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Sequential Suzuki–Miyaura Cross-coupling Reactions of 4-Halopyrazolyl MIDA 3-Boronates: A Modular Synthetic Entry to 3,4-Bis(hetero)aromatic Pyrazoles

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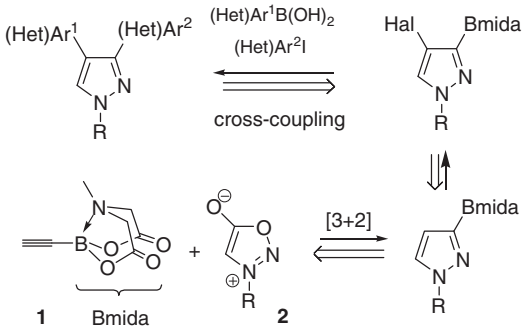
The 1,3-dipolar cycloaddition of *N*-arylsydnones with ethynyl MIDA boronate produces mixtures of the corresponding regioisomeric pyrazolyl 3(4)-boronates, with the pyrazolyl 3-boronates predominating by a factor of 7:3. Further C-4 iodination of the latter opened access to 4-iodopyrazolyl MIDA 3-boronates as valuable scaffolds for the elaboration of unsymmetrically 1,3,4-trisubstituted pyrazole derivatives via Suzuki cross-coupling reactions.

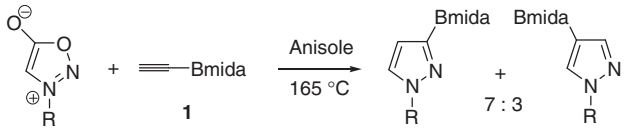
Pyrazole derivatives have found numerous applications as pharmaceuticals and agrochemicals.[1] As a part of our ongoing research program devoted to the synthesis of diverse poly(hetero)aromatic pyrazoles for biological screening, we needed an efficient and modular synthetic strategy to assemble a series of 3,4-bis(hetero)aromatic derivatives.[2] To this end, flexible protocols allowing the sequential introduction of (hetero)aryl substituents on the prefunctionalized pyrazole nucleus via transition-metal-catalyzed site-selective C–C bond forming processes were highly desirable.[3] Notably, the Suzuki-type reactions were particularly attractive as they are largely unaffected by the presence of water and are tolerant to a wide range of functional groups. They also take advantage of the commercial availability of numerous boronic acids.[4] However, one major drawback of this strategy is the poor synthetic accessibility of 3,4-dihalogenated pyrazoles. Indeed, while C-4 halogenation of the pyrazole nucleus is relatively easy,[5] selective halogenation at the C-3 carbon atom adjacent to nitrogen remains a rather difficult task.[3,6] In addition, issues of cross-coupling site-selectivity would also need to be addressed.

Within this context, we became interested in the potential synthetic utility of 4-halopyrazole-3-boronates as alternative scaffolds. Our approach is inspired by Harrity's pioneering work[2a,7] on the synthesis of pyrazolyl pinacol boronates via sydnone 1,3-dipolar cycloadditions with alkynylboronates. Interestingly, it was reported that terminal alkynylboronate cycloaddition provided the corresponding pyrazole-3-boronates with good levels of regiocontrol, whereas substituted alkynes afforded almost exclusively 4-boronates. Based on these results, we envisaged a rapid access to 4-halopyrazole-3-boronates via sydnone cycloaddition with a terminal alkynyl boronate ester followed by C-4 halogenation. Besides, in order to avoid self coupling reactions, it was decided to make use of masked boronic acids[8] that would allow us to first cross-couple at C-4 and then release the boronic acid to finally cross-couple at C-3. The commercially available ethynyl *N*-methyliminodiacetic acid (MIDA) boronate (**1**) developped by Burke[9] was the perfect candidate to gauge the present strategy (Scheme 1). We report herein our preliminary results toward this goal.



Scheme 1.

