Crystallization Induced Amide Bond Formation Creates a Boron-Centred Spirocyclic System.

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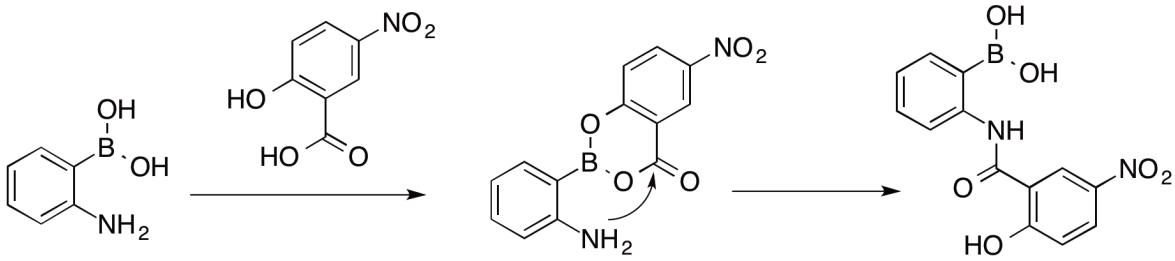
Abstract: We report the 5-nitrosalicylate ester of 2-acetamidophenylboronic acid ($C_{15}H_{10}BN_2O_6$) forms under crystallization conditions and the boron exists as a tetrahedral complex produced by a dative bond with the amide via B—O=C coordination. The perpendicular shape produces an unusual packing structure including a bifurcated hydrogen bond between the amide hydrogen and carbonyl groups on two neighbouring molecules. We propose that this reaction occurs due to increased Lewis acidity of the nitrosalicylate ester of 2-aminophenylboronic acid.

Keywords: amidation, boronate ester, crystal structure, dative bond, Lewis acid

Introduction:

Boron acids are useful catalysts for many transformations including amidation and esterification reactions.[1-3] In the first known example where 2-aminophenylboronic acid was used in amidations, it was shown by Groziak in 1994 that this compound could form a formamide by refluxing in formic acid.[4] It is unclear whether the boronic acid plays a role in catalyzing the amidation as the reaction can occur thermally at temperatures greater than 100˚C.[5] Previously, we have demonstrated that boric acid is an effective catalyst for esterification of α-hydroxycarboxylic,[6,7] malonic[8] or salicylic acids.[9] By chelating the carboxylate and the alcohol (or second carboxylate), boron activates the carbonyl group toward esterification.[10] We reasoned that such chelation would allow for direct, facile amide bond formation between 2-aminophenylboronic acid and α-

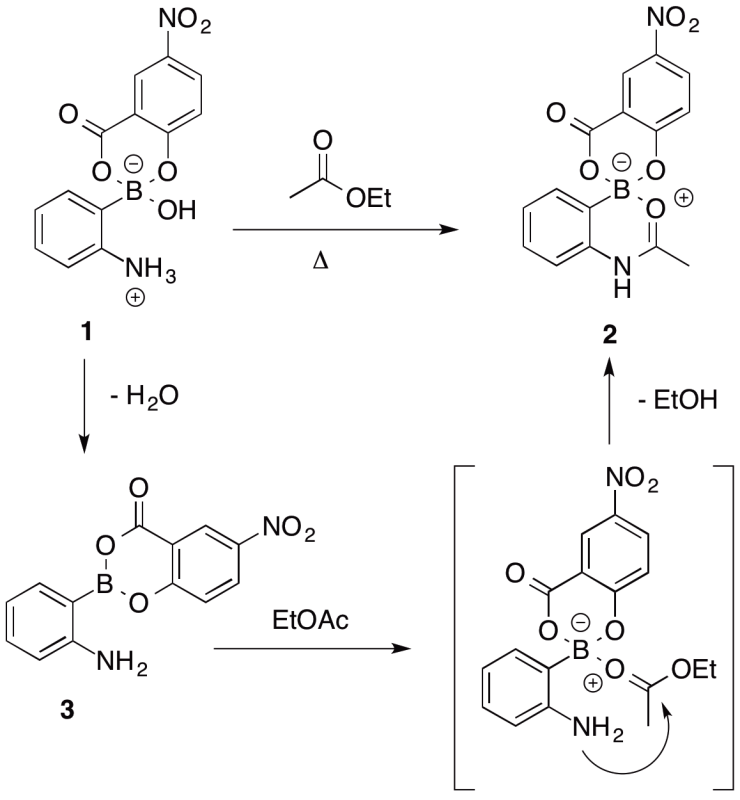
hydroxycarboxylic acids or salicylic acids (Scheme 1). Boron ester formation would place the activated carbonyl six atoms away from the amine.



Scheme 1: Proposed direct amide formation between 2-aminophenylboronic acid and 5-nitrosalicylic acid.

Results and Discussion:

Heating 2-aminophenylboronic acid and 5-nitrosalicylic acid in acetonitrile at 50˚C resulted in formation of **1** as a light brown precipitate rather than the desired amide. Attempted recrystallization of **1** from EtOAc/hexane produced the unexpected crystalline product **2** (Scheme 2). This amidation reaction with ethyl acetate does not occur when 2-aminophenylboronic acid alone is heated in this solvent system suggesting the nitrosalicylate ester plays a role in this reaction.



Scheme 2: Postulated mechanism for amidation reaction of **1**.

We propose that **1** likely dehydrates to form a free amine and neutral boronate ester **3** that can subsequently activate the ester carbonyl as shown in the bracket. The nitrosalicylate ester of the boronate would make the boron more Lewis acidic than its parent boronic acid allowing it to better activate the carbonyl group of ethyl acetate.[11,12] Compound **2** does not accumulate in solution and thus its formation appears to be a result of the crystallization process. The ORTEP diagram for the X-ray crystal structure of **2** is shown below in Figure 1.

