Oxidative Routes to the Heterocyclic Cores of Benzothiazole Natural Products

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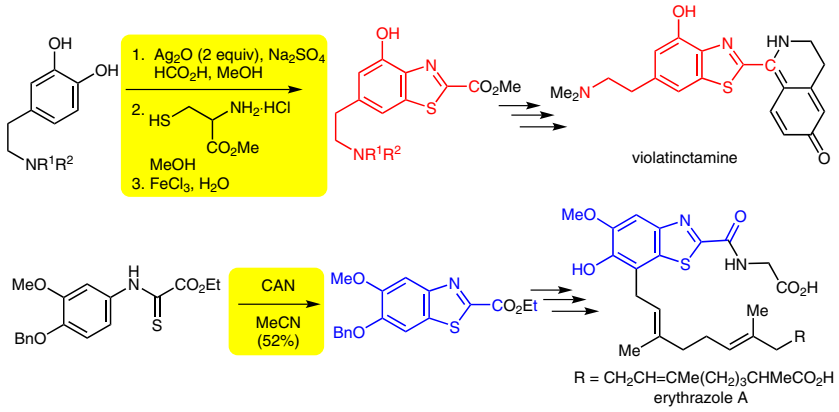
Dedicated to Professor Steve Ley FRS in celebration of his 70th birthday, and of his many outstanding contributions to organic synthesis



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Abstract Methyl 6-(2-acetylaminoethyl)-4-hydroxy-benzothiazole-2-carboxylate, the benzothiazole core of the natural product violatinctamine, was prepared in a biomimetic oxidative route from *N*-acetyldopamine and cysteine methyl ester. In an alternative oxidative cyclization, ethyl 6-benzyloxy-5-methoxybenzo[*d*]thiazole-2-carboxylate, the heterocyclic core of erythrazole A, was also prepared.

Key words heterocycles, natural products, amino acids, quinones, oxidation

Amino acids serve as precursors to a wide range of naturally occurring substances including alkaloids and antibiotics, many of which contain heterocyclic rings. One interesting subset of these heterocyclic natural products is biosynthesized from cysteine, and therefore contains both nitrogen and sulfur atoms. Whilst the simplest N,S-heterocycle – thiazole – is relatively common in nature, benzothiazoles, on the other hand, are relatively rare as natural products, possibly because the biosynthetic route to the ring system is more complex than for thiazoles themselves. Nevertheless, well-known examples include firefly luciferin (**1**) and rifamycin P (**2**, Figure 1). We now report oxidative routes to the heterocyclic core of two more recently isolated benzothiazoles, violatinctamine (**3**),[1] and erythrazole A (**4**, Figure 1).[2]

Violatinctamine (**3**) was isolated from the Kenyan marine tunicate *Cystodytes cf. violatinctus* and exists as a mixture of two tautomers, the amino quinone methide (shown) and the iminophenol. By analogy with the biosynthesis of luciferin,[3] and of the red hair pigments pheomelanins,[4] the

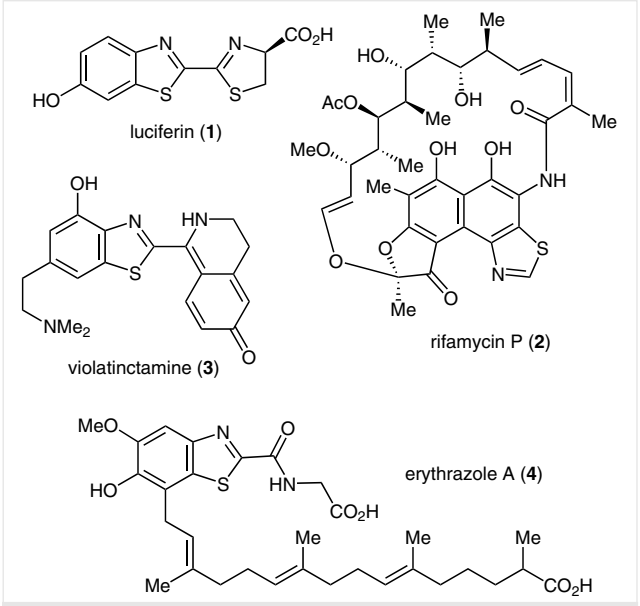
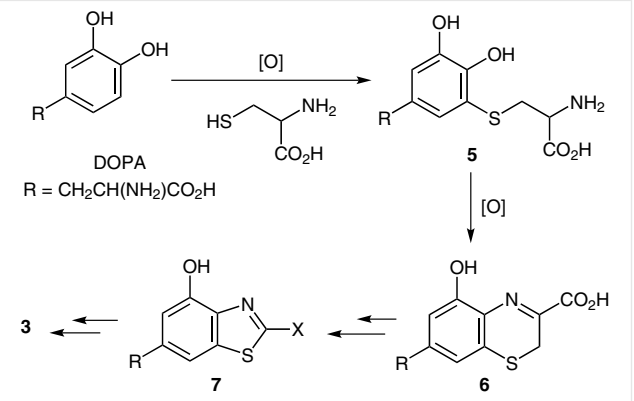
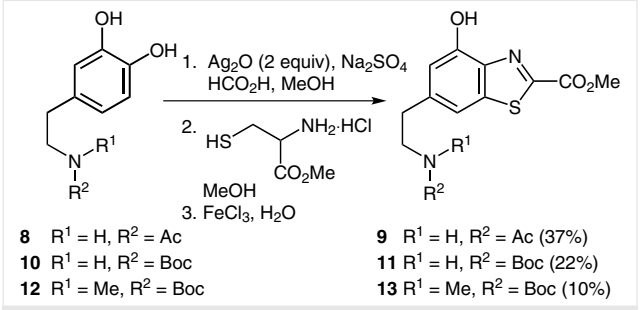


