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Short Note

1-Tosyl-6-vinyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole-2-amine

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Abstract: The alkene functionalised 2-aminobenzimidazole ring found in terrazoanthine natural products was synthesized in 3 steps from 1,2-epoxy-4-vinylcyclohexane via epoxide ring opening with toluenesulphonamide yielding 2 regioisomeric, separable amino alcohols. One isomer was oxidized to the corresponding ketone and subsequently condensed with cyanamide to furnish the title compound, which was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords: natural products; synthesis; NMR spectroscopy; condensation; 2-aminoimidazole

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1. Introduction

The terrazoanthines (A–C) are a family of 2-aminoimidazole alkaloids isolated from the marine invertebrate group, the zoantharians, off the coast of Ecuador by Thomas et al. [1] These compounds give an insight into the chemical content of *Terrazoanthus onoi*. Terrazoanthine A and B both contain a previously unknown 6-(imidazol-5-yl)benzo[d]imidazole skeleton (Figure 1).

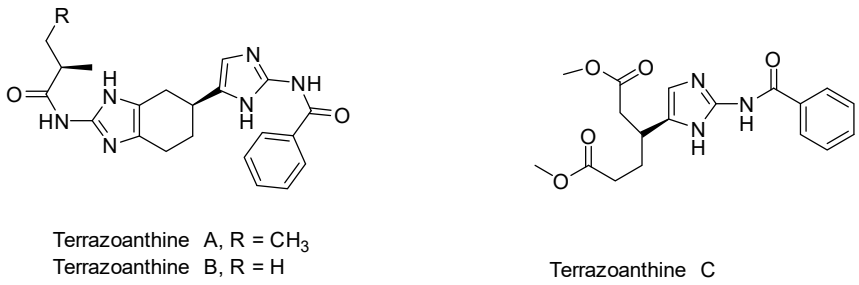


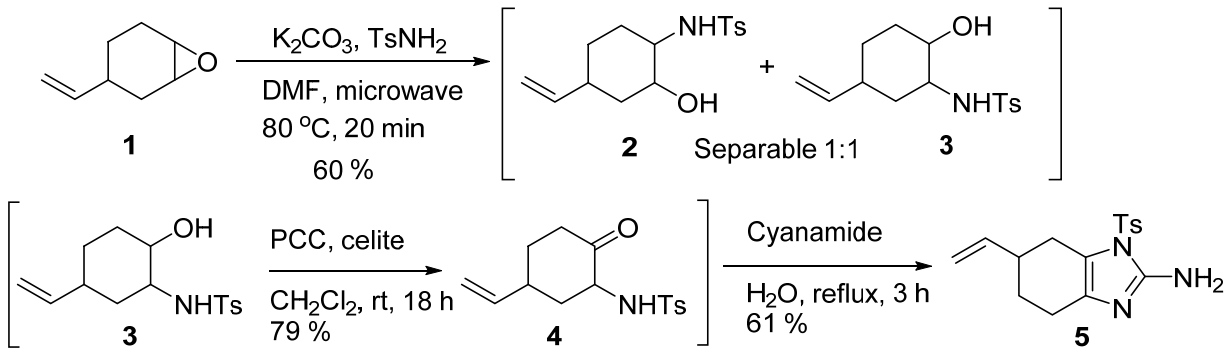
Figure 1. Structure of Terrazoanthines A–C.

The 2-aminoimidazole ring is an interesting structural moiety in medicinal chemistry. Biological targets containing glutamate and aspartate residues can interact with the 2-aminoimidazole ring via four hydrogen bonds. [2] It has also been utilized as a bioisostere for the replacement of guanidine, benzamidine and triazole groups in biologically active compounds [3–5]. There have been several 2-aminoimidazole natural products that have been the synthesized including sceptrin [6,7], ageliferin [7,8] and dragmacidins D and F [9,10]. We envisaged that the 2-aminoimidazole ring could be installed via a condensation strategy using an α-amino ketone. Alternative strategies have been reported for 2-aminoimidazole synthesis, including reaction of α-halo ketones with guanidine salts [11], or lithiation of imidazoles and subsequent quenching with an electrophilic source of azide and subsequent hydrogenolysis to yield the 2-aminoimidazole functionality [12].