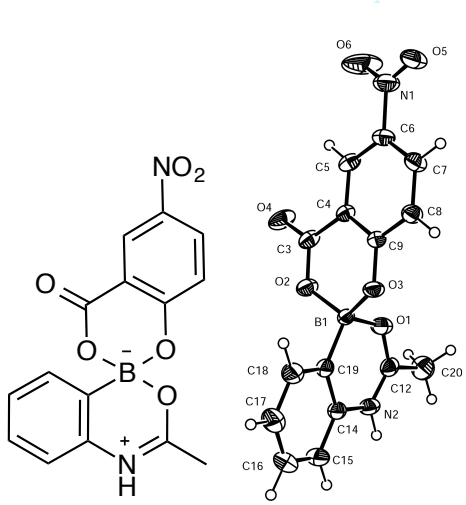


Figure 1: ORTEP diagram of **2**.

Compound **2** demonstrates some interesting supramolecular features in its crystal lattice (Figure 2). The main hydrogen bond supporting the packing structure is a bifurcated hydrogen bond between the hydrogen on the nitrogen in the amide (N^1) and two neighbouring carbonyl oxygen (O^4) from two other molecules. This hydrogen bond brings together two planar systems and two perpendicular systems together. The boron has put torsional strain on some bond lengths in the molecule, but the bond length of the B^1—C^1 of 1.577A° is consistent with typical values in the literature.[13] Coordination of an amide oxygen to create a spirocyclic centre at boron via a five-membered ring has also been observed;[14] However, the extended supramolecular topology of compound **2** appears unique.

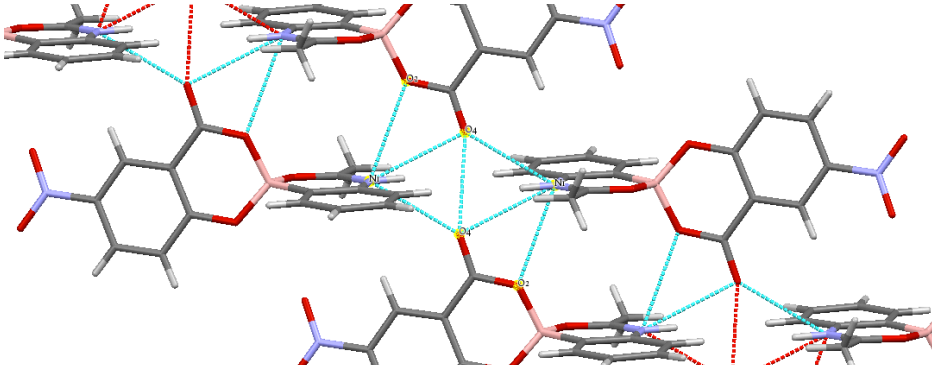


Figure 2. Hydrogen bonding network in X-ray crystal structure of **2**.

Conclusion:

Formation of compound **2** occurs via amidation of **1** with ethyl acetate during the crystallization process. It is unclear at present whether amide bond formation is induced by the rich hydrogen bonding network within the crystal lattice, or whether compound **2** has a strong propensity to crystallize once formed. Nonetheless, we are exploring the proposed Lewis acid activation toward nucleophilic attack by the adjacent amine in other systems and will report on success in this arena in due course.

Experimental:

4'-hydroxy-3-methyl-6'-nitro-4'*H*-spiro[benzo[*c*][1,5,2]oxazaborinine-1,2'-benzo[*d*][1,3,2]dioxaborinin]-1-uide (**2**): To a stirring solution of 2-aminophenylboronic acid (50.0mg, 0.37mmols) in acetonitrile (3.65ml) was added 5-nitrosalicylic acid (66.9mg, 0.37mmols). The reaction was allowed to react at 323K for 1 hour from which the precipitated product **1** as a light brown powder was then collected via vacuum filtration (109.2mg, 99%). ^{11}B NMR (DMSO-d_5): δ 5.59 ppm vs. BF_3-OEt_2/$CDCl_3$ standard. MS (ES–) 301.1 [M–H$^+$]; calcd for $C_{13}H_{10}BN_2O_6^-$: 301.06 m/z. Crystallisation occurred via a slow evaporation process at room temperature from hot 1:1 EtOAc/hexane solvent system after purification with activated charcoal. The solution stood for 3 days producing crystals that were clear, small and rectangular in appearance. The crystals were identified as compound **2** by proton NMR, MS and X-ray crystallography. ^{1}H NMR (DMSO-d_5): δ 2.35 (s, 3H, C**H**$_3$), 7.10 (d, 1H, Ar**H**), 7.16 (d, 1H, Ar**H**), 7.27 (m, 1H, Ar**H**), 7.42 (m,

2H, Ar**H**), 8.32 (dd, 1H, Ar**H**), 8.61 (s, 1H, Ar**H**) ppm. MS (ES–) 324.9 [M–H^+]; calcd for $C_{15}H_{10}BN_2O_6^-$: 325.06 m/z.

Crystal data for **2**: $C_{15}H_{11}BN_2O_6$. M = 326.1, monoclinic, space group $P2_1/n$, a = 8.6642(4), b = 11.2685(8), c = 16.0267(10) Å, β = 101.689(6)o, U = 1532.3(2) $Å^3$, Z = 4, D_c = 1.41 g cm^{-3}, μ = 0.110 mm^{-1}, Crystal size: 0.30 Å~ 0.20 Å~ 0.20 mm. $T_{min/max}$ =0.89, 1.00. 67970 reflections collected, 4092 unique (R_{int} = 0.040), R = 0.068 [2187 reflections with $I > 2s(I)$], wRF^2 = 0.123 (all data).

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