An Efficient Synthesis of Thalifoline

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Received 11 June 2002; revised 27 July 2002

Abstract: An efficient multi-step approach for the synthesis of the isoquinolin-1-one alkaloid thalifoline (1) is described. The key intermediate carbamate 8a underwent a modified Bischler–Napieralski-type cyclization using Banwell’s Tf₂O/DMAP conditions to form the lactam 9a under mild conditions and in excellent yield.

Key Words: alkaloids, thalifoline, quinolines, heterocycles, isoquinoline, ring closure, cyclizations

Thalifoline (1),¹ first isolated from Thalictrum minus L. var. adiantifolium Hort by Doskotch et al. in 1969, is a member of a small group of naturally-occurring tetrahydroisoquinolones (Figure 1). This group of alkaloids is present in only minor amounts. Based upon the few biogenetic studies that have been conducted, they are presumed to result from the biochemical oxidation of the more prevalent alkaloid components including benzyltetrahydroisoquinoline units.²,³ Thalifoline is structurally related to a subunit of more complex alkaloids such as baluchistanamine (2)⁴,⁵ and (−)-tejedine (3).⁵ We herein describe an efficient multi-step synthesis of thalifoline from vanillin (4). Using modified Bischler–Napieralski cyclization conditions developed by Banwell et al.,⁶ thalifoline was obtained in 37% overall yield from vanillin. The methodology reported herein appears to be a general one which could be applicable to other 6,7-disubstituted 3,4-tetrahydroisoquinolin-1-ones.

Scheme 1  Reagents and conditions: i) BnBr/K₂CO₃, acetone, reflux (98%); ii) MeNO₂/NH₄Ac, HOAc, reflux (90%); iii) LiAlH₄, THF, reflux (used directly in step iv); iv) HCO₂Et, reflux (78% from steps iii and iv); v) BH₃/THF/BF₃·OEt₂, THF, reflux (used directly in step vi); vi) ClCO₂Et/NaHCO₃, CH₂Cl₂–H₂O, 0 °C (60% from steps v and vi); vii) 8a + Tf₂O/DMAP, CH₂Cl₂, 0 °C, (90%); viii) 9a + H₂/Pd/C, MeOH (>98%).

Figure 1
The conversion of vanillin to 4-benzyloxy-3-methoxy-phenethylamine (6) was achieved in 84% overall yield using a standard procedure (Scheme 1). Benzylation of vanillin with benzyl bromide using K₂CO₃ in refluxing acetonite afforded 4a in 98% yield. Condensation of 4a with nitromethane using either aqueous sodium hydroxide at 0 °C, methylammonium chloride and Na₂CO₃ in ethanol, or dimethylammonium chloride and KF in toluene, only afforded the β-nitrostyrene 5 in less than 50% yields and presented difficulties in purifying the product. The reaction of 4a with nitromethane in refluxing acetic acid with ammonium acetate however, produced crystalline 5 in 90% yield. Reduction of 5 using LiAlH₄ in refluxing THF affording 6 in 84% overall yield from vanillin. Without further purification, 6 was converted to N-formyl-N-4-benzyloxy-3-methoxyphenethylamine (7) in 78% yield by reaction with ethyl formate in refluxing conditions. Reduction of 7 using LiAlH₄ afforded the desired N-methyl-N-4-benzyloxy-3-methoxyphenethylamine (7a) in only low yields. However with BH₃·THF/ BF₃·OEt₂ in refluxing THF, 7a could be obtained in >90% yields and pure enough to be used directly in the subsequent step. Schotten–Baumann reaction with ethyl chloroformate afforded the key intermediate N-ethoxycarbonyl-N-methyl-4-benzyloxy-3-methoxyphenethylamine (8a) in 60% overall yield from 7.

Cyclization of either carbamates 8a or 8b, or formamide 7 under typical, or modified Bischler–Napieralski conditions proved to be difficult. These substrates were treated with P₂O₅/POCl₃ (2:1) as described by Wang. Such conditions reportedly usually give cyclized isoquinolin-1-carboxylic acid (4a, 1.5 g, 15.1 mmol), nitromethane (6 mL, 87.3 mmol), and glacial HOAc was refluxed for 1.5 h. After cooling to r.t., the crystalline product was filtered and recrystallized from EtOH to afford 5.