2. Results and Discussion

The synthesis was commenced from commercially available 4-vinyl-1-cyclohexene 1,2-epoxide, mixture of isomers 1. The epoxide underwent aminolysis with *p*-toluenesulfonamide

under microwave irradiation, using conditions similar to those reported by Yang and Murray [13], giving two separable, regioisomeric amino alcohols 2 and 3. The more polar isomer 3 (R_f 0.22, EtOAc-cyclohexane, silica plates) was isolated and then oxidised with PCC in dichloromethane and the resulting ketone 4 was condensed with cyanamide by heating at reflux in H_2O to give the 2-aminoimidazole 5 containing the fused ring of terrazoanthine A/B (Scheme 1). Efforts to transform the alkene 5 into functional groups that would enable a second 2-aminoimidazole ring to be incorporated have not been successful to date in our hands. Reactions investigated have included aziridination with chloramine-t hydrate-trimethylphenyl ammonium bromide (decomposition); dihydroxylation with OsO_4 (recovered reactant), $RuCl_3$-$NaIO_4$-$CeCl_3$ (decomposition), I_2-AgOAc (decomposition), epoxidation with mCPBA (recovered reactant) and halohydrin formation with NBS/NIS/NCS (recovered reactant). The structural assignment is supported by gHMBCAD experiments combined with gHSQCAD in 4. The CH_2 signals between the CHs with the vinyl and Ts groups appear as 2 multiplets at δ 2.63 and δ 1.78 ppm. In the gHMBCAD this CH_2 signal (ms at δ 2.63 (weak) and δ 1.78 (strong)) ppm show crosspeaks to the ^{13}C signal for the CH bonded to the NHTs group (δ 56.95 ppm). The signal at δ 1.78 ppm also showed strong crosspeaks with the signal for the C = O (δ 205.86 ppm) and the alkene CH (δ 138.5 ppm) indicating this proton is located on the CH_2 between the NHTs and vinyl groups. In addition, the NMR assignments for **5** determined by 2D gCOSY, gHSQCAD and gHMBCAD and 2D-NOESY are shown in Figure 2. In the NOESY a cross peak between the multiplet at δ 2.76–2.84 ppm and the Ts protons supported the placement of the Ts group on the nitrogen atom closest to this proton.



Scheme 1. Synthesis of **5**.

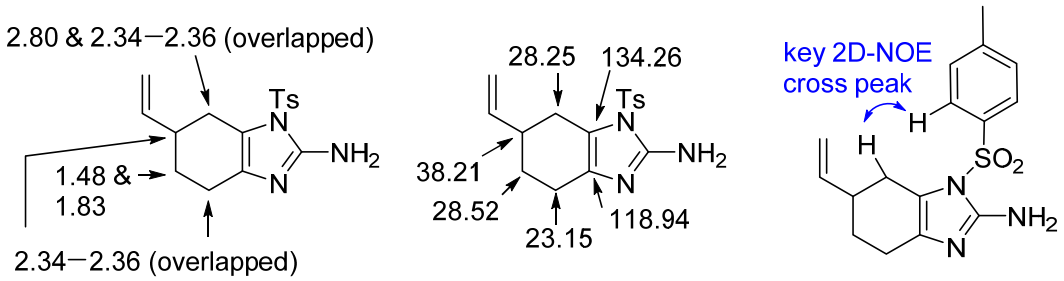


Figure 2. Selected ^1H-NMR (left) and ^{13}C-NMR assignments (middle) and observed NOE (right). All values given are chemical shifts (δ) in ppm.

3. Conclusions

The fused core of terrazoanthines A/B natural products were synthesized in 3 steps via epoxide aminolysis, oxidation and condensation strategy to yield the fused 2-aminoimidazole heterocycle, with the structure determined by a combination of 1D and 2D NMR spectroscopic techniques (Supplementary Materials).

