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Mass spectrometric studies on the formation of chiral *N*-sulphonylated oxazaborolidinones

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Abstract

The formation of *N*-tosyl-2-phenyl-1,3,2-oxazaborolidin-5-one **1** as a result of a condensation reaction between *N*-tosyl valine **2** and phenyl boronic acid was studied as a model of the formation of chiral oxazaborolidines used as Lewis acidic catalysts for various enantioselective syntheses. Intermediates of the formation of **1** along with those arising from further reactions (of **1**) were investigated by electrospray ionization mass spectrometry (ESI-MS). Results of the study indicate that one phenyl boronic acid may react with one or two molecules of **2** and/or with one or two molecules of phenyl boronic acid. In addition, side-products implying dephenylation of **1** and self-condensation of phenyl boronic acid (formation of triphenylboroxine) were found. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

A number of chiral *N*-sulphonylated 1,3,2-oxazaborolidin-5-ones (e.g. **1**; Scheme 1) are known as efficient catalysts for asymmetric Diels–Alder,[1] Mukaiyama aldol,[2] and 1,3-dipolar cycloaddition[3] reactions of nitrones to ketene acetals. Parent compounds of these catalysts (**1**, R=H; Scheme 1) were prepared by allowing borane to react with the corresponding *N*-sulphonylated amino acid (**2**; Scheme 1), whereas other analogs (e.g. **1**, R=butyl;[4] Scheme 1) were prepared by condensing[4] *N*-sulphonylated amino acids with the corresponding boronic acids R–B$(OH)_2$ (Scheme 1). The formation of **1** (R·H) may involve the neutral and anionic intermediates **3**–**6** (Scheme 1). Because Lewis acidic compounds, such as **1**, have a strong propensity to coordinate to Lewis bases (including self-aggregation), **1** will, as soon as it is formed, form adducts with its own precursors [i.e. coordinate at the most Lewis basic site of **2** or R–B$(OH)_2$; Scheme 2]. Little is known about the properties of these intermediate adducts.

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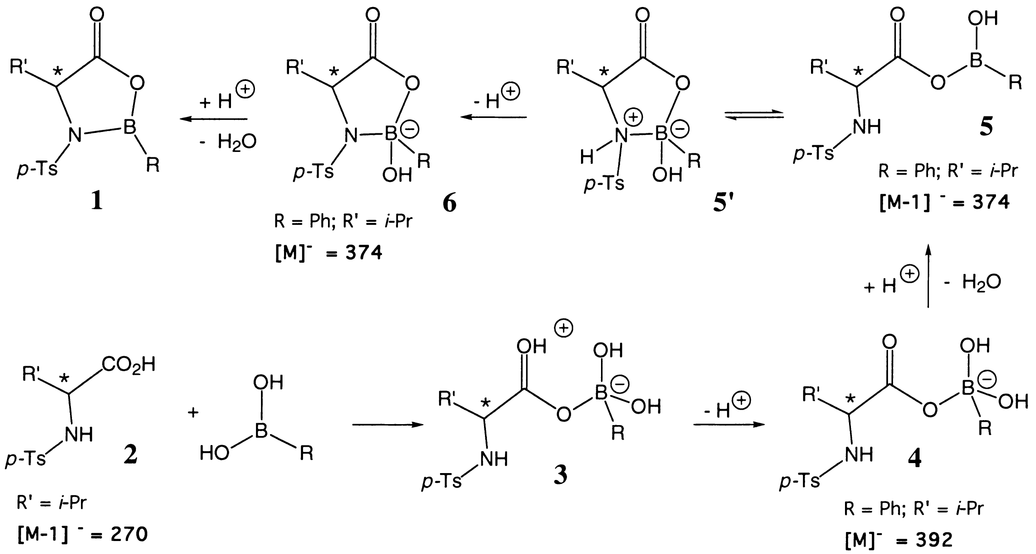
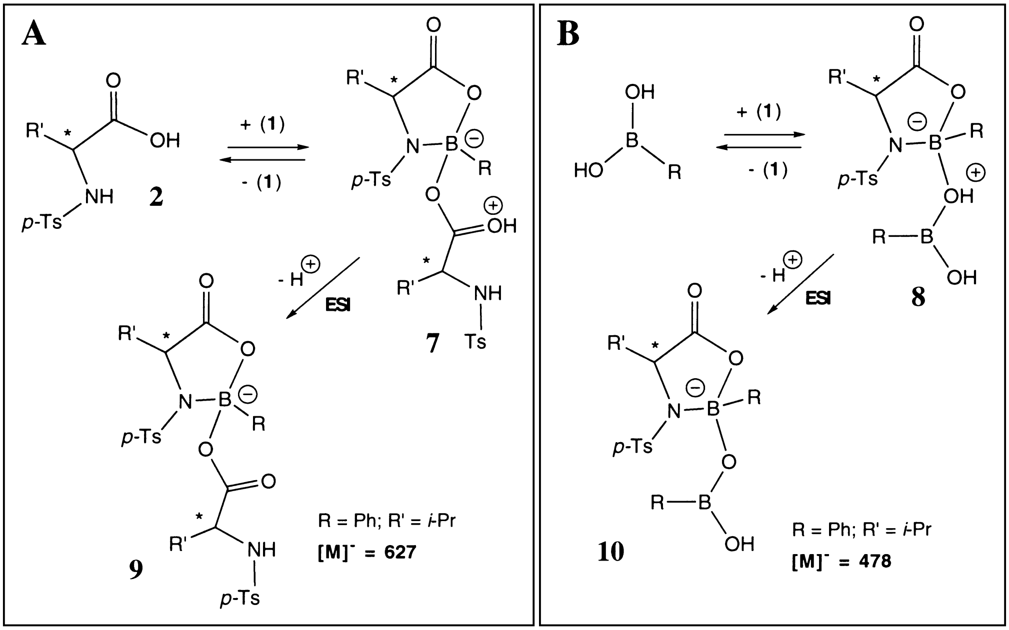


