Short Note

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

Fiach B. Meany*, Sarah O’Rourke and Paul V. Murphy

School of Chemistry, National University of Ireland, H91 TK33 Galway, Ireland; f.meany1@nuigalway.ie (F.B.M.); sarahor21@gmail.com (S.O.)
* Correspondence: paul.v.murphy@nuigalway.ie; Tel.: +353-91-492-465

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 1H-NMR and 13C-NMR spectroscopy.

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

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.](https://doi.org/10.3390/M1262)

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 biosostere 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 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-toluenesulphonamide...
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 (Rf 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 H₂O 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 OsO₄ (recovered reactant), RuCl₃-NaIO₄-CeCl₃ (decomposition), I₂-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 CH₂ 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 CH₂ signal (ms at δ 2.63 (weak) and δ 1.78 (strong)) ppm show crosspeaks to the 13C 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 CH₂ 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.](image)

**Figure 2.** Selected ¹H-NMR (left) and ¹³C-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$_4$Si ($\delta$ 0.00). NMR spectra were processed and analysed using MestReNova software. Signals from $^1$H and $^{13}$C spectra were assigned using 2D gCOSY, gHSQCAD & gHMBCAD spectroscopy and 2D-NOESY. J values are reported as observed. CDCl$_3$ ($\delta$ 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-1H-benzo[d]imidazole-2-amine (5)

A 35 mL microwave tube was charged with p-toluenesulfonylamine (1.7 g, 10 mmol, 1 equiv) and K$_2$CO$_3$ (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 (mixture 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$_2$O-H$_2$O (500 mL, 1:1). The mixture was shaken and the aqueous portion was further extracted with Et$_2$O (2 x 100 mL). The combined organic portions were washed with saturated aqueous NH$_4$Cl (50 mL), brine (50 mL), dried over anhydrous Na$_2$SO$_4$, 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-methylbenzenesulfonylamine, which co-eluted with a small amount of the p-toluenesulfonylamine, was carried forward to the next stage. Analytical data for 3. IR 3355, 3292, 2930, 1638, 1517, 1325, 1158 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (aptd, J = 8.3 Hz, 2H, Ar-H), 7.32 (apt d, J = 8.5 Hz, 2H, Ar-H), 5.62 (ddddd, J = 17.4, 10.7, 5.2, 1.9 Hz, 1H, alkene CH), 4.97 (d, J = 10.7 Hz, 1H, alkene CH(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, CH(OH)), 3.12 (m, 1H, CH-CH = CH$_2$), 2.33 (m, 1H, CH-CH = CH$_2$), 1.31–1.85 (overlapped signals and ms, 6H, cyclohexene CH$_2$ signals); $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$ 143.8 (aromatic C), 140.49 (alkene CH), 137.3 (aromatic C), 129.79 (Ar-CH), 127.22 (Ar-CH), 129.01 (CH(OH)), 55.01 (CHN), 39.14 (CHNH$_2$); HRMS calc. for C$_{15}$H$_{22}$O$_3$NS 294.1164 found [M + H]$^+$ 294.1319.

A solution of this intermediate 3 (1.8 g, 6.1 mmol) in CH$_2$Cl$_2$ (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$_2$O and filtered through silica gel, eluting with CH$_2$Cl$_2$. 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$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 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, CH-CH(NH$_2$)), 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 (td, J = 13.0, 4.7, 2.1 Hz, 1H); $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$ 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 (CHNCH$_2$CH(=vinyl)CH$_2$), 36.81 (CH$_2$C = O), 34.77 (CHCH$_2$CH$_2$), 30.76 (CH$_2$), 21.51 (CH$_3$). HRMS calc. for C$_{15}$H$_{20}$O$_3$NS 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$_2$O (30 mL) and the mixture was heated to reflux for 3 h, then cooled to room temperature and extracted with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic portions were washed with brine (2 × 10 mL), dried over anhydrous Na$_2$SO$_4$, 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$_2$N$_5$S 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.

Funding: The material presented herein was funded in part by Science Foundation Ireland (Grant No. 16/1A/4419 to PM).

