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A Modular Sydnone Cycloaddition/ Suzuki−Miyaura Cross-Coupling Strategy to Unsymmetrical 3,5-Bis(hetero)aromatic Pyrazoles

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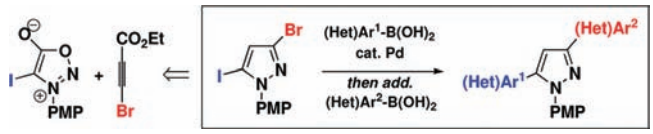
ABSTRACT



The [3 + 2] dipolar cycloaddition of 4-halosydnones with 1-haloalkynes opens a straightforward access to 3,5-dihalopyrazoles, valuable scaffolds for the elaboration of unsymmetrically 3,5-substituted pyrazole derivatives via site-selective Pd-catalyzed cross-coupling reactions. For instance, the flexible introduction of different (hetero)aryl substituents at the C-5 and C-3 positions of the PMP-protected pyrazole nucleus was achieved in a one-pot operation via sequential reactions with various boronic acids.

Pyrazoles are important core structures of many pharmaceutical and agrochemical substances.[1] In conjunction with a recent drug development program, we needed an efficient and modular synthetic strategy to assemble a series of 3,5-bis(hetero)aromatic pyrazoles. Classical approaches to 3,5-disubstituted pyrazoles are essentially based on the cyclocondensation of hydrazine derivatives with 1,3-disubstituted three-carbon units, including 1,3-diketones and α,β-unsaturated ketones (i.e., ynones).[2,3] Because such procedures generally suffer from a lack of commercially available derivatives and flexibility, the development of new protocols, allowing the sequential introduction of (hetero)aryl substituents on prefunctionalized pyrazoles via regioselective cross-coupling reactions, would be highly desirable.[4] However, while C-5 functionalization of the pyrazole nucleus via metalation is well documented,[5] the higher difficulty of metalation at the C-3 position makes the functionalization of this position more challenging.[6] Recently, McLaughlin[7] suggested the use of the tetrahydropyranyl (THP) group as a switchable metal-directing *N*-protecting group to achieve successive arylations of the pyrazole nucleus at the C-3 and C-5 positions by the lithiation/boronation/cross-coupling method.[8] In this letter, we propose a conceptually different strategy based on the direct assembly of *N*-substituted

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(1) (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley & Sons: New York, 2003; p 179.

(2) (a) Stanovnik, B.; Svete, J. *Pyrazoles, In Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Neier, R., Ed.; Georg Thieme Verlag: Stuttgart, 2002; Vol. 12, p 15. For recent developments in this area, see: (b) Deng, X.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2412. (c) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675. Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, 3267. (d) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487.

(3) For an overview of recent advances in the synthesis of pyrazoles, see: Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253.

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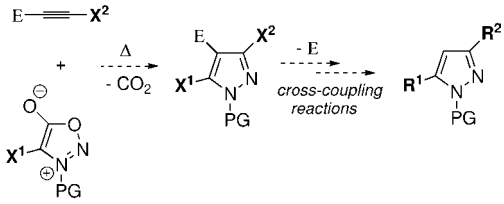
pyrazoles bearing distinguishable halides at the C-3 and C-5 positions via cycloaddition of 4-halosydnones with 1-haloalkynes and subsequent site-selective Suzuki−Miyaura cross-coupling reactions. Our approach requires the use of haloalkynes substituted by a removable functional group that would enable access to pyrazole derivatives with a free C-4 position (Scheme 1).

Scheme 1. Sydnone Cycloaddition/Cross-Coupling Strategy to 3,5-Bisfunctionalized Pyrazoles



X = Leaving group (halide)
E = Removable functional group
PG = Protecting group

The 1,3-dipolar cycloaddition of *N*-substituted sydnones with acetylenic derivatives has proven to be a powerful method for the construction of a variety of functionalized pyrazoles, albeit this procedure often suffers from low regioselectivities when unsymmetrical alkynes are involved.[9] Although 4-halosydnones have been shown to participate effectively in such a process to yield 5-halopyrazoles,[10,11] to the best of our knowledge the use of haloalkynes in sydnone cycloadditions has not been investigated to date.[12,13]