4. Materials and Methods

4.1. General Information

All reagents used were from commercial sources and used without further purification. TLC experiments were performed using aluminum sheets pre-coated with silica gel 60 (HF254, E. Merck, Darmstadt, Germany). NMR experiments were carried out in $CDCl_3$ using a 500 MHz spectrometer (Varian Ltd (Agilent), CA, Palo Alto, USA), with the chemical shifts reported relative to internal Me_4Si (δ 0.00). NMR spectra were processed and analysed using MestReNova software. Signals from ^1H and ^{13}C spectra were assigned using 2D gCOSY, gHSQCAD & gHMBCAD spectroscopy and 2D-NOESY. J values are reported as observed. $CDCl_3$ (δ 77.16) and signals were used for assignment of ^{13}C signals. HRMS data were obtained using a Waters LCT Premier XE Spectrometer. Chromatography was performed with silica gel 60 (Sigma Aldrich, Wicklow, Ireland). IR spectra were measured for films on KBr plates.

*4.2. Tosyl-6-vinyl-4,5,6,7-tetrahydro-1 H-benzo[d]imidazole-2-amine (**5**)*

A 35 mL microwave tube was charged with *p*-toluenesulfonamide (1.7 g, 10 mmol, 1 equiv) and K_2CO_3 (2.7 g, 20 mmol, 2 equiv). *N*,*N*-Dimethylformamide (DMF, 20 mL) was then added followed by 4-vinyl-1-cyclohexene-1,2-epoxide **1** (mixure of isomers, 3.9 mL, 30 mmol, 3 equiv). The tube was sealed with a septum and heated to 80 °C under microwave irradiation for 20 min. The resulting black solution was poured into a biphasic mixture of Et_2O-H_2O (500 mL, 1:1). The mixture was shaken and the aqueous portion was further extracted with Et_2O (2 x 100 mL). The combined organic portions were washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield a dark brown oily residue. This was a mixture of two regioisomeric products (1.8 g, 1:1, 60%) with Rf values (1:1 EtOAc-cyclohexane) of 0.27 (**2**) and 0.22 (**3**). Silica gel chromatography was used to separate the products and the more polar isomer **3**, *N*-(2-hydroxy-5-vinylcyclohexyl)-4-methylbenzenesulfonamide, which co-eluted with a small amount of the p-toluenesulfonamide, was carried forward to the next stage. Analytical data for **3**: IR 3355, 3259, 3064, 1638, 1299, 1152, 1095 cm^{-1}; [^1H-NMR (500 MHz, $CDCl_3$) δ 7.78 (apt d, *J* = 8.3 Hz, 2H, Ar-H), 7.32 (apt d, *J* = 8.5 Hz, 2H, Ar-H), 5.62 (dddd, *J* = 17.4, 10.7, 5.2, 1.9 Hz, 1H, alkene C-H), 4.97 (d, *J* = 10.7 Hz, 1H, alkene C*H*(H)), 4.92 (d, *J* = 6.8 Hz, 1H, -NH), 4.80 (d, *J* = 17.4 Hz, 1H, alkene CH(H)), 3.41 (broad signal, 1H, C*H*-OH), 3.12 (m, 1H, CH-N), 2.43 (s, 3H, tosyl CH_3), 2.33 (m, 1H, C*H*-CH = CH_2), 1.31–1.85 (overlapped signals and ms, 6H, cyclohexane CH_2 signals); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 143.8 (aromatic C), 140.49 (alkene CH), 137.3 (aromatic C), 129.79 (Ar-CH), 127.22 (Ar-CH), 114.56 (Alkene CH_2), 72.40 (*C*H-O), 55.01 (*C*H-N), 35.40 (*C*H-CH = CH_2), 34.02 (CH_2), 28.42 (CH_2), 27.13 (CH_2, 21.54 (Tosyl CH_3); HRMS calc. for $C_{15}H_{22}O_3NS$ 296.1320 found $[M + H]^+$ 296.1319.