Institutional Review Board Statement: Not applicable.

Data Availability Statement: The data is reported in the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Guillen, P.O.; Jaramillo, K.B.; Genta-Jouve, G.; Sinniger, F.; Rodriguez, J.; Thomas, O.P. Terrazoanthines, 2-Aminoimidazolodialkooids from the Tropical Eastern Pacific Zoantharian Terrazoanthus Onoi. Org. Lett. 2017, 19, 1558–1561. [CrossRef] [PubMed]

2. Arita, K.; Hashimoto, H.; Shimizu, T.; Nakashima, K.; Yamada, M.; Sato, M. Structural Basis for Ca(2+)-Induced Activation of Human PAD4. Nat. Struct. Mol. Biol. 2004, 11, 777–783. [CrossRef] [PubMed]

3. Pitts, W.J.; Wityak, J.; Smallheer, J.M.; Tobin, A.E.; Jetter, J.W.; Buynitsky, J.S.; Harlow, P.P.; Solomon, K.A.; Corjay, M.H.; Mousa, S.A.; et al. Oxazolines as Potent Antagonists of the Integrin αβ3. J. Med. Chem. 2000, 43, 27–40. [CrossRef] [PubMed]

4. Huigens, R.W.; Reyes, S.; Reed, C.S.; Bunders, C.; Rogers, S.A.; Steinhauer, A.T.; Melander, C. The Chemical Synthesis and Antibiotic Activity of a Diverse Library of 2-Aminobenzimidazole Small Molecules against MRSA and Multidrug-Resistant A. Baumannii. Bioorganic Med. Chem. 2010, 18, 663–674. [CrossRef] [PubMed]

5. Rogers, S.A.; Bero, J.D.; Melander, C. Chemical Synthesis and Biological Screening of 2-Aminoimidazolodialkooids Based on Aromatic and Fungal Antibiofilm Agents. ChemBioChem 2010, 11, 396–410. [CrossRef] [PubMed]

6. Baran, P.S.; Zografos, A.L.; O’Malley, D.P. Short Total Synthesis of (±)-Sceptrin. J. Am. Chem. Soc. 2004, 126, 3726–3727. [CrossRef] [PubMed]

7. Baran, P.S.; Li, K.; O’Malley, D.P.; Mitsos, C. Short, Enantioselective Total Synthesis of Sceptrin and Ageliferin by Programmed Oxaquaricyclane Fragmentation. Angew. Chem. Int. Ed. 2005, 44, 249–252. [CrossRef] [PubMed]

8. Baran, P.S.; O’Malley, D.P.; Zografos, A.L. Sceptrin as a Potential Biosynthetic Precursor to Complex Pyrrole-Imidazole Alkaloids: The Total Synthesis of Sceptrin. Angew. Chem. Int. Ed. 2004, 43, 2674–2677. [CrossRef] [PubMed]

9. Garg, N.K.; Sarpong, R.; Stoltz, B.M. The First Total Synthesis of Draggmacidin D Protocols from a Number of Deep Water Sponges Including. J. Am. Chem. Soc. 2002, 124, 13179–13184. [CrossRef] [PubMed]

10. Garg, N.K.; Caspi, D.D.; Stoltz, B.M. The Total Synthesis of (+)-Drgagmacidin F. J. Am. Chem. Soc. 2004, 126, 9552–9553. [CrossRef] [PubMed]

11. Little, T.L.; Webber, S.E. A Simple and Practical Synthesis of 2-Aminoimidazoles. J. Org. Chem. 1994, 59, 7299–7305. [CrossRef]
12. Sullivan, J.; Giles, R.; Looper, R. 2-Aminoimidazoles from Leucetta Sponges: Synthesis and Biology of an Important Pharmacophore. *Curr. Bioact. Compd.* 2009, 5, 39–78. [CrossRef]

13. Yang, S.M.; Murray, W.V. Microwave Assisted Ring-Opening of Epoxides with N-Biaryl Sulfonamides in the Synthesis of Matrix Metalloproteinase-9 Inhibitors. *Tetrahedron Lett.* 2008, 49, 835–839. [CrossRef]