We initially planned to develop 3(5)-bromo-5(3)-iodopyrazole model substrates **3a,b** as the most favorable scaffold candidates for regioselective cross-coupling reactions. We therefore selected PMP-protected 4-halosydnones **1a,b** and ethyl halopropiolates **2a,b** as potential cycloaddition partners, anticipating that the carboxylic ester group would subsequently be easily removed. However, at this point, predictions regarding the regioselectivities of the envisioned cycloadditions were not obvious.[14,15] As a preliminary experiment, an equimolar mixture of iodosydnone **1a** and bromoalkyne **2a** was heated at 140 °C in xylenes. Delightfully, the reaction was completed within 15 h, giving rise to a 3:1 mixture of regioisomeric 5-iodopyrazoles **3a** and **4a** in 84% combined yield (Table 1, entry 1). The pyrazoles were easily separated by silica gel chromatography, and the structure assignment of the desired major isomer **3a** (63% isolated yield) was made on the basis of the ^{1}H NMR spectrum of the corresponding decarboxylated 3-bromo-5-iodopyrazole **5** that revealed a sharp singlet at 6.6 ppm characteristic of the proton at C-4 of the pyrazole ring. The latter compound **5**, our target candidate for site-selective cross-coupling reactions, was easily obtained in 65% isolated yield upon treatment of **3a** with 50% aq sulfuric acid at refluxing temperature (Scheme 2). It deserves mention that this cycloaddition strategy could not provide the regioisomeric 5-bromo-3-iodopyrazoles, which may reflect the thermal instability of the required 4-bromosydnone **1b** (Table 1, entry 2).[16] However, the strategy applied nicely to the preparation of diiodopyrazoles

(4) For reviews on site-selective cross-coupling reactions of polyhalogenated heteroarene derivatives, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. (c) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405. For a recent insight into the origin of regioselectivities, see: (d) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664.

(5) See for examples: (a) Heinisch, G.; Holzer, W.; Pock, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1829. (b) Larsen, S. D. *Synlett* **1997**, 1013. (c) Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665. (d) Iddon, B.; Tønder, J. E.; Hosseini, M.; Begtrup, M. *Tetrahedron* **2007**, *63*, 56.

(6) For recent achievements in this area, see: (a) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326. (b) Paulson, A. S.; Eskildsen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2002**, *67*, 3904.

(7) McLaughlin, M.; Marcantonio, C.; Chen, C.-Y.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309.

(8) Recently, bisarylic pyrazoles have also been obtained via direct C−H bond arylations: Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042.

(9) For an overview of recent sydnone chemistry, see: Browne, D. L.; Harrity, J. P. A. *Tetrahedron* **2010**, *66*, 553.

(10) (a) Dickopp, H. *Chem. Ber.* **1974**, *107*, 3036. (b) Dumitraşcu, F.; Drăghici, C.; Dumitrescu, D.; Tarko, L.; Răileanu, D. *Liebigs Ann./Recueil* **1997**, 2613. (c) Dumitraşcu, F.; Mitan, C. I.; Dumitrescu, D.; Drăghici, C.; Căproiu, M. T. *ARKIVOC* **2002**, *ii*, 80. (d) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2010**, *75*, 984.

(11) The capability of 4-halosydnones to undergo palladium-catalyzed cross-coupling reactions has drawn recent attention on these mesionic compounds; see: (a) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396. (b) Turnbull, K.; Krein, D. M.; Tullis, S. A. *Synth. Commun.* **2003**, *33*, 2209.

(12) Recently, Harrity reported the synthesis of pyrazoleboronic esters via sydnone cycloaddition with alkynylboranes and their subsequent use in cross-coupling reactions allowing functionalization at the pyrazole C-4 position: (a) Browne, D. L.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8656. Recent reports feature examples of sydnone cycloadditions with alkynylstananes: (b) González-Nogal, A. M.; Calle, M.; Cuadrado, P.; Valero, R. *Tetrahedron* **2007**, *63*, 224. (c) Nicolaou, K. C.; Pratt, B. A.; Arseniyadis, S.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Chem. Med. Chem.* **2006**, *1*, 41.

