Cycloaddition Reactions

DOI: 10.1002/anie.200703767

A Sydnone Cycloaddition Route to Pyrazole Boronic Esters**

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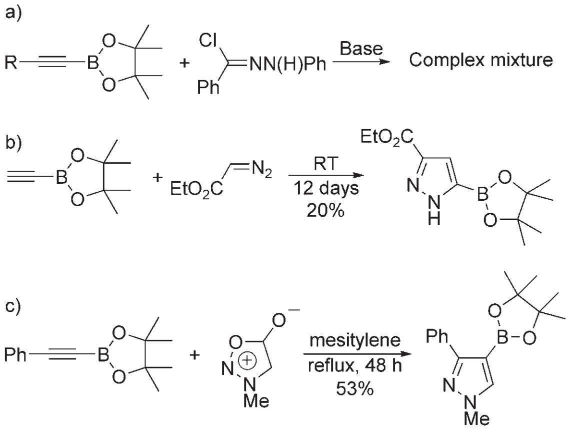
Aromatic and heteroaromatic boronic esters are among the most valuable synthetic intermediates in modern organic chemistry.[1] They are used throughout both industry and academia, largely because of their ability to form carbon–carbon bonds to various aromatic substrates through a Pd-catalyzed cross-coupling reaction.[2] However, they also participate in carbon–heteroatom bond formation to provide amines and ethers as well as undergoing nucleophilic addition reactions to imines, aldehydes, and enones.[3] Despite their popularity, their synthesis generally requires a functional group transformation from a starting organohalide or triflate.[4] The requirement for these precursors can become problematic if one wishes to generate highly functionalized aromatic boronates because the starting halide/triflate may be difficult to access or the substrate's functionality may be incompatible with conditions required to transform the substrate into the boronic ester product. An alternative and increasingly popular approach to these compounds is through cycloaddition reactions of alkynylboronates.[5] To date, metal-mediated[6] and metal-catalyzed[7] processes have been developed, as well as techniques based on pericyclic[8] reactions.

In an effort to expand the scope of hetereoaromatic compounds available by this strategy, we were attracted to the preparation of pyrazole boronic esters. Pyrazoles are commonly employed in the pharmaceutical and agrochemical industries;[9] therefore, a direct and flexible route for the synthesis of pyrazole boronic esters would allow a broad range of analogues to be made available by exploiting the rich chemistry available to these organoboron reagents.[10] We contemplated three approaches towards this goal: 1) [3+2] cycloadditions of diazoalkanes; 2) [3+2] cycloadditions of nitrile imines; and 3) cycloaddition/retrocycloaddition of sydnones. We set out to establish the potential of each approach, and our preliminary results are highlighted in Scheme 1. Attempts to prepare nitrile imines and perform the cycloaddition in situ[11] were unsuccessful, and a complex mixture of unidentifiable products was obtained (Scheme 1 a). The [3+2] cycloaddition of diazoalkane derivatives appeared to be a more promising alternative as Matteson had demonstrated the feasibility of this reaction through the cycloaddition of a terminal alkyne boronic ester with ethyl diazoacetate.[12] Although we were able to repeat these findings, the reaction was extremely slow and limited only to the terminal alkyne substrate (Scheme 1 b). We next turned our attention to the cycloaddition of alkynylboronates with sydnones.[13] Although there was no precedent for the reaction of alkynylboronates with this class of reagent, successful cycloadditions of these mesoionic compounds were reported during the course of this work with alkynylstannanes and -silanes.[14] To our delight, heating a mixture of the alkynylboronate derived from phenylacetylene and *N*-methylsydnone in refluxing mesitylenes provided the corresponding pyrazole in good yield (Scheme 1 c). Moreover, only a single regioisomer could be identified from the reaction mixture.[15] We therefore decided to carry out further investigations into the scope of this promising transformation.



Scheme 1. Cycloaddition approaches to pyrazoles.