Table 1. Synthesis of pyrazolyl MIDA 3-boronates **3**[a]



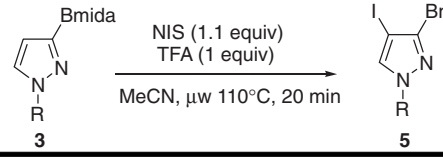
Entry	Sydnone R =	Time /h	Yield /%[b]	Yield of **3**[c]/%	Yield of **4**[c]/%
1	Ph	24	34	24 (**3a**)	10 (**4a**)
2	*p*-FPh	18	65	41 (**3b**)	24 (**4b**)
3	*p*-NO_2Ph	12	67	47 (**3c**)	20 (**4c**)

[a]Reactions conducted in sealed glass tubes on 2 mmol scale. [b]Combined isolated yields. [c]Isolated yields.

Our studies began with an initial investigation of the efficiency of sydnone cycloadditions with ethynyl MIDA boronate (**1**). A series of *N*-arylsydnones **2** were thus prepared and reacted with equimolar amounts of **1** at 165 °C in anisole (Table 1). As expected the reactions gave rise to mixtures of regioisomeric pyrazolyl boronates **3**/**4** easily separated by silica gel chromatography, with the pyrazole-3-boronate predominating by a factor of 7:3 as determined by ^{1}H NMR analysis of the crude mixture of **3** and **4**. These results also showed that sydnones bearing electron-poor aryl groups at N-1 gave the best result. The *N*-*p*-nitrophenylpyrazole **3c** was of special interest as it may ultimately open access to *N*H-pyrazoles upon cleavage of the PNP group.[10] The latter compound was isolated with an acceptable 47% yield.

With the pyrazole-3-boronates in hand, we next focused our efforts on establishing a convenient, high yielding procedure for the preparation of 4-halopyrazole-3-boronates. Early experiments following literature protocols[5] based on the use of *N*-halosuccinimides as halogenation reagents were disappointing.

Table 2. Synthesis of 4-iodopyrazolyl MIDA 3-boronates[a]



Entry	MIDA boronate R =	Yield/%[b]
1	Ph (**3a**)	95 (**5a**)
2	*p*-FPh (**3b**)	78 (**5b**)
3	*p*-NO_2Ph (**3c**)	79 (**5c**)

[a]Reactions conducted on 0.7 mmol scale. [b]Isolated yields.

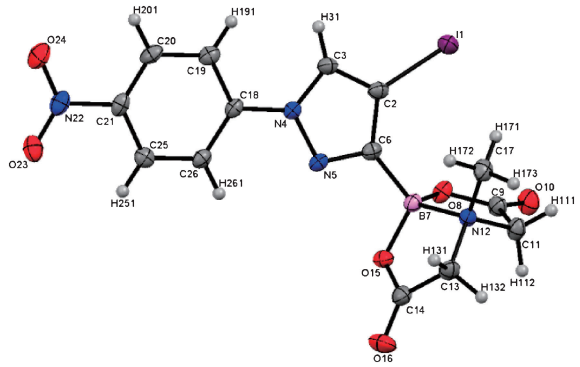


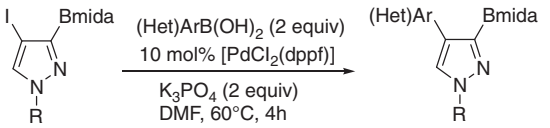
Figure 1. ORTEP view of **5c**.

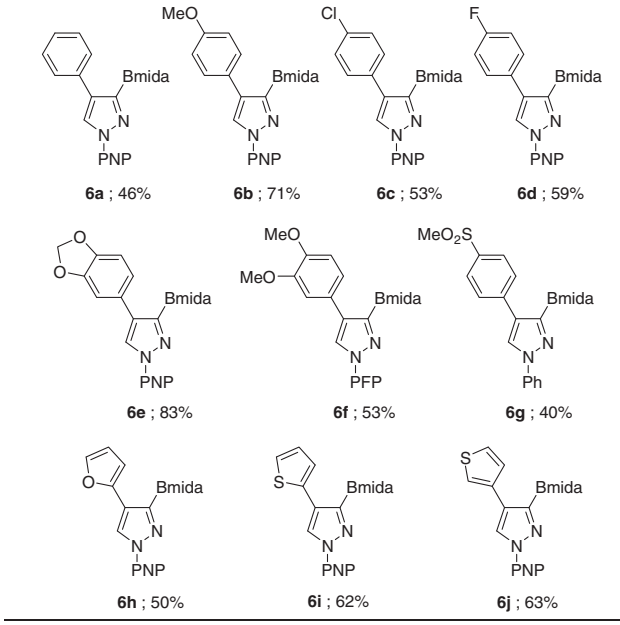
Reactions conducted in chlorinated solvents[5a] proved rather sluggish and low yielding owing to the poor solubility of the MIDA boronates in these solvents. Noticeable improvements came from the use of acetic acid as solvent under microwave irradiation.[5b] However, after further experimentation, the best conditions we could establish consisted of performing the reaction in acetonitrile as solvent using NIS–TFA (*N*-iodosuccinimide–trifluoroacetic acid) as iodonium donating system[11] under microwave irradiation (110 °C, 20 min). Under these conditions, a series of 4-iodopyrazole-3-boronates **5a**–**5c** could be obtained in 78–95% isolated yield (Table 2). The structure of **5c** has been secured by X-ray analysis (Figure 1).[12]

