Palladium-Catalyzed Synthesis of 1,2,3,4-Tetrahydro-4-oxo-β-carbolines

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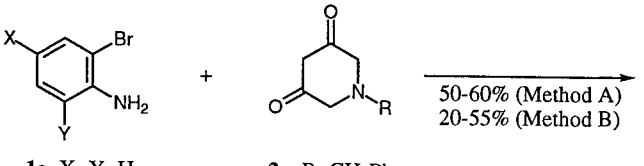
The synthesis of 1,2,3,4-tetrahydro-4-oxo-β-carbolines from bromoenaminones derived from 1-substituted piperidine-3,5-dione is described. The reaction proceeds by the intramolecular cyclization of bromoenaminones involving arylpalladium complexes.

Organometallic reagents are currently used in the synthesis of various heterocyclic ring systems;[1] hence palladium catalysis is extensively studied, and many promising new developments in palladium-catalyzed organic synthesis are in the field of carbon–carbon bond formation.[2,3] In the catalytic arylation of olefins via arylpalladium σ-complexes, most olefins employed were limited to simple or typical ones including styrenes, allyl alcohols, and acrylic acid derivatives,[4] and most reactions have been carried out in an intermolecular manner.[5,6]

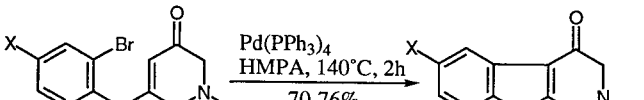
We have been interested in the utilization of enaminones, the character of which is significantly different from those of both enamines and ketones with respect to physical properties and chemical behavior. The enaminone system, $N_c-C_e=C_b-C_d=O_a$ is tridentate (site a, b, and c) toward electrophiles and bidentate (site d and e) toward nucleophiles and thus opens the possibility of a wide variety of reactions which are interesting and sometimes complicated. Despite the abundant literature[7] on alkylation and acylation at these reaction sites, there have been only few reports of arylation, although such a process would be potentially useful.[8] We report here a method of utilization of arylpalladium intermediate-catalyzed intramolecular cyclization of bromoenaminones **3** to prepare 1,2,3,4-tetrahydro-4-oxo-β-carbolines **4**.

The required bromoenaminones **3** were prepared based on the previously reported method.[9] Thus, 1-benzylpiperidine-3,5-dione **(2a)** was reacted as its trifluoroacetate[10] with dimethyl sulfide/*N*-chlorosuccinimide (DMS/NCS) complex followed by treatment with bromoanilines **1a–c** (method A) to give the corresponding bromoenaminones **3a–c**. In the case of 1-ethoxycarbonylpiperidine-3,5-dione **(2b)**,[11] both method A and the direct reaction with bromoanilines **1a–c** in refluxing methanol (method B) gave moderate yields of the corresponding bromoenaminones **3d–f** (Table 1).



1a X=Y=H
b X=Me, Y=H
c X=Y=Me

2a R=CH_2Ph
b R=CO_2Et



3a-f **4a-f**

3, 4	X	Y	R
a	H	H	CH_2Ph
b	Me	H	CH_2Ph
c	Me	Me	CH_2Ph
d	H	H	CO_2Et
e	Me	H	CO_2Et
f	Me	Me	CO_2Et

