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Syntheses of Three Mono-Brominated Enamide Analogs of Natural Alkaloids Isolated from the Tasmanian Marine Bryozoan Amathia Wilson

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Abstract. Synthesis of three brominated enamides, analogs of natural alkaloids isolated from the Tasmanian marine bryozoan Amathia Wilson, were prepared by a sequence of reactions starting from 3-hydroxybenzaldehyde.

Keywords: brominated enamides, amathamides.

Introduction

The enamides form an important group of naturally occurring compounds which have been isolated from a number of different sources, including terrestrial plants [1-3], microorganisms [4-6] and marine organisms [7-11]. In general, compounds belonging to this class of enamides show an array of biological effects including antibiotic [4], protein kinase inhibition [5] and antitumor activity [12].

Marine invertebrates are currently the focus of an intense worldwide search for new pharmacologically activity cytotoxic and antineoplastic agents. The amathamides are brominated proline-derived alkaloids which differ from each other by the degree of bromination or methylation and by their double bond geometry (Figure 1) [13-15].

Biological activity of this type of enamide alkaloids has not been fully studied and only a limited biological activities such as, nematocidal, antifungal, and antibacterial activity has been described for amathamides A, B, G, H, and I isolated from A. wilsoni and A. convolute species [16-17].

Results and discussion

Bromination of 3-hydroxybenzaldehyde (Scheme 1), gave a mixture of 8a-c (Br₂ in CHCl₃, rt) in a ratio of 87:3:10. Recrystallization of the mixture from acetic acid gave pure 8a in 65% yield.

However, similar bromination of 3-hydroxybenzaldehyde (Br₂ in silica gel/CH₂Cl₂, rt) (Scheme 1), gave 8a-c in ratio (68:7:25). Compounds were separated by column chromatography and recrystallization of 8c from acetic acid gave a single crystal X-ray structure (figure 2), confirming the position of bromine atom in 8c [20]. Mono-brominated compounds 8b and 8c were separated by chromatography in 7% and 25% yields respectively.

Aldehydes 8a-c were treated with methyl iodide in DMF in the presence of K₂CO₃ to give methyl ethers 9a-c respectively (Scheme 2). Subsequent condensation with nitromethane in the presence of ammonium acetate gave the nitroolefins 10a-c in 80-85% yields. Michael addition of thiophenol with a catalytic amount of N-isopropylcyclohexylamine to each nitroolefin gave adducts 11a-c in 85-92% yields. Reduction of the nitro...
Scheme 2. Reagents and conditions: a) CH₃I, DMF, K₂CO₃; b) CH₃NO₂, AcOH, AcONH₂; c) PhSH, N-isopropylcyclo hexylamine, CH₂Cl₂; d) Zn, HCl, AcOH; e) PhCOCl, DMAP, CH₂Cl₂; f) i. NaO₂; MeOH; ii. Toluene K₂CO₃ Reflux.

Fig. 2. X-ray crystal structure of 4-bromo-3-hydroxybenzaldehyde 8c [20].

compounds 11a-c, with Zn in acid conditions gave amines 12a-c in 33-47% yields. We previously made the reduction with samarium diiodide (SmI₂), however is a very expensive reagent and used 10 equivalents [18]. Acylation of amines with benzoyl chloride gave the products 13a-c in 81-95% yields. Oxidation of 13a-c with sodium periodate and subsequent elimination of thiophenol led to the desired enamides 14a-c in 36-56% yields.

