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Short Note

5-Amino-3-(diethylamino)-5*H*-benzo[4,5]imidazo [1,2-*b*][1,2,4,6]thiatriazine 1,1-Dioxide

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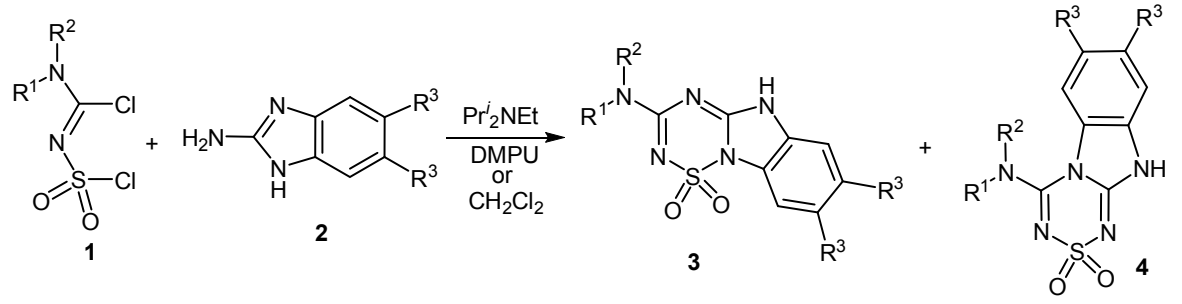
Abstract: In the quest for discovery of novel bioactive molecules, new heterocyclic ring systems provide templates for exploration of uncharted chemical space. Herein, we describe the synthesis of a new benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine derivative from readily available 1,2-diaminobenzimidazole and *N*,*N*-diethyl-*N*′-chlorosulfonyl chloroformamidine. The product structure, confirmed by X-ray crystallography, bears an exocyclic NH_2 group, which should enable synthesis of an extended range of derivatives of this unusual scaffold.

Keywords: heterocycle; *N*,*N*-dialkyl-*N*′-chlorosulfonyl chloroformamidine; aminobenzimidazole; thiatriazine; X-ray crystallography

1. Introduction

The immense biological and industrial significance of heterocyclic compounds [1] ensures that considerable research effort continues to be directed toward the discovery of convenient and efficient synthetic routes to such molecules. Importantly, the construction of new heterocyclic ring systems can provide templates and building blocks for exploration of uncharted chemical space, which is free of competing intellectual property claims.

During the course of an ongoing research program which produced a cornucopia of new and unusual heterocyclic ring systems from *N*,*N*-dialkyl-*N*′-chlorosulfonyl chloroformamidines (**1**) [2], we established that the regioselective reaction of dichlorides **1** with 2-aminobenzimidazoles (**2**), in the presence of Hünig's base, afforded benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine 1,1-dioxides (**3**) and, on occasion, minor proportions of the isomeric benzo[4,5]imidazo[2,1-*c*][1,2,4,6]thiatriazine 2,2-dioxides (**4**) (Scheme 1) [3].



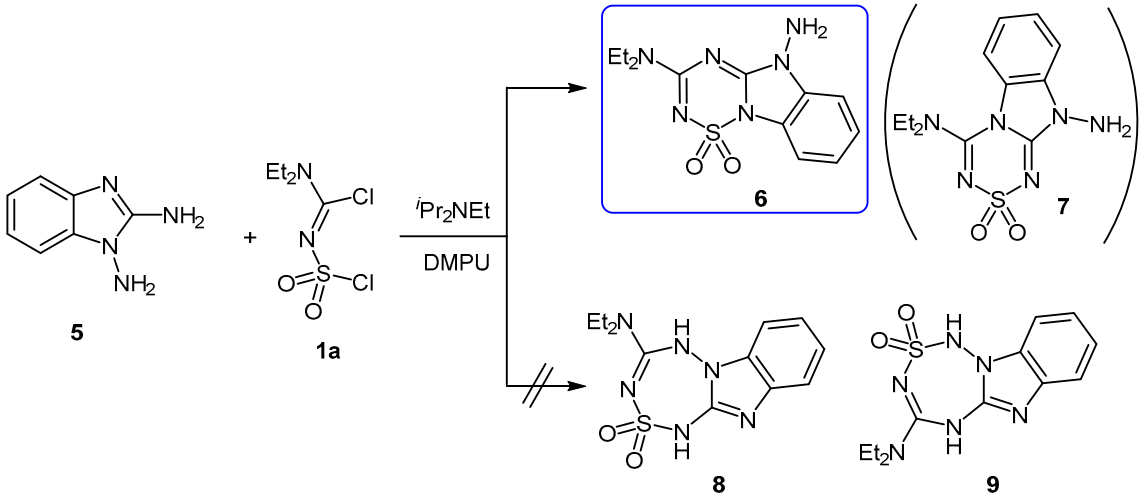
Scheme 1. Synthesis of fused [1,2,4,6]thiatriazines **3** and **4**.

