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One-pot oxidative hydrolysis-oxidative cleavage of 7-borylindoles enables access to *o*-amidophenols and 4-acylbenzoxazoles†

Kirsty Anderson, Andrew S. Eastabrook and Jonathan Sperry *

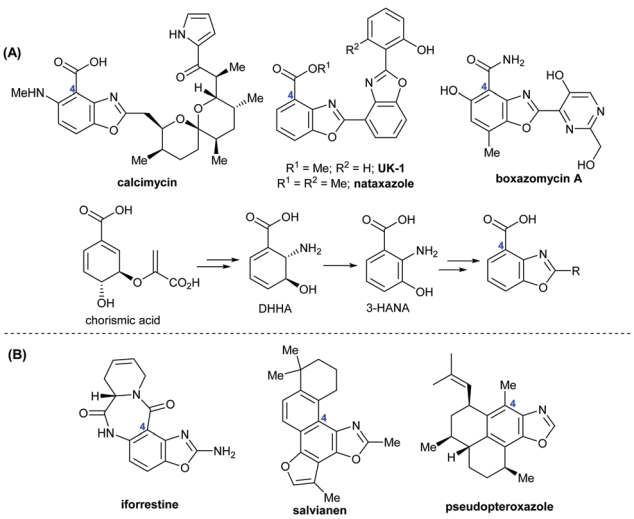
7-Borylindoles undergo a one-pot oxidative-hydrolysis of the arylboronate and oxidative cleavage of the indole C2–C3 double bond to afford *o*-amidophenol derivatives. Subsequent cyclisation delivers benzoxazoles bearing an acyl group at C4, a substitution pattern common to fungal-derived benzoxazole alkaloids. Using 7-borylindoles as substrates to access functionalised *o*-amidophenols circumvents the difficult preparation of these compounds from arenes, streamlining access to substituted 4-acylbenzoxazoles in the process.

Benzoxazole natural products derived from fungi display a wide range of structural diversity and biological properties. Due to their common biosynthesis from 3-hydroxyanthranilic acid (3-HANA) *via* the shikimate pathway, these alkaloids always possess an acyl group at the benzoxazole C4 position (Scheme 1A).[1,2] Moreover, a number of 4-substituted benzoxazoles have also been isolated from both plant and marine sources (Scheme 1B).[1,2]

Most synthetic approaches to 4-acylbenzoxazoles mimic the biosynthesis and involve the condensation of an *o*-aminophenol bearing an acyl substituent with an aldehyde or ester (or equivalent),[1–3] a straightforward process when the 4-acylbenzoxazole does not possess any additional substituents. However, accessing substituted 4-acylbenzoxazoles such as many of those shown in Scheme 1, or for medicinal chemistry studies, requires access to densely functionalised *o*-aminophenols, substrates that are not readily attainable. For example, procedures for the synthesis of substituted 3-HANA's are quite rare and are generally limited to the derivatisation of 3-HANA.[4,5] Similarly, facile synthetic routes to substituted 2-amino-3-hydroxybenzaldehydes and 2-amino-3-hydroxyacetophenones are also few in number.[6]

A proposal for a distinct route to substituted 4-acylbenzoxazoles that circumvent these issues is shown in Scheme 2. Iridium-catalysed C7–H borylation[7] of indole **1** would give the 7-borylindole **2**. A one-pot oxidation-hydrolysis of the arylboronate and oxidative cleavage of the indole 2,3-bond[8,9] would generate the *o*-amidophenol **3** that upon cyclisation would give the 4-acylbenzoxazole **4**, the common heteroaromatic unit found in the fungal benzoxazoles shown in Scheme 1. Given that substituted indoles are easy to prepare and a vast number are commercially available, this methodology should enable access to 4-acylbenzoxazoles bearing a variety of different substituents that would be otherwise cumbersome to prepare using existing methods.