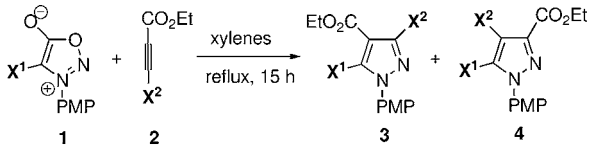
(13) For previous 1,3-dipolar cycloaddition reactions of 1-haloalkynes, see: (a) Kuijpers, B. H. M.; Dijkmans, G. C. T.; Groothuys, S.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Synlett* **2005**, 3059. (b) Letourneau, J. J.; Riviello, C.; Ohlmeyer, M. H. J. *Tetrahedron Lett.* **2007**, *48*, 1739. (c) Takenaka, K.; Nakatsuka, S.; Tsujihara, T.; Koranne, P. S.; Sasai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2492. (d) Hein, J. E.; Tripp, J. C.; Krasnova, L.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018. For other heterocycloadditions of alkynyl halides, see: (e) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205. (f) Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2007**, *64*, 874.

(14) Previous reports dealing with 3-phenylsydnone cycloaddition involving unsymmetrical alkynyl esters have essentially concerned the case of unsubstituted propiolates. It was established that regioisomeric mixtures where the cycloadduct having the ester group in the 3-position predominated were normally formed in these reactions. The observed selectivities have been explained in terms of HOMO−LUMO interactions, the dipole LUMO and dipolarophile HOMO interaction being suggested to be the controlling term: (a) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (b) Gotthardt, H.; Reiter, F. *Chem. Ber.* **1979**, *112*, 1193. (b) Gotthardt, H.; Reiter, F. *Chem. Ber.* **1979**, *112*, 1635. (c) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786. See also ref 10b.

(15) Quantum chemistry calculation using DFT suggested a favorable interaction between the dipole HOMO and the dipolarophile LUMO for the cycloaddition of 4-halosydnones (**1**) with ethyl halopropiolates (**2**). However, simple consideration of orbital lobe sizes did not allow a quantitative prediction of regioselectivity. See Supporting Information for details.

(16) In accordance with literature precedents (ref 10a), bromosydnone **1b** was found to be fairly unstable under the reaction conditions (elevated temperature and non-polar solvent), although some 3-aryl-4-bromosydnones have been previously successfully reacted with dimethyl acetylenedicarboxylate under similar conditions (refs 10b, c).

Table 1. [3 + 2]-Cycloaddition of PMP-Protected Halosydnones with Halopropiolates



1 2 3 4

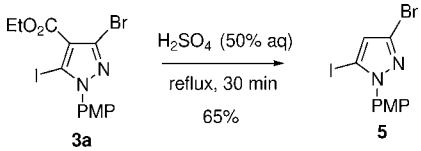
PMP = *p*-Methoxyphenyl

entry	sydnone	alkyne	ratio	yield of **3** (%)[b]	yield of **4** (%)[b]
	X^1 (**1**)	X^2 (**2**)	**3**:**4**[a]		
1	I (**1a**)	Br (**2a**)	3:1	**3a**; 63	**4a**; 21
2	Br (**1b**)	I (**2b**)	*c*	**3b**; ND[d]	**4b**; ND
3	I (**1a**)	I (**2b**)	1.5:1	**3c**; 58	**4c**; 28

[a] Ratio determined by ^{1}H NMR analysis of the crude product mixture. [b] Isolated yields. [c] See text. [d] ND: not detected

3c/**4c** in good yield (86%), albeit with poorer regioselectivity (Table 1, entry 3).

