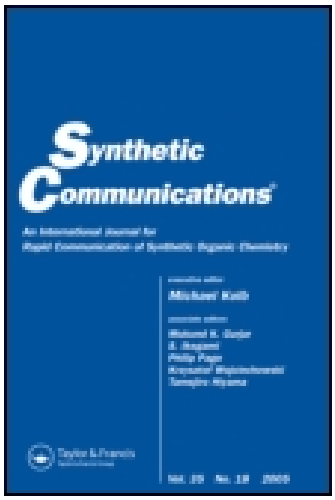

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Facile Synthesis of 7-Amino-1,2,3,4-tetrahydro-β-carboline

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Facile Synthesis of 7-Amino-1,2,3,4-tetrahydro-β-carboline

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ABSTRACT

7-Amino-1,2,3,4-tetrahydro-β-carboline has been prepared by a short efficient synthetic sequence based on a regioselective nitration of a fully protected 1,2,3,4-tetrahydro-β-carboline.

Key Words: Tetrahydro-β-carboline; Regioselective; Nitration; Phase-transfer.

In the process of searching for new biologically active compounds, we became interested in the preparation of 7-amino-1,2,3,4-tetrahydro-β-carboline on a multigram scale. Tetrahydro-β-carbolines are a class of

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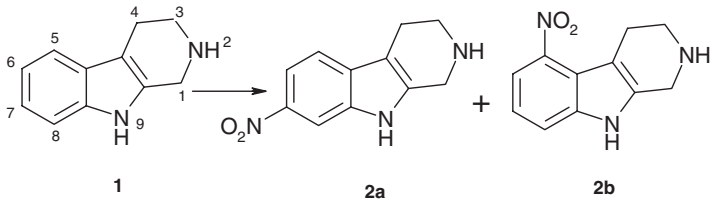
compounds that have been widely investigated due to their biological properties. In fact, molecules belonging to this class are known as analgesics, anxiolytics, antidepressants, antihypertensives[1] etc. This notwithstanding, very few examples of amino-1,2,3,4-tetrahydro-β-carbolines are reported in the literature[2] and in particular 5- and 7-nitro and 5- and 7-amino-1,2,3,4-tetrahydro-β-carbolines have not been yet reported in the literature. Therefore we set out to devise a synthetic procedure to obtain 7-amino-1,2,3,4-tetrahydro-β-carboline on a 10 g scale. As a first approach to prepare our target compound, we considered the nitration of the commercially available *noreleagnine* (**1**).

Treatment of compound **1** with different nitrating agents, under a variety of conditions, gave the expected 7-nitro and 5-nitro isomers,[2] but with unsatisfactory yield and low regioselectivity (Sch. 1). Moreover, regioisomers **2a** and **2b** could not be separated with standard chromatographic procedure.[3] As an attempt to improve the recovery of the regioisomers we converted *noreleagnine* into its 2-acetyl derivative **3** (Sch. 2).

Compound **3** was subjected to nitration under various reaction conditions (Table 1). The desired 7-nitro derivative **4a** was obtained in only 12% isolated yield by using nitronium tetrafluoborate,[4] generated in situ reacting nitric acid with trifluoromethansulfonic acid and dichloromethane as solvent. The regioisomer ratio was 2:1 in favor of the 7-nitro derivative. However, the yield of compound **4a** was far too low for our purposes.

