INTRAMOLECULAR CYCLIZATION OF ENAMINONES INVOLVING ARYLPALLADIUM COMPLEXES. SYNTHESIS OF 4-OXO-1,2,3,4-TETRAHYDRO-β-CARBOLINES

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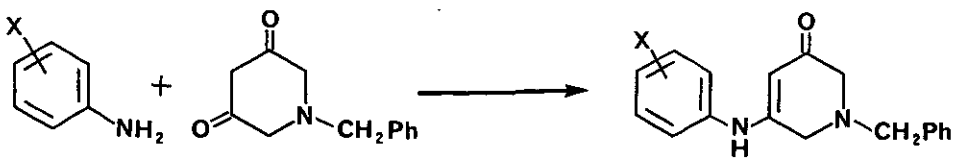
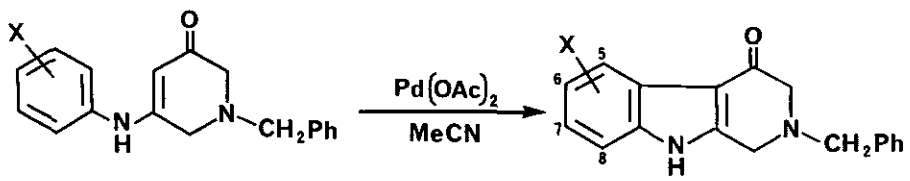
Abstract——The synthesis of 4-oxo-1,2,3,4-tetrahydro-β-carbolines from enaminones derived from 1-benzylpiperidine-3,5-dinoe is described. The reaction proceeds by the intramolecular cyclization of enaminones involving arylpalladium complexes.

Enaminones are of current interest[1] because of their unique characteristics different from those of both enamines and ketones with respect to physical properties and chemical behavior. The enaminone system, N-C=C-C=O, consists of three conjugated functional groups, i.e., amino, double bond, and carbonyl, and thus possesses five reaction sites. Despite the rather abundant literature[2] on alkylation and acylation at this sites, there appear to have been remarkably few reports of arylation, although such a process would be potentially useful.[3] We would like to report a method for the direct introduction of the aryl group into the enaminone system to prepare 4-oxo-1,2,3,4-tetrahydro-β-carbolines.
The enaminones were prepared by condensation of anilines with the known 1-benzylpiperidine-3,5-dione.[4]



1a, X= H
b, X= *o*-OMe
c, X= *p*-OMe
d, X= *m*-OMe

The direct introduction of the aryl group into the enaminone system with a stoichiometric amount of palladium salt was investigated. When the enaminones (1a, 1b, 1c) reacted with equimolar amount of palladium(II) acetate in refluxing acetonitrile, the cyclization occurred to give the corresponding β-carbolines 2a, 2b, and 2c in 25%, 21%, and 23% yields, respectively.



1a-d

2a, X= H
b, X= 8-OMe
c, X= 6-OMe
d, X= 5-OMe
e, X= 7-OMe

The methoxy substituent shows significant influences in this cyclization reaction. The *m*-methoxy substituted substrate (1d) afforded significantly higher total yield (64%) of cyclized products compared with *o*- or *p*-methoxy substituted substrate, 1b or 1c. In the case of aromatic substitution of simple olefins with palladium(II) salts, it has been suggested that the reaction involves electrophilic palladation[5] and the direction of the palladation is thus affected by substituents shch as OMe or NO_2 on the benzene ring, as observed in other electrophilic substitution reaction.[6] On this basis, the position of the methoxy group may be accounted for electrophilic aromatic substitution by palladium(II). Thus in the substrate with ortho-para directing OMe group at the meta position, the positions where electrophilic palladation occurs with a preference for ortho and para to the methoxy group are consistent with the cyclization sites: it means that the substrate can be caused to undergo the subsequent cyclization more readily than substrates with methoxy substitution at other positions.

Finally, the mechanism of this stoichiometric cyclization appears to be closely related to the Heck arylation reaction.[7] It involves the direct electrophilic palladation of the aromatic ring to generate the arylpalladium acetate to which the vinyl group in the enaminone system presumably coordinates in an intramolecular manner. The reactive intermediate thus produced can be subsequently incorporated into a sequence similar to that of olefinic arylation[8] to give the 4-oxo-1,2,3,4-tetrahydro-β-carboline.

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EXPERIMENTAL

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

1-Benzyl-3-anilino-5-oxo-3,4-dehydropiperidine (1a): A mixture of the aniline (926 mg, 9.94 mmol) and 1-benzylpiperidine-3,5-dione (2 g, 9.84 mmol) was heated at 100°C for 30 min. The reaction mixture was allowed to cool to room temperature, and the solidified product was crushed and washed with acetone. Recrystallization from methanol gave 1.80 g (65%) of 1a, mp 160-162°C (lit.[9] mp 160-162°C).

1-Benzyl-3-(*o*-methoxyanilino)-5-oxo-3,4-dehydropiperidine (1b): Reaction of *o*-methoxyaniline (1.22 g, 9.94 mmol) with 1-benzylpiperidine-3,5-dione (2 g, 9.84 mmol) as described for 1a gave a solid, which was recrystallized from ethyl acetate to give 1.35 g (67%) of 1b, mp 114-115°C. Ir ($CHCl_3$) ν 3425, 1615, 1590 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.17 (s, 2H, NCH_2), 3.36 (s, 2H, NCH_2), 3.68 (s, 2H, NCH_2Ph), 3.80 (s, 3H, OMe), 5.74 (s, 1H, CH=), 6.80-7.50 (m, 9H, ArH); m/z 308 (M^+), Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.05; H, 6.55; N, 9.05.