Scheme 1.



Scheme 2.

Experimental evidence on the role of these intermediates (**3**–**6**; Scheme 1), the adduct of **1** to **2** (formation of **7**; Scheme 2, **A**), or the adduct of **1** to R–B(OH)$_2$ (formation of **8**; Scheme 2, **B**) appears not to have been published (with the exception of our preliminary note[5]). Therefore, the aim of this study was to detect the anionic species related to the formation of **1** by means of mass spectrometric (MS) methods. Raw products of condensation reactions used[4] to prepare **1** were charged for the MS analysis using electrospray ionization (ESI)[6] which is a very mild ionization method and allows the ion formation to occur in solution. With ESI we believe we could detect both species: those which are present as anions (if any) in the sample solution; and those arising from complexes (e.g. **3**, **5′**, **7** and **8**; Schemes 1 and 2) which are deprotonated under ESI conditions.

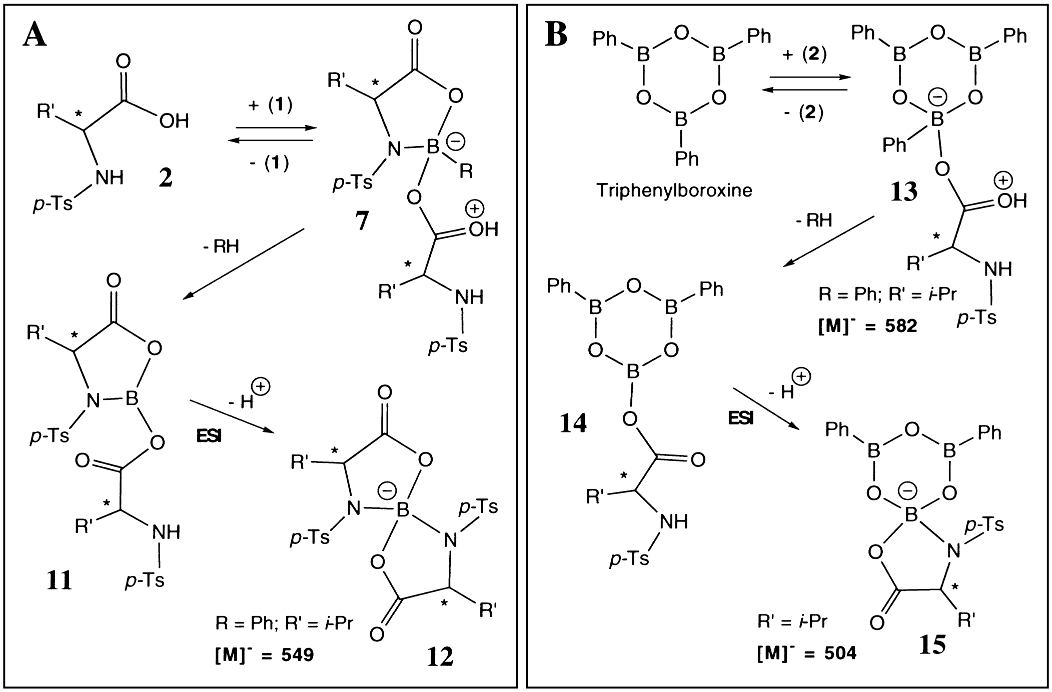
2. Results and discussion

The anionic adducts **4** (m/z=392; Scheme 1), **6** (or M-1 of **5**, m/z=374; Scheme 1), **9** (m/z=627; Scheme 2, **A**) and **10** (m/z=478; Scheme 2, **B**) along with the acid residue of **2** (m/z=270) were all observed in a number of ESI-MS[6] experiments conducted.[7] The relative stability of these anions was studied by allowing the ESI process to occur in the presence of two different solvents (acetonitrile, THF) and salt (NaCl) added into the sample solution just before taking measurements. As a consequence of the variation in the chemical environment of the anions, only a very small change in the relative abundance of the ions was observed. In addition to these anions, the adducts of the acid residue of **2** (m/z=270; Scheme 1) to one or two molecules of the parent acid **2** (giving rise to ions, m/z=541 and 812) were also observed.

