Synthetic Methods

Synthesis of Highly Substituted Pyridazines through Alkynyl Boronic Ester Cycloaddition Reactions**

*Matthew D. Helm, Jane E. Moore, Andrew Plant, and Joseph P. A. Harrity**

Aryl boronic acids and esters represent one of the most heavily used classes of synthetic intermediates in recent times.[1] The versatility of the C–B bond allows the organoboron species to be transformed into numerous new synthetic compounds through various functional group interconversions and C–C bond-forming reactions. In an effort to develop new strategies toward the synthesis of highly substituted and functionalized aromatic boronic esters, we have embarked on a program that endeavors to access these compounds through a series of benzannulation protocols. Specifically, we have prepared benzenoid-derived boronic esters through a chromium-mediated benzannulation reaction[2] and isoxazole boronic esters through a [3+2] cycloaddition.[3] More recently, we investigated the use of [4+2] cycloaddition reactions to broaden the scope of our approach. Previous studies in this area have demonstrated that alkynyl boronic esters, alkynyl dihaloboranes, and alkynyl dialkyl boranes can all function as dienophiles.[4] We report herein our efforts to exploit this strategy for the synthesis of pyridazine boronic esters.

The inverse-electron-demand Diels–Alder reaction of 3,6-disubstituted 1,2,4,5-tetrazines (developed by Carboni and Lindsey) is an effective method for the synthesis of highly substituted pyridazines and other aromatic systems.[5,6] We envisaged that employing alkynyl boronic esters in this reaction would allow the rapid assembly of highly substituted pyridazine boronic esters with potential control of the regiochemistry around the heteroaromatic ring (Scheme 1). Indeed, Seitz and Haenel gave three examples of cycloaddition reactions of ethynyl boronic esters with symmetrical tetrazines that provided the corresponding pyridazines in good yield.[7] The authors did not explore the use of more heavily substituted alkynyl boronic esters or investigate the regiochemistry of this reaction. Nonetheless, it is notable that, to the best of our knowledge, this report is the only

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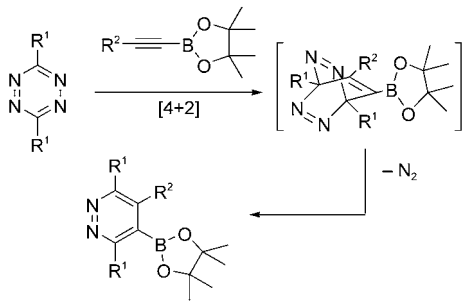


Scheme 1. Synthesis of pyridazine boronic esters through cycloaddition reactions of tetrazines.

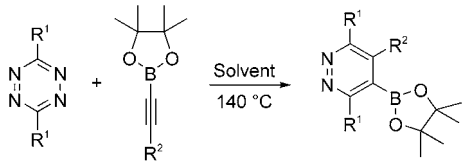
documented method for the preparation of pyridazine boronic esters.

We began our studies by investigating the cycloaddition reactions of some substituted alkynyl boronic esters with the readily prepared symmetrical tetrazines **1** and **2**[8] (the results are summarized in Table 1). The preliminary results were encouraging, and we were pleased to find that the ester-substituted tetrazine **1** participated smoothly in the cycloaddition process at 140 °C to form the corresponding pyridazine boronic esters **9**–**12** in moderate to high yield. An interesting solvent effect was also observed, whereby the reactions proceeded more quickly and cleanly when conducted in nitrobenzene (Table 1, compare entries 1, 3, 5, and 7 with entries 2, 4, 6, and 8). Furthermore, the bis(3,5-dimethylpyrazol-1-yl) (DMPY) substituted tetrazine **2** furnished the corresponding heteroaromatic boronic esters **13**–**15** in high yield; moreover, these substrates were stable to chromatography on silica gel, whereas the purification of the ester-substituted boronic esters was more successful when florisil was used. Finally, the parent tetrazine **3** also participated in cycloaddition reactions with alkynes **5** and **7** to provide the simpler pyridazines **16** and **17** in good yield.

We next turned our attention to investigating the cycloaddition reactions of unsymmetrical tetrazines with a view to developing a regioselective method for preparing the corresponding pyridazine boronic esters. It has been reported that the DMPY group can be readily displaced with a variety of O- and N-containing nucleophiles,[9] and therefore **2** was employed as a common intermediate for the preparation of unsymmetrical tetrazines (Scheme 2). The treatment of **2** with ammonia followed by Boc_2O furnished a Boc-protected tetrazine **18**. Furthermore, oxazolidinone-substituted tetrazines **19** and **20** were readily prepared by addition of the appropriate amino alcohol followed by acylation with triphosgene.

