An alkynylboronic ester cycloaddition route to functionalised aromatic boronic esters†

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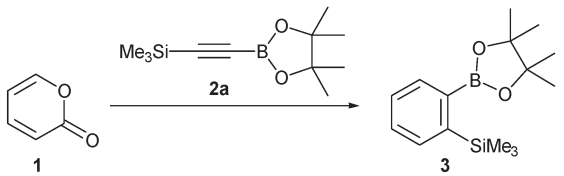
A series of functionalised aromatic boronic esters have been prepared *via* the regioselective cycloaddition of 2-pyrones with alkynylboronates.

Aromatic and heteroaromatic boronic acids and esters have enjoyed widespread use in both academia and industry because they combine a common and important core motif with a highly versatile functional group.[1] Current methods of accessing these intermediates can be crudely classified as functional group interconversion processes,[2] C–H activation techniques[3] and cycloaddition strategies.[4] In the context of the latter approach, we have recently reported a series of benzannulation processes of readily available alkynylboronates that allow heteroaromatic boronic esters to be made available with excellent levels of regiocontrol.[5] In contrast, the employment of this strategy towards benzenoid based systems has uncovered some notable limitations. Specifically, whilst the Dötz benzannulation reaction provides highly functionalised hydroquinone and quinone based boronic esters with excellent levels of regiocontrol,[6] the requirement of stoichiometric quantities of toxic organochromium reagents is undesirable from an economical and environmental standpoint. A cyclopentadienone cycloaddition approach provided a metal-free alternative, however, this was limited by a poor substrate scope and low levels of regioselectivity.[7] In an effort to uncover a more general and regioselective method for the synthesis of functionalised aromatic boronic esters, we have been investigating the cycloaddition reaction of alkynylboronates with 2-pyranones and wish to report our preliminary observations herein.

2-Pyrones have long been known to undergo [4 + 2] cycloaddition reactions with alkynes to generate functionalised benzene derivatives following an *in situ* loss of CO_2.[8] In the context of our study, it was particularly interesting that arylstannanes had been prepared *via* a cycloaddition of the corresponding alkynylstannanes, however, there were no reports of the analogous arylboronic ester synthesis by this means.[9] Accordingly, we began our investigations by examining the cycloaddition of the parent 2-pyrone **1** with trimethylsilylethynyl boronate **2a**; the results are outlined in Table 1. We were pleased to observe that heating a mixture of alkyne and diene in mesitylene at 140 °C provided the desired aromatic boronic ester **3** in good yield over a 48 h period. Pleasingly, the use of a sealed tube allowed us to employ an elevated reaction temperature that resulted in a slight increase in product yield within a reduced reaction time. Switching solvents to diphenyl ether resulted in a drop in yield, however, running the cycloaddition in the absence of solvent gave the desired product in high yield.

Table 1 Preliminary cycloaddition studies



Solvent	Conditions	Yield **3**
Mesitylene	140 °C, 48 h	56%
Mesitylene	170 °C, 17 h	64%[a]
Diphenyl ether	170 °C, 17 h	56%[a]
—	170 °C, 17 h	86%[b]

[a] Reactions conducted in a sealed vial using 1.5 equiv. of alkyne. [b] Reaction employed 2 equiv. of alkyne.

We next turned our attention to the key regioselectivity studies and opted to investigate the cycloaddition reaction of a series of alkynylboronates with pyranones **4** and **5** (Fig. 1).[10] These isomeric dienes would give rise to the same two regioisomeric aromatic products and would therefore allow us to establish the effect of the positioning of the electron withdrawing substituent on reaction efficiency and regioselectivity.