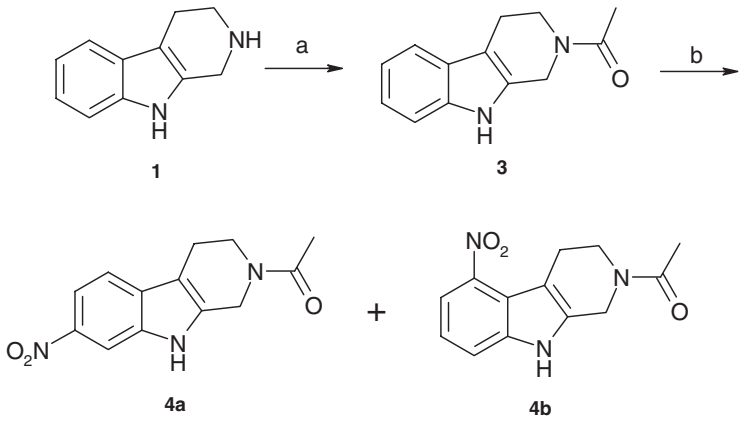
Degradation of compound **3** was observed under all experimental conditions, possibly due to instability of the unprotected indole moiety in an acidic/oxidative environment.[6] Therefore, we turned our attention toward the nitration of the fully protected 1,2,3,4-tetrahydro-β-carboline system **6** (Sch. 3).

The acetyl group on the tetrahydropyridine nitrogen **4a** proved to be resistant to acid and alkaline hydrolysis, and was therefore replaced by the more labile trifluoroacetyl group. Trifluoroacetamide **5** was obtained



1 2a 2b

Scheme 1.



a) Ac_2O, Py, 98%; b) see Tab. 1

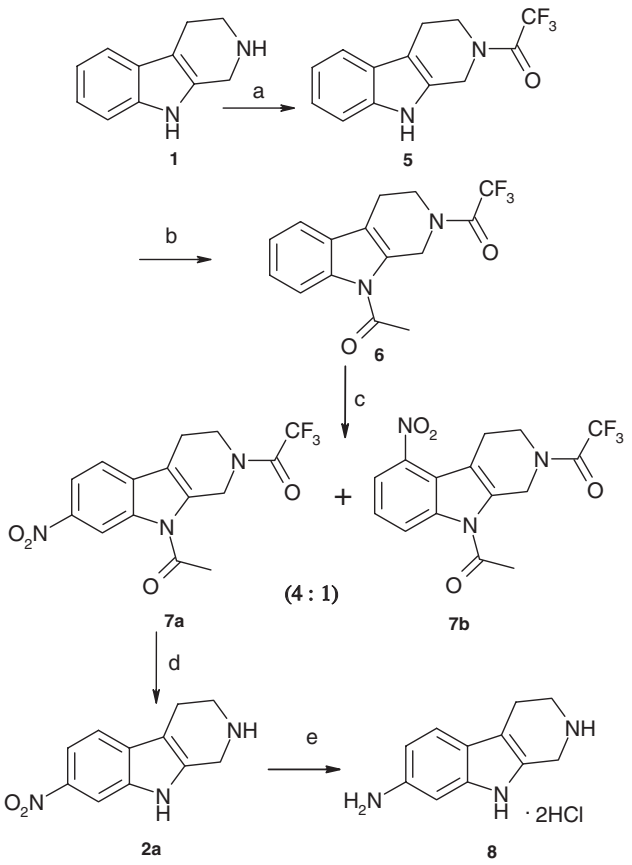
Scheme 2.

Table 1.

Nitrating agent	Solvent	Temperature	Result
$CF_3SO_3NO_2$	CH_2Cl_2[a]	−78 to −30°C	18% of a mixture of 7-nitro and 5-nitro isomers (2:1)
BF_4NO_2[b]	CH_2Cl_2[c]	−78 to −20°C to RT	12% of a mixture of isomers
NH_4NO_3[d], TFAA	CH_2Cl_2[e]	0 to RT	Only traces of product

[a]When the reaction was carried out in CH_3CN, DME, or AcOEt only degradation of **3** was observed.
[b]See Ref.[4]
[c]Only degradation of **3** was observed using DME as solvent.
[d]See Ref.[5]
[e]Only degradation of **3** was observed using TFAA as solvent.

from **1** in 98% yield applying a standard procedure (TFAA, DCM, 0°C to R.T.). Compound **5** was then acetylated at the indole nitrogen under phase transfer conditions, as reported by Illi[7] and Ottoni et al.,[8] in almost quantitative yield. The phase-transfer procedure, run in the absence of water, prevented the reversion of the reaction, due to the high reactivity of *N*-acyl indoles towards nucleophiles, as well as



a) TFAA, DCM, 0°C to rt, 98%; b) NaOH pellets, cetrimide, DCM, 96%; c) $CF_3SO_3NO_2$, DCM, -78°C to 0°C,40%; d)NaOH (1N), EtOH, 90%; e) H_2, Pd/C, MeOH, HCl (1N), 85%.

