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Alkyne [3 + 2] Cycloadditions of Iodosydnones Toward Functionalized 1,3,5-Trisubstituted Pyrazoles

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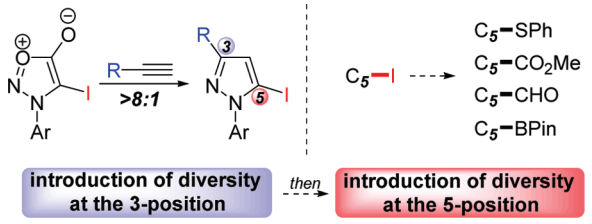
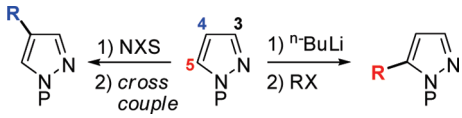


The cycloaddition of 4-iodosydnones with terminal alkynes proceeds with excellent regiocontrol to provide 5-iodo pyrazoles. These products participate smoothly in subsequent C−C and C−heteroatom bond forming processes.

The synthesis and reactions of pyrazoles continues to gain growing interest within both academic and industrial laboratories. This diazole core is finding increasing importance as a biologically active agent and can be found in a number of pharmaceutical and agrochemical products.[1] Pyrazoles are also gaining interest as ligands for transition metals and within materials chemistry.[2] The search for new bioactivity and pyrazole reactivity will be aided by the development of new and complementary synthetic approaches to such molecules. In this context, pyrazoles are generally accessed either via ring synthesis or by ring functionalization.[3] With regard to the latter approach, typical methods of pyrazole functionalization involve the regioselective halogenation at the C-4 position followed by metalation or cross-coupling, or by selective ring lithiation at C-5 with a subsequent electrophilic quench (Scheme 1).[4] While there are no direct methods of functionalization at C-3, McLaughlin and Sames have employed an elegant protecting group transposition concept that provides a regiocontrolled method for achieving this goal.[5]

SCHEME 1



Recent studies in our laboratories have also been aimed at developing regiocontrolled methods for the synthesis of highly functionalized pyrazoles.[6] We have largely opted to target pyrazole boronic acid derivatives because of the associated versatility of the boronate motif.[7] Accordingly, we have conducted several studies on the cycloaddition of sydnones with alkynylboronates for the synthesis of pyrazole boronic esters (Figure 1). The regiochemical outcome of these cycloadditions has been delineated and interrogated by both practical and theoretical examination.[6a,c] We have also extended this to a flexible divergent approach through the discovery of a cross-coupling strategy from an intermediate 4-bromosydnone.[6b] A potentially powerful extension of the pyrazole forming strategy outlined in Figure 1 would be the direct cycloaddition of alkynes with 4-halosydnones to provide the corresponding halopyrazoles. In connection with this concept, we report herein the regioselective synthesis of 5-iodo pyrazoles with specific emphasis on the flexible introduction of substituents at the C-3 position.

A literature survey suggested that bromosydnones are unstable at elevated temperatures in nonpolar solvents[8] although their participation in cycloaddition processes with activated alkynes (e.g., dimethylacetylene dicarboxylate and

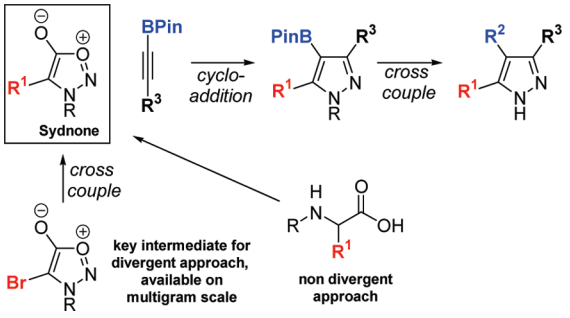


FIGURE 1. A sydnone cycloaddition stratgey to pyrazoles.

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(2) (a) Trofimenko, S. *Prog. Inorg. Chem.* **1986**, *34*, 115. (b) Danel, A.; He, Z.; Milburn, G. H. W.; Tomasik, P. *J. Mat. Chem.* **1999**, *9*, 339.
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(6) (a) Browne, D. L.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8656. (b) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396. (c) Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7762.
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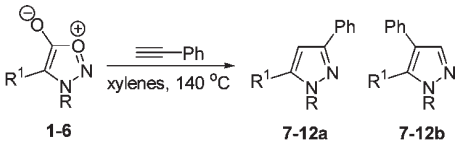
TABLE 1. 4-Iodo Sydnone Cycloaddition Reactivity and Regioselectivity Studies



