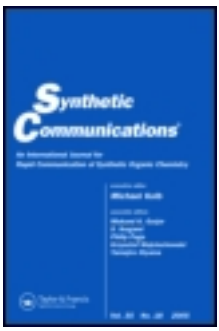

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β-Carboline Alkaloids, Part 8.[1] Regioselective Homolytic Acetylation of β-Carbolines

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β-CARBOLINE ALKALOIDS, PART 8.[1]

REGIOSELECTIVE HOMOLYTIC ACETYLATION OF β-CARBOLINES

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Homolytic acetylation of 3-ethoxycarbonyl-ß-carboline and norharmane occurs selectively at 1-position. Better yields are obtained by generation of the acetyl radical from acetaldehyde than by oxidative decarboxylation of pyruvic acid.

1-Substituted β-carbolines are a large class of biologically active alkaloids.[2] Consequently, the total synthesis of these alkaloids has found widespread interest in the last decades. The classical approaches starting from tryptophan or tryptamine derivatives (Bischler-Napieralski,[3] Pictet-Spengler[4]) offer an easy access to 1-aryl- and 1-alkyl-β-carbolines. In contrast, 1-*acyl*-β-carbolines cannot be readily prepared by these methodologies. In the last years several synthetic approaches to 1-*acyl*-β-*carbolines* have been published, e. g. reaction of Grignard reagents with 1-cyano-β-carboline[5] or 1-methoxycarbonyl-β-carboline[6] and cyclization of tryptamine derived α-ketoimidoyl chlorides.[7] Very recently, we described two

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alternative strategies *via* Pd-catalyzed cross coupling of 1-chloro-β-carboline with a stannylated enol ether[8] and reaction of 1,9-dimetalated β-carboline with electrophiles.[1]

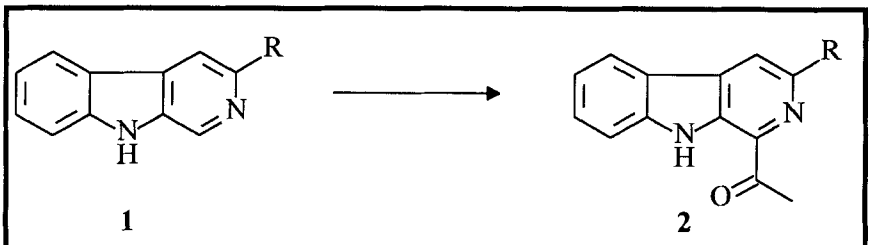
In this communication we describe a one-step preparation of 1-acyl-β-carbolines *via* regioselective homolytic acylation (Minisci-reaction) of β-carbolines by means of acetyl radical. The Minisci-reaction[9] is a convenient strategy for substitution of protonated nitrogen heteroaromates (pyridines, pyrazines, quinolines, quinoxalines ...) by nucleophilic radicals generated *in situ*. Substitution occurs selectively at the *ortho*- and/or *para*-positions of the protonated ring nitrogen. Electron withdrawing substituents strongly enhance the reactivity of the heterocyclic ring towards nucleophilic radicals. Homolytic acylations of β-carboline derivatives have not yet been described in the literature.

For first experiments we selected commercially available 3-ethoxycarbonyl-β-carboline (**1a**) as a starting material, since according to the regioselectivity described above acylation should occur selectively at C-1. Moreover, the ester group should strongly activate the ring system for acylation.

In fact, reaction of protonated **1a** with acetyl radical generated from acetaldehyde by the $FeSO_4$/*t*-BuOOH redox system[10] gave the expected 1-acetyl derivative **2a**[11] in 85% yield (entry 1).