Having secured a reliable preparative method to the 4-iodopyrazole-3-boronates, we next focused our attention on their application in Suzuki cross-coupling reactions at the halide terminus. Anhydrous conditions would normally prevent premature hydrolysis of the boronate esters. Gratifyingly, under the optimum set of reaction conditions (10 mol % [$PdCl_2$(dppf)], 2 equiv of K_3PO_4, DMF, 60 °C), a variety of electron-poor and electron-rich arylboronic acids, as well as a series of heteroarylboronic acids, including 2-furyl and 2(3)-thienylboronic acids furnished the corresponding coupling products **6a**–**6j** in moderate to good yields after chromatographic purification (Table 3).

Finally, we evaluated the effectiveness of the Suzuki cross-coupling reactions at the C-3 position. To this end, in situ slow-release of the corresponding boronic acids through hydrolysis of the MIDA boronates under aqueous basic conditions was envisaged in order to minimize any undesired protodeboronation. We thus applied to a series of pyrazolyl MIDA 3-boronates reaction conditions similar to those developed by Burke and co-workers[13] and consisting of $Pd(OAc)_2$/S-Phos as catalyst system and K_3PO_4 as base in aqueous DMF. Under these conditions, a small array of 3,4-bis(hetero)aromatic pyrazoles **7a**–**7e** could be produced in acceptable yields (Table 4).

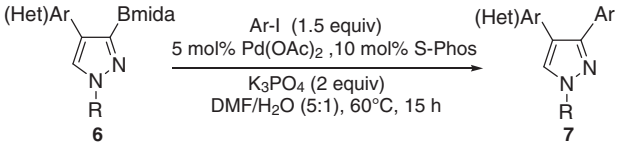
Table 3. Reaction of 4-iodopyrazolyl MIDA 3-boronates with various (hetero)aromatic boronic acids[a]

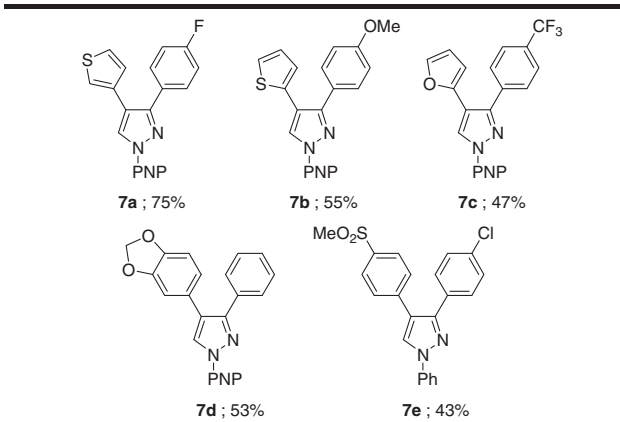




[a]Reactions conducted on 0.2 mmol scale (isolated yields); PNP = *p*-NO_2Ph; PFP = *p*-F-Ph.

Table 4. Reaction of pyrazolyl MIDA 3-boronates with various aryl iodides[a]





[a]Reactions conducted on 0.2 mmol scale (isolated yields).

In summary, 4-iodopyrazolyl MIDA 3-boronates are readily accessible in two steps from sydnones and commercially available ethynyl MIDA boronate. They have been shown to be valuable scaffolds for the rapid elaboration of 3,4-bis(hetero)-arylpyrazole derivatives by means of sequential Suzuki cross-coupling reactions and should find broader applications in the preparation of chemical libraries of potentially biologically active compounds.[14]

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