We performed the cycloaddition of a series of alkynylboronates with *N*-aryl sydnones to establish the reaction scope and regioselectivity; our results are summarized in Table 1. We were pleased to find that *N*-phenylsydnone **1a** reacted smoothly with a range of alkynylboronates to provide the corresponding pyrazoles in good to high yield (entries 1–4). We were surprised to find significant variation in reaction regioselectivity. Whereas phenyl alkynylboronate **2a** provided a single regioisomer, more modest regiocontrol was observed with alkynes **2b** and **2c**, and a switch in regiochemistry was found when terminal alkyne **2d** was employed. We were intrigued by the possibility of modulating reaction rate and regiochemistry by changing the electronic nature of the sydnone and therefore opted to investigate the cycloaddition of substrates bearing electron-rich/-deficient aryl groups. We found that electron-rich sydnone **1b** was rather sluggish in the

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[**] The authors are grateful to the EPSRC and Syngenta for financial support.

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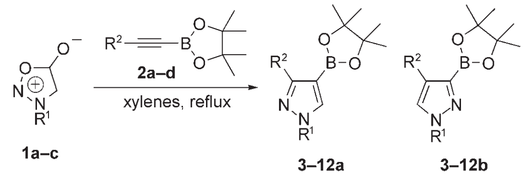
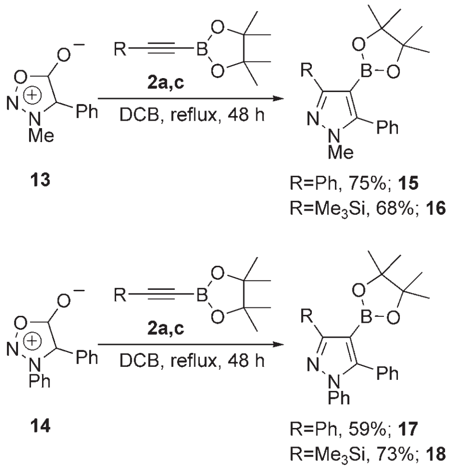
Table 1: Cycloaddition reactions of alkynyl boronic esters with *N*-phenyl sydnone.

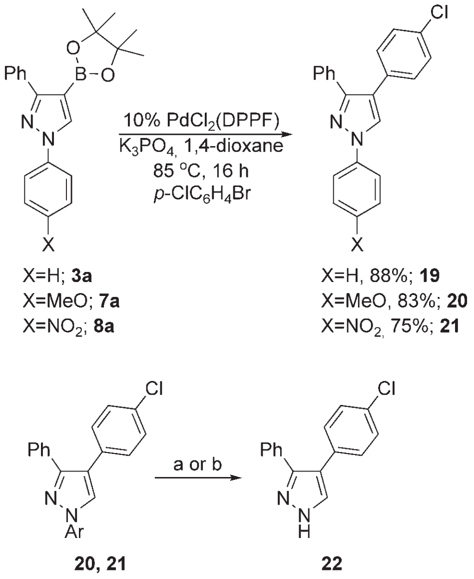


Entry	R^1	$R^{2[b]}$	*t* [h]	Product	Yield [%] (**a**:**b**)[c]
1	Ph (**1a**)	Ph (**2a**)	16	**3**	58 (>98:2)
2	Ph (**1a**)	Bu (**2b**)[a]	16	**4**	64 (5:2)
3	Ph (**1a**)	Me_3Si (**2c**)	16	**5**	76 (2:1)
4	Ph (**1a**)	H (**2d**)[a]	16	**6**	54 (1:7)
5	*p*-$MeOC_6H_4$ (**1b**)	Ph (**2a**)	24	**7**	58 (>98:2)
6	*p*-$NO_2C_6H_4$ (**1c**)	Ph (**2a**)	4	**8**	70 (>98:2)
7	*p*-$MeOC_6H_4$ (**1b**)	Bu (**2b**)[b]	24	**9**	55 (5:1)
8	*p*-$NO_2C_6H_4$ (**1c**)	Bu (**2b**)[a]	8	**10**	62 (5:1)
9	*p*-$MeOC_6H_4$ (**1b**)	Me_3Si (**2c**)	22	**11**	61 (2:1)
10	*p*-$NO_2C_6H_4$ (**1c**)	Me_3Si (**2c**)	4	**12**	83 (3:2)

[a] Reactions run in refluxing mesitylenes. [b] Reaction run in refluxing *o*-dichlorobenzene.



Scheme 2. Cycloaddition with C-substituted sydnones. DCB: *o*-dichlorobenzene.