Conclusion

In conclusion using specific bromination techniques we have synthesized three monobromobenzaldehydes, which were subsequently converted via a series of reactions involving, nitrofen formation, followed by Michael addition of thiophenol, reduction, acylation and elimination of sulfoxide to give the desired enamides 14a-c. Future work towards the synthesis of amathanamides C, E and F are under progress.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR Spectra were taken on a Perkin Elmer FT-IR 1600 spectrometer. ¹H-(200 MHz) spectra were recorded on a Varian Oxford 200 MHz spectrometer. Spectra were recorded in CDCl₃ with tetramethylsilane (TMS) used as internal standard. The EIMS data were obtained on a Finnigan MAT-90 instrument and all experiments were performed in the electron-impact mode (EI) at 70 eV using a direct insertion probe. All starting materials were research grade chemical, commercially available and used without further purification. Silica gel 60 F₂₅₄ was used for TLC. Compound visualization was effected by UV light (252 nm).

2-Bromo-5-hydroxybenzaldehyde 8a

To a solution of 3-hidroxybenzaldehyde (5.00 g, 40.94 mmol) in CHCl₃ (50 mL) was added bromine (2.05 mL, 40.94 mmol) in CHCl₃ (30 mL). The resulting solution was stirred at rt for 1 h. The excess bromine was removed with a saturated solution of sodium thiosulfate (20 mL), the organic phase was washed with water and dried over anhydrous Na₂SO₄. Removal of solvent gave a brown solid, which was recrystallized from acetic acid (7.16 g, 87%); mp 132-134 °C. IR (film): 3325, 3064, 1682, 1592 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 10.30 (s, 1H), 7.50 (d, 8.7 Hz, 1H), 7.44 (d, 3.0 Hz, 1H), 7.03 (dd, 8.7, 3.17 Hz, 1H) ppm. ¹³C NMR: (CDCl₃, 200 MHz): δ 192.5, 159.2, 155.8, 135.1, 123.6, 118.0, 115.9. ppm. MS (EI) m/z (%): 202 (M⁺, 96); 200 (M⁺+2, 100).

Monobromo-3-hydroxybenzaldehydes 8b, c

To a solution of 3-hidroxybenzaldehyde (10.00 g, 81.88 mmol) in CH₂Cl₂ (100 mL), was added silica gel (10.00 g) and bromine (4.10 mL, 81.88 mmol) in CH₂Cl₂ (30 mL). The resulting solution was stirred at rt for 1 h. The excess bromine was removed with a saturated solution of sodium thiosulfate (30 mL), and filtered. The organic phase was washed with water and dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica, eluting with CH₂Cl₂:Hexane (1:1).

2-Bromo-3-hydroxybenzaldehyde 8b

Obtained from 3-hidroxybenzaldehyde as white solid which was recrystallized from acetic acid (1.15 g, 7%); mp 147-148 °C. IR (film): 3143, 3064, 1654, 1566 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 10.29 (s, 1H), 7.51 (dd, 7.4, 2 Hz, 1H), 7.36 (t, 1H).
Syntheses of Three Mono-Brominated Enamide Analogs of Natural Alkaloids Isolated from the Tasmanian Marine

7.4 Hz, 1H), 7.28 (dd, 7.32, 2.01 Hz, 1H), 5.97 (s, 1H) ppm.

1H NMR. (CDCl3, 50 MHz): δ 191.4, 153.2, 134.7, 129.1, 122.9, 121.9, 114.2 ppm. MS (EI) m/z (%) 200 (M+, 86); 202 (M++2, 100).

4-Bromo-3-hydroxybenzaldehyde 8c

Obtained from 3-hydroxybenzaldehyde as white solid which was recrystallized from acetic acid (4.11 g, 25%); mp 71-72 °C. IR (film): 3281, 3064, 1684, 1585 cm⁻¹. 1H NMR (CDCl3, 200 MHz): δ 9.93 (s, 1H), 7.66 (d, 8.2 Hz, 1H), 7.50 (d, 1.8 Hz, 1H), 7.34 (dd, 8.19, 1.7 Hz, 1H), 5.97 (s, 1H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 191.5, 159.2, 134.7, 129.1, 117.6, 112.6 ppm. MS (EI) m/z (%) 214 (M+, 45); 259 (M++2, 48), 63 (100).