We initially examined if a 2,3-disubstituted indole could proceed through the route outlined in Scheme 2. 2,3-Dimethylindole (**5**) underwent facile iridium-catalysed C–H borylation to give the 7-borylindole **6**,[10] setting up the pivotal step in the proposed route; the simultaneous oxidative cleavage of the indole C2–C3 double bond and oxidative hydrolysis of the



Scheme 1 (A) Fungal benzoxazole natural products and their general biosynthesis (3-HANA = 3-hydroxyanthranilic acid; DHHA = *trans*-2,3-dihydro-3-hydroxyanthranilic acid); (B) non-fungal benzoxazole alkaloids with a substituent at C4.

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand. E-mail: j.sperry@auckland.ac.nz

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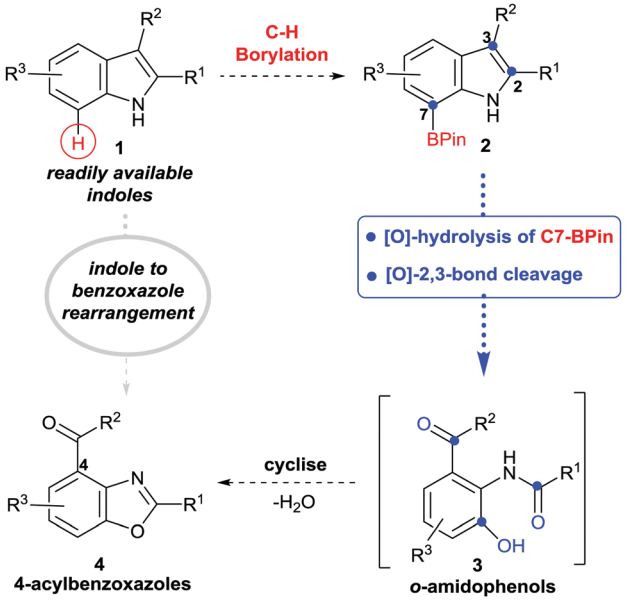
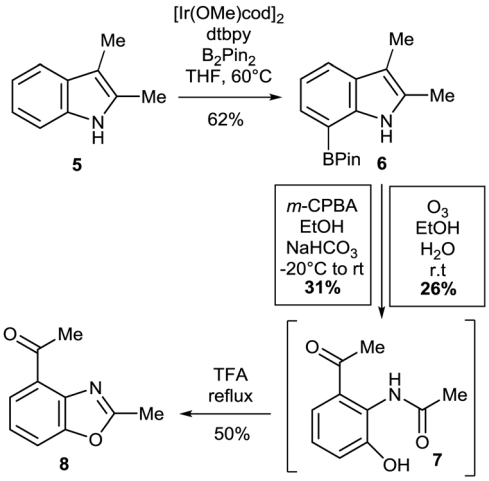


Scheme 2 Proposed route to 4-acylbenzoxazoles from indoles.