Yield: 3.2 g (90%); mp 121–122 °C (lit. 121–123 °C).

4-Benzoyloxy-3-methoxy-β-nitrostyrene (5) A mixture of 4-benzylovanilline (4.0 g, 16.5 mmol), ammonium acetate (1.2 g, 15.1 mmol), nitromethane (6 mL, 87.3 mmol), and glacial HOAc was refluxed for 1.5 h. After cooling to r.t., the crystalline product was filtered and recrystallized from EtOH to afford 5.

Yield: 775 mg (78%); colorless oil.

1H NMR (CDCl₃, 500 MHz): δ = 2.51 (q, J = 7.0 Hz, 2 H), 2.75 (t, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 5.11 (s, 2 H), 5.72 (br s, 1 H), 6.65 (dd, J = 1.5, 8.0 Hz), 6.73 (d, J = 1.5 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 7.29–7.43 (m, 5 H), 8.08 (s, 1 H).

13C NMR (CDCl₃, 125 MHz): δ = 35.5, 37.8, 39.7, 43.6, 53.9, 56.5, 71.6, 112.9, 113.1, 114.8, 114.9, 121.1, 121.3, 127.6, 128.3, 129.0, 131.2, 132.2, 137.6, 137.6, 147.3, 147.6, 150.3, 150.3, 161.6, 164.8.

MS: m/z (%) = 285 (M⁺, 6), 240 (14), 149 (20), 91 (100).

All reactions were performed under N₂ or Ar. All compounds were purified by either flash chromatography using Scientific Adsorbents Inc. (SAI) silica gel (63–200 μm) or preparative thin layer chromatography (PLC) plates, which were made from SAI silica gel (5–15 μ) with gypsum. TLC was performed on precoated silica gel 60 F 254 (SAI). Chemical reagents were purchased from Sigma–Aldrich. Solvents were dried using standard procedures. Mps were determined on a Fisher–Johns apparatus and are uncorrected. IRspectra were recorded on a Mattson Polaris FT instrument. MS data were presented as follows: m/z, intensity. 1H NMR spectra were at 300 MHz or 500 MHz, and chemical shifts are relative to internal TMS.

1% C NMR spectra were recorded at 75 MHz or 125 MHz and chemical shifts are relative to the solvent (δ = 77.0 for CDCl₃).

O-Benzylanillin (4a) A solution of anhyd K₂CO₃ (31 g, 0.23 mol) in CHCl₃ (60 mL) and MeOH (30 mL) was refluxed for 15 min and then vanillin 4 (7.6 g, 0.05 mol) and benzyl bromide (8.9 mL, 0.08 mol) were added. After heating at reflux for 4 h, the reaction mixture was filtered, the organic phase was washed with water, dried (MgSO₄), filtered, and concentrated in vacuo. The product was recrystallized from hexane–CH₂Cl₂ to give pure 4a.

Yield: 12 g (96%); crystalline needles; mp 63–64 °C (lit. 61–64 °C).

4-Benzoyloxy-3-methoxy-β-nitrostyrene (5) A mixture of 4-benzylovanilline (4.0 g, 16.5 mmol), ammonium acetate (1.2 g, 15.1 mmol), nitromethane (6 mL, 87.3 mmol), and glacial HOAc was refluxed for 1.5 h. After cooling to r.t., the crystalline product was filtered and recrystallized from EtOH to afford 5.

Yield: 3.2 g (90%); mp 121–122 °C (lit. 121–123 °C).

4-Benzoyloxy-3-methoxyphenethylamine (6) A solution of 4-benzyloxy-3-methoxy-β-nitrostyrene (5) (1.0 g, 3.5 mmol) in anhyd THF (5 mL) was added dropwise to a stirred solution of LiAlH₄ (0.7 g, 17.5 mmol) in anhyd THF (15 mL). The reaction mixture was refluxed for 3 h followed by addition ofaq KOH (20%) to destroy the excess LiAlH₄. The mixture was then extracted with EtOAc (3 × 20 mL), washed with brine (3 × 20 mL), dried (K₂CO₃), concentrated in vacuo. The oily residue was used directly in the next step.

