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A [4 + 2] Cycloaddition Strategy to Pyridine Boronic Ester Derivatives

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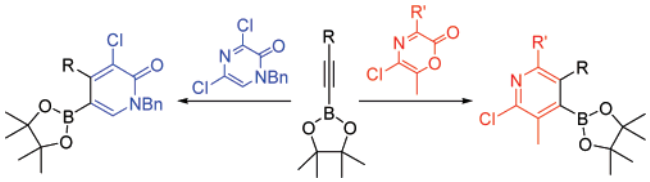
ABSTRACT



Alkynylboronate cycloadditions of 1,4-oxazin-2-ones and 2-pyrazinones provide a direct and regioselective route to functionalized pyridine boronic ester derivatives.

Aromatic and heteroaromatic boronic esters are an extremely valuable class of synthetic intermediates in modern organic chemistry.[1] Although these compounds undergo many transformations, the Suzuki-Miyaura cross-coupling with aryl/heteroaryl halides is arguably the most widely studied within academia and the fine chemicals industry.[2] Moreover, among the plethora of biaryl compounds that can be prepared by this strategy, pyridine-containing compounds are of significant importance because of their biological activity[3] and widespread employment in catalysis both as ligands[4] and as nucleophilic promoters.[5] However, the use of pyridines as the boronic acid component in Suzuki coupling is relatively uncommon, most likely because of problems associated with their preparation. For example, they can show significant water solubility, thereby necessitating an additional step to convert from the boronic acid to the corresponding ester. Moreover, Li−halogen exchange-based approaches can be hampered by the acidity of the substrate bromopyridines.[6] We envisaged an alternative strategy to pyridine boronic esters that employed an alkynylboronate cycloaddition as outlined in Scheme 1. Such cycloadditions have become increasingly popular,[7] and to-date, metal-mediated[8] and metal-catalyzed[9] processes have been developed, as well as

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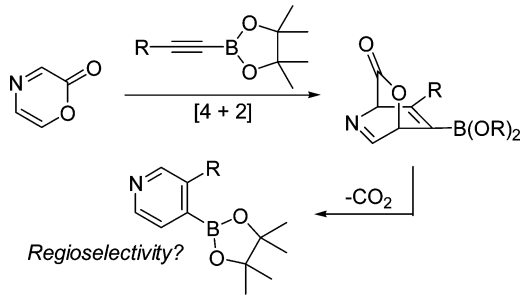
Scheme 1

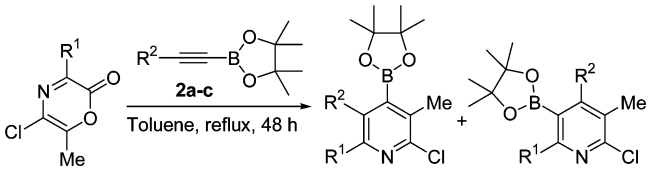


techniques based on pericyclic[10] reactions. In the context of pyridine synthesis, we envisaged that the cycloaddition of an alkynylboronate with a 1,4-oxazin-2-one would furnish the desired heteroaromatic product after loss of CO_2. This scheme provided the prospect of a direct synthesis of pyridine boronic esters under neutral conditions that avoided aqueous workup steps. We report herein our preliminary studies on this novel strategy with regard to its scope and regioselectivity.

We first decided to investigate the scope and regioselectivity of cycloadditions of readily accessible 1,4-oxazin-2-ones **1a**−**c** with alkynylboronates of varying steric size.[11] Indeed, heating a toluene solution of **1a** with phenylacetylene-derived substrate **2a** resulted in smooth cycloaddition and generation of pyridine boronic ester **3** in high yield (entry 1, Table 1). Moreover, we were pleased to find that the reaction provided useful levels of regiocontrol for isomer **3a**. The 3-chloro-oxazin-2-one gave very similar results (entry 2). However, 3-bromo-oxazin-2-one provided the corresponding product with enhanced regiocontrol for the 4-boronate isomer **5a** (entry 3). Changing alkyne substrates to **2b** provided **6** in good yield but with disappointing levels of regioselectivity. Interestingly, oxazinone **1b** provided significantly better regiocontrol whereas, again, **1c** proved to generate the pyridine boronic ester **8** in high yield and with excellent levels of control for regioisomer **a**. Finally, the terminal alkyne **2c** reacted with dienes **1a**−**c** in excellent yield but with poor selectivity. Nonetheless, we were interested to note that once again, a preference for regioisomer **a** was strongest when bromide **1c** was employed.[12]

