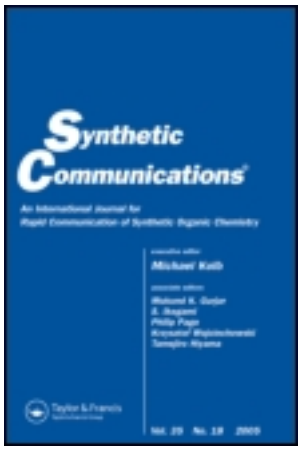

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Unexpected ipso-Substitutions at the β-Carboline Nucleus

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Unexpected *ipso*-Substitutions at the β-Carboline Nucleus

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ABSTRACT

Minisci-type radical carbamoylation of 1-bromo-β-carboline (**1**) gives the 3-substituted product in low yield, whereas 1-acetyl-β-carboline (**3a**) reacts under *ipso*-substitution of the acetyl group. Cyanations of the *N*-oxides of **1** and **3a** occur under clean *ipso*-substitution of the groups in 1-position. 1-Methyl derivatives show no tendency to react under *ipso*-substitution.

Key Words: β-Carbolines; *ipso*-Substitution; *N*-oxides; *Minisci* reaction; Cyanation.

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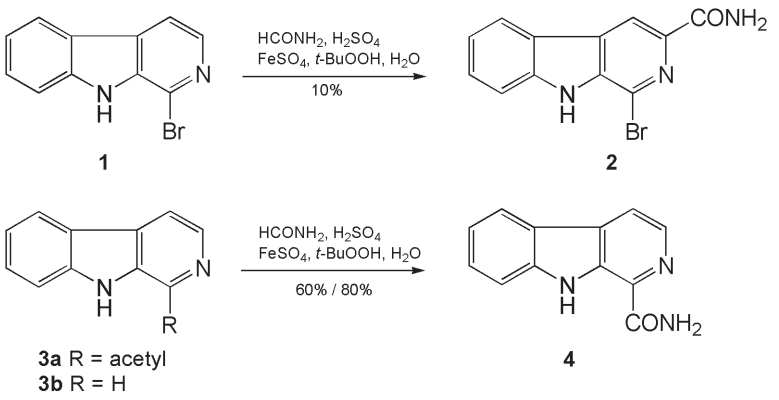
β-Carbolines represent a large group of biologically active alkaloids widespread in nature.[1] The majority of these alkaloids is substituted only in 1-position, and numerous synthetic approaches to 1-substituted β-carbolines have been published.[2] In continuation of our work on biologically active β-carboline alkaloids[3] we focussed our interest on 1,3-disubstituted β-carbolines. Compounds of this type occur in nature (e.g., the antibiotic pyridindolol[4]) and synthetic β-carbolines with electron attracting groups in 3-position have been shown to have antifilarial activity[5] and affinity to brain benzodiazepine receptors.[6]

In order to develop a general access to 1,3-disubstituted β-carbolines, we planned to start from readily available 1-bromo-β-carboline (**1**) and 1-acetyl-β-carboline (**3a**). These building blocks have reactive functional groups in 1-position, that can be converted to a large number of substituents using methods developed in our laboratories.[3] For the introduction of substituents at C-3 without prior activation of this position we wanted to take advantage from the special reactivites of the pyridine ring. Protonated pyridines can undergo ring substitution with nucleophilic radicals on ortho or para position to the ring nitrogen (*Minisci* reaction[7]). So we expected that the 1-substituted β-carbolines **1** and **3a** should give the desired 3-carbamoyl product on reaction with a radical generated from formamide. On the other hand pyridine *N*-oxides can be converted to 2-cyano derivatives with trimethylsilanecarbonitrile and diethylcarbamoyl chloride.[8] Thus, β-carbolines **1** and **3a** should give the corresponding 3-cyano derivatives.

Both the carbamoyl and the cyano groups would offer the possibility for further modification at 3-position.