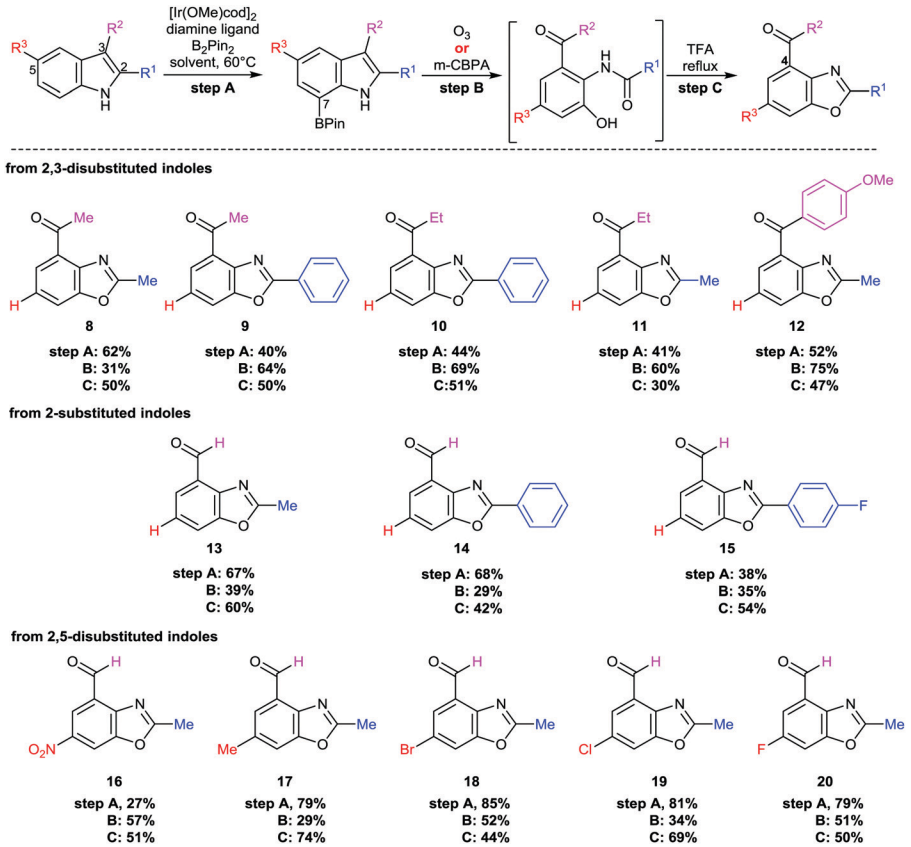
heteroarylboronate at C7. Subjecting **6** to a wide variety of different oxidants including $NaIO_4$, $VO(acac)_2$, CrO_3, salcomine, $RuCl_3$ and $CuCl_2$ was met with universal failure, with the desired *o*-amidophenol **7** not observed. The only two oxidants



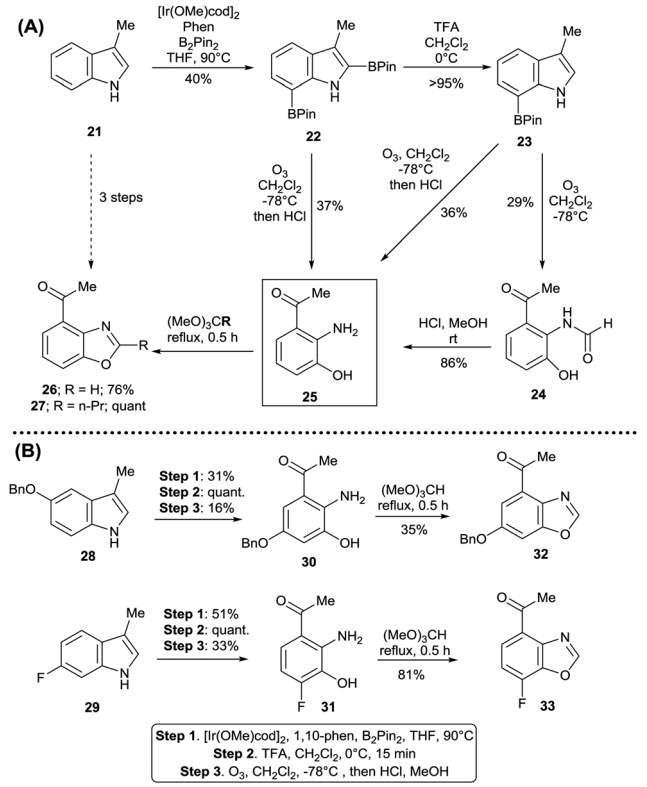
Scheme 3 Initial proof of concept.

that were found to be capable of converting **6** into **7** were *m*-CPBA[11] and ozone,[12] with the former giving a slightly better yield in this instance. Cyclisation of **7** with TFA gave 4-acetyl-2-methylbenzoxazole (**8**) in good overall yield.

