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Investigation of the scope of a [3+2] cycloaddition approach to isoxazole boronic esters

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Abstract—The [3+2] cycloaddition reaction of nitrile oxides and alkynylboronates provides direct access to a wide variety of isoxazole boronic esters. Specifically, this technique has been employed to generate trisubstituted isoxazole 4-boronates and disubstituted isoxazoles where the boronic ester moiety can be installed at C-4 or C-5 with high levels of regiocontrol. The application of this methodology in the synthesis of non-steroidal antiinflammatory agents is also described.

1. Introduction

The versatility of organoboron reagents renders them one of the most popular classes of synthetic intermediates in modern organic chemistry.[1] Among the many transformations that these compounds will undergo, the Pd-catalysed cross-coupling reaction has found widespread use in academia and industry because of the relatively mild conditions used in this carbon–carbon bond forming process and the relative non-toxicity of the reagents employed.[2] In the context of aromatic boronic acids and esters, these compounds are typically prepared from the appropriate Grignard or organolithium species,[1] or more recently, via Pd-catalysed C–B bond forming processes.[3] An alternative strategy that is of significant potential in the synthesis of these substrates is the use of transition metal catalysts that promote C–H activation processes.[4] Both of these approaches constitute C–X to C–B bond transformations and therefore require an appropriately functionalised starting aromatic compound. Recent work in our laboratories has focused on an alternative strategy whereby aromatic boronic esters are prepared by benzannulation processes of readily available alkynylboronates.[5] In this case, incorporation of the boronic ester and any additional functionality is carried out in a convergent sense via the cycloaddition of simple starting materials. These three strategies are outlined in Figure 1. We report herein, the scope and limitations of this strategy in the synthesis of heteroaromatic boronic esters based on the isoxazole ring via a [3+2] cycloaddition reaction of nitrile oxides with alkynylboronates.[6]

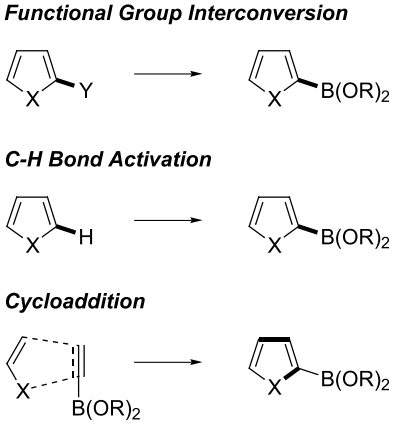

Figure 1.

2. Results and discussion

At the outset of our studies, we were aware of only a single report describing the [3+2] cycloaddition of some benzonitrile oxides with dibutyl ethynylboronate.[7] Notably,

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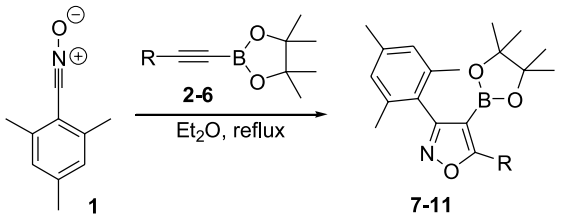
Table 1.



Entry	R	Yield
1	Bu; **2**	**7**; 73%
2	Ph; **3**	**8**; 64%
3	Me_3Si; **4**	**9**; 65%
4	$BnOCH_2$; **5**	**10**; 61%
5	$PhSCH_2$; **6**	**11**; 60%