1-6 7-12a 7-12b

entry	R	R^1	reaction time (h)	yield % (a:b)
1	PNP[a]	H; **1**	8	60 (19:1); **7**
2	PNP	I; **2**	8	84 (10:1); **8**
3	Ph	H; **3**	16	35 (>19:1); **9**
4	Ph	I; **4**	16	73 (>19:1); **10**
5	PMP[b]	H; **5**	24	30 (10:1); **11**
6	PMP	I; **6**	24	72 (10:1); **12**

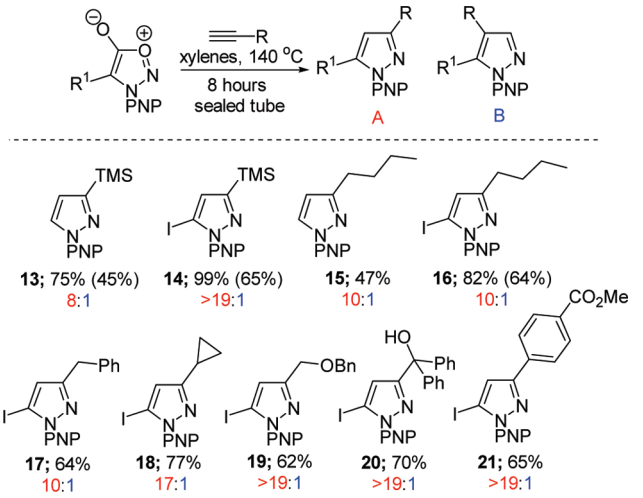
[a]PNP: *p*-nitrophenyl. [b]PMP: *p*-methoxyphenyl.

ethyl propiolate) has been documented.[9] There were no reports of thermal instability in the analogous 4-iodosydnones, although again reports of their cycloaddition chemistry were similarly limited to activated alkynes.[9] In addition, the outcome of the cycloadditions of 4-iodosydnones and propiolates suggested little scope for regiocontrol.[10] Nonetheless, we decided to explore the cycloaddition efficiency and regioselectivity of a series of nonactivated terminal alkynes with sydnones bearing an I-atom at C-4. Moreover, we conducted the cycloaddition reactions of the appropriate C-4 unsubstituted sydnones to highlight any advantageous/deleterious effects of the iodide substituent on the cycloaddition process.[11] We chose to begin our studies by using phenylacetylene as the dipolarophile, and our results are summarized in Table 1. *N*-*p*-Nitrophenyl substituted sydnone **1** underwent efficient cycloaddition to provide the corresponding 1,3-disubstituted pyrazole **7** with excellent regiocontrol (entry 1). The corresponding iodide **2** reacted similarly but gave an improved overall yield of 1,3,5-trisubstituted pyrazole **8** (entry 2). Changing the *N*-substituent to more electron rich aromatic groups resulted in reduced reaction rates but had little effect on the cycloaddition regiocontrol (entries 3−6). Overall however, the C-4 iodo substituted sydnones appeared to give a consistently improved yield of pyrazole products over their C-4 unsubstituted counterparts.

The high selectivities observed in this preliminary study were extremely encouraging as this strategy represented a potentially powerful and effective method for installing substituents at the pyrazole C-3 position, while providing scope for elaboration at C-5. Moreover, given that this substituent ultimately emanates from a terminal alkyne, this approach promised to show significant generality. To confirm this, we next turned our attention to assessing the scope of the pyrazole forming chemistry with respect to the terminal alkyne, and our results are highlighted in Table 2.

Surprisingly, the cycloaddition of trimethylsilylacetylene and PNP-protected sydnones **1** and **2** proceeded in modest yield when conducted under refluxing xylenes. We envisaged that this relatively low yield was due to the volatility of this alkyne, and so we opted to perform the reaction in a sealed

TABLE 2. Scope of the Alkyne Cycloaddition Partner



entry	R	R^1	yield %[a]	A:B
1	TMS	H	75 (45); **13**	8:1
2	TMS	I	99 (65); **14**	>19:1
3	^{n}Bu	H	47; **15**	10:1
4	^{n}Bu	I	82 (64); **16**	10:1
5	Bn	I	64; **17**	10:1
6	cyclopropyl	I	77; **18**	17:1
7	CH_2OBn	I	62; **19**	>19:1
8	$C(OH)Ph_2$	I	70; **20**	>19:1
9	*p*-$MeO_2CC_6H_4$	I	65; **21**	>19:1

[a]Yields in parentheses represent that when the reaction was conducted under reflux.

tube. Pleasingly, the desired pyrazoles **13** and **14** were delivered in greatly increased yields (entries 1, 2). Primary alkyl substituted alkynes (1-hexyne and 3-phenyl-1-propyne) displayed good selectivity in the cycloaddition reaction, giving rise to a 10:1 ratio of pyrazole isomers (entries 3−5). Cycloaddition with cyclopropylacetylene provided an interesting pyrazolyl-3-cyclopropane scaffold **18** in good yield (entry 6). The latter secondary alkyl substituted alkyne displayed improved regioselectivity over the primary congeners (compare entries 4−6), suggesting an element of steric control in these cycloadditions. Finally, propargyl alcohol derivatives and functionalized arylacetylenes were also found to participate smoothly in the cycloaddition with **2** to provide the pyrazoles **19**−**21** in good yields and with excellent regiocontrol (entries 7−9).