In the syntheses outlined in Scheme 1, the 2-aminobenzimidazoles **2** acted as 1,3-bis-nucleophiles in reactions with the 1,3-bis-electrophilic dichlorides **1** to produce six-membered ring products, the fused thiatriazines **3** (and **4**), which are representatives of very rare ring systems.

We envisaged that replacement of 2-aminobenzimidazoles **2** with 1,2-diaminobenzimidazole (**5**) (readily produced from **2** (R^3=H) by N-amination [4]) in a similar reaction to those outlined in Scheme 1 might result in the production of a new fused seven-membered ring system via the action of **5** as a 1,4-bis-nucleophile.

2. Results and Discussion

Treatment of **5** [4] with *N*,*N*-diethyl-*N*′-chlorosulfonyl chloroformamidine **1a** [2] in *N*,*N*′-dimethylpropyleneurea (DMPU) in the presence of Hünig's base at room temperature afforded the 5-amino-benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine derivative (**6**) as the major product. The crude product, obtained as a precipitate directly from the reaction mixture by simple addition of ethyl acetate and water, was a ~7:1 mixture of **6** and an isomeric compound, presumably the 10-amino-benzo[4,5]imidazo[2,1-*c*][1,2,4,6]thiatriazine (**7**) (vide infra, Scheme 2). Recrystallization from aqueous 1,2-dimethoxyethane afforded a pure sample of **6**.



Scheme 2. Synthesis of 5-amino-3-(diethylamino)-5*H*-benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine 1,1-dioxide (**6**).

NMR and mass spectral analyses alone did not allow an unambiguous structural assignment for fused thiatriazine **6**; however, a signal at 5.88 ppm integrating for 2H in the ^{1}H-NMR spectrum of **6** was indicative of an NH_2 group, thereby narrowing the possibilities to either of structures **6** or **7**. An unequivocal determination of the structure of **6** was achieved via X-ray crystallography (Figures 1 and 2). In the ^{1}H-NMR spectrum of the crude product (see Supplementary Materials), an additional minor resonance at 5.80 ppm, also indicative of an NH_2 group, suggested that the minor isomer had structure **7**. Neither of the expected seven-membered ring products **8** or **9** were observed. No obvious additional spots were noted during thin-layer chromatography (TLC) analysis of the mother liquor.

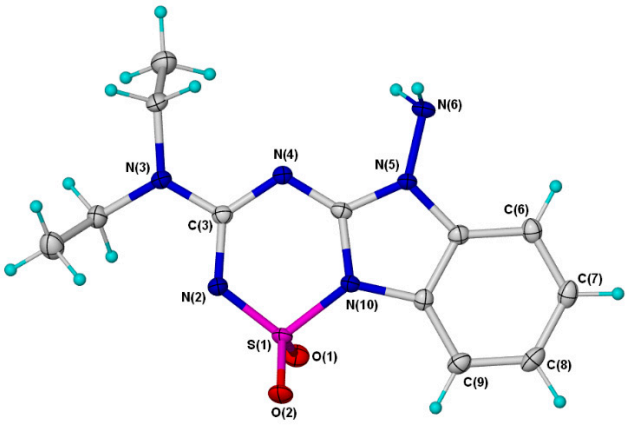


Figure 1. Crystal structure of **6**. The molecular diagram is shown with 50% thermal ellipsoids. Only one of the two unique molecules is shown. The other molecule is essentially the same as that shown, apart from the relative orientations of the ethyl groups of the NEt_2 substituent at C3.

The crystal structure of **6** shows linear chain packing, formed by hydrogen bonding between the exocyclic amino groups and sulfonyl oxygen atoms of adjacent molecules (Figure 2).

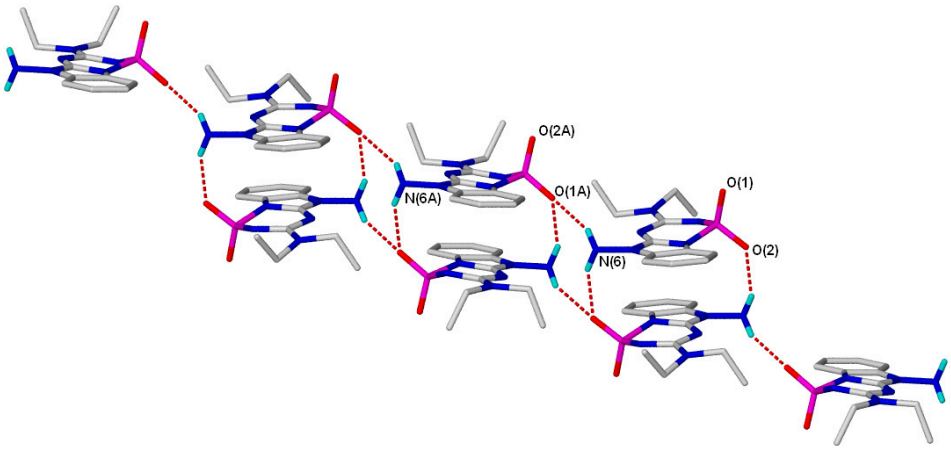


Figure 2. Stick plot of the linear chain crystal packing of **6**.

