd, 1 H, J = 8.2, 1.2 Hz), 8.33 (dd, 1 H, J = 4.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 23.3, 37.9, 111.4, 117.5, 119.4, 129.7, 142.7, 143.9, 155.4, 195.1. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.94; H, 5.42; N, 15.05. Found: C, 70.79; H, 5.61; N, 14.89

6,7,8,9-Tetrahydro-5*H*-pyrido[3,4-*b*]indol-9-one (12): mp >260 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (m, 2 H), 2.50 (t, 2 H, J = 5.1 Hz), 2.96 (t, 2 H, J = 5.5 Hz), 4.15 (br s, 1 H), 7.96 (d, 1 H, J = 4.5 Hz), 8.18 (d, 1 H, J = 5.4 Hz), 8.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.37 (2 carbons), 37.9, 112.5, 115.9, 130.6, 133.1, 133.5, 140.4, 155.7, 194.8. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.94; H, 5.42; N, 15.05. Found: C, 70.81; H, 5.51; N, 14.97.

Photocyclization of Enaminone 11. General Method. A solution of enaminone **11** (250 mg, 1.0 mmol) in the appropriate

(20) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949.

(21) Chen, L.-C.; Yang, S.-C.; Wang, H.-M. *Synthesis* **1995**, *4*, 385.

(22) For general experimental details see ref 6.

solvent (150 mL) was irradiated for the time indicated in Table 2. The solvents were then evaporated under reduced pressure. All compounds were purified by flash chromatography on silica gel using a CH_2Cl_2/MeOH mixture as eluent (95/5).

5-Ethyl-6,7,8,9-tetrahydropyrido[3,2-*b*]indol-9-one (13): brown paste; MS *m*/*z* (rel intensity) 214 (68), 186 (63), 158 (100), 157 (29); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3 H, J = 7.3 Hz), 2.20 (m, 2 H), 2.50 (t, 2 H, J = 7.5 Hz), 2.95 (t, 2 H, J = 5.6 Hz), 4.10 (q, 2 H, J = 7.3 Hz), 7.10 (dd, 1 H, J = 8.3, 4.8 Hz), 7.56 (dd, 1 H, J = 8.3, 1.4 Hz), 8.56 (dd, 1 H, J = 8.3, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 21.9, 22.7, 37.9, 38.3, 111.9, 116.4, 117.1, 129.2, 143.0, 145.1, 153.4, 192.5. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08. Found: C, 72.52; H, 6.62; N, 12.89.

5-Ethyl-6,7,8,9-tetrahydropyrido[4,3-*b*]indol-9-one (14): mp 149−151 °C; MS *m*/*z* (rel intensity) 214 (57), 186 (82), 158 (100), 157 (18), 83 (95); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (t, 3 H, J = 7.0 Hz), 2.25 (m, 2 H), 2.56 (t, 2 H, J = 5.0 Hz), 2.95 (t, 2 H, J = 5.7 Hz), 4.20 (q, 2 H, J = 7.0 Hz), 8.05 (d, 1 H, J = 5.3 Hz), 8.37 (d, 1 H, J = 5.3 Hz), 8.69 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 21.8, 22.8, 37.6, 38.7, 112.0, 115.6, 130.0, 132.0, 133.0, 141.6, 153.6, 193.5. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08. Found: C, 72.92; H, 6.42; N, 13.01.

5-Ethyl-4-methoxy-6,7,8,9-tetrahydropyrido[4,3-*b*]indol-9-one (15): mp 174−176 °C; MS *m*/*z* (rel intensity) 244 (100), 229 (41), 215 (34), 188 (45), 187 (38), 158 (34); ^{1}H NMR ($CDCl_3$,, 400 MHz) δ 1.36 (t, 3 H, J = 7.5 Hz), 2.22 (m, 2 H), 2.55 (t, 2 H, J = 5.6 Hz), 2.92 (t, 2 H, J = 5.0 Hz), 4.06 (s, 3 H), 4.36 (q, 2 H, J = 7.5 Hz), 7.71 (d, 1 H, J = 5.4 Hz), 7.86 (d, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 21.9, 23.1, 37.8, 41.1, 53.1, 110.7, 112.9, 120.8, 132.3, 138.2, 151.0, 152.0, 193.7. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 68.82; H, 6.61; N, 11.47. Found: C, 68.98; H, 6.42; N, 11.23.