Scheme 2. Decarboxylation of 4-Ethoxycarbonylpyrazole **3a**

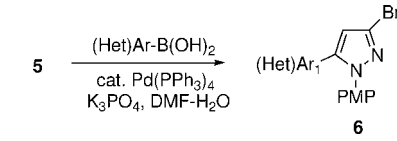


3a **5**

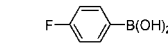
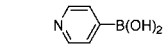
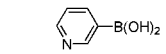
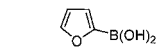
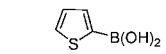
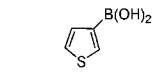
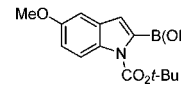
Having secured a reliable preparative method to the dihalogenopyrazole **5**, we next focused our attention on its application in Suzuki−Miyaura reactions. Gratifyingly, early investigations involving a series of aryl and heteroaryl boronic acids as coupling partners including 3-pyridyl, 4-pyridyl, 2-furyl, 2-thienyl, and 3-thienyl boronic acids established the cross-coupling reaction to be highly site-selective of the C-5 position, the desired monocoupled products being exclusively formed. Thus, an optimal set of reaction conditions (1.1 equiv of the boronic acid, 10 mol % $Pd(PPh_3)_4$, 2 equiv of K_3PO_4, DMF−H_2O (4:1), 50 °C, 2−3 h) was determined that allowed access to a diversity of 5-(hetero)aromatic pyrazoles **6** in good to excellent isolated yields. Illustrative examples are shown in Table 2. It should be noted that the poor yield obtained in the case of indolylpyrazole **6g** is due to the inherent instability of the requisite *N*-Boc(2-indolyl)boronic acid (Table 2, entry 7).

We then investigated the reactivity of the remaining halogen atom at C-3 toward Suzuki−Miyaura cross-coupling reactions. As we anticipated the possibility of introducing two different (hetero)aryl substituents at the C-5 and C-3 positions of the pyrazole nucleus in a one-pot sequential fashion, preliminary test experiments were made using the same set of reaction conditions and, preferably, using the same Pd catalyst. The cross-coupling of 3-bromo-5-(2-thienyl)-pyrazole **6e** with 3-pyridylboronic acid was thus

Table 2. Suzuki Site-Selective Coupling of 3-Bromo-5-iodopyrazole **5** with Various Boronic Acids[a]



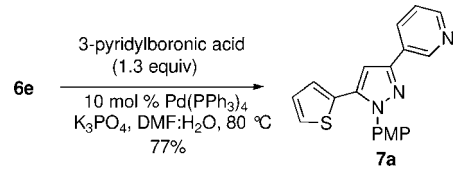
6

entry	boronic acid	product	yield[b] (%)
1		**6a**	87
2		**6b**	69[c]
3		**6c**	83
4		**6d**	95
5		**6e**	91
6		**6f**	91
7		**6g**	30

[a] Reactions conducted on 0.2 mmol scale. Conditions: 1.1 equiv of (Het)Ar^{1}B(OH)$_2$, 10 mol % $Pd(PPh_3)_4$, 3 equiv of K_3PO_4, DMF−H_2O (4:1), 50 °C, 2−3 h. [b] Isolated yields. [c] Reaction performed at 80 °C.

investigated as a model reaction. Pleasingly, the desired coupling reaction proceeded as expected with optimal conditions being 1.3 equiv of the boronic acid and 80 °C for the reaction temperature. Under these conditions, the bis-heteroaromatic pyrazole **7a** was obtained in 77% isolated yield (Scheme 3).

