Synthesis of 3-Haloisoxazole Boronic Esters: Novel Heterocyclic Synthetic Intermediates Containing Independently Variable Functionality

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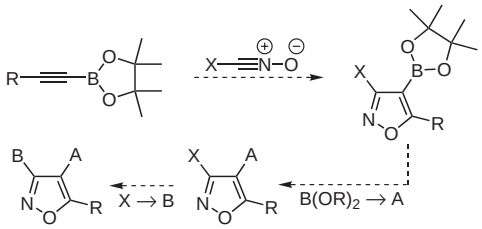
Abstract: The regioselective cycloaddition reaction of nitrile oxides with alkynylboronates has been exploited in the preparation of 3-bromo- and 3-chloroisoxazolyl-4-boronates. The synthetic potential of these intermediates has been explored through a number of cross coupling reactions of the boronic ester unit and some representative reactions of the heteroaryl halide moiety.

Key words: regioselective, cycloadditions, Suzuki coupling, isoxazole



Scheme 1

The development of parallel synthesis for the high throughput screening of biologically active compounds has provided much impetus for the design of intermediates, which may be manipulated in an independent and orthogonal manner.[1] In terms of synthetic flexibility, aromatic and heteroaromatic boronic esters are particularly noteworthy. They participate readily in Pd-catalysed coupling reactions with aryl and vinyl halides (Suzuki coupling reaction),[2] they permit carbon-heteroatom bond formation to provide amines and ethers[3] and they have also been shown to participate in nucleophilic addition reactions to imines, aldehydes and enones.[4] We have recently been investigating a new approach to aryl boronic esters through the employment of cycloaddition reactions of alkynylboronates and have found this approach to be particularly powerful for the concise preparation of these valuable synthetic intermediates.[5] Indeed, we have reported that the [3+2] cycloaddition reaction of nitrile oxides with alkynylboronates provides a regioselective method for the synthesis of isoxazole boronic esters.[5c] Whilst these compounds proved to be good precursors to further isoxazole derivatives through Suzuki coupling reactions, the cycloadducts were limited to a single point of diversity arising from the boronate functional group. We were therefore intrigued by the notion of employing an alternative nitrile oxide substrate which would furnish isoxazoles with two readily and independently manipulated points for further elaboration, thus enhancing the diversity of compounds which may potentially arise from these intermediates (Scheme 1).

We were aware of the ability of bromo- and chloronitrile oxides to react with alkynes to generate the corresponding 3-haloisoxazoles[6] and surmised that the utilisation of alkynylboronates in this process would furnish an isoxazole with boronic ester and halide groups which would act as suitable points for further manipulation of the heteroaromatic cycloadduct. We therefore initiated our studies by examining the cycloaddition reaction of bromonitrile oxide (generated in situ from **1**) with 2-phenylethynyl-4,4,5,5-tetramethyl[1,3,2]dioxaborolane **2a**, an air stable and readily prepared crystalline solid, the results are summarised in Table 1. We initially employed a slow addition of triethylamine to the reaction mixture in an effort to generate a low concentration of bromonitrile oxide (and hence minimise unwanted nitrile oxide dimerisation). We were pleased to find that the desired cycloaddition had taken place and, by analogy to our previous studies, that a single regioisomer **3a** was produced. Unfortunately, the product yields could not be raised above 10–15% and from a practical viewpoint; the necessity of a syringe pump for controlled slow addition limited the progress of our optimisation studies. With a view to circumventing these practical problems, we were intrigued by reports which employed a suspension of a metal bicarbonate in a solution of dibromoformaldoxime **1** and alkyne.[7] Presumably, the low basicity and low solubility of the bicarbonate permits the slow generation of nitrile oxide and minimises dimerisation. Indeed, the employment of sodium bicarbonate in CH_2Cl_2 proved to dramatically enhance the efficiency of the desired cycloaddition reaction and we were pleased to isolate a 56% yield of **3a**. Finally, after further optimisation we found that heating a suspension of the substrates in DME at 50 °C in the presence of $KHCO_3$ resulted in an increased yield of 69% over a reduced reaction time of 16 h. The employment of these conditions was also found to provide *n*-Bu- and Me-substituted isoxazoles **3b**–**c** as single regioisomers.[8] The regiochemistry of the cycloaddition was established by

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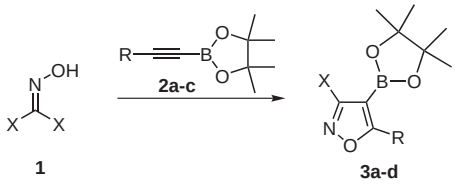
Table 1 Synthesis of Bromoisoxazole Boronic Esters