A solution of this intermediate 3 (1.8 g, 6.1 mmol) in CH_2Cl_2 (40 mL) was added to a flame dried 100 mL round bottom flask containing pyridinium chlorochromate (3.27 g, 15.2 mmol, 2.5 equiv) and celite. The resulting mixture was stirred overnight at room temperature, then diluted with Et_2O and filtered through silica gel, eluting with CH_2Cl_2. The filtrate was concentrated under reduced pressure and silica gel column chromatography (30% EtOAc in cyclohexane) gave 1.4 g of ketone 4 (4.8 mmol, 79% yield); IR 3292, 2930, 1716, 1639, 1417, 1325, 1158 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H, aromatic H), 7.27 (d, *J* = 8.4 Hz, 2H, aromatic H), 5.92 (dddd, *J* = 14.9, 10.7, 4.1, 2.0 Hz, 1H, alkene CH), 5.69 (d, *J* = 4.6 Hz, 1H, NH), 5.38–5.20 (overlapped signals, 2H, alkene CH_2), 3.91 (dt, *J* = 12.1, 5.0 Hz, 1H, C*H*-NHTs), 2.71–2.59 (overlapping signals, 2H), 2.40 (s, 3H, tosyl CH_3), 2.35 (overlapping signals, 2H), 2.15–2.05 (broad doublet (*J* = 13.0 Hz) or m, 1H), 1.93–1.83 (m, 1H), 1.78 (tdd, *J* = 13.0, 4.7, 2.1 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.86 (C1), 143.59 (Ar-C), 138.55 (alkene CH), 136.75 (Ar-C), 129.74 (Ar-CH), 127.00 (Ar-CH), 116.15 (alkene CH_2), 56.92 (CHN), 39.14 ($CHNHCH_2CH(vinyl)CH_2$), 36.81 (CH_2C = O), 34.77 (CHCH = CH_2), 30.76 (CH_2), 21.51 (CH_3). HRMS calc. for $C_{15}H_{20}O_3NS$ 294.1164 found $[M + H]^+$ 294.1150.

To a round bottom flask containing this ketone (1.4 g, 4.8 mmol) was added cyanamide (1.22 g, 29 mmol), H_2O (30 mL) and the mixture was heated to reflux for 3 h, then cooled to room temperature and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic portions were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Silica gel column chromatography (100% EtOAc) gave the title compound **5** as a greenish solid (925 mg, 2.9 mmol, 61%); IR 3463, 3072, 1638, 1561, 1362, 1162 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.82 (m, 1H, alkene CH), 5.45 (s, 2H, NH_2), 5.04 (br d, *J* = 17.3 Hz, 1H, alkene CH), 4.99 (br d or m, *J* = 10.3 Hz, 1H, alkene H), 2.84–2.76 (m, 1H), 2.42 (s, 3H, tosyl CH_3), 2.34–2.36 (overlapping signals, 4H), 1.83 (apt d or br d, *J* = 11.6 Hz, 1H), 1.52–1.44 (m, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 148.45 (imidazole C, *C*-NH_2), 145.71 (Ar-C), 142.10 (alkene C-H), 135.85 (Ar-C), 134.26 (imidazole C, C = *C*-NTs), 130.28 (Ar CH), 127.05 (Ar CH), 118.94 (imidazole C-CH_2), 113.74 (Alkene CH_2), 38.22 (CH), 28.52 (CH_2), 28.25 (CH_2), 23.15 (CH_2), 21.82 (Tosyl CH_3). HRMS calc. for $C_{16}H_{20}O_2N_3S$ 318.1276 found $[M + H]^+$ 318.1269.

Supplementary Materials: The following are available online, Various 1D and 2D NMR spectra of compounds **3**–**5**.

Author Contributions: F.B.M. conceived and designed the experiments, drafted the manuscript and made revisions; F.B.M. & S.O. performed the experiments; F.B.M., S.O. and P.V.M. analysed the data; P.V.M. is principal investigator and project director and contributed to the target selection, synthesis route design as well as correcting drafts and finalising the manuscript. All authors have read and agreed to the published version of the manuscript.

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