We investigated the cycloaddition of a representative series of alkynes with 2-pyrones **4** and **5** and the results are outlined in Table 2. Trimethylsilyl-substituted alkyne **2a** was found to participate smoothly in the cycloaddition reaction with both dienes to provide the corresponding benzenoid products in high yield. Interestingly, whilst **4** provided **6a** with a 3:1 regioselectivity, the isomeric **5** provided an equal mixture of regioisomers. In contrast, Ph-substituted alkyne participated in a non-selective cycloaddition with **4** but was highly selective for **7b** when 2-pyrone **5** was used. We next turned our attention to an alkyl substituted alkyne and were pleased to find that the reaction was regioselective with both dienes **4** and **5** to provide the isomeric products **8a/b**, each with modest to high levels of regiocontrol. Finally, we

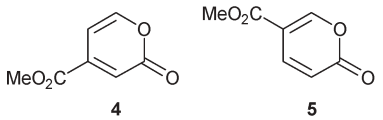


Fig. 1 Isomeric 2-pyrone substrates.

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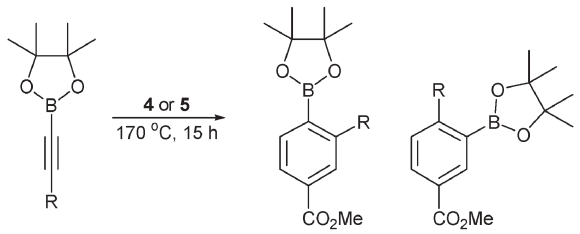
Table 2 Regioselective cycloaddition studies



2a-d **6-9a** **6-9b**

Pyranone	R	Yield	a:b
4	Me_3Si **2a**	**6**; 70%	3:1
5	Me_3Si **2a**	**6**; 85%	1:1
4	Ph **2b**	**7**; 42%	1:1
5	Ph **2b**	**7**; 57%	1:14
4	*n*-Bu **2c**	**8**; 24%	10:1
5	*n*-Bu **2c**	**8**; 59%	1:3
4[a]	H **2d**	—	—
5[a]	H **2d**	**9**; 77%	5:1

[a] Reactions conducted in diphenyl ether.

investigated the cycloaddition of terminal alkyne **2d** and were surprised to note that this substrate was completely unreactive towards **4** but underwent efficient and regioselective cycloaddition with the isomeric diene **5**.

These preliminary studies raised some interesting observations: (1) the cycloaddition reaction is generally more efficient for 2-pyrones bearing the electron withdrawing group at the 5-position (substrate **5**). (2) The regiochemistry of the cycloaddition of substituted alkynes appears to be largely dictated by the 2-pyrone, with the ester group acting as a selectivity modulating unit. Specifically, the reactions are either non-selective or selective for the addition mode shown in Fig. 2.

In order to improve the synthetic versatility of our methodology, we felt that it was important to uncover a class of dienes that gave improved levels of regioselectivity whilst maintaining useful functionality for further elaboration. Towards this end, we began to study the cycloaddition of 3,5-dibromo-2-pyrone **10**[11] and 3-bromo methyl coumalate **11**,[12] our results are highlighted in Table 3.

Once again, the trimethylsilyl substituted acetylene was found to participate efficiently in the cycloaddition, however, we were disappointed to find that an equal mixture of regioisomers **12a/b** was generated. However, the Ph- and Bu-substituted alkynes provided more encouraging results, furnishing the corresponding aromatic boronic esters **13** and **14** with excellent levels of regiocontrol. Finally, cycloaddition of alkyne **2b** with **11** also proved to be highly regioselective, generating **15a** only in good yield. Notably, the mode of addition in all cases was found to proceed in an analogous fashion to those with pyrones **4** and **5** (see Fig. 2).‡

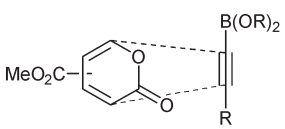
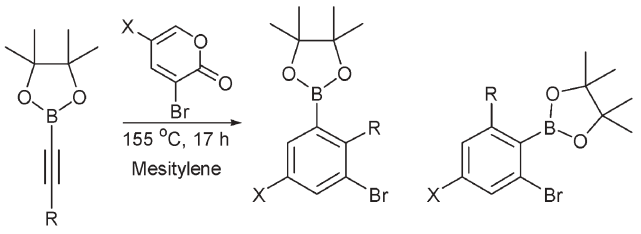


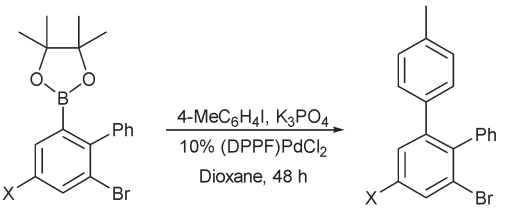
Fig. 2 Cycloaddition regiochemistry.

