

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

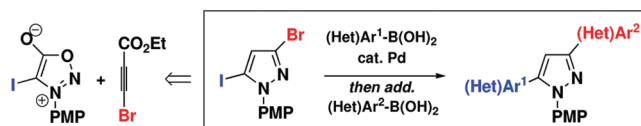
Thierry Delaunay,[†] Pierre Genix,[‡] Mazen Es-Sayed,[‡] Jean-Pierre Vors,[‡]
Nuno Monteiro,^{*,†} and Geneviève Balme^{*,†}

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS, UMR 5246 du CNRS), ESCPE Lyon, Université Lyon 1, 43, Bd du 11 Novembre 1918, 69622 Villeurbanne, France, and Bayer SAS, Bayer CropScience, 14 impasse Pierre Baizet, BP9163, 69263 Lyon Cedex 09, France

balme@univ-lyon1.fr; monteiro@univ-lyon1.fr

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ABSTRACT



The [3 + 2] dipolar cycloaddition of 4-halosydnone 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, McLaughlin⁷ 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

[†] Université Lyon 1.

[‡] Bayer SAS, Bayer CropScience.

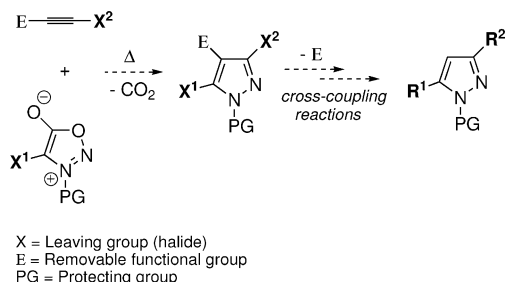
(1) (a) Lamberth, C. *Heterocycles* **2007**, 71, 1467. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley & Sons: New York, 2003; p 179.

(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.

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pyrazoles bearing distinguishable halides at the C-3 and C-5 positions via cycloaddition of 4-halosydnone 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



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 reac-

tions. 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 ¹H 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

(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.; Dijkman, 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.; Strozio, 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).

(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. I* **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) Dumitrașcu, F.; Drăghici, C.; Dumitrescu, D.; Tarko, L.; Răileanu, D. *Liebigs Ann./Recueil* **1997**, 2613. (c) Dumitrașcu, F.; Mitran, C. I.; Dumitrescu, D.; Drăghici, C.; Căprioiu, 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.

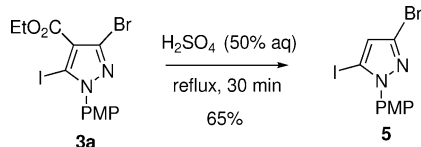
(11) The capability of 4-halosydnones to undergo palladium-catalyzed cross-coupling reactions has drawn recent attention on these mesionic compounds; see: (a) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396. (b) Turnbull, K.; Krein, D. M.; Tullis, S. A.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

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

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 ¹H 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**

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(PPh₃)₄, 2 equiv of K₃PO₄, DMF–H₂O (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).

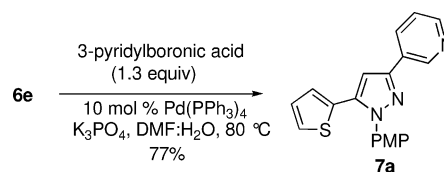
We then investigated the reactivity of the remaining halogen atom at C-3 toward Suzuki–Miyaura cross-coupling reactions. As we anticipated the possibility of introducing two different (hetero)aryl substituents at the C-5 and C-3 positions of the pyrazole nucleus in a one-pot sequential fashion, preliminary 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

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)Ar¹B(OH)₂, 10 mol % Pd(PPh₃)₄, 3 equiv of K₃PO₄, DMF–H₂O (4:1), 50 °C, 2–3 h. ^b Isolated yields. ^c Reaction performed at 80 °C.

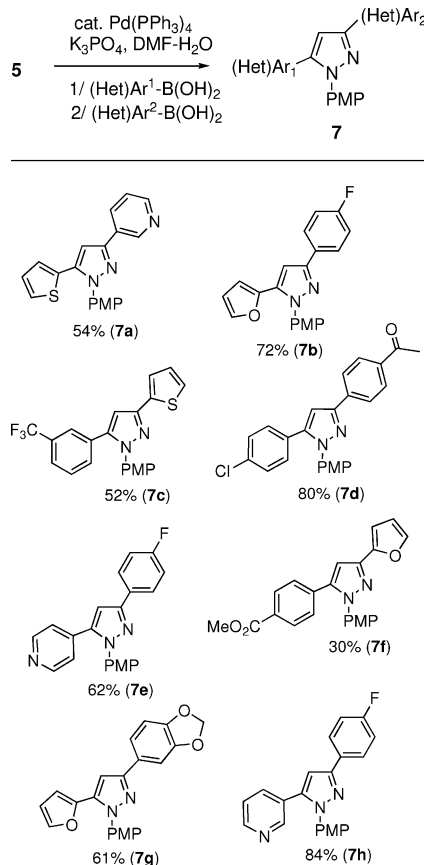
investigated as a model reaction. Pleasingly, the desired coupling reaction proceeded as expected with optimal conditions being 1.3 equiv of the boronic acid and 80 °C for the reaction temperature. Under these conditions, the bis-heteroaromatic pyrazole **7a** was obtained in 77% isolated yield (Scheme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

Scheme 3

One-pot double Suzuki–Miyaura cross-coupling reactions are rare¹⁷ 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(PPh₃)₄, 2 equiv of K₃PO₄, DMF–H₂O (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)arylpiperazines in satisfying yields. It is worth noting that yields of illustrative examples shown in Scheme 4 refer to

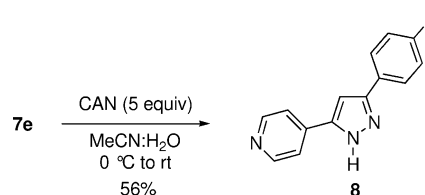
Scheme 4. One-Pot Suzuki Bis-Coupling of 3-Bromo-5-iodopyrazole **5** with Different Boronic Acids^a



^a Reactions conducted on 0.2 mmol scale. Conditions: 1.1 equiv of (Het)Ar¹B(OH)₂, 10 mol % Pd(PPh₃)₄, 3 equiv of K₃PO₄, DMF-H₂O (4:1), 50 °C, 3 h; then 1.3 equiv of (Het)Ar²B(OH)₂, 80 °C, 18 h

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*-CO₂Me)phenyl boronic acid under the reaction conditions.

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-halosydnone, 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**; ¹H and ¹³C 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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