Figure 1 Some naturally occurring benzothiazoles

isolation chemists suggested that the benzothiazole core of violatinctamine (**3**) could derive by addition of cysteine to a benzoquinone.[1] In this proposal, cysteine adds to the *ortho*-quinone, formed by oxidation of DOPA, to give 5-*S*-cysteinyl-DOPA (**5**), which upon further oxidation gives the benzothiazine **6** that undergoes ring contraction to the key benzothiazole **7** (X = CHO or CO_2H, Scheme 1). Therefore, inspired by the possibility of a biomimetic route to violatinctamine (**3**), we undertook the preparation and oxidation of a number of dopamine derivatives.



Scheme 1 Proposed biosynthesis of violatinctamine (**3**)[1]



Scheme 2 Biomimetic oxidative route to benzothiazole core of violatinctamine (**3**)

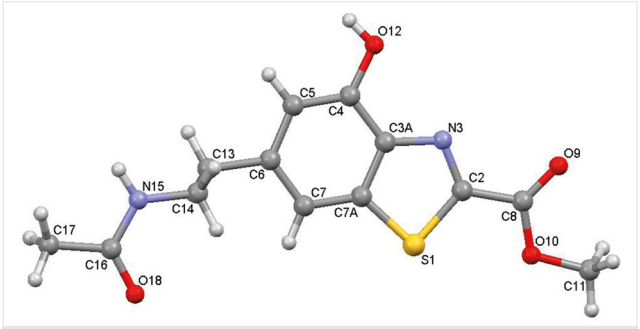
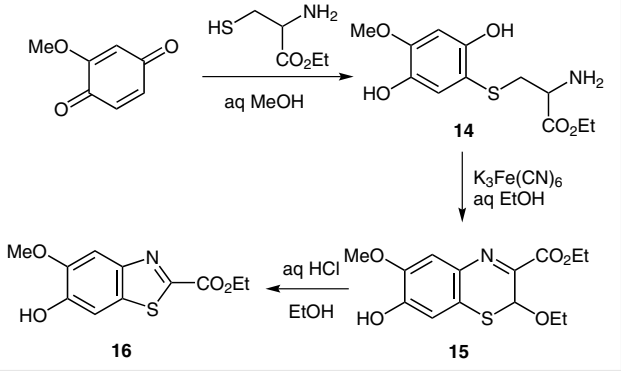


Figure 2 X-ray crystal structure of methyl 6-(2-acetylaminoethyl)-4-hydroxybenzothiazole-2-carboxylate (**9**)