General procedure to obtained nitroolefins of 10a-c

To a solution of 9a, 9b or 9c (1.00 g, 4.65 mmol) in glacial AcOH (10 mL) was added AcONH2 (0.36 g, 4.65 mmol) and nitromethane (1.73 mL). The solution was heated under reflux for 1 h. The mixture was cooled to rt. and treated with water (20 mL). A precipitate was formed which was collected by filtration. The solid was dissolved with methylene chloride, filtered through a plug of silica gel and dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a yellowish solid which was recrystallized with methylene chloride.

(E)-1-bromo-4-methoxy-2-(2-nitrovinyl)benzene 10a

Obtained from 9a as with crystals (956 mg, 80%); mp 106-107 ºC. IR (film): 3110, 2837, 1589, 1510 cm⁻¹; 1H-NMR: δ 8.45 (d, 14.0 Hz, 1H), 7.51 (d, 14.0 Hz, 1H), 7.34 (t, 8.0 Hz, 1H), 7.16 (dd, 7.7, 2.0 Hz, 1H), 7.01 (dd, 7.5, 2.0 Hz, 1H), 3.94 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 156.5, 138.4, 137.7, 135.1, 134.5, 128.7, 120.4, 116.1, 114.4, 56.7 ppm. MS (EI) m/z (%) 257 (M+, 45); 259 (M++2, 48), 63 (100).

(E)-2-bromo-1-methoxy-3-(2-nitrovinyl)benzene 10b

Obtained from 9b as with crystals (991 mg, 83%); mp 106-107 ºC. IR (film): 3111, 2838, 1632, 1512 cm⁻¹; 1H-NMR: δ 8.45 (d, 14.0, 1H), 7.51 (d, 14.0 Hz, 1H), 7.34 (t, 8.0 Hz, 1H), 7.16 (dd, 7.7, 2.0 Hz, 1H), 7.01 (dd, 7.5, 2.0 Hz, 1H), 3.94 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 156.9, 139.1, 138.2, 129.2, 128.7, 120.4, 116.1, 114.4, 56.7 ppm. MS (EI) m/z (%) 257 (M+, 45); 259 (M++2, 23), 63 (100).

(E)-2-bromo-2-methoxy-4-(2-nitrovinyl)benzene 10c

Obtained from 9c as with crystals (1015 mg, 85%); mp 166-167 ºC. IR (film): 3116, 2942, 1629, 1502 cm⁻¹; 1H-NMR: δ 7.95 (d, 13.8 Hz, 1H), 7.62 (d, 7.8 Hz, 1H), 7.58 (d, 13.4 Hz, 1H), 7.04 (dd, 8.1, 1.8 Hz, 1H), 6.99 (d, 1.6 Hz, 1H), 3.95 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 156.5, 138.4, 137.7, 135.1, 134.5, 122.7, 121.4, 111.6, 114.4, 56.7 ppm. MS (EI) m/z (%) 257 (M+, 15); 259 (M++2, 14), 63 (100).

General procedure to obtained compounds 11a-c

To a solution of 10a, 10b or 10c (1.0 g, 3.87 mmol) in CH2Cl2 (20 mL) was added thioiphenol (5.25 mmol, 0.54 mL) and 4 drops of N-isopropylicyclo hexylamine. The resulting mixture was stirred for 1 h at rt. The mixture was concentrated and subjected to flash chromatography on silica gel using hexane/CH2Cl2 (80:20) as eluting solvent to give a brownish oil.

