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A regioselective cycloaddition route to isoxazoleboronic esters†

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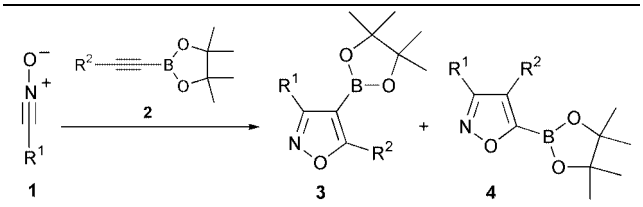
Alkynylboronates participate in 1,3-dipolar cycloaddition reactions with nitrile oxides to provide isoxazoleboronic esters with excellent levels of regiocontrol; additionally, these potentially valuable synthetic intermediates have been shown to participate efficiently in Suzuki coupling reactions.

Aromatic boronic esters are amongst the most valuable and widely used synthetic intermediates in modern organic chemistry due to their ability to participate in functional group transformations and carbon–carbon bond forming reactions.[1] These compounds are generally accessed *via* a functional group interconversion strategy from a starting aryl halide or triflate.[2] However, the requirement of these precursors can prove problematic when more highly substituted or heavily functionalised boronic ester products are required. Accordingly, in an effort to develop novel and efficient routes to complex arylboronates, we have recently been exploring the possibility of employing cycloaddition/benzannulation reactions of boron containing alkynes.[3] In connection with this study, we wish to report herein our recent findings on the [3+2] cycloaddition reaction of alkynylboronates with nitrile oxides towards the assembly of highly substituted isoxazoleboronic esters.

The cycloaddition reaction of nitrile oxides with alkynylboronates has received scant attention in the literature to-date. Indeed, we are aware of only a single report whereby dibutyl ethynylboronate provided the corresponding isoxazole as a single regioisomer.[4] However and importantly, only this terminal alkynylboronate was examined and the effect of acetylenic alkyl substituents on regioselectivity was not described. In contrast, the employment of alkynylstannanes is well documented.[5] However, this approach suffers from ready protodestannylation of the heterocyclic product, as well as the associated problems of handling toxic organotin species. In an effort to further clarify the effectiveness of alkynylboronates as precursors to isoxazoleboronic esters, to examine the regiochemistry of substituted boron containing alkynes and to establish the utility of isoxazoleboronic esters in carbon–carbon bond forming processes, we undertook a study of the scope of the cycloaddition reaction as outlined in Table 1.

We decided to initiate our studies on the scope of alkynylboronate [3+2] cycloaddition reactions with mesitylenecarbonitrile oxide **1** (R^1 = Mes), which is known to be stable towards dimerisation.[6] As outlined in Entry 1, we were pleased to find that 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[7] **2** (R^2 = H), underwent a smooth cycloaddition reaction to provide the isoxazole **4a** bearing the boronic ester unit in the 5-position in 59% yield, with only 23% of the alternative regioisomer **3a**. On changing the alkyne substituent R^2 = H to R^2 = Me (Entry 2) the reaction proceeded cleanly to provide a *single regioisomer* of **3b**, remarkably, with complete reversal in regiochemistry. Finally, the use of longer chain alkyl and phenyl substituents also provided the 4-substituted boronic esters as single regioisomers in good yield.[8] We briefly examined the scope of nitrile oxides in the cycloaddition process and were pleased to find that this technique was applicable to phenyl and alkyl substituted 1,3-dipole substrates (Entries 5–7), the isoxazole

Table 1 1,3-Dipolar cycloadditions[a]



Entry[b]	R^1	R^2	Product	Yield (%)
1	Mes	H	**4a**	59%[c]
2	Mes	Me	**3b**	90%
3	Mes	Bu	**3c**	73%
4	Mes	Ph	**3d**	64%
5	Ph	H	**4e**	53%[c]
6	Ph	Me	**3f**	54%
7	*t*-Bu	Me	**3g**	27%[e]

[a] Regiochemical assignments made on the basis of diagnostic ^{13}C resonances. Additionally, these assignments have been supported by X-ray data for compounds **3b** and **3c**, which will be the subject of a future disclosure. [b] For experimental conditions, see ref. 8. [c] 23% of **3a** was isolated. [d] 6% of **3e** was islolated. [e] Estimated by ^1H NMR.[9]

† Electronic supplementary information (ESI) available: full experimental procedures. See http://www.rsc.org/suppdata/cc/b1/b103319k/

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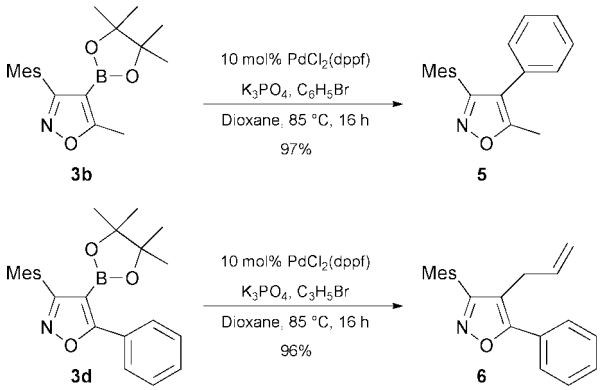
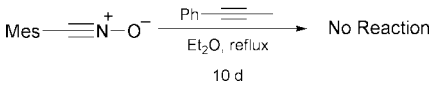
products **4e**, **3f–g**, were again formed with excellent levels of regioselectivity and followed the same insertion pattern established with the mesitylenecarbonitrile oxide in Entries 1–4. Notably, and in contrast to the stannylated isoxazoles, boronic esters **3** and **4** were isolated as white crystalline solids which could be readily purified by standard chromatographic techniques without problematic protodeboronation side reactions.

The regiochemical outcomes outlined in Table 1 are consistent with literature reports of electron deficient alkyne [3+2] cycloaddition reactions with nitrile oxides. Specifically, whereas terminal propiolates generally give a mixture of regioisomers which favours that bearing the ester moiety in the 5-position,[10] substituted propiolates and alkynyl ketones provide the regioisomeric products with the electron withdrawing group in the 4-position with high levels of selectivity.[11] Nonetheless, from a synthetic standpoint, this methodology provides a quick and direct method for the assembly of isoxazoleboronic esters which avoids problematic metallation of the heterocyclic nucleus.[12]

With a rapid and efficient entry into isoxazoleboronic esters in hand, we decided to confirm their effectiveness as synthetic intermediates for Suzuki coupling reactions. As outlined in Scheme 1, isoxazoles **3b** and **3d** were found to undergo smooth and efficient Pd-catalysed coupling with bromobenzene and allyl bromide to give **5** and **6** respectively in excellent yields. We therefore anticipate that this efficient two step procedure holds great promise for the regioselective assembly of a range of functionalised highly substituted isoxazole products.[13] Additionally, as exemplified in Scheme 2, attempts to prepare **5** by direct [3+2] cycloaddition of prop-1-ynylbenzene failed to produce any of the cycloaddition product, even after prolonged reaction times. Therefore, not only does the cycloaddition–coupling technique permit the regioselective formation of highly substituted isoxazole products, it also circumvents limitations associated with preparing 4,5-dialkyl or -diaryl substituted isoxazoles through the employment of unactivated alkyne substrates.



Scheme 1 Suzuki coupling reactions.



Scheme 2

In conclusion, we report a novel and flexible approach to highly substituted isoxazoles through a key [3+2] cycloaddition reaction of nitrile oxides with alkynylboronates. The investigation of related cycloaddition reactions is currently underway in our laboratories and will be reported in due course.

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