5-Ethyl-4-phenyl-6,7,8,9-tetrahydropyrido[4,3-*b*]indol-9-one (16): yellow oil; MS *m*/*z* (rel intensity) 290 (100), 275 (39), 262 (27), 235 (25), 213 (8); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.9 (t, 3 H, J = 7.0 Hz), 2.30 (m, 2 H), 2.65 (t, 2 H, J = 6 Hz), 2.95 (t, 2 H, J = 5.5 Hz), 3.85 (q, 2 H, J = 7.0 Hz), 7.47−7.55 (m, 5 H), 8.20 (d, 1 H, J = 5.0 Hz), 8.46 (d, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_{CH} 15.4, 22.7, 23.1, 37.9, 40.0, 115.1, 128.3, 128.7, 129.1, 141.2. Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.51; H, 6.43; N, 9.44.

3-[(2-Methoxy-3-pyridinyl)ethylamino]cyclohex-2-en-1-one (21): brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, 3 H, J = 7.5 Hz), 1.80−2.10 (m, 4 H), 2.20 (t, 2 H, J = 5.5 Hz), 3.41 (br s, 2 H), 3.85 (s, 3 H), 5.25 (br s, 2 H), 6.84 (dd, 1 H, J = 7.4, 4.9 Hz), 7.27 (dd, 1 H, J = 7.4, 1.8 Hz), 8.05 (dd, 1 H, J = 4.9, 1.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_{CH} 13.0, 22.2, 27.7, 38.0, 99.9, 117.0, 138.3, 146.3. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.25; H, 7.37; N, 11.38. Found: C, 68.11, H, 7.43; N, 11.34.

Palladium-Catalyzed Cyclization: Method A. 3-[(3-Pyridinyl)ethylamino]cyclohex-2-en-1-one (20). To a stirred solution of palladium acetate (6 mg, 0.03 mmol), triphenylphosphine (15 mg, 0.06 mmol), and sodium hydrogencarbonate (235 mg, 2.79 mmol) in dry dimethylformamide (21 mL) was added 350 mg (1.4 mmol) of **11** under nitrogen. The resulting mixture was refluxed for 15 h 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 **20** as a brown oil (23%): ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.12 (t, 3 H, J = 7.1 Hz), 1.66−2.36 (m, 6 H), 3.58 (q, 2 H, J = 7.1 Hz), 5.26, (s, 1 H), 7.40 (m, 2 H), 8.36 (d, 1 H, J = 1.6 Hz), 8.51 (dd, 1 H, J = 4.4 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 11.9, 22.5, 28.4, 35.8, 47.5, 101.0, 124.1, 135.5, 140.1, 148.5, 149.4, 163.5, 197.5. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.18; H, 7.56; N, 12.96. Found: C, 71.96; H, 7.23; N, 12.78.

Palladium-Catalyzed Cyclization: Method B. To a stirred solution of freshly prepared palladium tetrakis(triphenylphosphine) (3 mg, 0.02 mmol) and sodium hydrogencarbonate (210 mg, 2.45 mmol) in freshly distilled hexamethylphosphoramide (HMPA, 13 mL) was added the required chloro enaminone (1.27 mmol) under nitrogen. The mixture was heated at 140 °C for 3 h and then diluted in water. The resulting solution was extracted with dichloromethane. The organic layers were dried over sodium sulfate and concentrated under reduced pressure.

Compound **7** was obtained from enaminone **6** (282 mg, 1.27 mmol); purification by flash chromatography on silica gel using a ether/methanol mixture as eluent (85/15) gave 92 mg (39%) of **7**, which was identical (^{1}H and ^{13}C NMR data) to the sample obtained by irradiaion of **6**.

Compound **13** was obtained from enaminone **11** (317 mg, 1.27 mmol) and purified by chromatography on silica gel using a dichloromethane/methanol mixture as eluent (85/15); 42%. This compound was identical (^{1}H and ^{13}C NMR data) to the sample obtained by irradiation of **11**.

JO970637+