COPPER(I) IODIDE-PROMOTED CYCLIZATION OF ENAMINONES. SYNTHESIS OF 1,2,3,4-TETRAHYDRO-4-OXO-β-CARBOLINES

Shyh-Chyun Yang, Huey-Min Wang, Ching-Shwu Kuo, and Ling-Ching Chen*
Graduate Institute of Pharmaceutical Sciences, Kaohsiung Medical College, 100, Shih-Chuan 1st Road, San Min Dist., Kaohsiung 80708, Taiwan, R.O.C.

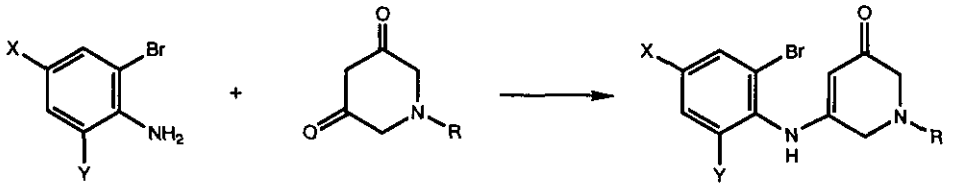
Abstract—— Anions derived from the *N*-2-bromoaryl-substituted enaminones were found to undergo smooth cyclization to give 1,2,3,4-tetrahydro-4-oxo-β-carbolines when heated with copper(I) iodide in hexamethylphosphoric triamide.

We have been interested in utilization of enaminones, the character of which is significantly different from those of both enamines and ketones,[1] as versatile synthons in the preparation of condensed heterocyclic systems. Previously, we reported a method for the direct introduction of the aryl group into the enaminone system via arylpalladium intermediates to afford 1,2,3,4-tetrahydro-4-oxo-β-carbolines in poor yields.[2] In this paper we would like to report a method for the improvement of cyclization.

It has been known for many years that copper(I) salts of heteroatom nucleophiles react with unactivated aryl halides under relatively mild conditions to give substitution.[3] In anticipation of utilizing the activating effect of cuprous ion for the cyclization of enaminones, we have found that *N*-2-bromoaryl-substituted enaminones undergo smooth cyclization to give 1,2,3,4-tetrahydro-4-oxo-β-carbolines by the aid of copper(I) iodide in hexamethylphosphoric triamide (HMPA).[4]

The required bromo enaminones were prepared by using the previously reported method.[5] Thus, 1-benzylpiperidine-3,5-dione (2a) trifluoroacetate[6] was reacted with DMS/NCS-complex followed by treatment with bromoanilines (1a, 1b, 1c) (method A) to give the corresponding bromo enaminones (3a, 3b, 3c). In the case of 1-ethoxycarbonyl-piperidine-3,5-dione (2b),[7] both method A and the direct reaction with bromoanilines (1a, 1b, 1c) in refluxing MeOH (method B) gave moderate yields of the corresponding

bromo enaminones (3d, 3e, 3f).

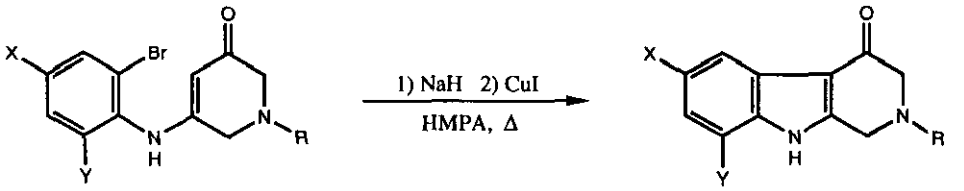


1a, X=Y=H
b, X=Me, Y=H
c, X=Y=Me

2a, R=CH_2Ph
b, R=CO_2Et

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

When the bromo enaminones (3a-f) treated with sodium hydride in HMPA, followed by heating in the presence of 2.0 equ. of copper(I) iodide at 120°C under nitrogen for 2 h, the cyclization occurred to give the 1,2,3,4-tetrahydro-4-oxo-β-carbolines (4a-f) in moderate yields (Table I). The yield is higher than that found with the more expensive palladium acetate.[2]



3a-f

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

In conclusion, this paper has described a convenient and useful method for the synthesis of 1,2,3,4-tetrahydro-4-oxo-β-carbolines.