1-Benzyl-3-(*p*-methoxyanilino)-5-oxo-3,4-dehydropiperidine (1c): *As described for* 1a, reaction of *p*-methoxyaniline (1.22 g, 9.94 mmol) and 1-benzylpiperidine-3,5-dione (2 g, 9.84 mmol) yielded 1.25 g (63%) of 1c, mp 163.5-164.5°C (from ethyl acetate). Ir ($CHCl_3$) ν 3430, 1600, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.07 (s, 2H, NCH_2), 3.31 (s, 2H, NCH_2), 3.62 (s, 2H, NCH_2Ph), 3.77 (s, 3H, OMe), 5.36 (s, 1H, CH=), 6.81 (d, *J*=8.9 Hz, 2H, ArH), 7.01 (d, *J*=8.9 Hz, 2H, ArH), 7.30 (s, 5H, Ph); m/z 308 (M^+), Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.02; H, 6.53; N, 9.07.

1-Benzyl-3-(*m*-methoxyanilino)-5-oxo-3,4-dehydropiperidine (1d): As described for 1a, reaction of *m*-methoxyaniline (1.22 g, 9.94 mmol) and 1-benzylpiperidine-3,5-dione (2 g, 9.84 mmol) yielded 1.23 g (61%) of 1d, mp 161-162°C (from chloroform-benzene). Ir ($CHCl_3$) ν 3440, 1610, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.14 (s, 2H, NCH_2), 3.32 (s, 2H, NCH_2), 3.66 (s, 2H, NCH_2Ph), 3.75 (s, 3H, OMe), 5.64 (s, 1H, CH=), 6.62-7.74 (m, 9H, ArH); m/z 308 (M^+), Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.85; H, 6.54; N, 9.05.

2-Benzyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (2a): A mixture of 1a (500 mg, 1.80 mmol) and palladium(II) acetate (403 mg, 1.80 mmol) in acetonitrile (15 ml) was refluxed for 6 h. After cooling to room temperature, the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with chloroform-ethyl acetate (3:1) as an eluting solvent to give 124 mg (25%) of 2a, mp 183-184°C. Ir ($CHCl_3$) ν 3460, 1650, 1605 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.44 (s, 2H, NCH_2), 3.82 (s, 2H, NCH_2), 3.89 (s, 2H, NCH_2Ph), 7.20-7.34 (m, 9H, ArH); m/z 276 (M^+), Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.39; H, 5.61; N, 9.87.

2-Benzyl-4-oxo-8-methoxy-1,2,3,4-tetrahydro-β-carboline (2b): As described for 2a, reaction of 1b (500 mg, 1.62 mmol) with palladium(II) acetate (364 mg, 1.62 mmol) in acetonitrile (15 ml) gave a solid, which was recrystallized from chloroform-benzene to give 104 mg (21%) of 2b, mp 190-191°C. Ir ($CHCl_3$) ν 3440, 1650, 1610 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.48 (s, 2H, NCH_2), 3.86 (s, 2H, NCH_2), 3.90 (s, 2H, NCH_2Ph), 3.95 (s, 3H, OMe), 6.73-7.79 (m, 8H, ArH); m/z 306 (M^+), Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.25; H, 6.18; N, 9.31.

2-Benzyl-4-oxo-6-methoxy-1,2,3,4-tetrahydro-β-carboline (2c): As described for 2a, reaction of 1c (500 mg, 1.62 mmol) and palladium(II) acetate (364 mg, 1.62 mmol) in acetonitrile (15 ml) yielded 114 mg (23%) of 2c, mp 174-175°C (from chloroform). Ir ($CHCl_3$) ν 3440, 1650, 1610 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.42 (s, 2H, NCH_2), 3.80 (s, 2H, NCH_2), 3.85 (s, 2H, NCH_2Ph), 3.87 (s, 3H, OMe), 6.88 (dd, J=8.8, 2.5 Hz, 1H, H-7), 7.24 (d, J=8.8 Hz, 1H, H-8), 7.34 (s, 5H, Ph), 7.65 (d, J=2.5 Hz, 1H, H-5); m/z 306 (M^+), Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.61; H, 5.82; N, 9.33.

2-Benzyl-4-oxo-5-methoxy-1,2,3,4-tetrahydro-β-carboline (2d) and 2-Benzyl-4-oxo-7-methoxy-1,2,3,4-tetrahydro-β-carboline (2e): As described for 2a, reaction of 1d (500 mg, 1.62 mmol) and palladium(II) acetate (364 mg, 1.62 mmol) in acetonitrile (15 ml) yielded 126 mg (31%) of 2d, and 134 mg (33%) of 2e. (2d): mp 220-221°C (from ethyl acetate). Ir ($CHCl_3$) ν 3420, 1650, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.36 (s, 2H, NCH_2), 3.75 (s, 5H, NCH_2, OMe), 3.79 (s, 2H, NCH_2Ph), 6.63-7.35 (m, 8H, ArH); m/z 306 (M^+), Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92: N, 9.15. Found: C, 74.23; H, 6.12; N, 9.31. (2e): mp 189-190°C (from chloroform-benzene). Ir ($CHCl_3$) ν 3440, 1645, 1605 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.37 (s, 2H, NCH_2), 3.76 (s, 2H, NCH_2), 3.79 (s, 5H, NCH_2Ph, OMe), 6.86 (dd, J=8.6, 2.0 Hz, 1H, H-6), 7.18 (d, J=2.0 Hz, H-8), 7.30 (s, 5H, Ph), 7.98 (d, J=8.6 Hz, H-5); m/z 306 (M^+), Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.31; H, 5.74; N, 9.37.

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