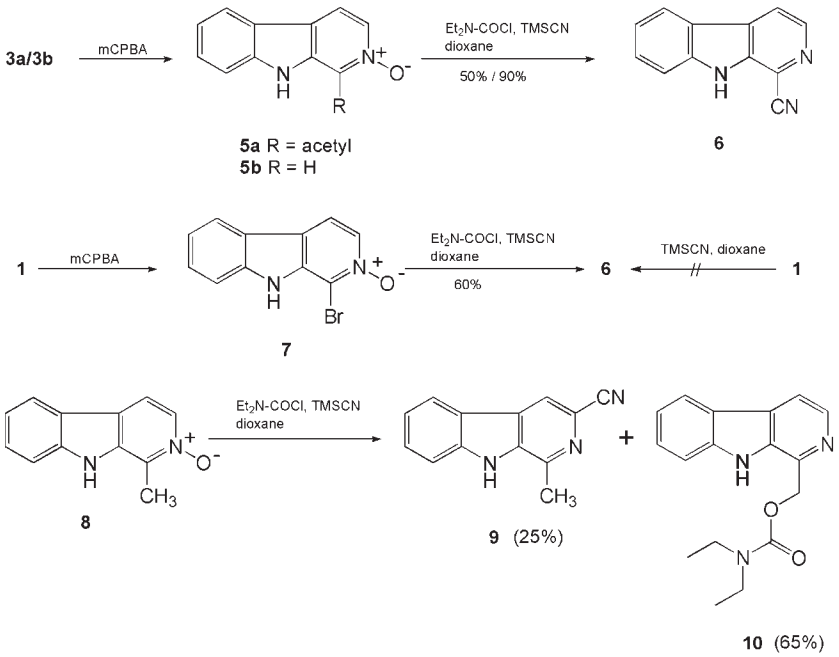


Scheme 1. Carbamoylations of 1-substituted β-carbolines under *Minisci* conditions.

In the present communication we describe unexpected results of our experiments aimed at the introduction of new substituents at C-3.

RESULTS AND DISCUSSION

Treatment of 1-bromo-β-carboline (**1**)[3e] with formamide, $FeSO_4$, and *tert*-butylhydroperoxide under standard conditions[9] gave the expected 3-carbamoyl derivative **2** in very poor yield. Large amounts of starting material were recovered. In contrast, 1-acetyl-β-carboline (**3a**)[3b,3f] did not give any 3-carbamoyl derivative. To our surprise we isolated the carboxamide **4** in 60% yield. **4** is a natural product isolated from several plants like *Nauclea diderrichii*, *Odyendea gabonensis*, *Neisosperma kilneri*, *Ailanthus altissima*, and *Ailanthus malabarica*.[10a–e] So this reaction gave a clean *ipso*-substitution of the acetyl group in 1-position. Few examples of *ipso*-substitutions of strongly electron-withdrawing substituents (mainly nitro and acyl groups) at aromatic and heteroaromatic ring systems by nuclephilic alkyl radicals have been described in literature.[11]



Scheme 2. Cyanations of 1-substituted β-carboline-*N*-oxides.

In order to explore the scope of this reaction, we also reacted harman (1-methyl-β-carboline) with formamide under the conditions used before, but there was absolutely no conversion. On the other hand, norharman (**3b**) gave the expected 1-substituted product **4** in 80% yield. This is in accordance with our former finding, that C-1 is the preferred position for substitution of β-carbolines with nucleophilic radicals.[3f]

For the ring cyanation experiments, **1** and **3a** were first converted to the corresponding *N*-oxides **7** and **5a** under standard conditions. Reactions of these *N*-oxides with trimethylsilanecarbonitrile and diethylcarbamoyl chloride[8] gave the same product, 1-cyano-β-carboline (**6**). So here again clean *ipso*-substitutions of substituents had occurred. In contrast to the experiments described above, not only the acetyl group, but also the bromo substituent was eliminated. In order to control, whether the *N*-oxide group was really involved in the replacement of bromine, we also reacted 1-bromo-β-carboline (**1**) with trimethylsilanecarbonitrile, but no conversion was observed at all.

As could be expected from these results, cyanation of norharman-*N*-oxide (**5b**)[12] gave **6** again. The yield was 90% and so our methodology represents a very short and effective approach to this important building block for alkaloid synthesis.[3d,13]

Finally, we also reacted harman-*N*-oxide (**8**)[14] with trimethylsilanecarbonitrile and diethylcarbamoyl chloride. We obtained a mixture of the 3-cyano product **9** and the carbamate **10**. Product **10** obviously results from reaction of the *N*-oxide with the carbamoyl chloride according to the Boekelheide reaction[15] without involvement of trimethylsilanecarbonitrile. In the original article[8] no substitutions at 2-methyl groups of pyridines have been described. In analogy to the radical reactions, 1-alkyl-β-carbolines show no tendency to undergo *ipso*-substitution at 1-position.

In conclusion, we have found surprising *ipso*-substitutions of 1-substitited β-carbolines and their *N*-oxides under different reaction conditions. Appropriate leaving groups (acetyl, bromine) can be substituted by carbamoyl or cyano groups. 1-Alkyl groups do not show this reactivity. In addition, the interesting building blocks **4** and **6** were obtained from norharman in unprecedented efficiency.

EXPERIMENTAL

General

Melting points were determined with Büchi B-50 apparatus. Infrared spectra were run on a Perkin Elmer IR-881 infrared spectrometer

as KBr plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Joel GSX 400 and Joel GSX 500 in DMSO-d_6 or $CDCl_3$ solution. Chemical shifts are expressed in ppm with reference to TMS as an internal standard. Mass spectra were measured on a Hewlett Packard 5989 A Mass Spectrometer. Flash chromatography was carried out using silica gel (Merck, Kieselgel 60).