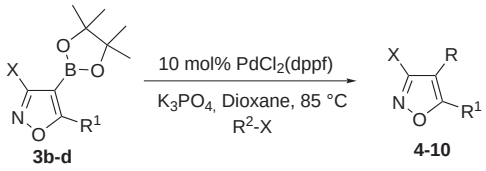
Entry	R	X	Conditions	Yield
1	Ph; **2a**	Br	Et_3N, Et_2O, 35 °C, 48 h	**3a**: 14%
2	Ph; **2a**	Br	$NaHCO_3$, CH_2Cl_2, 25 °C, 72 h	**3a**: 56%
3	Ph; **2a**	Br	$KHCO_3$, DME, 50 °C, 16 h	**3a**: 69%
4	*n*-Bu; **2b**	Br	$KHCO_3$, DME, 50 °C, 16 h	**3b**: 44%
5	Me; **2c**	Br	$KHCO_3$, DME, 50 °C, 16 h	**3c**: 40%
6	*n*-Bu; **2a**	Cl	$KHCO_3$, DME, 50 °C, 16 h	**3d**: 44%

X-ray crystallographic analysis of **3a**[9,10] and was found to mirror that observed in previous studies in our laboratories.[5c] Unsurprisingly, chloroisoxazole boronic ester **3d** was generated by following the same reaction course.

With a reliable method for the synthesis of 3-haloisoxazole boronic esters in hand, we turned our attention to the independent elaboration of both functional groups. In considering which of these groups to examine first, we felt that the sensitivity of the isoxazole boronic esters to protodeboronation under basic conditions would thwart most attempts to manipulate the halide in compounds **3**. In contrast, we felt confident that we could carry out selective Pd-catalysed coupling reactions at the isoxazole boronate whilst avoiding unwanted reactions at the adjacent bromide or chloride by judicious choice of the substrate aryl halide. As outlined in Table 2, initial attempts to couple isoxazole **3b** with bromobenzene provided a modest yield of **4** together with minor amounts of protodeboronated isoxazole as the only identifiable products (entry 1). Notably however, the mass balance of this reaction seldom exceeded 60% and we were unable to clarify the fate of the remaining isoxazole material. Accordingly, we investigated the coupling reaction of the more reactive iodobenzene and were pleased to observe that the Suzuki cross coupling reaction took place to provide **4** in an improved 98% yield (entry 2). Examination of similarly activated systems proved to be successful although notably lower yields were observed when an electron rich aryl iodide was employed (entry 6).[11]

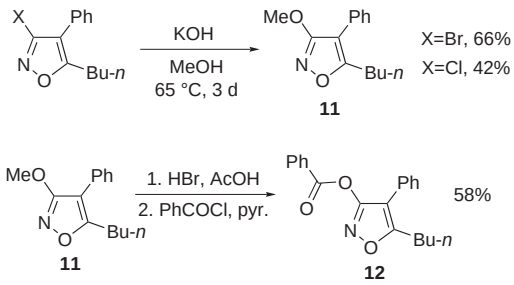
It now only remained to explore the scope of elaboration of the remaining isoxazole bromide and chlorides. Given the relative simplicity with which alkyl/aryl groups can be

Table 2 Suzuki Cross-Coupling Reactions



Entry	R^1; X	R^2X	Yield
1	*n*-Bu; Br **3b**	PhBr	**4**: 47%
2	*n*-Bu; Br **3b**	PhI	**4**: 98%
3	Me; Br **3c**	PhI	**5**: 89%
4	*n*-Bu; Br **3b**	*p*-$NO_2C_6H_4I$	**6**: 73%
5	*n*-Bu; Br **3b**	*o*-$NO_2C_6H_4I$	**7**: 87%
6	*n*-Bu; Br **3b**	*p*-$MeOC_6H_4I$	**8**: 70%
7	*n*-Bu; Cl **3d**	PhI	**9**: 99%
8	*n*-Bu; Cl **3d**	*p*-$NO_2C_6H_4I$	**10**: 92%

incorporated in the 3-position from the appropriate nitrile oxides,[5c] we were particularly attracted to the installment of heteroatom containing groups via S_NAr reactions. Accordingly, treatment of bromoisoxazole **4** with methanolic-KOH resulted in smooth conversion to ether **11** in good yield.[12] The corresponding chloride **9** was found to be less reactive and furnished **11** in lower yield. Unfortunately, all attempts to introduce amines and thiols by this route failed and resulted in the return of starting material or decomposition.[13] Finally, we were pleased to find that ester functionality could be readily introduced at C-3 via the isoxol-3-one intermediate. Therefore, hydrolysis of **11** followed by benzoylation[14] provided ester **12** in good overall yield (Scheme 2).