2-(2-Bromo-5-methoxyphenyl)-2-(thiophenyl)-1-nitrothane 11a

Obtained from 10a (1207 mg, 85%). IR (film): 3005, 2936, 1593 cm⁻¹; 1H-NMR: δ 7.50-7.20 (m, 6H, 6H), 6.72 (bs, 2H), 5.35 (t, 7.4 Hz, 1H), 4.88 (dd, 13.0, 8.8 Hz, 1H), 4.71 (dd, 13.0, 7.0 Hz, 1H), 3.94 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 191.4, 153.2, 134.7, 129.1, 121.9, 114.2 ppm. MS (EI) m/z (%) 257 (M+, 40); 259 (M++2, 48), 63 (100).
H-NMR: δ 7.44 (d, 8.8 Hz, 1H), 7.30-7.21 (m, 5H), 1.66 (bs, 2H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 156.2, 140.9, 131.8, 129.1, 128.3, 127.2, 121.0, 114.66, 110.9, 56.6, 55.4, 47.0 ppm. MS (EI) m/z (%) 337 (M⁺, 5); 369 (M⁺+2, 5), 258 (100).

2-(4-bromo-3-methoxyphenyl)-2-(phenylthio)ethanamine 12b

Obtained from 11a (200.25 mg, 40%). IR (film): 3372, 3057, 2936 cm⁻¹. 1H-NMR: δ 744 (d, 8.0 Hz, 1H), 7.30-7.21 (m, 5H), 6.77-6.72 (m, 2H), 4.12 (t, 8.0 Hz, 1H), 3.87-382 (m, 2H), 3.82 (s, 3H), 1.99 (bs, 2H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 156.0, 141.3, 133.8, 133.4, 132.9, 129.1, 121.4, 111.7 110.8, 56.3, 56.3, 48.0 ppm. MS (EI) m/z (%) 337 (M⁺, 5); 369 (M⁺+2, 5), 258 (100).

General procedure to obtained amides 13a-c

To a solution of 12a, 12b or 12c (300.0 mg, 0.88 mmol) in CH₂Cl₂ (10 mL) and added a catalytic amount of DMAP and benzoyl chloride (136.23 mg, 0.97 mmol) and stirred for 3 h. The mixture was concentrated in vacuo, and the residue was purified by circular chromatography using hexane/CH₂Cl₂ (1:1) as eluting solvent. Removal of the solvent gave colorless oils

N-(2-(4-bromo-3-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13a

Obtained from 12a (372.7 mg, 95%). IR (film): 3329, 3059, 2967, 1639, 1542 cm⁻¹. 1H-NMR: δ 7.66-7.22 (m, 11H), 6.95 (d, 3.0 Hz, 1H), 6.69 (dd, 8.9, 3.0 Hz, 1H), 6.36 (bs, 1H), 5.00 (t, 8.0 Hz, 1H), 3.91 (t, 7.0 Hz, 2H), 3.73 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 167.7, 159.4, 139.4, 134.9, 133.8, 132.3, 131.7, 130.3, 129.3, 128.7, 127.8, 127.1, 115.6, 115.2, 114.4, 55.7, 51.1, 44.2 ppm. MS (EI) m/z (%) 441 (M⁺, 69); 443 (M⁺+2, 67), 105 (100).

N-(2-(4-bromo-3-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13b

Obtained from 12b (334.8 mg, 86%). IR (film): 3224, 3059, 2932, 1645, 1574 cm⁻¹. 1H-NMR: δ 7.63-7.60 (m, 2H), 7.50-7.35 (m, 5H), 7.29-7.21 (m, 4H), 7.07 (dd, 8.0, 1.4 Hz, 1H), 6.82 (dd, 8.0, 1.4 Hz, 1H), 6.37 (bs, 1H), 5.16 (t, 7.0 Hz, 1H), 3.93 (t, 7.0 Hz, 2H), 3.90 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 167.6, 156.2, 142.0, 133.7, 132.1, 131.7, 130.3, 129.3, 128.7, 128.5, 127.7, 127.1, 120.8, 114.6, 111.3, 56.6, 51.1, 44.3 ppm. MS (EI) m/z (%) 441 (M⁺, 35); 443 (M⁺+2, 64), 105 (100).