Cycloaddition reactions with model alkynes were carried out under the conditions optimized in the earlier studies (Scheme 3). Accordingly, heating a solution of **18** and a phenyl-substituted alkynyl boronic ester in nitrobenzene resulted in smooth conversion into pyridazine **21**, which was isolated as the free amine[10] and, notably, as a single regioisomer. NOE interaction studies were used to determine the regiochemistry of this cycloaddition reaction, and it was

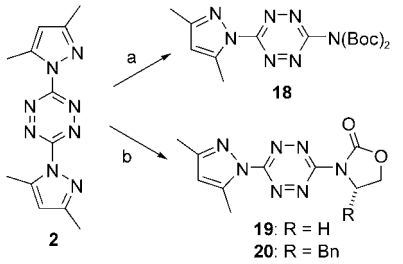
Table 1: Cycloaddition reactions of alkynyl boronic esters with symmetrical tetrazines.



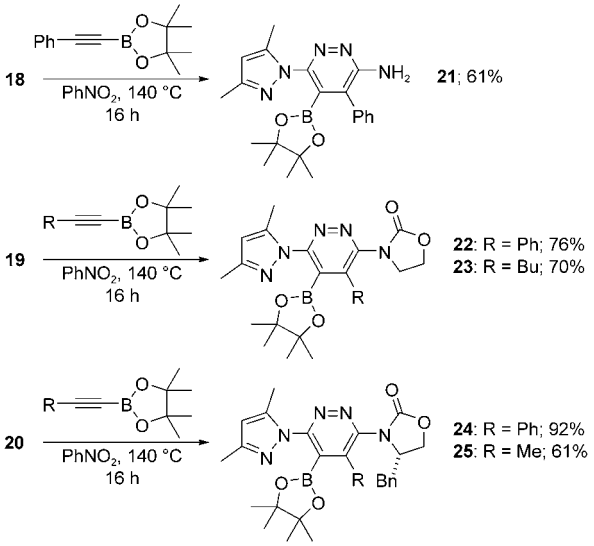
1–3 **4–8** **9–17**

Entry	R^1	$R^{2[a]}$	Solvent	*t* [h]	Product	Yield [%]
1	CO_2Me (**1**)	Me (**4**)	xylene	16	**9**	39
2	CO_2Me (**1**)	Me (**4**)	nitrobenzene	3	**9**	44
3	CO_2Me (**1**)	*n*Bu (**5**)	xylene	16	**10**	62
4	CO_2Me (**1**)	*n*Bu (**5**)	nitrobenzene	6	**10**	75
5	CO_2Me (**1**)	Ph (**6**)	xylene	16	**11**	68
6	CO_2Me (**1**)	Ph (**6**)	nitrobenzene	4	**11**	75
7	CO_2Me (**1**)	TMS (**7**)	xylene	16	**12**	62
8	CO_2Me (**1**)	TMS (**7**)	nitrobenzene	4	**12**	89
9	DMPY (**2**)	Me (**4**)	xylene	16	**13**	82
10	DMPY (**2**)	Me (**4**)	nitrobenzene	7	**13**	81
11	DMPY (**2**)	Ph (**6**)	xylene	16	**14**	80
12	DMPY (**2**)	Ph (**6**)	nitrobenzene	6	**14**	84
13	DMPY (**2**)	TMS (**7**)	xylene	16	**15**	70
14	DMPY (**2**)	TMS (**7**)	nitrobenzene	8	**15**	69
15	H (**3**)	Ph (**6**)	nitrobenzene	6	**16**	60
16	H (**3**)	H (**8**)	nitrobenzene	6	**17**	64

[a] TMS = trimethylsilane.



Scheme 2. a) 1. NH_3 (excess), toluene, 98%; 2. Boc_2O (2.2 equiv), DMAP (10 mol%), THF (**18**: 70%); b) 1. $H_2N(CH_2)_2OH$ (1.2 equiv), MeOH; 2. triphosgene (1.2 equiv), Et_3N (2.1 equiv), CH_2Cl_2 (**19**: 73% over 2 steps); or 1. (*S*)-$H_2NCH(Bn)CH_2OH$ (1.2 equiv), MeOH; 2. triphosgene (1.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2 (**20**: 63% over 2 steps). Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, Bn = benzyl.