Scheme 3.

the cleavage of the alkaline-labile trifluoroacetamide. Compound **6** turned out to be more stable than 2-acetyl *noreleagnine* **3** under nitrating conditions. Nitration of **6** was carried out by treatment with 1.1 equiv. of $CF_3SO_3NO_2$ in CH_2Cl_2 at $-78^{\circ}C$, then allowing the reaction mixture to warm up to $0^{\circ}C$. The two regioisomers were obtained in 40% isolated yield. Moreover, a higher degree of regioselectivity was observed, the ratio of 7-NO_2 vs. 5-NO_2 being increased to 4:1.

The pure regioisomer **7a** was isolated by flash chromatography and, after simultaneous removal of the protective groups (1N NaOH/

EtOH; 96% yield), the 7-nitro-1,2,3,4-tetrahydro-β-carboline **2a** was catalytically hydrogenated in acidic medium (50 psi H_2, Pd/C 10%, MeOH, 1N HCl) to afford pure 7-amino-1,2,3,4-tetrahydro-β-carboline dihydrochloride **8** in 84% yield.

CONCLUSION

In this communication we disclosed a convenient procedure suitable for a large-scale preparation of 7-amino-1,2,3,4-tetrahydro-β-carboline. Starting from the commercially available 1,2,3,4-tetrahydro-β-carboline (*noreleagnine*), we were able to obtain, in five steps, and with only one chromatographic purification, the pure 7-amino-1,2,3,4-tetrahydro-β-carboline in 31% overall yield.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Mercury-Vx 600 MHz, 500 MHz, 400 MHz, or 300 MHz, spectrometers. Mass spectra were recorded on a Finnigan LCQ ion trap mass spectrometer using the electrospray (ESI) ionization technique with positive and negative ion detection. Elemental analyses were recorded by EA 1110 CHNS-O C.E. Instruments Elemental Analyzer. Melting points have been measured on a Buchi 510 apparatus and are uncorrected.

2-(Trifluoroacetyl)-1,2,3,4-tetrahydro-9H-β-carboline (5)

In a three-necked round-bottomed flask, equipped with a mechanical stirrer, a suspension of 1,2,3,4-tetrahydro-9H-β-carboline (25 g, 0.145 mol) in dichloromethane (1.3 L) was stirred and cooled to 0°C. To this suspension TFAA (174 mL, 1.25 mol) was then added dropwise. After the addition was complete[a], the reaction mixture was stirred and cooled for an additional hour, then neutralized by slow addition of a pre-cooled $NaHCO_3$ saturated aqueous solution (1.6 L). The organic phase was then separated, washed with water (100 mL), dried over

[a]Initial formation of TFA salt of unreacted 1,2,3,4-tetrahydro-β-carboline gave rise to a white precipitate that disappeared once the addition of TFAA was complete.

Na_2SO_4, and evaporated to afford 38.12 g (98%) of pure 2-(trifluoroacetyl)-1,2,3,4-tetrahydro-9H-β-carboline (**5**) as white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) (*syn*/*anti* mixture): 2.95 (m, 2H), 3.95–4.06 (two t, $J = 5.7$ Hz, 2H, *syn*/*anti* 1/2.5), 4.83–4.88 (two s, 2H), 7.0–7.6 (m, 4H), 7.9 (bs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) (*syn*/*anti* mixture): 22.22, 42.20, 44.58, 107.99, 111.39, 114.93, 118.49, 118.74, 120.10, 122.48, 122.67, 126.73, 126.78, 128.44, 136.52, 156.24, 156.63, 157.11, 157.59. MS: $m/z = 260$ $(M-H)^-$. CHN: Anal. calcd. for $C_{13}H_{11}F_3N_2O$: C, 58.21%; H, 4.13%; N, 10.44%. Found: C, 57.66%; H, 4.13%; N, 10.18%. M.p. = 135–140°C decomposition.