Although we were encouraged by the potential of oxazinones to furnish functionalized pyridines, we decided to investigate alternative heterodienes in an effort to expand the product scope and in the hope of uncovering processes

Table 1. Cycloaddition Reactions of Alkynyl Boronic Esters with 3,5-Dihalo-2*H*-1,4-oxazin-2-ones



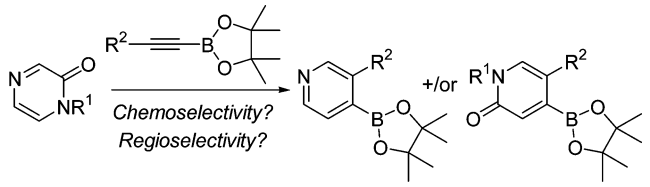
1a-c **3a-11a** **3b-11b**

entry	R^1	R^2	product	yield (**a**:**b**)
1	H (**1a**)	Ph (**2a**)	**3**	72% (5:1)
2	Cl (**1b**)	Ph (**2a**)[a]	**4**	78% (5:1)
3	Br (**1c**)	Ph (**2a**)	**5**	74% (20:1)
4	H (**1a**)	Bu (**2b**)	**6**	67% (2:1)
5	Cl (**1b**)	Bu (**2b**)[a]	**7**	82% (9:1)
6	Br (**1c**)	Bu (**2b**)	**8**	82% (10:1)
7	H (**1a**)	H (**2c**)	**9**	88% (1:2)
8	Cl (**1b**)	H (**2c**)[a]	**10**	84% (1:1)
9	Br (**1c**)	H (**2c**)	**11**	83% (3:2)

[a] Reaction run in *o*-dichlorobenzene (DCB) at 190 °C for 4 h.

that delivered generally higher levels of regiocontrol. In this context, the Hoornaert group demonstrated that substituted pyridines and pyridones could be prepared by the cycloaddition of alkynes with 2[1*H*]-pyrazinones;[13] we therefore decided to explore this chemistry in an effort to uncover the reaction chemoselectivity (formation of pyridine versus pyridone) and regioselectivity (Scheme 2).

Scheme 2



We prepared azadiene **12**[13a] and explored its cycloaddition with alkynylboronates **2a**−**d**. Our results are highlighted in Table 2. We were delighted to find that the cycloadditions proceeded in high yield to provide the 2-pyridone boronic ester rather than the pyridine product.[14] Moreover, we observed a single regioisomer in each case where the boronic ester was incorporated in the 5-position.[15] The 2-pyridone boronic esters prepared by this route have little precedent in

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(12) The regiochemistry of compounds **5**, **7**, **8** were determined by nOe and that of **9** was based on ^{1}H NMR coupling constants. The regiochemistry of compound **3** was assigned by ^{1}H NMR coupling constants after protodeboronation with CsF/EtOH/MeCN. The regiochemistry of **6**, **10**, and **11** are tentatively made by analogy. Compounds **4** and **5** were analyzed by X-ray crystallography. This assignment data is available in the Supporting Information.

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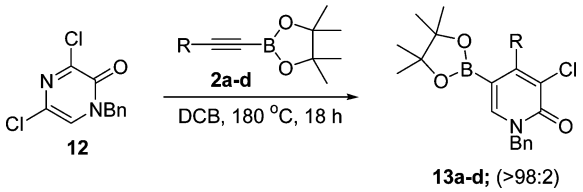
(14) The cycloaddition of alkyne **2d** (Table 2, entry 4) provided a minor amount (~5%) of the corresponding pyridine product.