Table I. 1,2,3,4-Tetrahydro-4-oxo-β-carbolines (4)

Product 4	Yield [%]	mp[a] [°C]	Ir[b] ν[cm^{-1}]	^{1}H-nmr[c] δ[ppm], J[Hz]
4a	60	183-184[2]	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	62	191-192	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, J=8.4, 1.2 Hz, 1H, H-7), 7.28 (d, J=8.4 Hz, 1H, H-8), 7.34 (s, 5H, Ph), 7.99 (d, J=1.2 Hz, 1H, H-5), 8.30 (br s, 1H, NH)
4c	64	193-194	3465, 1655	2.42 (s, 6H, $ArCH_3$ x 2), 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	61	211-212	3460, 1690, 1660	1.32 (t, J=7 Hz, 3H, OCH_2CH_3), 4.24 (q, J=7 Hz, 2H, 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	65	203-204	3460, 1690, 1660	1.32 (t, J=7 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, $ArCH_3$), 4.23 (q, J=7 Hz, 2H, OCH_2CH_3), 4.33 (s, 2H, NCH_2), 4.94 (s, 2H, NCH_2), 7.12 (dd, J=8.2, 1.8 Hz, 1H, H-7), 7.28 (d, J=8.2 Hz, 1H, H-8), 8.00 (d, J=1.8 Hz, 1H, H-5), 9.00 (br s, 1H, NH)
4f	67	248-249	3465, 1690, 1660	1.32 (t, J=7 Hz, 3H, OCH_2CH_3), 2.43 (s, 3H, $ArCH_3$), 2.47 (s, 3H, $ArCH_3$), 4.24 (q, J=7 Hz, 2H, 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) Uncorrected.
b) Measured in $CHCl_3$.
c) Measured in $CDCl_3$.

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EXPERIMENTAL

All melting points are uncorrected. The ir absorption spectra were recorded on a Shimadzu IR-27G spectrophotometer, and ^{1}H-nmr spectra on a Varian Gemini-200 spectrometer. Ms were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Chemical shifts were measured in ppm (δ) with respect to TMS.

1-Benzyl-3-(*o*-bromoanilino)-3,4-dehydro-5-oxopiperidine (3a): Method A— A solution of 2a (406 mg, 2 mmol) and trifluoroacetic acid (228 mg, 2 mmol) in dry methylene chloride (4 ml) was added to a separately prepared cloudy solution of *N*-chlorosuccinimide (294 mg, 2.2 mmol) and dimethyl sulphide (0.18 ml, 2.5 mmol) in dry methylene chloride (20 ml) at -20°C under argon. To the cloudy solution, *o*-bromoaniline (516 mg, 3 mmol) was added at -20°C. The reaction mixture was allowed to warm slowly to room temperature, stirred for 3 h, neutralized with 10% aqueous sodium hydroxide (3 ml), and extracted with methylene chloride (10 ml x 4). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulphate, and concentrated in vacuo to give a solid which was purified by column chromatography on silica gel with chloroform-ethyl acetate (3:1) as an eluting solvent to give 392 mg (55%) of 3a, mp 108-109°C (from ethyl acetate). Ir ($CHCl_3$) ν 3410, 1615, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 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); m/z 357 (M^+), Anal. Calcd for $C_{18}H_{17}N_2OBr$: C, 60.51; H, 4.80; N, 7.84. Found: C, 60.42; H, 4.98; N, 7.73.
Method B— A mixture of 2a (300 mg, 1.48 mmol) and *o*-bromoaniline (508 mg, 2.95 mmol) in methanol (15 ml) was refluxed for 10 h and the mixture was concentrated in vacuo to give a solid which was purified by column chromatography as above to give 106 mg (20%) of 3a.

1-Benzyl-3-(2-bromo-4-methylanilino)-3,4-dehydro-5-oxopiperidine (3b): As described for 3a by method A, reaction of 2a (406 mg, 2 mmol) with 2-bromo-4-methyaniline (558 mg, 3 mmol) in the presence of trifluoroacetic acid (228 mg, 2 mmol) gave a solid,

which was purified by column chromatography on silica gel with ethyl acetate as an eluting solvent to give 386 mg (52%) of 3b, mp 92-93°C (from chloroform-benzene). Ir ($CHCl_3$) ν 3405, 1615, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 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); m/z 371 (M^+), Anal. Calcd for $C_{19}H_{19}N_2OBr$: C, 61.46; H, 5.16; N, 7.55. Found: C, 61.32; H, 5.28; N, 7.69.

1-Benzyl-3-(2-bromo-4,6-dimethylanilino)-3,4-dehydro-5-oxopiperidine (3c): Reaction of 2a (406 mg, 2 mmol) with 2-bromo-4,6-dimethylaniline (600 mg, 3 mmol) in the presence of trifluoroacetic acid (228 mg, 2 mmol) as described for 3a gave a solid, which was recrystallized from ethyl acetate to give 385 mg (50%) of 3c, mp 136-137°C. Ir ($CHCl_3$) ν 3400, 1610, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 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); m/z 385 (M^+), Anal. Calcd for $C_{20}H_{21}N_2OBr$: C, 62.34; H, 5.49; N, 7.27. Found: C, 62.48; H, 5.31; N, 7.39.