N-(2-(4-bromo-3-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13c

Obtained from 12c (315.3 mg, 81%). IR (film): 3342, 3059, 2928, 1639, 1577 cm⁻¹. 1H-NMR: δ 7.66-7.24 (m, 11H), 6.82-6.77 (m, 2H), 6.51 (t, 6.0 Hz, 1H), 4.49 (t, 8.0 Hz, 1H), 3.93-
Syntheses of Three Mono-Brominated Enamide Analogs of Natural Alkaloids Isolated from the Tasmanian Marine

383 (m, 2H), 3.79 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz); δ 167.8, 156.1, 140.5, 133.8, 133.6, 132.5, 131.9, 130.3, 129.3, 128.8, 128.6, 127.0, 121.2, 111.7, 111.1, 56.3, 52.3, 44.7 ppm. MS (EI) m/z (%) 441 (M+, 14); 443 (M+2, 17), 105 (100).

**General procedure to obtained enamides 14a-c**

To a solution of 13a, 13b or 13c (100.0 mg, 0.22 mmol) in methanol (7 mL) was added a solution of sodium periodate (70.6 mg, 0.33 mmol) in water (7 mL) and the resulting mixture heated under reflux for 1 h. The methanol was removed in vacuo and the aqueous residue was extracted with methylene chloride (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a brownish oil. The crude product was then used in the next step without purification. The sulfoxide was dissolved in toluene (15 mL), sodium carbonate was added (30 mg) and the mixture heated under reflux for 3 h. The solvent was removed under vacuum, added water (15 mL) and extracted into methylene chloride (3 X10 mL), dried over anhydrous sodium sulfate and the solvent removed to give an oil. The residue was purified by circular chromatography using CH2Cl2/Methanol (95:5) to give a brownish oil

(E)-N-(2-bromo-5-methoxystyryl)benzamide 14b

Obtained from 13b (40.92 mg, 56%). IR (film): 2942, 1592, 1547 cm−1. 1H-NMR: δ 8.18 (d, 11 Hz, 1H), 7.9-7.8 (m, 2H), 7.72 (dd, 14.0, 11.0 Hz, 1H), 7.60-7.45 (m, 3H), 7.25-7.20 (m, 2H), 6.77 (ddd, 7.0, 1.2 Hz, 1H), 6.70 (d, 14.0, Hz 1H), 3.91 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 164.7, 159.2, 133.6, 133.3, 133.2, 129.0, 127.3, 125.2, 115.2, 114.0, 112.5, 110.5, 55.7 ppm. MS (EI) m/z (%) 331 (M+, 29); 333 (M+2, 14), 77 (100).

(E)-N-(4-bromo-3-methoxystyryl)benzamide 14c

Obtained from 13c (26.3 mg, 36%). IR (film): 3059, 3010, 2942, 1592, 1547 cm−1. 1H-NMR: δ 8.04 (d, 11Hz, 1H), 7.88-7.83 (m, 2H), 7.75 (dd, 14.4, 11.0 Hz, 1H), 7.52-7.42 (m, 4H), 6.89 (d, 1.8 Hz, 1H), 6.78 (dd, 8.0, 1.8 Hz, 1H), 6.21 (d, 14.4, Hz 1H) 3.91 (s, 3H) ppm. 13C NMR: (CDCl3, 50 MHz): δ 164.7, 156.1, 133.5, 133.4, 132.5, 129.2, 129.0, 127.3, 128.8, 119.8, 112.9, 110.0, 108.5, 56.4 ppm. MS (EI) m/z (%) 331 (M+, 29); 333 (M+2, 22), 77 (100).

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**References**

20. Data collected at 294 K using highly oriented graphite crystal monochromated MoKα radiation. The structure was solved by direct methods and non-hydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 7.79%, wR2 = 20.77%. The crystal data are a = 7.790(3) Å b = 9.113(2) Å c = 9.968(4) Å, α = 90°, β = 97.06 (3°), γ = 90°, V = 702.2(4) Å3, space group P21/n. CCDC number 779842 for compound 8c.