A range of ten N-protected derivatives of dopamine was prepared (see Supporting Information), and their oxidation in the presence of cysteine methyl ester investigated. A number of reagents are reported to oxidize DOPA derivatives to the corresponding *ortho*-quinones, including cerium(IV) ammonium nitrate (CAN),[5] DDQ,[6] and tyrosinase,[7] but we elected to use silver(I) oxide.[8] Thus, silver(I) oxide was added to *N*-acetyldopamine (**8**) in methanol; after 15 minutes the black suspension was filtered to give a red solution of the *ortho*-quinone that was immediately added to a solution of cysteine methyl ester in methanol to give the corresponding cysteinyl dopamine. The oxidative cyclization of such compounds is often carried out using potassium ferricyanide,[4] but in our hands this was unsatisfactory. In the event, the intermediate cysteinyl acetyldopamine was not isolated, but treated with aqueous iron(III) chloride to give the desired benzothiazole **9** in 37% yield from dopamine **8** (Scheme 2),[9] the structure being confirmed by X-ray crystallography (Figure 2). The intermediate benzothiazine analogous to compound **6** was not observed. Similarly, *N*-Boc dopamine (**10**) and *N*-Boc epinine (**12**) gave the corresponding benzothiazoles **11** and **13**, but in poor yield (Scheme 2), whilst the remaining dopamine derivatives (see Supporting Information) did not deliver the required heterocycles. Nevertheless, despite the modest 37% yield, this biomimetic oxidative route does give access to the benzothiazole core **9** of violatinctamine (**3**) in a fascinating sequence of reactions from simple, readily available starting materials, and paved the way for a similar approach to the benzothiazole core of erythrazole A (**4**).

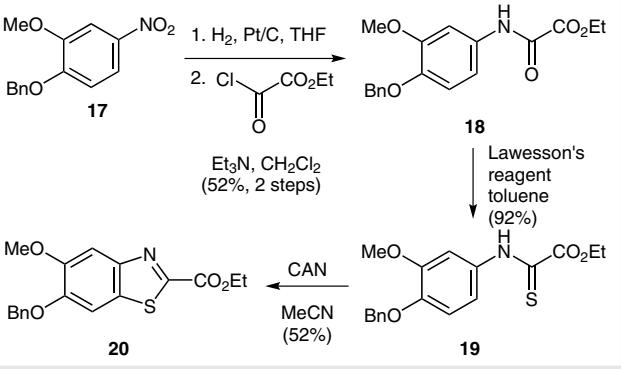
Erythrazole A (**4**) was isolated from an *Erythrobacter* strain of marine-derived bacteria as a 1.0:0.6 mixture of enantiomers.[2] Again, by analogy with the biosynthesis of luciferin,[3] it was proposed that the natural product arose from addition of cysteine to a 6-substituted 2-methoxy-1,4-benzoquinone.[2] Indeed the addition of cysteine ethyl ester to 1,4-benzoquinone itself is a well-established route to ethyl 6-hydroxybenzothiazole-2-carboxylate,[3,10] and therefore seemed an ideal starting point for a biomimetic synthesis of the benzothiazole core of erythrazole A (**4**). Addition of cysteine ethyl ester hydrochloride to 2-methoxy-1,4-benzoquinone proceeded smoothly but the isolated yield of the cysteine adduct **14** was extremely poor (14%). Therefore the sequence was repeated without isolation of the intermediate **14** by direct oxidation of the reaction mixture with potassium ferricyanide, the preferred oxidant for such reactions,[3,10] giving an inseparable mixture of benzothiazine **15** and the desired benzothiazole **16** (Scheme 3). Treatment of the mixture with hydrochloric acid[10] led to the ring contraction of the benzothiazine **15** to giving the desired benzothiazole **16** in an overall of 9% over three steps from 2-methoxy-1,4-benzoquinone. Although the yield of the benzothiazole core of erythrazole A (**4**) is poor, the sequence does establish the viability of a biomimetic oxidative route.

In view of the poor yield in the above biomimetic route to benzothiazole **16**, we investigated an alternative oxidative cyclization from a thioamide. The cyclization of thioamides to benzothiazoles does have some precedent, and was used in the first synthesis of firefly luciferin.[11] The route started from 4-benzyloxy-3-methoxynitrobenzene (**17**) that was reduced and acylated to give the oxalamide **18**. Conversion into the corresponding thioamide **19** proceeded in excellent yield, and the key oxidative cyclization



Scheme 3 Biomimetic oxidative route to benzothiazole core of erythrazole A (**4**)

step was attempted using potassium ferricyanide as reported in the firefly luciferin synthesis.[11] Unfortunately, this failed to deliver the desired benzothiazole, and therefore a change in oxidant was instigated. Two alternatives were considered – cerium(IV) ammonium nitrate and phenyliodine(III)diacetate – but based on a recent comparative study,[12] we elected to use CAN. Treatment of the thioamide **19** with CAN in acetonitrile at 0 °C resulted in cyclization to the benzothiazole **20** in 52% yield (Scheme 4),[13] thereby completing a practical route to the heterocyclic core of erythrazole A (**4**).