3-(o-Bromoanilino)-1-ethoxycarbonyl-3,4-dehydro-5-oxopiperidine (3d): Method A— Reaction of 2b (370 mg, 2 mmol) with *o*-bromoaniline (516 mg, 3 mmol) in the absence of trifluoroacetic acid gave 352 mg (52%) of 3d, mp 132-133°C (from benzene). Ir ($CHCl_3$) ν 3410, 1690, 1615, 1580 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 1.27 (t, *J*=7 Hz, 3H, OCH_2CH_3), 4.12 (s, 2H, NCH_2), 4.18 (q, *J*=7 Hz, 2H, 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); m/z 339 (M^+), Anal. Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.65; H, 4.59; N, 8.12.
Method B— A mixture of 2b (300 mg, 1.62 mmol) and *o*-bromoaniline (557 mg, 3.24 mmol) was refluxed for 10 h and the mixture was concentrated in vacuo to give a solid which was purified by column chromatography on silica gel with chloroform-ethyl acetate (3:1) as an eluting solvent to give 275 mg (50%) of 3d.

3-(2-Bromo-4-methylanilino)-1-ethoxycarbonyl-3,4-dehydro-5-oxopiperidine (3e): As described for 3d by method B, reaction of 2b (300 mg, 1.62 mmol) with 2-bromo-4-methylaniline (603 mg, 3.24 mmol) in methanol (15 ml) as described for 3c gave a solid, which was recrystallized from ethyl acetate to give 315 mg (55%) of 3e, mp 50-51°C. Ir ($CHCl_3$) ν 3410, 1690, 1620, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 1.26 (t, *J*=7 Hz, 3H, OCH_2CH_3), 2.34 (s, 3H, $ArCH_3$), 4.11 (s, 2H, NCH_2), 4.21 (q, *J*=7 Hz, 2H, 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); m/z 353 (M^+), Anal. Calcd for $C_{15}H_{17}N_2O_3Br$: C, 51.01; H, 4.85; N, 7.93. Found: C, 51.18; H, 4.71; N, 7.81.

3-(2-Bromo-4,6-dimethylanilino)-1-ethoxycarbonyl-3,4-dehydro-5-oxopiperidine (3f): Reaction of 2b (300 mg, 1.62 mmol) with 2-bromo-4,6-dimethylaniline (648 mg, 3.24 mmol) in methanol (15 ml) as described for 3d gave a solid, which was recrystallized from ethyl acetate to give 315 mg (53%) of 3f, mp 173-174°C. Ir ($CHCl_3$) ν 3410, 1690, 1615, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$); 1.21 (t, J=7 Hz, 3H, OCH_2CH_3), 2.16 (s, 3H, $ArCH_3$), 2.29 (s, 3H, $ArCH_3$), 4.06 (s, 2H, NCH_2), 4.08 (q, J=7 Hz, 2H, 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); m/z 367 (M^+), Anal. Calcd for $C_{16}H_{19}N_2O_3Br$: C, 52.33; H, 5.22; N, 7.63. Found: C, 52.47; H, 5.10; N, 7.78.

2-Benzyl-1,2,3,4-tetrahydro-4-oxo-β-carboline (4a); Typical procedure: To a solution of 3a (357 mg, 1 mmol) in HMPA (5 ml) was added 50% sodium hydride (96 mg, 2 mmol). After being stirred for 30 min at room temperature, copper(I) iodide (380 mg, 2 mmol) was added to the above mixture, which was heated at 120°C for 2 h with stirring in a current of nitrogen. After being colled, the mixture was diluted with water and the product was extracted with ether. The extract was dried over sodium sulphate and evaporated to afford the residue, which was purified by column chromatography on silica gel with chloroform-ethyl acetate (3:1) as an eluting solvent to give 166 mg (60%) of 4a, mp 183-184°C (lit.,[2] mp 183-184°C).

2-Benzyl-1,2,3,4-tetrahydro-6-methyl-4-oxo-β-carboline (4b): This was prepared from 3b (1 mmol) in HMPA (5 ml). m/z 290 (M^+), Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.41; H, 6.38; N, 9.79.

2-Benzyl-1,2,3,4-tetrahydro-6,8-dimethyl-4-oxo-β-carboline (4c): This was prepared from 3c (1 mmol) in HMPA (5 ml). m/z 304 (M^+), Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.76: H, 6.78; N, 9.38.

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-4-oxo-β-carboline (4d): This was prepared from 3d (1 mmol) in HMPA (5 ml). m/z 258 (M^+), Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.29; H, 5.41; N, 10.79.

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-4-oxo-β-carboline (4e): This was prepared from 3e (1 mmol) in HMPA (5 ml). m/z 272 (M^+), Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.25; H, 5.81; N, 10.35.

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-6,8-dimethyl-4-oxo-β-carboline (4f): This was prepared from 3f (1 mmol) in HMPA (5 ml). m/z 286 (M^+), Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.28; H, 6.27; N, 9.61.

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