From the perspective of library synthesis, we felt that it was important to demonstrate that the chemistry is amenable to being performed in a microwave reactor and on gram scale. We found this to be the case and an illustrative example of each is provided in Scheme 2.

We concluded from these cycloaddition studies that the iodosydnone generally undergoes cycloaddition in high yield (and typically in higher yield than the C-4 unsubstituted sydnone) and with excellent levels of regiocontrol. To highlight the potential value of these synthetic intermediates, we next explored a selection of transformations of the iodide. Unsurprisingly, these compounds participated smoothly in the Suzuki−Miyaura cross-coupling reaction.[12] However,

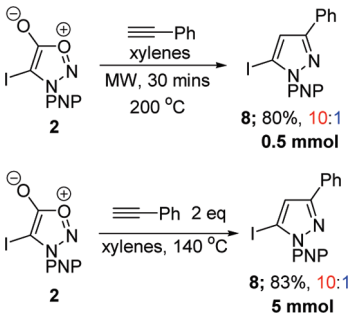
(9) Dumitraşcu, F.; Mitan, C. I.; Dumitrescu, D.; Drăghici, C.; Căproiu, M. T. *ARKIVOC* **2002**, *2*, 80.

(10) Jiang, Q.; Ryan, M.; Zhichkin, P. *J. Org. Chem.* **2007**, *72*, 6618.

(11) Terminal alkynes were reported to undergo cycloaddition with excellent regiocontrol by Huisgen in his seminal report of this chemistry: Huisgen, R.; Grashey, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 48.

(12) Pyrazoles **8**, **14**, **18**, underwent cross-coupling with a selection of boronic acids in yields of >79%. Details of these reactions can be found in the Supporting Information.

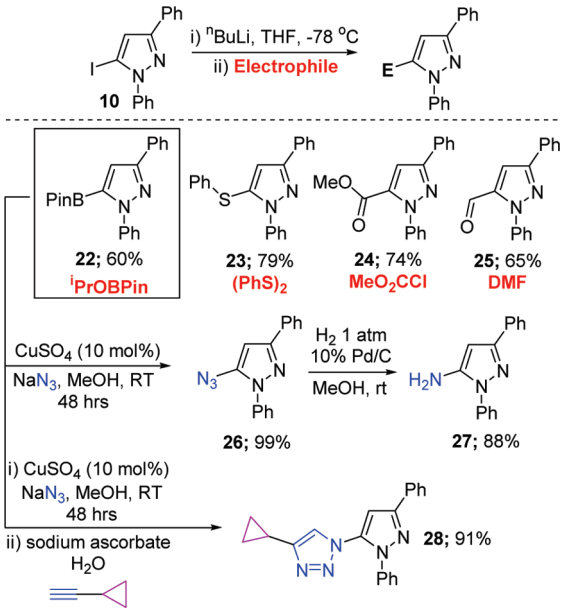
SCHEME 2. Gram Scale Cycloadditions



we opted to focus our attention on replacing the iodide substituent with other heteroatoms. We were particularly keen to introduce a nitrogen atom at the 5-position. Initial efforts toward this end consisted of a host of unsuccessful palladium and copper mediated amination reactions. Notably, in the case of the copper mediated couplings, the oxidative insertion appeared facile (even at room temperature), as evidenced by the near quantitative recovery of protodeiodonated pyrazoles following a number of protocols.[13] While the exact reasons for the failure of this chemistry are to date unclear, to the best of our knowledge there are no reports of the coupling of 5-halopyrazoles mediated by copper. Moving to a different tact, we assessed the lithium−halogen exchange reaction toward the introduction of heteroatoms. To our delight, treatment of 5-iodo pyrazole **10** with *n*-butyllithium at −78 °C for 2 h followed by quenching with diphenyldisulfide gave the 5-pyrazolylsulfide **23** in excellent yield (Scheme 3).[14] Pyrazolyl ester **24** and aldehyde **25** could be isolated by treatment of the lithiated intermediate with methylchloroformate (74%) and DMF (65%), respectively. Moreover, pyrazolyl-5-boronic ester **22** was synthesized in 60% yield by the in situ treatment of the lithiated intermediate with isopropoxypinacol boronate. This product was particularly intriguing as it represented an alternative means to introduce an amine. Specifically, a recent report from Liu, Guo, and co-workers described the transformation of boronic acids to azides at room temperature in the presence of a copper sulfate catalyst.[15] Indeed, treatment of the pyrazole boronic ester **22** under these conditions for 48 h at room temperature delivered the azide **26** in 99% yield. Furthermore, the pyrazolyl-azide was successfully reduced to its amino analogue **27** in 88% yield on the employment of palladium catalyzed hydrogenation. Lastly, a one-pot azidation/click reaction delivered the corresponding biheteroaryl product **28** in excellent yield (Scheme 3, 91%).