Table 2. Synthesis of Di-, Tri-Substituted Pyridone Boronic Esters



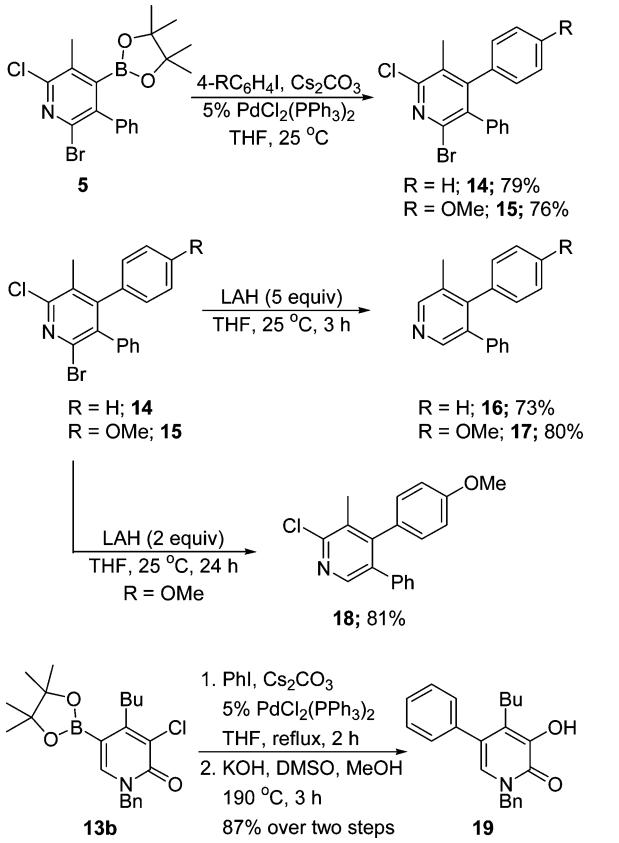
entry	R	product	yield
1	Ph (**2a**)	**13a**	64%
2	Bu (**2b**)	**13b**	81%
3	H (**2c**)	**13c**	77%
4	Me_3Si (**2d**)	**13d**	84%

the literature, and further studies into the scope of this interesting transformation are ongoing in our laboratories.

Having developed two complementary approaches to pyridine-based boronic esters, we wished to confirm that these intermediates could be further elaborated and chose to investigate representative cross-coupling reactions. This process was of particular significance given the congested nature of the boronic esters and/or the presence of halide groups in these substrates that could potentially give rise to competing dimerization processes. We began by investigating the cross-coupling of substrate **5**. As outlined in Scheme 3, we were pleased to find that the Suzuki-Miyaura reaction of pyridine **5** proceeded efficiently to provide **14** and **15**, and we were unable to detect products resulting from homocoupling. In addition, we found that the cross-coupled products could be efficiently de-halogenated to provide 3,4,5-trisubstituted pyridines **16** and **17**. Moreover, partial reduction to the 2-chloropyridine **18** was successfully achieved in the case of **15** by carrying out the reduction with fewer equivalents of LAH. Finally, with regard to the 2-pyridone boronic esters, we confirmed the potential of these intermediates as substrates for Suzuki coupling by performing the Pd-catalyzed cross-coupling of **13b**. Subsequent substitution at the chloride was also feasible but required rather harsh conditions to provide **19** in good overall yield.

(15) The regiochemistry of compounds **13b**, **d** was determined by nOe and that of **13c** was based on ^{1}H NMR coupling constants. The regiochemistry of **13a** is tentatively made by analogy.

Scheme 3



In conclusion, we report herein a new approach to functionalized pyridine-based boronic esters that exploits [4 + 2] cycloaddition reactions of alkynylboronates. This strategy allows a diverse range of intermediates to be generated in good yield and obviates many of the problems associated with using strong bases or aqueous workup procedures.

Acknowledgment. We are grateful to the EPSRC and GSK for financial support.

Supporting Information Available: Full experimental details for the syntheses reported are provided together with spectroscopic and X-ray crystallographic assignment data. This material is available free of charge via the Internet at http://pubs.acs.org

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