The polynucleophilicity of **5** allows for either the 1,3-NCN or 1,4-NCNN bis-nucleophilic modes of reaction with dielectrophilic reagents and both types of reaction of **5** with 1,3-bis-electrophiles are described in the literature. For example, treatment of **5** with either of *N*-arylitaconimides or *N*-arylmaleimides in refluxing 2-propanol in the presence of catalytic amounts of acetic acid afforded 10-amino-tetrahydropyrimido[1,2-*a*]benzimidazole derivatives, the products of a 1,3-NCN reaction [5,6]. Similarly, treatment of **5** with malonic or β-ethoxymethylenemalonic acid derivatives gave pyrimido[1,2-*a*]benzimidazole derivatives, again from a 1,3-NCN reaction [7]. However, reactions of diamine **5** as a 1,4-NCNN bis-nucleophile with β-dicarbonyl compounds, under acid catalysis, to provide 1,2,4-triazepino[2,3-*a*]benzimidazoles, were also reported [8].

It appears that, in the present work, the reaction of diamine **5** with dichloride **1a** under basic conditions, favors the 1,3-NCN bis-nucleophilic mode of reaction, affording the 5-amino-benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine **6**.

The free NH_2 moiety on the newly formed and rare fused [1,2,4,6]thiatriazine ring system of **6** should offer prospects for various *N*-substitution reactions. Such synthetic chemistry, in addition to the ring NH substitution methodology previously demonstrated on compounds **3** [3], should enable

the production of an extended range of derivatives of this unusual scaffold, with potential application in bioactive molecule discovery projects.

3. Experimental Section

3.1. Materials and Methods

All chemicals were commercially available except those whose synthesis is described. The reaction mixture was monitored by TLC using commercial aluminium-backed TLC plates (Merck Kieselgel 60 F254, Darmstadt, Germany). The plates were observed under UV light at 254 nm. The melting point was determined using a Büchi B-545 apparatus and is uncorrected. High resolution mass spectrometric analyses were performed on a Thermo Scientific Q Exactive mass spectrometer (Thermo Scientific, Waltham, MA, USA) fitted with an ASAP ion source (M&M Mass Spec consulting) [9]. The design and method of ionisation have been described previously [10,11]. Positive and negative ions were recorded in an appropriate mass range at 140,000 mass resolution. The APCI probe was used without flow of solvent. The nitrogen nebulizing/desolvation gas used for vaporization was heated to 350 °C. The sheath gas flow rate was set to 25, the auxiliary gas flow rate to 5 and the sweep gas flow rate to 2 (all arbitrary units). The discharge current was 4 mA and the capillary temperature was 320 °C. The UV-vis spectrum was collected in methanol solution on a Lambda 1050 UV-Vis-NIR Spectrometer (Perkin Elmer, Waltham, MA, USA) with a standard detector in the 250–800 cm^{-1} range. The IR spectrum was collected from a solid sample on a laminated diamond in the 4000–600 cm^{-1} range with a resolution of 4 cm^{-1} using a Nicolet 6700 FT-IR spectrometer (Thermo Scientific, Waltham, MA, USA). ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Av400 instrument (Bruker Biospin, Rheinstetten, Germany) at 400 and 100.6 MHz, respectively. Deuterated dimethyl sulfoxide (DMSO-d_6) was used as the solvent and also as an internal lock. LC-MS analyses were performed on a Waters Acquity UPLC i-Class (Waters Corporation, Milford, MA, USA) with QDa performance mass detector with adjustment-free atmospheric pressure ionisation (API) electrospray (ES) interface. Positive and negative ions were recorded simultaneously with full scan analysis in m/z range 50 to 1000. High purity nitrogen (>95%) nebulizing/desolvation gas was used for vapourization with the pressure regulated at 650–700 kPa. The probe temperature was set at 600 °C, the source temperature at 120 °C, the cone voltage was 10 V whilst the capillary voltage was 0.8 kV for both positive and negative ion modes. The chromatographic conditions were as follows: column—Waters Acquity UPLC BEH C_{18} (50 × 2.1 mm, 1.7 µm particle size); flow rate—0.4 mL/min; column temperature 30 °C; mobile phase A—100% Milli-Q Water with 0.1% formic acid; mobile phase B—100% acetonitrile with 0.1% formic acid; gradient—95% A to 100% B over 4.5 min, hold at 100% B for 1 min, change to 95% A over 0.5 min, then hold for 1 min. MS data were collected for the complete 7 min run. Spectral analysis was from 190 to 350 nm with chromatograms extracted using a wavelength of 254 nm.