Because many anions are formed under ESI conditions,[6] a question arises as to whether the anionic adducts **4**, **6**, **9** and **10** (Schemes 1 and 2) were formed as a consequence of the chemical process used to remove water from the mixture of **2** and R–B$(OH)_2$, or whether they arise from reactions potentially taking place in spray particles generated by the ESI process[6]. In the latter case, new anionic adducts should be observable if another carboxylic acid residue capable of forming adducts with **1**, **5** or Ph–B$(OH)_2$ (reactions competing with the formation of **4**, **6**, **9** and **10**) was added into the sample proposed to contain **4**, **6**, **9** and **10** (Schemes 1 and 2). However, when a reaction mixture (used to detect anions of **4**, **6**, **9** and **10** as discussed earlier) was treated with a large amount of propionic acid,[8] only anions related to the propionate residue (m/z=73) along with its adduct to the parent acid (m/z=147) and Ph–B$(OH)_2$ (m/z=195) were observed. The relative abundance of the anionic adducts **4**, **6**, **9** and **10** was hardly affected at all. These results allow us to conclude that, for instance, free phenyl boronic acid is present in the solution studied and that it can be trapped by propionate (as indicated by m/z=195). In addition, it looks as if the precursors **3**, **5**, **5′**, **7** and **8** of the adducts **4–6**, **9** and **10** (Schemes 1 and 2) could be stable enough for them not to exchange acid residues in the time scale (max. 15 min)[8] of the measurement. If those exchange reactions had occurred, a clear change in the relative abundance of **4**, **6** (m/z=392 and 374; Scheme 1), **9** and **10** (m/z=627 and 478; Scheme 2) would have been seen, but was not observed. Therefore, it looks as if the precursors (**3**, **5**, **5′**, **7** and **8**) of the anionic adducts **4**, **6**, **8** and **10** could have been present in the raw product of **1**. Interestingly, an X-ray structure of an adduct of H_3C–B$(OH)_2$ to oxazaborolidine derived from diphenyl prolinol supports our conclusions on the formation of **8** (Scheme 2, **B**) in that an oxygen of the acid residue of H_3C–B$(OH)_2$ was found to coordinate to the boron of the oxazaborolidine ring and the proton of the acid bound to one of the atoms adjacent to the boron.[9]

Two other side-reactions were predicted to take place under the conditions of the condensation of **2** and Ph–B$(OH)_2$ described earlier. Namely, boronic acids may undergo self-condensation to form cyclic anhydrides[10] (e.g. triphenylboroxine) and undergo dephenylation. Products of related reactions (in the case of the preparation of **1** discussed earlier) could be those illustrated in Scheme 3.

If dephenylation (i.e. elimination of Ph–H) takes place in intermediate **7**, a cyclic boronate **11** could be formed (Scheme 3, **A**). Deprotonation of **11** under ESI[6] conditions could lead (via an intramolecular reaction) to the formation of spiro boronate **12** of which the m/z ratio would be 549 (Scheme 3, **A**). Indeed, an intensive signal at m/z=549 was observed[7] in the case of all reaction mixtures studied. With regard to the formation of triphenylboroxine, an ion corresponding to the adduct **13** (Scheme 3, **B**) was



Scheme 3.

observed. Further support for the proposed formation of **13** was obtained (as an elimination of R–H in **13** followed by a deprotonation which should give rise to the formation of **14**; Scheme 3, **B**) by detection of an anion of which the m/z value was 504. This value could be related to the spiro adduct **15** (Scheme 3, **B**).[7]

3. Conclusions

The results of this study indicate that ESI-MS techniques[6] can be very useful for the detection of labile anionic systems such as those derived from reactive intermediates. Chemical results obtained suggest that conventional condensation of *N*-sulphonylated amino acids and alkyl/aryl boronic acids may give rise to the formation of mixtures of products and that the resulting oxazaborolidines may form 1:1 adducts with either the *N*-sulphonylated amino acids, with the alkyl/aryl boronic acids or with both of these. In addition, a loss of the alkyl/aryl moiety of the oxazaborolidine formed in the condensation may take place in the presence of the *N*-sulphonylated amino acid. Self-condensation of the alkyl/aryl boronic acid may also occur to give rise to the formation of related boroxines. The boroxines could then react with the *N*-sulphonylated amino acid giving rise to dealkylation/dephenylation at the boroxine ring. Further studies on the use of ESI and MS in order to characterize other analogous anionic systems are in progress.

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7. Isotopic patterns (indicating the presence of boron) and daughter ion analysis were used to confirm the structural assignations.
8. Feeding the sample into the ESI-MS inlet was started immediately after the acid was added into the sample with stirring. This treatment together with the subsequent measurement took about 5–15 min, respectively.
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