Scheme 4 Oxidative cyclization of thioamide to benzothiazole core of erythrazole A (**4**)

Hence we have developed routes to the heterocyclic cores of two naturally occurring benzothiazoles – violatinctamine and erythrazole A – based on oxidative cyclization reactions. Further studies towards a total synthesis of the natural products are in progress.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560722.

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(9) **Methyl 6-(2-Acetylaminoethyl)-4-hydroxy-benzothiazole-2-carboxylate (9)**
Ag_2O (256 mg, 1.1 mmol) and Na_2SO_4 (251 mg, 1.8 mmol) were added to a solution of *N*-acetyldopamine (**8**, 60 mg, 0.3 mmol) and formic acid (42 µL, 1.1 mmol) in MeOH (4 mL), and the black suspension was stirred for 15 min in the dark at r.t. then filtered through a pad of Celite®. The filter cake was washed with MeOH (2 × 6 mL), and the combined red filtrates were immediately added dropwise to a solution of cysteine methyl ester hydrochloride (57 mg, 0.3 mmol) in MeOH (2 mL). After addition had completed the pale green solution was concentrated to give the cysteine adduct as a pale yellow–green foam that was used directly without purification {HRMS: *m/z* calcd for $C_{14}H_{21}N_2O_5S^+$: 329.1166; found [M + H$^+$]: 329.1160}. The above foam was dissolved in H_2O (0.7 mL) and a solution of $FeCl_3{\cdot}6H_2O$ (442 mg, 1.6 mmol) in H_2O (1.8 mL) was slowly added dropwise with vigorous stirring. The mixture was stirred for 72 h at r.t., then diluted with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was subjected to flash column chromatography on silica gel, eluting with EtOH–AcOH (1:9) to give the title compound as yellow solid (34 mg, 37% over two steps); mp 143–144 °C. HRMS: *m/z* calcd for $C_{13}H_{15}N_2O_4S^+$: 295.0747; found [M + H$^+$]: 295.0742. IR ($CHCl_3$): ν_{max} = 3522, 3011, 2414, 1722, 1603, 1497, 1192 cm^{-1}. UV-Vis (MeCN): λ_{max} = 264 (log ε 3.15), 312 (log ε 3.58) nm. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.44 (1 H, br s), 7.79 (1 H, br s), 7.46 (1 H, s), 6.94 (1 H, s), 4.01 (3 H, s), 3.57–3.53 (2 H, m), 2.96–2.93 (2 H, m), 2.02 (3 H, s). ^{13}C NMR (100 MHz, acetone-d_6): δ = 172.8 (C), 161.5 (C), 155.5 (C), 153.7 (C), 143.0 (C), 124.9 (C), 139.1 (C), 113.9 (CH), 113.6 (CH), 53.7 (Me), 41.8 (CH_2), 36.4 (CH_2), 20.9 (Me).
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(13) **Ethyl 6-Benzyloxy-5-methoxybenzo[*d*]thiazole-2-carboxylate (20)**

To a solution of ethyl 2-(4-benzyloxy-3-methoxyphenyl)amino)-2-thioxoacetate (**19**, 2.5 g, 7.2 mmol) in MeCN (175 mL) at 0 °C was added CAN (9.86 g, 18 mmol) in H_2O (175 mL). The reaction mixture was stirred for 1.5 h, then diluted with H_2O (200 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were combine, washed with brine (2 × 200 mL), then dried over $MgSO_4$ to give the title compound as a beige solid (1.28 g, 52%); mp 116 °C. HRMS: *m/z* calcd for $C_{18}H_{18}NO_4S$: 344.0951; found $[M + H]^+$: 344.0961. IR ($CHCl_3$): ν_{max} = 3009, 1714, 1607, 1497 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (1 H, s), 7.45–7.31 (6 H, m), 5.24 (2 H, s), 4.52 (2 H, q, *J* = 7.1 Hz), 3.97 (3 H, s), 1.47 (3 H, t). ^{13}C NMR (100 MHz, $CHCl_3$): δ = 160.7 (C), 156.2 (C), 150.9 (C), 149.9 (C), 148.2 (C), 136.1 (C), 129.8 (C), 128.7 (CH), 128.2 (CH), 127.3 (CH), 106.0 (CH), 104.1 (CH), 71.3 (CH_2), 62.8 (CH_2), 56.2 (Me), 14.3 (Me).