3.2. 5-Amino-3-(diethylamino)-5H-benzo[4,5]imidazo[1,2-b][1,2,4,6]thiatriazine 1,1-Dioxide (**6**)

A mixture of **5** [4] (0.74 g, 5 mmol), the dichloro compound **1a** [2] (1.52 g, 6.5 mmol), *N*,*N*-diisopropylethylamine (2.25 mL, 13 mmol), and DMPU (5 mL) was stirred at room temperature for 6 h. Ethyl acetate (15 mL) was added with stirring, followed by water (30 mL), and the mixture was stirred vigorously for a few min. The precipitate was collected by filtration and washed sequentially with water, ethyl acetate, and diethyl ether to afford a mixture of compounds **6** and **7** (~7:1, 687 mg, 45%) as an off-white solid. A sample (100 mg) was recrystallized from aqueous 1,2-dimethoxyethane to afford the title compound **6** (61 mg) as small, off-white, nacreous plates, melting point 273–275 °C. (Found: [M + H] 309.1127, $M^{+\cdot}$ 308.1051. $C_{12}H_{16}N_6O_2S$ requires [M + H] 309.1128, $M^{+\cdot}$ 308.1050). λ_{max} (MeOH)/nm 255, 306, 297 (shoulder). ν_{max} (solid)/cm^{-1} 3343 (weak), 2942 (weak), 1616, 1550, 1435, 1407, 1377, 1304, 1224, 1171, 1006, 883, 750, 720, 658, 611. δ_H 7.60 (1H, d, 7.9 Hz, ArH), 7.52 (1H, d, 7.5 Hz, ArH), 7.43 (1H, ddd, 8.0, 7.5, 1.1 Hz, ArH), 7.34 (1H, ddd, 7.9, 7.6, 1.3 Hz, ArH), 5.88 (2H, br s,

NH_2), 3.72 (2H, q, *J* 7.2 Hz, NCH_2), 3.52 (2H, q, *J* 7.2 Hz, NCH_2), 1.22 (3H, t, *J* 7.2 Hz, CH_3), 1.17 (3H, t, *J* 7.2 Hz, CH_3). δ_C 156.5, 151.3, 130.7, 125.2, 123.6, 122.4, 111.8, 110.1, 42.0, 41.9, 13.5, 12.9.

3.3. X-ray Crystallography

A second recrystallization from ethyl acetate afforded small, colorless prisms, suitable for X-ray studies. X-ray crystallographic data were collected on a Nonius KAPPA diffractometer equipped with a charge-coupled device (CCD) detector, utilizing Mo-Kα radiation (λ = 0.071073 Å). A representative crystal attached to a glass fiber using a viscous hydrocarbon oil and was transferred to a goniostat and cooled to 123 K. The data were collected and processed, including a multi-scan absorption correction collection, using proprietary software [12–14]. The structure was solved and refined on F^2 using full-matrix least squares with SHELX2016 [15]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms attached to carbon were placed in calculated positions using a riding model. Initial positions of the hydrogen atoms attached to the exocyclic amino group were located in the difference Fourier map and were refined without restraint.

Crystal and refinement data (**6**): (CCDC-1860349): $C_{12}H_{16}N_6O_2S$, M = 308.37, monoclinic, space group $P2_1/c$, a = 15.3907(2) Å, b = 14.9210(2) Å, c = 13.2368(1) Å, β = 114.424(1)°, V = 2767.73(6) Å^3, Z = 8, T = 123(2) K, ρ_{calcd} = 1.480 g·cm^{-3}, $2\theta_{max}$ = 55.0°. Refinement of 395 parameters on 6221 unique reflections (N_{total} 25,274, R_{int} 0.046) led to $R1$ = 0.0431 for 4480 reflections with $I > 2\sigma(I)$, w$R2$ = 0.1220 (all data) and S = 1.058 with the largest difference peak and hole of 0.319 and −0.503 e·Å^{-3}, respectively. Crystallographic data for **6** were deposited with the Cambridge Crystallographic Data Centre with the deposit number CCDC-1860349. The data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax +44-1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary Materials: The following are available online: ^{1}H, ^{13}C-NMR, LC-MS, high-resolution MS, UV-vis, infrared (IR), and single-crystal X-ray data for 5-amino-benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine **6** and ^{1}H-NMR spectrum and LC-MS data for the crude precipitate.

Author Contributions: V.T. performed the experiments. C.M.F. collected, analyzed, and interpreted the X-ray crystallography data. C.L.F. conceived the experiments, analyzed the data, and wrote the paper.

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

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