9-Acetyl-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline (6)

In a three-necked round-bottomed flask, equipped with a mechanical stirrer, NaOH pellets[b] (190 g, 4.75 mol) and *N*-cetyl-*N*,*N*,*N*-trimethyl-ammonium bromide (4.68 g, 0.013 mol) were suspended in dry dichloromethane (1.5 L). After cooling to 0°C, 2-(trifluoroacetyl)-1,2,3,4-tetrahydro-9H-β-carboline (**2**) (36.5 g, 0.136 mol) was added under vigorous stirring. To the mixture was then added acetyl chloride (173 mL, 2.4 mol) dropwise, and the reaction mixture was kept under stirring and cooling until no starting material was left. The reaction mixture was then filtered, the filtrate was washed with water (100 mL) and the pH adjusted to neutrality by slow addition of $NaHCO_3$ saturated aqueous solution. Finally, the organic phase was separated, washed with brine (300 mL), dried over Na_2SO_4 and evaporated to afford 40.5 g (96%) of pure 9-acetyl-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline (**6**) as yellowish solid.

^{1}H-NMR (400 MHz, d^6-DMSO) (*syn*/*anti* mixture): 2.76–2.78 (two s, 3H), 2.82 (m, 2H), 3.89–3.93 (two t, $J = 5.5$ Hz, 2H, *syn*/*anti* 1/2.5), 5.05–5.08 (two s, 2H), 7.2–7.6 (m, 3H), 7.89–7.92 (two d, $J = 7.3$ Hz, 1H). ^{13}C-NMR (75 MHz, d^6-DMSO) (*syn*/*anti* mixture): 22.07, 27.22, 41.05, 44.50, 111.34, 115.16, 115.54, 118.98, 119.08, 122.80, 123.62, 125.02, 129.41, 131.34, 135.34, 154.98, 155.44, 155.90, 156.36, 170.48. MS: m/z 310 (M^+). CHN: Anal. calcd. for $C_{15}H_{13}F_3N_2O_2$: C, 8.07%; H, 4.22%; N, 9.03%. Found: C, 59.13%; H, 4.55%; N, 8.99%. M.p. = 99–102°C.

[b]**CAUTION** using finely grounded NaOH instead of pellets led to a strongly exothermic reaction when acetyl chloride was added.

9-Acetyl-7-nitro-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline (7a)

In a three-necked round-bottomed flask, equipped with a mechanical stirrer, trifluoromethanesulfonic acid (22.9 mL, 0.26 mol) was dissolved in dichloromethane (1.3 L) under nitrogen at room temperature. To the milky solution, 90% nitric acid (6.1 mL, 0.13 mol) was added, and the mixture was stirred at room temperature until the initially formed white precipitate was dissolved, giving rise to a yellow–green solution. The mixture was cooled to −50°C, then a solution of 9-acetyl-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline (**6**) (40 g, 0.13 mol) in dichloromethane (500 mL) was added dropwise. Once the addition was completed, the reaction mixture was allowed to warm to 0°C then quenched by pouring it into a vigorously stirred saturated aqueous solution of $NaHCO_3$ (3 L). After 15 min, the organic layer was separated, washed with brine (2 × 200 mL) and dried. Separation of the two regioisomers was performed by flash chromatography of the crude residue (40 g) using AcOEt as eluent and afforded 4.6 g of 5-nitro and 19.02 g of 7-nitro-regioisomer that was further purified by suspending it in AcOEt (200 mL); the solid was then collected and dried to give 18.41 g (40%) of pure 9-acetyl-7-nitro-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline as yellow solid.