Under identical reaction conditions norharmane (**1b**) gave the alkaloid 1-acetyl-β-carboline[8] (**2b**) in 48% yield (entry 2). The lower yield can be explained by the lacking activation of the ester group. A significantly higher yield (79%) of **2b** could be obtained by prolongation of the reaction time and addition of a second portion of the radical precursors after 1 hour (entry 3). Alternatively, **2b** could be prepared in 33% yield from **1b** by using silver-catalyzed decarboxylation of pyruvic acid by sodium persulfate[12] in a two-phase system as the source of acetyl radical (entry 4). Performing this oxidative decarboxylation in homogeneous

solution gave **2b** only in traces (entry 5). No acetylation at C-3 was observed in entries 2-5. Comparable regioselectivity had been found in homolytic substitutions of isoquinoline with alkyl, carbamoyl and trioxanyl radicals.[9a] In contrast, homolytic alkylation of isoquinoline with cyclohexyl radical generated from a xanthate gave a mixture of 1- and 3-cyclohexyl derivatives.[13]



1 **2**

entry	educt	R	source of acetyl radical	product	yield
1	**1a**	$COOC_2H_5$	CH_3-CHO/$FeSO_4$/*t*-BuOOH	**2a**	86%
2	**1b**	H	CH_3-CHO/$FeSO_4$/*t*-BuOOH (once)	**2b**	48%
3	**1b**	H	CH_3-CHO/$FeSO_4$/*t*-BuOOH (twice)	**2b**	79%
4	**1b**	H	CH_3-CO-COOH/$AgNO_3$/$Na_2S_2O_8$/ TFA/CH_2Cl_2/H_2O	**2b**	33%
5	**1b**	H	CH_3-CO-COOH/$AgNO_3$/$Na_2S_2O_8$/ 1M H_2SO_4	**2b**	4%

In conclusion, regioselective homolytic acetylation of β-carbolines provides a convenient one-step approach to 1-acetyl-β-carbolines. The synthetic route described here appears quite capable of extension to the synthesis of other 1-acyl-β-carbolines.

Experimental

NMR spectra: Bruker AM 400. FT-IR spectra: Philips Analytical PU 98000. Mass spectra: Finnigan MAT 8430 (EI, 70 eV). Norharmane and 3-ethoxycarbonyl-β-carboline were purchased from Aldrich.

1-Acetyl-3-ethoxycarbonyl-β-carboline (2a)

3-Ethoxycarbonyl-β-carboline (**1a**) (120 mg, 0.5 mmol) was suspended in an ice cooled mixture of water (1.2 ml), glacial acetic acid (1.2 ml) and conc. sulfuric acid (0.25 ml) by means of ultrasound irradiation and acetaldehyde (132 mg, 3.0 mmol) was added. Then a solution of $FeSO_4$*7 H_2O (420 mg, 1.5 mmol) in water (1 ml) and *t*-BuOOH (70% solution in water; 0.205 ml, 1.5 mmol) were added simultaneously with stirring. After 30 minutes of additional stirring at 0°C the mixture was poured into water (100 ml) followed by neutralization with K_2CO_3 and extraction with ethyl acetate (3x100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was purified by flash column chromatography (silica; eluent: ethyl acetate/hexanes 1:1) to give 120 mg (85%) **2a** as pale yellow crystals, m.p. 210°C (decomp.). MS (m/z, %): 282 (M^+, 78), 236 (19), 210 (100), 208 (33), 194 (24), 182 (40); IR (KBr, $\tilde{\nu}$, cm^{-1}): 3346, 2980, 1713, 1670, 1373, 1334, 1263, 739; ^1H NMR (DMSO-d_6, δ, ppm): 12.3 (br. s, 1H, NH), 9.17 (s, 1H, 4-H), 8.47 (br. d, J = 7.8 Hz, 1H, 5-H), 7.86 (d, J = 8.3 Hz, 1H, 8-H), 7.64 (m, 1H, 7-H), 7.37 (m, 1H, 6-H), 4.44 (q, J = 7.0 Hz, 2H, CH_2), 2.84 (s, 3H, CO-CH_3), 1.41 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 201.0, 164.8, 142.3, 135.7, 135.2, 135.0, 131.4, 129.3, 122.2, 121.1, 121.0, 120.2, 113.4, 60.9, 25.6, 14.3; Anal. Calcd. for $C_{16}H_{14}N_2O_3$ (282.30): C 68.08, H 5.00, N 9.92; Found: C 67.85, H 5.04, N 9.57.