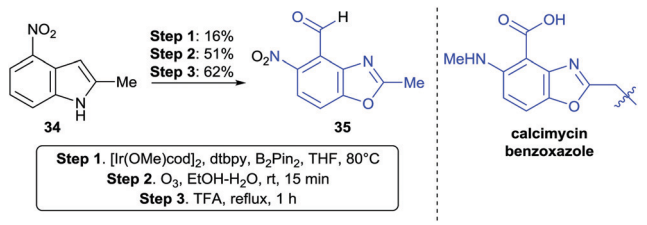
With the example shown in Scheme 3 successful, we subjected a variety of 2-substituted indoles to this process (Scheme 4). By using 2,3-disubstituted indoles, benzoxazoles harbouring a ketone at C4 are readily attainable, exemplified by



Scheme 4 Synthesis of 4-acylbenzoxazoles from 2-substituted indoles.



Scheme 5 (A) Preparation of benzoxazoles **26** and **27** from skatole (**21**); (B) synthesis of the 6-benzyloxybenzoxazole **32** and the 7-fluorobenzoxazole **33** from commercially available skatole derivatives.



Scheme 6 Application of the methodology towards the calcimycin benzoxazole.

the synthesis of 4-acylbenzoxazoles **8–12**. Next, a series of 2-substituted indoles with a vacant C3 site were trialled; 2-methylindole, 2-phenylindole and 2-(4-fluorophenyl)indole all proceeded through the sequence smoothly, affording the 4-formylbenzoxazoles **13–15**. 2,5-Disubstituted indoles also work well in this process, enabling access to 4-acylbenzoxazoles bearing a variety of substituents on the benzenoid ring, including nitro (**16**), methyl (**17**) and a variety of halogens (**18–20**).

With a series of mono- and disubstituted indoles bearing a C2-substituent successfully transformed into their corresponding *o*-amidophenols and hence 4-acylbenzoxazoles, attention turned to incorporating 3-substituted indoles into this process. 3-Substituted indoles present a challenge as the vacant C2-position will undergo C–H borylation along with the C7-site. Iridium-catalysed diborylation of skatole **21** gave the 2,7-diborylindole **22** that upon selective protodeborylation at C2[13] gave the 7-borylindole **23** (Scheme 5A). Subjecting **23** to ozone led to the *o*-amidophenol **24** in acceptable yield. Facile cleavage of the formamide in **24** gave 2′-amino-3′-hydroxyacetophenone (**25**), which could also be obtained in one-pot from **23** by ozonolysis followed by acidic workup. Interestingly, **25** was directly attainable from the 2,7-diborylindole **22** by ozonolysis followed by acidic workup. Treatment of **25** with trimethyl orthoformate and trimethyl orthobutyrate gave the 4-acetylbenzoxazoles **26**[14] and **27**, respectively. 5-Benzyloxyskatole (**28**) and 6-fluoroskatole (**29**) both proceeded through this sequence, affording the *o*-aminophenols **30** and **31**, that upon heteroannulation with trimethyl orthoformate gave the benzoxazoles **32** and **33**, respectively (Scheme 5B).

Finally, the methodology was used to access a benzoxazole related to the natural product calcimycin (Scheme 6). 2-Methyl-4-nitroindole (**34**)[15] underwent the established sequence to give the benzoxazole **35**, which itself is structurally related to the calcimycin benzoxazole. Moreover, the 2,4-disubstituted indole **34** harbours a substitution pattern that complements the examples shown in Schemes 4 and 5.

Indoles serve as readily available substrates for the synthesis of substituted *o*-amidophenols and hence a range of 4-acylbenzoxazoles. Iridium-catalysed C–H borylation of the indole gives a 7-borylindole that undergoes a one-pot oxidative hydrolysis and oxidative cleavage in the presence of either *m*-CPBA or ozone. The resulting *o*-amidophenol derivatives undergo cyclisation to give the desired 4-acylbenzoxazoles bearing a variety of different substituents. A variety of substituents tolerate this process, and the final cyclisation in TFA is compatible with aldehydes, ketones, halogens and the nitro group. The use of 7-borylindoles as templates to access functionalised *o*-aminophenol derivatives circumvents the difficulty in preparing these compounds, simultaneously streamlining access to substituted 4-acylbenzoxazoles in the process.

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Conflicts of interest

There are no conflicts to declare.

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