General Procedure for Carbamoylation

One mmol of the β-carboline derivative is suspended at room temperature in a mixture of 5 mL formamide and 0.5 mL conc. sulfuric acid by means of ultrasound irradiation. Then a solution of $FeSO_4 \times 7\,H_2O$ (420 mg, 1.5 mmol) in 1 mL water and *tert*-BuOOH (70% solution in water; 0.205 mL, 1.5 mmol) are added simultaneously over a period of 10 min and stirring is continued for 15 min. The addition of *t*-BuOOH and $FeSO_4 \times 7\,H_2O$ can be repeated until there is no starting material left (TLC control). The reaction mixture is poured into water (100 mL) followed by neutralization with K_2CO_3 and extraction with ethyl acetate (3×50 mL). The combined organic layers are washed twice with brine (100 mL), dried with Na_2SO_4 and evaporated. The residue is purified by flash column chromatography (ethyl acetate/ hexanes 1:1).

1-Carbamoyl-β-carboline (4) from norharman (3b). Yield: 169 mg (80%); m.p. 228°C (Lit.[10d] 230°C); analytical data in accordance with Lit.[10e]

1-Carbamoyl-β-carboline (4) from 1-acetyl-β-carboline (3a). Yield: 127 mg (60%).

1-Bromo-3-carbamoyl-β-carboline (2). Yield: 20 mg (7%). M.p. 303°C. MS (*m*/*z*, %): 291 (M^+, 80), 289 (M^+,74), 248 (61), 246 (67), 182 (46), 166 (66). IR, ν (cm^{-1}): 3443, 3303, 2924, 1692, 1629, 1580, 1535, 1375, 1248, 1202, 745. ^{1}H NMR (DMSO-d_6): 12.14 (s, 1 H, N-H), 8.86 (s, 1 H, 4-H), 8.38 (d, $J = 7.9$ Hz, 1 H, 5-H), 7.91 (s, 1 H, N-H), 7.68 (d, $J = 8.0$ Hz, 1 H, 8-H), 7.62 (m, 1 H, 7-H), 7.57 (s, 1 H, N-H), 7.33 (m, 1 H, 6-H). ^{13}C NMR (DMSO-d_6): 166.1 (C=O), 141.6 (C-8a), 141.0 (C-3), 136.5 (C-9a), 130.1 (C-4a), 129.7 (C-7), 123.1 (C-5), 122.6 (C-1),122.0 (C-4b), 121.3 (C-6), 114.9 (C-4), 113.2 (C-8).

General Procedure for *N*-Oxidation

One mmol of the β-carboline derivative is dissolved in a mixture of 5 mL chloroform and 5 mL ethanol and 3 mmol (670 mg) of 3-chloroper-

oxybenzoic acid is added. The reaction mixture is refluxed for 2 h, then allowed to cool to room temperature. Three milliliters of 0.1 M NaOH are added and stirring is continued for 30 min. The organic layer is dried with Na_2SO_4 and the solvents are evaporated. The residue is purified by flash column chromatography (ethyl acetate/MeOH 95:5).

Norharman-2-oxide (5b). Yield: 156 mg (85%). M.p. 256°C (Lit.[12] 268–271°C).

Harman-2-oxide (8). Yield: 184 mg (93%). M.p. 237°C (Lit.[14] 182–184°C, Lit.[12] 246–248°C).

1-Acetyl-β-carboline-2-oxide (5a). Yield: 57 mg (25%). M.p. 180°C. MS (*m*/*z*, %): 226 (M^+, 15), 210 (57), 168 (100), 140 (28); IR, ν (cm^{-1}): 3315, 1653, 1427, 1319, 1185, 1040, 735. ^{1}H NMR (DMSO-d_6): 11.80 (s, 1 H, N-H), 8.31 (d, $J = 6.5$ Hz, 1 H, 3-H), 8.17 (m, 2 H, 4-H and 5-H), 7.71 (d, $J = 8.0$ Hz, 1 H, 8-H), 7.48 (m, 1 H, 7-H), 7.27 (m, 1 H, 6-H), 2.84 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): 196.5 (C=O), 142.5 (C-8a), 136.4 (C-1), 132.5 (C-4), 131.5 (C-9a), 127.9 (C-7), 121.3–121.2 (C-4a, C-5, C-6), 120.8 (C-4b), 119.9 (C-3), 113.2 (C-8), 32.7 (CH_3).