1-Acetyl-β-carboline (2b)

a) Acetaldehyde as radical precursor (entry 3)

Norharmane (**1b**) (200 mg, 1.19 mmol) was suspended in an ice cooled mixture of water (3 ml), glacial acetic acid (3 ml) and conc. sulfuric acid (0.6 ml) by means of ultrasound irradiation and acetaldehyde (0.32 g, 7.26 mmol) was added. Then a

solution of $FeSO_4$*7 H_2O (1.0 g, 3.6 mmol) in water (3.6 ml) and *t*-BuOOH (70% solution in water; 0.5 ml, 3.6 mmol) were added simultaneously with stirring. After stirring at 0°C for 1 hour the same amounts of acetaldehyde, $FeSO_4$*7 H_2O and *t*-BuOOH were added again in the manner described above and stirring was continued for one more hour at 0°C. Workup was performed as described above. Flash column chromatography of the crude product (silica; eluent: ethyl acetate/hexanes 1:4) gave 197 mg (79%) **2b** as a pale yellow solid, m.p. 203-205°C (from cyclohexane). The product was identified by comparison (m.p., IR, NMR) with an authentical sample.[8]

b) Pyruvic acid as radical precursor (entry 4)

A solution of norharmane (**1b**) (84 mg, 0.5 mmol) and pyruvic acid (132 mg, 1.5 mmol) in dichloromethane (5 ml) was added to a solution of $Na_2S_2O_8$, (178 mg, 0.75 mmol), $AgNO_3$ (8.5 mg, 0.05 mmol) and trifluoroacetic acid (86 mg, 0.75 mmol) in water (5 ml). The mixture was stirred at 40°C for 5 h, then poured into water (10 ml), made alkaline with 2M NaOH and extracted with dichloromethane (3x20 ml). The combined organic layers were dried (Na_2SO_4) and evaporated. Purification by flash column chromatography, as described above, gave 35 mg (33%) **2b**.

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References and notes

1. Part 7: Bracher, F. and Hildebrand, D., Tetrahedron, in print.
2. Allen, J. R. F. and Holmstedt, B. R., Phytochemistry, 1980, 19, 1573.

3. Whaley, W. M. and Govindachari, T. R., Org. React., 1951, 6, 74.
4. Whaley, W. M. and Govindachari, T. R., Org. React., 1951, 6, 151.
5. a) Rinehart, K. L., Kobayashi, J., Harbour, G. C., Gilmore, J., Mascal, M., Holt, T. G., Shield, S. L. and Lafargue, F., J. Am. Chem. Soc., 1987, 109, 3378; b) Bracher, F., Hildebrand, D. and Ernst, L., Arch. Pharm. (Weinheim, Ger.), 1994, 327, 121.
6. a) Still, I. W. J. and McNulty, J., Heterocycles, 1989, 29, 2057; b) see also: Razmilic, I., Castillo, M. and Lopez, J. T., J. Heterocyclic Chem., 1980, 17, 595.
7. VanWagenem, B. C. and Cardellina, J. H., Tetrahedron Lett. 1989, 30, 3605.
8. Bracher, F. and Hildebrand, D., Liebigs Ann. Chem., 1993, 837.
9. a) Minisci, F., Vismara, E. and Fontana, F., Heterocycles, 1989, 28, 489; b) Minisci, F., Synthesis, 1973, 1.
10. Caronna, T., Fronza, G., Minisci, F. and Porta, O., J. Chem. Soc., Perkin Trans. II, 1972, 2035.
11. The corresponding carboxylic acid and methyl ester have been identified as constituents of *Vestia lycioides* (Solanaceae): Faini, F., Torres, R., Delle Monache, F., Marini-Bettolo, G. B. and Castillo, M., Planta Medica, 1980, 38, 128.
12. Fontana, F., Minisci, F., Nogueira Barbosa, M. C. and Vismara, E., J. Org. Chem., 1991, 56, 2866.
13. Coppa, F., Fontana, F., Minisci, F., Pianese, G., Tortoreto, P. and Zhao, L., Tetrahedron Lett., 1992, 33, 687.

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