Table 1. Bromoenaminones **3** Prepared

Product[a]	Yield[b] (%)		mp (°C)	IR ($CHCl_3$) ν [cm^{-1}]	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
	Method A	Method B			
3a	55	20	108–109	3410, 1615, 1585	3.22 (s, 2H, NCH_2), 3.40 (s, 2H, NCH_2), 3.73 (s, 2H, NCH_2Ph), 5.59 (s, 1H, CH=), 6.12 (br s, 1H, NH), 7.02–7.75 (m, 9H, ArH)
3b	52	24	92–93	3405, 1615, 1585	2.33 (s, 3H, $ArCH_3$), 3.23 (s, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 3.73 (s, 2H, NCH_2Ph), 5.53 (s, 1H, CH=), 5.90 (br s, 1H, NH), 7.07–7.75 (m, 8H, ArH)
3c	50	22	136–137	3400, 1610, 1585	2.22 (s, 3H, $ArCH_3$), 2.30 (s, 3H, $ArCH_3$), 3.23 (s, 2H, NCH_2), 3.39 (s, 2H, NCH_2), 3.74 (s, 2H, NCH_2Ph), 4.81 (s, 1H, CH=), 5.65 (s, 1H, NH), 7.00 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.36 (s, 5H, Ph)
3d	52	50	132–133	3410, 1690, 1615, 1580	1.27 (t, 3H, $J=7$, OCH_2CH_3), 4.12 (s, 2H, NCH_2), 4.18 (q, 2H, $J=7$, OCH_2CH_3), 4.49 (s, 2H, NCH_2), 5.53 (s, 1H, CH=), 6.70 (br s, 1H, NH), 7.05–7.68 (m, 4H, ArH)
3e	60	55	50–51	3410, 1690, 1620, 1600	1.26 (t, 3H, $J=7$, OCH_2CH_3), 2.34 (s, 3H, $ArCH_3$), 4.11 (s, 2H, NCH_2), 4.21 (q, 2H, $J=7$, OCH_2CH_3), 4.42 (s, 2H, NCH_2), 5.53 (s, 1H, CH=), 6.05 (br s, 1H, NH), 7.00–7.50 (m, 3H, ArH)
3f	57	53	173–174	3410, 1690, 1615, 1600	1.21 (t, 3H, $J=7$, OCH_2CH_3), 2.16 (s, 3H, $ArCH_3$), 2.29 (s, 3H, $ArCH_3$), 4.06 (s, 2H, NCH_2), 4.08 (q, 2H, $J=7$, OCH_2CH_3), 4.54 (s, 2H, NCH_2), 4.75 (s, 1H, CH=), 6.98 (s, 1H, ArH), 7.26 (s, 1H, ArH), 8.07 (s, 1H, NH)

[a] All compounds gave satisfactory microanalyses (C ± 0.17, H ± 0.18, N ± 0.15).
[b] Yield of isolated product.

Table 2. 1,2,3,4-Tetrahydro-4-oxo-β-carbolines **4** Prepared

Product[a]	Yield[b] (%)	mp (°C)	IR ($CHCl_3$) ν [cm^{-1}]	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	72	183–184[c]	3460, 1650	3.44 (s, 2H, NCH_2), 3.82 (s, 2H, NCH_2), 3.89 (s, 2H, NCH_2Ph), 7.20–8.23 (m, 9H, ArH), 8.75 (br s, 1H, NH)
4b	70	192–192	3460, 1650	2.47 (s, 3H, $ArCH_3$), 3.44 (s, 2H, NCH_2), 3.81 (s, 2H, NCH_2), 3.86 (s, 2H, NCH_2Ph), 7.09 (dd, 1H, J = 8.4, 1.2, 1H, H-7), 7.28 (d, 1H, J = 8.4, 1H, H-8), 7.34 (s, 5H, Ph), 7.99 (d, 1H, J = 1.2, 1H, H-5), 8.30 (br s, 1H, NH)
4c	74	193–194	3465, 1655	2.42 (s, 6H, 2 × $ArCH_3$), 3.41 (s, 2H, NCH_2), 3.78 (s, 2H, NCH_2), 3.84 (s, 2H, NCH_2Ph), 6.89 (s, 1H, ArH), 7.33 (s, 5H, Ph), 7.81 (s, 1H, ArH), 8.64 (br s, 1H, NH)
4d	73	211–212	3460, 1690, 1660	1.32 (t, 3H, J = 7, OCH_2CH_3), 4.24 (q, 2H, J = 7, OCH_2CH_3), 4.34 (s, 2H, NCH_2), 4.97 (s, 2H, NCH_2), 7.15–8.25 (m, 4H, ArH), 9.02 (br s, 1H, NH)
4e	75	203–204	3460, 1690, 1660	1.32 (t, 3H, J = 7, OCH_2CH_3), 2.47 (s, 3H, $ArCH_3$), 4.23 (q, 2H, J = 7, OCH_2CH_3), 4.33 (s, 2H, NCH_2), 4.94 (s, 2H, NCH_2), 7.12 (dd, 1H, J = 8.2, 1.8, 1H, H-7), 7.28 (d, 1H, J = 8.2, 1H, H-8), 8.00 (d, 1H, J = 1.8, 1H, H-5), 9.00 (br s, 1H, NH)
4f	76	248–249	3465, 1690, 1660	1.32 (t, 3H, J = 7, OCH_2CH_3), 2.43 (s, 3H, $ArCH_3$), 2.47 (s, 3H, $ArCH_3$), 4.24 (q, 2H, J = 7, OCH_2CH_3), 4.32 (s, 2H, NCH_2), 4.98 (s, 2H, NCH_2), 6.93 (s, 1H, ArH), 7.83 (s, 1H, ArH), 9.46 (br s, 1H, NH)