7a. ^{1}H-NMR (400 MHz, d^6-DMSO) (*syn*/*anti* mixture): 2.84–2.87 (two s, 3H), 2.91 (m, 2H), 3.95 (m, 2H), 5.14 (s, 2H), 7.77 (m, 1H), 8.17 (m, 1H), 8.77–8.85 (two d, $J = 1.8$ Hz, 1H, *syn*/*anti* 2.5/1). ^{13}C-NMR (75 MHz, d^6-DMSO) (*syn*/*anti* mixture): 22.00, 27.06, 41.05, 44.46, 111.28, 111.85, 115.08, 115.65, 118.88, 118.89, 119.42, 122.68, 133.99, 134.29, 137.15, 144.73, 155.03, 155.50, 155.97, 156.44, 170.49. MS: *m*/*z* 353 $(M-H)^-$. CHN: Anal. calcd. for $C_{15}H_{12}F_3N_3O_4$: C, 50.71%; H, 3.40%; N, 11.83%. Found: C, 50.73%; H, 3.44%; N, 11.56%. M.p. = 168–171°C.

7b. ^{1}H-NMR (300 MHz, $CDCl_3$) (*syn*/*anti* mixture): 2.84–2.87 (two s, 3H), 3.03 (m, 2H), 3.87–3.92 (two t, $J = 5.7$ Hz, 2H), 5.15–5.17 (two s, 2H), 7.42 (m, 1H), 7.9 (dd, $J = 0.7$ Hz, $J = 8.1$ Hz, 1H), 8.03–8.16 (two dd, $J = 0.7$ Hz, $J = 8.6$ Hz, 1H, *syn*/*anti* 0.4/1.1). ^{13}C-NMR (150 MHz, $CDCl_3$) (*syn*/*anti* mixture): 25.32, 27.58, 43.39, 44.52, 113.81, 119.45, 120.20, 122.32, 123.90, 135.60, 137.27, 142.92, 155.87, 156.11, 156.35, 156.59, 168.94. MS: *m*/*z* 353 $(M-H)^-$. CHN: Anal. calcd. for $C_{15}H_{12}F_3N_3O_4$: C, 50.71%; H, 3.40%; N, 11.83%. Found: C, 50.75%; H, 3.45%; N, 11.52%.

Along the same procedure, products **4a** and **4b** were prepared:

4a. (as yellow solid). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.28 (s, 3H), 2.92 (m, 2H), 3.86 (m, 2H), 4.90 (s, 2H), 7.50 (d, 1H, $J = 8.8$), 8.03 (dd, 1H,

$J = 2.15, 8.8$), 8.32 (d, 1H, $J = 2.15$), 9.00 (bs, 1H). ^{13}C-NMR (150 MHz, d^6-DMSO): 21.89, 22.04, 22.61, 44.44, 108.50, 114.74, 118.30, 118.75, 131.96, 134.96, 139.27, 139.69, 169.82. MS: m/z 258 $(M-H)^-$. CHN: Anal. calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23%; H, 5.05%; N, 16.21%. Found: C, 60.20%; H, 4.97%; N, 16.15%.

4b. (as yellow solid). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.28 (s, 3H), 3.19 (m, 2H), 3.76 (m, 2H), 4.90 (s, 2H), 7.20 (t, 1H, $J = 8.09$), 7.62 (d, 1H, $J = 8.09$), 7.94 (d, 1H, $J = 8.09$), 9.00 (bs, 1H). ^{13}C-NMR (150 MHz, d^6-DMSO): 21.13, 21.95, 25.25, 44.70, 109.21, 117.40, 118.36, 120.40, 131.83, 135.14, 137.92, 142.17, 169.82. MS: m/z 258 $(M-H)^-$. CHN: Anal. calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23%; H, 5.05%; N, 16.21%. Found: C, 60.21%; H, 4.95%; N, 16.18%.