Scheme 2

In conclusion, the [3+2] cycloaddition reaction of halonitrile oxides with alkynylboronates provides an expedient route to functionalised isoxazole products. Whilst the Suzuki coupling reaction of these intermediates proceeds in high yield with aromatic iodides, functionalisation of the 3-isoxazolyl halide was found to be more limited. A thorough investigation of the elaboration of these intermediates is underway and will be described in a full account of this work.

Acknowledgement

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(8) **Representative experimental procedure for cyclo-addition reactions: 3-Bromo-5-butyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoxazole 3b**: A solution of 2-hexyn-1-yl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (0.90 g, 4.32 mmol), dibromoformaldoxime (0.877 g, 4.32 mmol) and $KHCO_3$ (0.866 g, 8.65 mmol) in dimethoxyethane (5 mL) was stirred for 12 h at 50 ºC. The reaction mixture was cooled, the residual solid removed by vacuum filtration and the solvent removed in vacuo. Purification by flash chromatography eluting with hexane–EtOAc, (15:1) followed by kugelrohr distillation 110 °C/ 0.4 mmHg gave the title compound as a colourless oil (0.627g, 44% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.91 (3 H, t, *J* = 7.0 Hz), 1.22–1.41 (2 H, m), 1.31 (12 H, s), 1.58–1.73 (2 H, m), 2.94 (2 H, t, *J* = 7.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.5, 22.0, 24.8, 26.8, 30.1, 83.8, 144.5, 183.6. FTIR ($CHCl_3$/cm^{-1}): 2978 (s), 2934 (s), 2874 (s), 1741 (m), 1589 (s). Anal. calcd for $C_{13}H_{21}BNO_3Br$: C, 47.31; H, 6.41; N, 4.24; Br, 24.21. Found: C, 47.33; H, 6.58; N, 4.23; Br, 24.18. HRMS calcd for $C_{13}H_{22}BNO_3{}^{79}Br$ (MH^+): 330.0871, Found: 330.0876. HRMS calcd for $C_{13}H_{22}BNO_3{}^{81}Br$ (MH^+): 332.0851, Found: 332.0847.
(9) The X-ray data for isoxazole **3a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 191718.
(10) For X-ray data of related isoxazole boronic esters see: Harrity, J. P. A.; Adams, H.; Davies, M. W.; Wybrow, R. A. J.; Johnson, C. N. *Acta Cryst.* **2002**, *C58*, o168.
(11) **Representative experimental procedure for Suzuki coupling reactions: 3-Bromo-5-butyl-4-(2-nitrophenyl)-isoxazole 7**: A solution of boronic ester **3b** (0.05 g, 0.15 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.012 g, 0.015 mmol), 1-iodo-2-nitrobenzene (0.075 g, 0.30 mmol) and K_3PO_4 (0.096 g, 0.45 mmol) in dioxane (1 mL) was stirred at 85 °C under N_2 atmosphere for 16 h. The reaction was quenched with deionised water (10 mL), and allowed to cool to room temperature. The product was extracted into CH_2Cl_2 (3 × 10 mL) and the organic layer washed with saturated brine (10 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo to give a brown solid. Purification by flash chromatography eluting with hexane–EtOAc (100:1) gave the title compound as yellow oil (0.043 g, 87% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.77 (3 H, t, *J* = 7.0 Hz), 1.13–1.31 (2 H, m), 1.46–1.61 (2 H, m), 2.61 (2 H, t, *J* = 7.0 Hz), 7.28 (1 H, dd, *J* = 7.0 Hz, 7.5 Hz), 7.51–7.73 (2 H, m), 8.10 (1 H, dd, *J* = 8.0 Hz, 1.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.5, 22.1, 25.9, 29.1, 114.8, 123.3, 125.2, 130.2, 133.4, 141.6, 149.1, 171.4. FTIR ($CHCl_3$/cm^{-1}): 2960 (m), 1633 (m), 1601 (m), 1529 (m), 1441 (m). Anal. calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.62; Br, 24.57. Found: C, 48.30; H, 4.12; N, 8.42; Br, 24.66. HRMS calcd for $C_{13}H_{14}N_2O_3{}^{79}Br$ (MH^+): 325.0188. Found: 325.0189. HRMS calcd for $C_{13}H_{14}N_2O_3{}^{81}Br$ (MH^+): 327.0168. Found: 327.0165.
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(13) Preliminary investigations indicate that 3-haloisoxazoles **4**–**10** are relatively unreactive towards Pd-catalysed coupling reactions, nonetheless, there is substantial scope for the optimisation of this process and these studies are ongoing in our labs. In contrast, the introduction of amines by S_NAr reactions has been demonstrated: Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minelli, J. L. *J. Med. Chem.* **1986**, *29*, 359.
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