Scheme 3. Functionalization of pyrazole boronic esters. a) **20:** CAN (5 equiv), MeCN, H_2O (3:2) (63%); b) **21:** i) $NH_2NH_2.H_2O$, 10% Pd/C, EtOH, 50°C, 3 h; ii) CAN (5 equiv), MeCN, H_2O (3:2) (48% over two steps). DPPF = bis(diphenylphosphanyl)ferrocene.

cycloaddition reaction (entries 5, 7, 9) whereas significantly faster reaction rates were observed when more-electron-deficient sydnone **1c** was employed (entries 6, 8, 10). This observation is in line with recent kinetics and computational studies from our labs that suggest that alkynylboronates participate as electron-rich components in cycloadditions.[16] Nonetheless, although the reaction rate was found to depend on the electronic nature of the mesoionic reagent, reaction regioselectivity was largely unaffected. Notably, the regioisomers generated in entries 2, 3, 4, and 9 were readily separable by chromatography; hence, essentially single isomers of pyrazole boronic esters could easily be obtained in seven of the ten reactions studied.

We next decided to explore the cycloaddition chemistry of more heavily substituted sydnones with a view to generating more-complex pyrazoles. We also anticipated that the increased steric bulk present in these substrates could lead to more generally regioselective cycloadditions. Accordingly, we prepared sydnones **13** and **14**; our cycloaddition studies are highlighted in Scheme 2. We were delighted to find that sydnone **13** underwent efficient cycloaddition to provide direct access to the fully substituted pyrazoles **15** and **16** and that these compounds were isolated as single regioisomers. Moreover, changing the sydnone to include an *N*-aryl substituent (**14**) did not have a deleterious effect on yield or regioselectivity.

Having demonstrated that the cycloaddition chemistry could provide tri- and tetrasubstituted pyrazole boronic esters, we wished to confirm that these intermediates could be further elaborated through Suzuki coupling reactions. Additionally, our reaction scope studies had provided functionalized *N*-arylpyrazoles (Table 1, entries 5–10) and we hoped to show that these provided a means for deprotection of the cross-coupled pyrazole products. In the event (Scheme 3), cross-coupling reactions of pyrazoles **3**, **7**, and **8** proceeded without incident to give the corresponding products in good to excellent yield. Moreover, we were able to demonstrate the utility of these intermediates by removing the *N*-aryl moiety in compounds **20** and **21**; specifically, oxidation of **20** with ceric ammonium nitrate (CAN) proceeded in 63% yield to provide pyrazole **22**. Moreover, reduction of the nitro group in **21** to the corresponding aniline allowed **22** also to be accessed by CAN oxidation.

In conclusion, we report the first example of alkynylboronate cycloadditions with sydnones as a means to the direct preparation of functionalized pyrazole boronic esters. Moreover, we have demonstrated that these compounds can be further functionalized by Pd-catalyzed cross-coupling reactions and N-deprotection processes.

Experimental Section

Typical cycloaddition procedure, as exemplified by the formation of **3**: 4,4,5,5-Tetramethyl-2-phenethynyl[1,3,2]dioxaborolane (**2a**; 228 mg, 1 mmol) and *N*-phenyl sydnone (**1a**; 81 mg, 0.5 mmol) were dissolved in xylenes (0.5 mL), heated at reflux for 16 h, and then rapidly cooled in an ice bath. The reaction mixture was purified by flash chromatography on silica gel (100 % petrol to 30 % ethyl acetate in petrol). Product **3** was isolated as a colorless solid (100 mg, 58 %). Further purification could be carried out by trituration with diethyl ether. M.p. 158–160 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.30$ (s, 1H), 8.02–8.10 (m, 2H), 7.75–7.83 (m, 2H), 7.25–7.50 (m, 6H), 1.34 ppm (s, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 157.9$, 139.8, 136.3, 133.9, 129.4, 128.44, 128.0, 126.6, 119.3 (2C), 83.6, 24.8 ppm; FTIR: 2978 (m), 1600 (m), 1532 (s), 1446 (m), 1356 (m), 1307 (m), 1217 (m), 1146 (m), 1126 (m), 1062 (m), 993 (m), 958 cm^{-1} (m). HRMS calcd for $C_{21}H_{23}BN_2O_2$: *m*/*z* 346.1853, found: 346.1866.

Received: August 16, 2007

Keywords: boronic esters · cycloaddition · heterocycles · regioselectivity

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