Table 3 3-Bromo-2-pyrone cycloaddition studies



2a-c **12-15a** **12-15b**

R	X	Yield	a:b
Me_3Si **2a**	Br **10**	**12**; 65%	1:1
Ph **2b**	Br **10**	**13**; 62%	100:0
n-Bu **2c**	Br **10**	**14**; 47%	17:1
Ph **2b**	CO_2Me **11**	**15**; 56%	100:0



X=Br; **13a**
X=CO_2Me; **15a**

X=Br 57%; **16**
X=CO_2Me 70%; **17**

Scheme 1 Suzuki coupling reactions.

The cycloadducts outlined in Table 3 have both arylbromide and arylboronic ester moieties and therefore potentially competing polymerisation could be envisaged during cross-coupling reactions. In an effort to address this issue, we carried out Suzuki coupling of compounds **13a** and **15a** and were pleased to observe smooth and selective cross-coupling with 4-iodotoluene without any detectable interference from the proximal arylbromide moiety (Scheme 1).[13]

In conclusion, we have developed a regioselective method for the synthesis of functionalised aromatic boronic esters through the cycloaddition of alkynylboronates with 2-pyrones. A regiochemistry pattern has emerged that suggests the most favoured mode of addition is as illustrated in Fig. 2, although selectivity is modulated by substituents on the alkyne and 2-pyrone substrates.

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Notes and references

‡ *Crystal data* for $C_{18}H_{19}BBr_2O_2$ (**13a**), M = 437.96; crystallises from petroleum ether–ethyl acetate solvent as colourless blocks; crystal dimensions 0.18 × 0.11 × 0.04 mm^3. Triclinic, a = 11.074(2), b = 11.835(2), c = 15.537(3) Å, α = 87.05(3)°, β = 86.80(3)°, γ = 63.69(3)°, U = 1821.7(6) $Å^3$, Z = 4, D_c = 1.597 Mg m^{-3}, space group $P\bar{1}$ (C_i^1, No. 2), Mo-K $_\alpha$ radiation (λ = 0.71073 Å), μ(Mo-K $_\alpha$) = 4.455 mm^{-1}, $F(000)$ = 872. 6590 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. Refinement converged at a final R = 0.0301 (wR_2 = 0.0577, for all 8635 data, 423 parameters, mean and maximum δ/σ 0.000, 0.002) with allowance for the thermal anisotropy of all non-hydrogen atoms. CCDC 608269. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607322k

Crystal data for $C_{20}H_{22}BBrO_4$ (**15a**), M = 417.10; crystallises from petroleum ether–ethyl acetate solvent as colourless needles; crystal dimensions 0.28 × 0.19 × 0.04 mm^3. Monoclinic, a = 8.0909(5),

b = 21.9946(12), c = 11.5867(7) Å, β = 106.399(3)°, U = 1978.0(2) Å^3, Z = 4, D_c = 1.401 Mg m^{-3}, space group $P2_1/c$ ($P2_1/c$ C_h, No.14), Mo-K $_\alpha$ radiation (λ = 0.71073 Å), μ(Mo-K $_\alpha$) = 2.099 mm^{-1}, F(000) = 856. 3641 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. Refinement converged at a final R = 0.0627 (wR_2 = 0.1546, for all 4548 data, 309 parameters, mean and maximum δ/σ 0.000, 0.000) with allowance for the thermal anisotropy of all non-hydrogen atoms. CCDC 608270. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607322k

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13 Notably, synthesis of a compound analogous to **16** was attempted by heating **10** with diphenylacetylene at 170 °C for 2 days, however, only a trace amount of the cycloadduct was observed.