Scheme 3

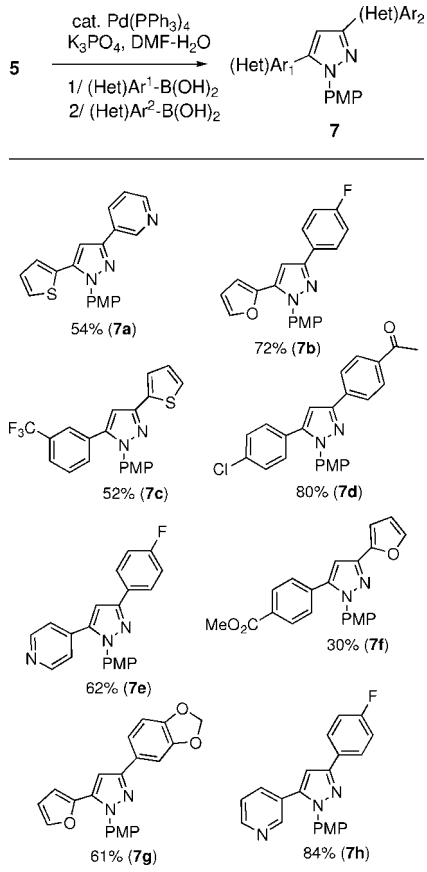


7a

One-pot double Suzuki−Miyaura cross-coupling reactions are rare[17] and often require additional base, catalyst, or ligand to cross-couple the second boronic acid efficiently. To our delight, a sequential addition, one-pot protocol for the synthesis of **7a** could be set up as follows: dihalogenopyrazole **5** (1.0 equiv) and 2-thienylboronic acid (1.1 equiv) underwent the Suzuki−Miyaura cross-coupling reaction under the previous conditions (10 mol % $Pd(PPh_3)_4$, 2 equiv of K_3PO_4, DMF−H_2O (4:1), 50 °C). Once the reaction had reached completion as judged by TLC (ca. 2 h), 3-pyridyl-

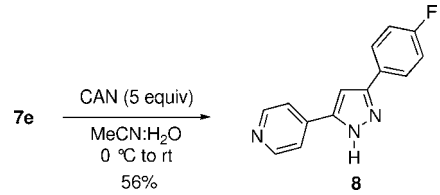
boronic acid (1.3 equiv) was added, and the reaction was left to stir overnight at 80 °C to afford **7a** in 54% isolated yield. Most importantly, the developed protocol was also efficient in the preparation of a large array of 3,5-bis(hetero)arylpyrazoles in satisfying yields. It is worth noting that yields of illustrative examples shown in Scheme 4 refer to single runs and are for pure, isolated products. The low yield obtained in the synthesis of **7f** was attributed to the poor stability of (*p*-CO_2Me)phenyl boronic acid under the reaction conditions.

Scheme 4. One-Pot Suzuki Bis-Coupling of 3-Bromo-5-iodopyrazole **5** with Different Boronic Acids[a]



[a] Reactions conducted on 0.2 mmol scale. Conditions: 1.1 equiv of (Het)$Ar^1B(OH)_2$, 10 mol % $Pd(PPh_3)_4$, 3 equiv of K_3PO_4, DMF−H_2O (4:1), 50 °C, 3 h; then 1.3 equiv of (Het)$Ar^2B(OH)_2$, 80 °C, 18 h

Scheme 5. Deprotection of *N*-PMP-Pyrazole **7e**



Finally, as illustrated with the synthesis of **8** (Scheme 5), it was shown that the PMP-protecting group may be easily removed with ceric ammonium nitrate,[18] thus expanding the synthetic potential of our strategy.

In summary, we have developed an efficient three-step synthetic entry to unsymmetrical 3,5-bis(hetero)aromatic pyrazole derivatives with an inherent scope for diversification. The procedures are simple and seem well suited for the rapid generation of compound libraries of analogues from a given set of readily available 4-halosydnones, 1-haloalkynes and boronic acids.

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Supporting Information Available: Experimental procedures and characterization for all new compounds; DFT calculations for compounds **1a,b** and **2a,b**; ^{1}H and ^{13}C NMR spectra for compounds **3a**, **5**, **6a**−**g**, **7a**−**h**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For illustrative examples, see: (a) Farooq, M. I.; Hussain, M.; Obaid-Ur-Rahman, A.; Ali, A.; Ullah, I.; Zinad, D. S.; Langer, P. *Synlett* **2010**, 411. (b) Tikad, A.; Routier, S.; Akssira, M.; Guillaumet, G. *Org. Biomol. Chem.* **2009**, *7*, 5113. (c) Beaumard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2009**, *11*, 1801. (d) Varello, S.; Handy, S. T. *Synthesis* **2009**, 138. (e) Handy, S. T.; Wilson, T.; Muth, A. *J. Org. Chem.* **2007**, *72*, 8496. (f) Handy, S. T.; Zhang, Y. *Synthesis* **2007**, 3883. (g) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537. (h) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493. (i) Couty, S.; Barbazanges, M.; Cossy, J. *Synlett* **2005**, 905. (j) Uozomi, Y.; Kikouchi, M. *Synlett* **2005**, 1775. (k) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 1363.

(18) Butler, R. N.; Hanniffy, J. M.; Stephens, J. C.; Burke, L. A. *J. Org. Chem.* **2008**, *73*, 1354.