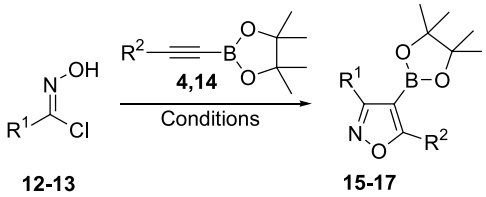
the boronic acid products obtained were unstable and not readily isolated. Additionally, the authors did not extend their study to more heavily substituted alkyne substrates. Accordingly, in an effort to assess the effectiveness of this strategy in the synthesis of these potentially useful organoboron intermediates, we decided to undertake a study of the scope of this process. We began by examining the cycloaddition reaction of mesitylenecarbonitrile oxide **1**—a stable and easily accessible dipole substrate, our results are outlined in Table 1. Upon warming an ether solution of **1** and various alkynylboronates we were pleased to find that the corresponding isoxazole boronic esters were isolated in high yield. Moreover, we were only able to detect a single regioisomer in each case (as judged by 250 MHz ^{1}H NMR spectroscopy of the crude reaction mixture) where the boronate unit was incorporated in the 4-position.[8]

These preliminary experiments confirmed that the [3+2] cycloaddition process could be employed for the synthesis of 3,4,5-trisubstituted isoxazoles with incorporation of the boronate at C-4 with excellent levels of regiocontrol. Furthermore, this technique allowed a reasonable variety of substituents to be installed at C-5. We therefore next addressed the issue of substituent scope at C-3, in this regard, various nitrile oxides would be needed to achieve good flexibility. Generally speaking, nitrile oxides are prone to dimerisation to furoxans and the rate of this process is dependent on the steric demands of the dipole.[9] Accordingly, these compounds are typically generated in situ from the corresponding hydroximic acid chlorides in low concentrations in an effort to promote dipolarophile cycloaddition over competing dimerisation. We decided to employ two protocols for the in situ formation of nitrile oxides; the slow addition of triethylamine to an ethereal solution of hydroximic acid chlorides and the use of a potassium bicarbonate/DME suspension. In the latter case, the sparing solubility of the bicarbonate in DME ensures that nitrile oxide formation proceeds relatively slowly.[10] The utilisation of these procedures in isoxazole boronic ester synthesis is outlined in Table 2. The formation of benzonitrile oxide under either set of conditions permitted a smooth cycloaddition reaction to take place with trimethylsilylethynylboronate **4** to furnish the corresponding isoxazole 4-boronate **15**, again as a single regioisomer (entires 1 and 2). The inorganic base conditions were readily extended to include *t*-Bu-substituted dipole (from **13**), however, attempts to carry out a similar cycloaddition using triethylamine with **13** resulted in a low yield of isoxazole **17** (entries 3 and 4).

In an effort to broaden the scope of substituents available at C-3 yet further, we decided to investigate the cycloaddition reaction of halonitrile oxides. These dipoles are also highly prone to dimerisation and are prepared in situ from the corresponding dihaloformaldoximes. We attempted the cycloaddition of representative alkynylboronates with these species and our results are outlined in Table 3. We began by comparing the efficiency of isoxazole formation in the presence of triethylamine versus potassium bicarbonate. As shown in entries 1 and 2, the latter base was considerably more efficient and we therefore employed these conditions for the remainder of the study. Indeed, we were pleased to find that this technique allowed us to access a wide range of 3-bromoisoxazoles in good yield, again a single regioisomer was detected in each case.[11] Finally, as outlined in entry 8, this process was also viable for the preparation of 3-chloroisoxazoles.

During the course of this work, we became aware of a study by Itoh et al. that outlined the formation of acetylnitrile oxide from acetone and ammonium cerium (IV) nitrate in the presence of formic acid.[12] Given that our investigations up to this point had demonstrated that the alkynylboronates were compatible with mild bases, it seemed that this process would provide the opportunity to demonstrate the acid stability of these reagents. As outlined in Eq. 1, subjecting

Table 2.



Entry	R^1	R^2	Conditions	Yield
1	Ph; **12**	Me_3Si; **4**	Et_3N, Et_2O, reflux	**15**; 72%
2	Ph; **12**	Me_3Si; **4**	$KHCO_3$, DME, 50 °C	**15**; 69%
3	Bu^t; **13**	Me_3Si; **4**	$KHCO_3$, DME, 50 °C	**16**; 58%
4	Bu^t; **13**	Me; **14**	Et_3N, Et_2O, reflux	**17**; 27%