In summary, iodo sydnones represent useful substrates for the regioselective synthesis of functionalized pyrazoles via [3 + 2] cycloadditions of terminal alkynes. This chemistry

SCHEME 3. Functionalization Reactions



offers access to a plethora of pyrazole scaffolds where diversity at the 3 position is seemingly only limited by the availability of the alkyne. Moreover, we have shown that the iodo pyrazole intermediates can be further functionalized by a selection of C−C and C−heteroatom bond forming processes.

Experimental Section

Representative Procedure for the Cycloaddition of Sydnones with Alkynes. 5-Iodo-1-(4-nitrophenyl)-3-phenyl-1*H*-pyrazole (8). To iodosydnone **2**[6c] (167 mg, 0.5 mmol) and phenylacetylene (0.11 mL, 1 mmol) was added xylenes (0.5 mL). The reaction was heated at reflux for 8 h before cooling and purifying by flash column chromatography (solvent gradient starting with petroleum ether, ending with 20% ethyl acetate in petroleum ether). Product **8** was isolated as a yellow oil (as a mixture of isomers 10:1, 165 mg, 84%). Further purification allowed **12** to be isolated as a single regioisomer, as a yellow solid, mp 115−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (1H, s), 7.40−7.50 (3H, m), 7.83−7.87 (2H, m), 7.92 (2H, d, J = 9.0 Hz), 8.39 (2H, d, J = 9.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 80.8, 116.8, 124.4, 125.8, 126.1, 128.9 (2C), 131.6, 144.9, 146.9, 155.6. FTIR: 1595 (m), 1522 (s), 1500 (m), 1456 (m), 1342 (s), 1111 (m), 971 (m), 854 (m) cm^{-1}. HRMS (ES): m/z $[MH]^+$ calcd for $C_{15}H_{11}IN_3O_2$ 391.9896, found 391.9899.

Representative Procedure for Lithiation of 4-Iodopyrazoles: Synthesis of 1,3-Diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (22). 5-Iodopyrazole **10** (100 mg, 0.29 mmol) was dissolved in THF (1 mL) and the reaction mixture cooled to −78 °C before the addition of *n*-butyllithium (2.2 M in hexanes, 290 μL, 0.638 mmol). The resulting reaction mixture was stirred at −78 °C for 2 h before the addition of *iso*-propoxypinacolboronate (237 μL, 1.16 mmol). The reaction mixture was stirred for a further 2 h before removal of the cold bath and allowing to warm to room temperature. After 30 min, the reaction was quenched with aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered, and concentrated to dryness before purification by flash column chromatography (solvent gradient starting with petroleum ether, ending with 10% ethyl acetate in petroleum ether). Product **22** was isolated as a colorless solid (60 mg, 60%), mp 114−117 °C. ^{1}H NMR

(13) Palladium mediated amination reactions: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (b) For a discussion of the challenges associated with Pd-catalyzed amination of iodoarenes, see: Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Org. Chem.* **2009**, *131*, 5766. Copper mediated amination reactions: (c) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337. (d) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(14) Lithiation of pyrazole **12** followed by quenching with PhSSPh provided the corresponding sulfide in low yield as an impure product. We speculate that lithiation of this pyrazole is complicated by side reactions at the *N*-*p*-nitrophenyl group.

(15) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 3525.

(400 MHz, $CDCl_3$): δ 1.32 (12H, s), 7.25 (1H, s), 7.32−7.50 (6H, m), 7.62−7.68 (2H, m), 7.90−7.96 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.6, 84.4, 114.9, 124.8, 125.9, 127.5, 127.8, 128.4, 128.6, 133.1, 141.5, 152.3. FTIR: 3063 (w), 2978 (m), 2931 (w), 1600 (m), 1544 (m), 1510 (m), 1439 (s), 1329 (s), 1240 (m), 1143 (s), 1009 (m), 854 (m) cm^{-1}. HRMS (ES): *m*/*z* $[MH]^+$ calcd for $C_{21}H_{24}BN_2O_2$ 347.1931, found 347.1935.

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

Supporting Information Available: Full experimental details and characterization data, copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.