1-Bromo-β-carboline-2-oxide (7). Yield: 150 mg (57%). M.p. 254°C. MS (*m*/*z*, %): 264 (M^+, 28), 262 (M^+, 25), 248 (100), 246 (100), 167 (96), 155 (38), 140 (73). IR, ν (cm^{-1}): 3060, 1606, 1480, 1455, 1426, 1318, 1194. ^{1}H NMR (DMSO-d_6): 11.90 (s, 1 H, N-H), 8.28 (d, $J = 6.4$ Hz, 1 H, 3-H), 8.17 (d, $J = 8.0$ Hz, 1 H, 5-H), 8.15 (d, $J = 6.4$ Hz, 1 H, 4-H), 7.60 (d, $J = 8.0$ Hz, 1 H, 8-H), 7.51 (m, 1 H, 7-H), 7.28 (m, 1 H, 6-H). ^{13}C NMR (DMSO-d_6): 141.5 (C-8a), 137.2 (C-9a), 131.9 (C-3), 127.5 (C-7), 121.5 (C-4b), 121.4 (C-5), 120.6 (C-6), 119.1 (C-4a), 116.1 (C-1), 115.5 (C-4), 112.2 (C-8).

General Procedure for Cyanation

To a stirred solution of 1 mmol of the β-carboline-2-oxide derivative in 10 mL dry dioxane are added 3 mmol (298 mg) of trimethylsilanecarbonitrile and 3 mmol (407 mg) of diethylcarbamoylchloride. The mixture is heated to 80°C and stirred under nitrogen for 16 h. After cooling to room temperature 3 mmol (834 mg) of $FeSO_4 \times 7\,H_2O$ in 1 mL H_2O and 1 mL of 0.1 M NaOH is added and stirring is continued for 15 min. The mixture is filtered through a celite pad and washed with ethyl acetate. The filtrate is dried with Na_2SO_4 and evaporated. The residue is purified by flash column chromatography (ethyl acetate/hexanes 1:4).

1-Cyano-β-carboline (6) from norharman-2-oxide (5b). Yield: 174 mg (90%). M.p. 222°C (Lit.[3d] 226°C); analytical data in accordance with Lit.[3d]

1-Cyano-β-carboline (6) from 1-acetyl-β-carboline-2-oxide (5a). Yield: 100 mg (50%).

1-Cyano-β-carboline (6) from 1-bromo-β-carboline-2-oxide (7). Yield: 115 mg (60%).

3-Cyanoharman (9) from harman-2-oxide (8). Yield: 52 mg (25%). M.p. 188°C. MS (*m*/*z*, %): 207 (M^+, 100), 179 (27), 105 (12). IR, ν (cm^{-1}): 3317, 2221, 1625, 1504, 1407, 1307, 1238, 735. ^{1}H NMR (DMSO-d_6): 12.21 (s, 1 H, N-H), 8.64 (s, 1 H, 4-H), 8.34 (d, $J = 8.0$ Hz, 1 H, 5-H), 7.70 (m, 2 H, 7-H, and 8-H), 7.38 (m, 1 H, 6-H). ^{13}C NMR (DMSO-d_6): 147.9 (C-9a), 142.2 (C-4), 141.4 (C-8a), 134.1 (C-1), 130.1 (C-7), 126.0 (C-4a), 121.8 (C-5), 120.9 (C-6), 119.3 (C-4b), 118.0 (C ≡ N), 113.2 (C-8), 97.7 (C-3), 21.4 (CH_3).

***N*,*N*-Diethyl-9*H*-pyrido[3,4-b]indol-1-ylmethylcarbamate (10) from harman-2-oxide (8).** Yield: 193 mg (65%). M.p. 118°C. MS (*m*/*z*, %): 297 (M^+, 35), 197 (100), 181 (57), 154 (26), 127 (13), 100 (17). IR, ν (cm^{-1}): 3299, 2976, 1671, 1627, 1428, 1274, 1173, 1072, 997, 751. ^{1}H NMR ($CDCl_3$): 10.32 (s, 1 H, N-H), 8.39 (d, $J = 5.0$ Hz, 1 H, 3-H), 8.07 (d, $J = 7.5$ Hz, 1 H, 5-H), 7.92 (d, $J = 5.0$ Hz, 1 H, 4-H), 7.52 (m, 2 H, 8-H, and 7-H), 7.24 (m, 1 H, 6-H), 5.68 (s, 2 H, CH_2-O), 3.32 (q, $J = 7.0$ Hz, 2 H, N-CH_2), 3.21 (q, $J = 7.0$ Hz, 2 H, N-CH_2), 1.11 (t, $J = 7.0$ Hz, 3 H, CH_3), 1.01 (t, $J = 7.0$ Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): 157.2 (C=O), 140.6 (C-8a), 139.6 (C-1), 138.2 (C-3), 135.3 (C-9a), 129.7 (C-4a), 128.5 (C-7), 121.6 (C-5), 121.5 (C-4b), 119.8 (C-6), 115.3 (C-4), 112.0 (C-8), 66.6 (CH_2-O), 42.3 (CH_2-N), 41.6 (CH_2-N), 13.9 (CH_3), 13.4 (CH_3).

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