7-Nitro-1,2,3,4-tetrahydro-9H-β-carboline (2a)

To a stirred suspension of 9-acetyl-7-nitro-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-β-carboline (**7a**) (11.9 g, 0.0335 mol) in ethanol (1.2 L), under nitrogen at room temperature, aqueous 2 M NaOH (149 mL) was added over 5 min, thus obtaining a deep red solution that was stirred for an additional hour. The reaction mixture was then diluted with water (1 L) and filtered. The orange solid obtained was washed with water (100 mL), collected, and dried to afford 6.54 g (90%) of pure 7-nitro-1,2,3,4-tetrahydro-9H-β-carboline (**2a**) as yellow solid.

^{1}H-NMR (300 MHz, d^6-DMSO): 2.62 (m, 2H), 2.95 (m, 2H), 3.9 (s, 2H), 7.4 (d, 1H, $J = 9.1$), 7.83 (dd, 1H, $J = 2.3, 9.1$), 8.2 (d, 1H, $J = 2.3$), 11.55 (bs, 1H). ^{13}C-NMR (150 MHz, d^6-DMSO): 22.54, 43.40, 43.63, 108.21, 111.45, 114.52, 117.76, 132.66, 134.48, 141.67, 142.96. MS: m/z 218 $(M+H)^+$. CHN: Anal. calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82%; H, 5.10%; N, 19.34%. Found: C, 60.86%; H, 5.15%; N, 19.30%.

7-Amino-1,2,3,4-tetrahydro-9H-β-carboline Dihydrochloride (8)

To a solution of 7-nitro-1,2,3,4-tetrahydro-9H-β-carboline (**2a**) (3.4 g, 0.016 mol) and aqueous 1M HCl (40 mL) in methanol (610 mL), 10% Pd/C (0.7 g) was added and the suspension was shaken in a Parr hydrogenation apparatus under hydrogen atmosphere (50 psi) for 2 h. The suspension was then filtered over Celite®, the volume of the filtrate was reduced in vacuo, than submitted to an azeotropic removal of residual water with absolute ethanol (2×250 mL).

Finally, the crude was suspended in absolute ethanol (200 mL), filtered, collected, and dried to afford 3.46 g (85%) of pure 7-amino-1,2,3,4-tetrahydro-9H-β-carboline (**8**) as dihydrochloride salt (white solid).

^{1}H-NMR (400 MHz, d^6-DMSO): 2.93 (m, 2H), 3.40 (m, 2H), 4.33 (s, 2H), 7.01 (dd, $J = 1.9$, 8.3 Hz, 1H), 7.46 (d, $J = 1.9$, 1H), 7.54 (d, $J = 8.3$, 1H), 9.67 (bs, 2H), 10.3 (bs, 3H), 11.44 (s, 1H). ^{13}C-NMR (75 MHz, d^6-DMSO): 18.61, 41.01, 41.87, 106.49, 106.98, 114.91, 119.42, 126.08, 126.14, 128.98, 136.25. MS: m/z 188 $(M + H)^+$. CHN: Anal. calcd. for $C_{11}H_{13}N_3$: 2HCl: C, 50.78%; H, 5.81%; N, 16.15%. Found: C, 50.80%; H, 5.86%; N, 16.12%. M.p. > 280°C.

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3. The mixture of **2a** and **2b**, obtained in 7% yield by reaction of **1** with $CF_3SO_3NO_2$ at 0°C in CH_2Cl_2, was hydrogenated, affording a crude mixture of amino derivatives which was treated with BOC anhydride to give 2-(*tert*-butoxycarbonyl)-7-[(*tert*-butoxycarbonyl)amino]-1,2,3,4 -tetrahydro-β-carboline and 2-(*tert*-butoxycarbonyl)-5-[(*tert*-butoxycarbonyl)amino]-1,2,3,4-tetrahydro-β-carboline (40% over two steps). The two isomers could be easily separated by conventional column chromatography regioisomer ratio 2:1 of 7-NO_2 vs. 5-NO_2) and the desired isomer reconverted quantitatively to the amino derivative **8** (1.8% overall yield).
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