N-Formyl-N-(4-benzyloxy-3-methoxyphenethylamine (7) 3-Methoxy-4-benzyloxyphenethylamine (6) (890 mg, 3.5 mmol) was dissolved in ethyl formate (40 mL), and the reaction mixture was refluxed for 1 h. After removal of the solvent, the residue was purified by flash chromatography (silica gel; CH₂Cl₂–MeOH, 96:4) to afford 7.

Yield: 775 mg (78%); colorless oil.

1H NMR (CDCl₃, 500 MHz): δ = 2.51 (q, J = 7.0 Hz, 2 H), 2.75 (t, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 5.11 (s, 2 H), 5.72 (br s, 1 H), 6.65 (dd, J = 1.5, 8.0 Hz), 6.73 (d, J = 1.5 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 7.29–7.43 (m, 5 H), 8.08 (s, 1 H).

13C NMR (CDCl₃, 125 MHz): δ = 35.5, 37.8, 39.7, 43.6, 53.9, 56.5, 71.6, 112.9, 113.1, 114.8, 114.9, 121.1, 121.3, 127.6, 128.3, 129.0, 131.2, 132.2, 137.6, 137.6, 147.3, 147.6, 150.3, 150.3, 161.6, 164.8.

MS: m/z (%) = 285 (M⁺, 6), 240 (14), 149 (20), 91 (100).
HRMS: m/z calc'd for C_{19}H_{23}NO_{4}: 329.1622; found: 329.1617.

**N-Ethoxycarbonyl-N-methyl-4-benzyloxy-3-methoxyphenethylamine (8a)**

To a solution of [7 (775 mg, 2.72 mmol) in THF (20 mL) under Ar was added BF_{3}OEt_{3} (0.14 mL, 1.09 mmol) via syringe. The solution was heated to a gentle reflux and then 

\[ \text{NH}_{2} \quad \text{THF} (7 \, \text{mL} \, 6.80 \, \text{mmol}) \quad \text{was added dropwise with stirring.} \]

The reaction mixture was stirred at 0 °C for 1 h, then at 25 °C for 1 h. The mixture was concentrated on a rotary evaporator to remove solvent, then cooled to 0 °C and made basic to pH 13 using solid KOH. Water and CH_{2}Cl_{2} were added to the resulting basic mixture to dissolve the potassium salts and the mixture was stirred at 0 °C for 1 h, then at 25 °C for 1 h. The mixture was filtered and the solvent was evaporated in the usual manner, to give a light brown solid. Purification by flash column chromatography (hexanes–EtOAc, 1:1) afforded 9a.

Yield: 90%; colorless solid; mp 114–115 °C.

1H NMR (CDCl_{3}, 500 MHz): \( \delta = 2.91 \) (t, \( J = 6.0 \, \text{Hz}, 2 \, \text{H} \)), 3.12 (s, \( 3 \, \text{H} \)), 3.51 (t, \( J = 6.0 \, \text{Hz}, 2 \, \text{H} \)), 3.89 (s, \( 3 \, \text{H} \)), 5.17 (s, \( 2 \, \text{H} \)), 6.63 (s, \( 1 \, \text{H} \)), 7.27–7.47 (m, \( 5 \, \text{H} \)), 7.67 (s, \( 1 \, \text{H} \)).

13C NMR (CDCl_{3}, 125 MHz): \( \delta = 28.0, 35.5, 48.8, 56.5, 71.3, 110.1, 113.2, 122.4, 128.0, 128.3, 129.0, 132.3, 137.3, 147.5, 152.7, 165.2.

**References**


(20) In ref. 18 J. Finkelstein reported this compound using a different procedure but did not quote a melting point. Sigma–Aldrich lists this compound as having a mp of 61–64 °C.