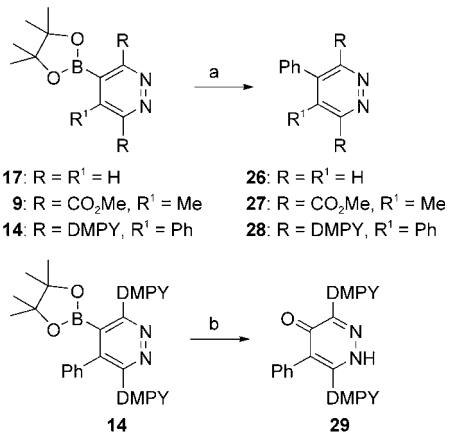


Scheme 3. Preparation of unsymmetrical tetrazines.

shown that the boronic ester is adjacent to the pyrazolyl ring. We extended this promising reaction to the oxazolidinone-substituted tetrazine **19** to afford **22** and **23** and were pleased that, once again, single regioisomers were isolated. Crystals of **22** suitable for X-ray crystallographic analysis were obtained, and it was confirmed that the boronic ester moiety was again incorporated adjacent to the pyrazole ring.[11] Finally, we extended the cycloaddition chemistry to the chiral oxazolidinone-substituted tetrazine **20** and synthesized chiral pyridazine boronic esters **24** and **25** with equally satisfying results.[12]

With a series of pyridazine boronic esters in hand, our final goal was to investigate functionalization reactions of the C–B bond. The primary objective was to establish the viability of these substrates for Suzuki cross-coupling reactions. It was anticipated that these reactions would require significant optimization as electron-deficient boronic acid derivatives are known to be prone to protodeboronation.[13] Also, the significant steric crowding around the boronate moiety in these compounds further suggested that they would be very challenging substrates. Accordingly, we initiated our studies by examining the cross-coupling of the parent pyridazine boronic ester **17** (Scheme 4). After significant optimization, we were pleased to find that **26** was successfully generated in high yield by employing the protocol of Netherton and Fu[14] for the Suzuki reaction. Pleasingly, these conditions could also be applied to the cross-coupling reaction of the hindered diester **9** to provide the coupled product **27** in 57% yield. Finally, the cross-coupling reaction of **14** with iodobenzene proved to be extremely difficult and resulted in the formation of a substantial quantity of protodeboronated material with a small amount of desired product. Nonetheless, the use of microwave irradiation allowed the desired product **28** to be isolated in 51% yield within a short reaction time.[15] Finally, we explored a simple oxidation of **14** to the 1*H*-pyridazin-4-one **29** and were pleased to find that this transformation proceeded smoothly and in high yield (Scheme 4).

In conclusion, we have reported that the cycloaddition of tetrazines with alkynyl boronic esters provides a direct and regioselective method for the synthesis of highly functionalized pyridazine boronic esters. We have also shown that these intermediates can undergo C–O and C–C bond-forming reactions; the latter transformation requires bulky and electron-rich phosphine ligands to promote catalytic cross-coupling over protodeboronation.



17: R = R¹ = H
9: R = CO_2Me, R¹ = Me
14: R = DMPY, R¹ = Ph

26: R = R¹ = H
27: R = CO_2Me, R¹ = Me
28: R = DMPY, R¹ = Ph

Scheme 4. a) **26**: $[Pd_2(dba)_3]$ (5 mol%), $[(t\text{Bu})_3\text{PH}]BF_4$ (12 mol%), PhI, K_3PO_4, MeCN, 85°C, 90 min (72%); **27:** $[Pd_2(dba)_3]$ (5 mol%), $[(t\text{Bu})_3\text{PH}]BF_4$ (12 mol%), PhI, K_3PO_4, MeCN, 50°C, 90 min (57%); **28:** $[Pd_2(dba)_3]$ (5 mol%), $[(t\text{Bu})_3\text{PH}]BF_4$ (12 mol%), PhI, K_3PO_4, MeCN, 170°C, microwave irradiation, 15 min (51%); b) *i*PrOH, H_2O_2, Na_2CO_3, 85°C (**29**: 96%).

Experimental Section

Typical cycloaddition procedure, as exemplified by the formation of **16**: 4,4,5,5-Tetramethyl-2-phenylethynyl[1,3,2]dioxaborolane (**6**; 306 mg, 1.34 mmol) and 1,2,4,5-tetrazine (**3**; 100 mg, 1.22 mmol) were dissolved in nitrobenzene (2 mL) and heated at 140°C for 6 h. The nitrobenzene was removed in vacuo, and the product recrystallized from ethyl acetate to give **16** (206 mg, 60%) as a light-yellow solid. M.p. 130.5–132.7°C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.25$ (s, 12H), 7.40–7.50 (m, 5H), 9.22 (d, $J = 1.0$ Hz, 1H), 9.31 ppm (d, $J = 1.0$ Hz, 1H); ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): $\delta = 24.4$, 84.8, 128.7, 129.0, 129.4, 136.0, 143.3, 150.8, 153.6 ppm; FTIR: 3063 (w), 2978 (m), 1573 (w), 1288 (w), 1148 (s), 1076 cm^{-1} (m). HRMS calcd for $C_{16}H_{19}N_2O_2B$: *m/z* 282.1540, found: 282.1550.

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