[a] All compounds gave satisfactory microanalyses (C ± 0.18, H ± 0.16, N ± 0.18).
[b] Yield of isolated product.
[c] Lit.[12] mp 183–184°C.

When the bromoenaminones **3a–f** were treated with 2 mol% of tetrakis[triphenylphosphine]palladium [$Pd(PPh_3)_4$] in hexamethylphosphoric triamide (HMPA) in the presence of sodium hydrogen carbonate, the direct introduction of the aryl group into the bromoenaminone system was subject to palladium-catalyzed cyclization to yield the corresponding 1,2,3,4-tetrahydro-4-oxo-β-carbolines **4a–f** in moderate yields (Table 2). The yield is higher than that found with the more expensive palladium acetate.[12]

In conclusion, we have described a convenient and useful method for the synthesis of 1,2,3,4-tetrahydro-4-oxo-β-carbolines **4**.

All melting points are uncorrected. IR absorption spectra were recorded on a Shimadzu IR-27G spectrophotometer, and ^1H NMR spectra on a Varian Gemini-200 spectrometer. Mass spectra (MS) were measured on a JEOL JMS D-300 instrument, with a direct inlet system.

Bromoenaminones 3; General Procedures:
Method A: A solution of β-diketone **2** (2 mmol) and CF_3CO_2H (228 mg, 2 mmol) in anhydr. CH_2Cl_2 (4 mL) was added to a separately prepared turbid solution of *N*-chlorosuccinimide (294 mg, 2.2 mmol) and dimethyl sulfide (0.18 mL, 2.5 mmol) in anhydr. CH_2Cl_2 (20 mL) at −20°C under N_2. To the turbid solution, bromoaniline (3 mmol) was added at −20°C. The reaction mixture was allowed to warm slowly to r.t., stirred for 3 h, neutralized with 10% aq NaOH (3 mL), and extracted with CH_2Cl_2 (4 × 10 mL). The extract was washed with H_2O (2 × 5 mL), and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was chromatographed on silica gel using $CHCl_3$/EtOAc (3:1) as an eluent to give **3**.

Method B: A solution of β-diketone **2** (1.48 mmol) and bromoaniline (2.95 mmol) in MeOH (15 mL) was refluxed for 10 h. The mixture was cooled and concentrated in vacuo, and worked up as described above in Method A to give **3**.

1,2,3,4-Tetrahydro-4-oxo-β-carbolines 4; General Procedure:
A solution of bromoenaminone **3** (1 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), and $NaHCO_3$ (168 mg, 2 mmol) in HMPA (10 mL) was heated at 140°C for 2 h with stirring under N_2. The mixture was cooled, diluted with H_2O, and extracted with Et_2O (4 × 10 mL). The extract was washed with H_2O (2 × 5 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel using $CHCl_3$/EtOAc (3:1) as an eluent to give **4**.

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