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# One-pot copper-catalyzed synthesis of N-functionalized pyrazoles from boronic acids

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ABSTRACT

A straight-forward route to prepare a diverse set of *N*-aryl pyrazoles via a one-pot copper-catalyzed boronic acid coupling and cyclization protocol is presented. A variety of aryl and heteroaryl N-functionalized pyrazoles not easily accessible by other means were formed in good yield from readily available boronic acid precursors in an operationally simple procedure.



Pyrazoles represent an important class of heterocycles as constituents of agro-chemicals,[1] polymeric materials[2] and as a unique ligand class[3] but are perhaps most prevalent as constituents of active pharmaceutical compounds.[4] Considering the lack of naturally occurring pyrazole-containing molecules, it is interesting that there are an extensive number of synthetic pyrazoles with profound biological activity[5] including the COX-2 inhibitor drug Celecoxib (Celebrex)™. In our ongoing drug discovery research efforts, we are interested in the development of efficient and general methods to access N-functionalized pyrazoles under mild conditions.

Typically, the construction of pyrazole compounds is performed via cyclocondensation of hydrazines and 1,3-dicarbonyls, or by direct N-functionalization of pre-formed 1*H*-pyrazoles by either nucleophilic substitution or metal-catalyzed/mediated C–N cross-coupling methods.[6–10] In regards to the latter, while transition-metal-catalyzed coupling or direct nucleophilic substitution of simple pyrazoles is known, these examples are limited to pyrazoles devoid of potentially useful halo-substitutions. In addition, while transition metal-catalyzed/mediated C–N bond formation routes have witnessed considerable advances in generality, 1*H*-pyrazoles remain difficult substrates in these reactions.[6] The cyclocondensation method can also be restricted in regards to the availability of the requisite hydrazine precursors. For example, a number of common heterocyclic hydrazines are not known, and preparation of multi-substituted aryl hydrazines can be difficult to access using conventional methods.[11] For these reasons, a general method for the preparation of these interesting pharmaceutically active cores from readily available materials with improved functional group scope (e.g., formation of halo-containing pyrazoles) is a desirable goal.

Recently, we have reported that a number of *N*-aryl pyrazoles, including those with pyrazole-ring halo-substituents, can be prepared in a simple one-pot protocol from aryl-bromides.[12] This reaction involves initial metal-halo exchange generating a reactive aryl-lithium species which reacts rapidly with di-*tert*-butylazodicarboxylate[13] providing a di-*N*-boc-protected aryl hydrazide intermediate which in the presence of a 1,3-dicarbonyl compound and in situ deprotection generated a number of useful *N*-aryl pyrazoles in good yield (Fig. 1).

While useful, the metallation conditions employed is not compatible with aryl-bromides containing sensitive groups. For

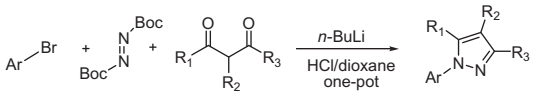
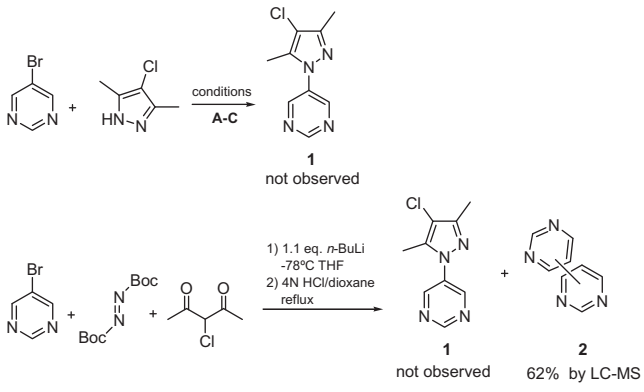



**Figure 1.** One-pot formation of *N*-aryl pyrazoles from aryl halides.




**Scheme 1.** Unsuccessful attempts towards a 5-pyrazole-pyrimidine synthesis from 5-bromo-pyrimidine. Reagents and conditions: (A) 1.2 equiv pyrazole, 1.5 equiv $iPr_2NEt$, DMSO 110 °C 24 h; (B) 1.8 equiv pyrazole, 5% Cu powder, 5% CuI 20% *rac*-BINOL, 2.3 equiv $Cs_2CO_3$, DMF 110 °C 24 h; (C) 1.5 equiv pyrazole, 10% CuO, 30% $Fe(acac)_3$, 2 equiv $Cs_2CO_3$, DMF 90 °C 24 h.

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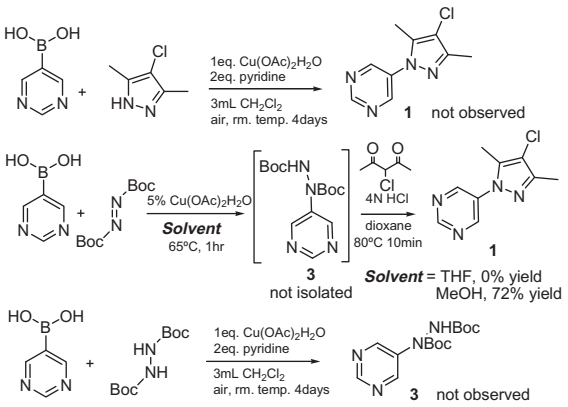
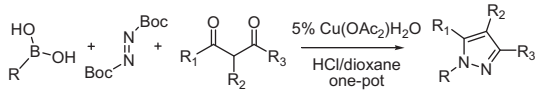



**Scheme 2.** A one-pot copper-catalyzed 5-pyrazole-pyrimidine synthesis from 5-pyrimidine boronic acid.

example, we considered the potential to access chloro-functionalized-5-pyrazole-substituted pyrimidines such as **1** via this method since the corresponding 5-hydrazine-pyrimidine is not known, and attempts at direct substitution of 5-bromo-pyrimidine with 4-chloro-3,5-dimethyl-1*H*-pyrazole[14] under conventional 1*H*-pyrazole cross-coupling conditions were unsuccessful.[8h,9] However, in the event, 5-Br-pyrimidine under our typical one-pot metallation/condensation conditions resulted in the undesired formation of a dimerized pyrimidine species **2** with no trace of the pyrazole product **1** by LC–MS analysis of the crude reaction mixture (Scheme 1).

Alternatively, we investigated whether the commercially available 5-pyrimidine-boronic acid would be compatible in a copper-mediated approach towards pyrazoles of type **1**. As shown in Scheme 2, the oxidative Chan-Lam-type coupling of 5-pyrimidine-boronic acid and 4-chloro-3,5-dimethyl-1*H*-pyrazole in the presence of stoichiometric copper was unsuccessful.[10] Considering that our one-pot metallation strategy to pyrazoles involved initial

**Table 1**
One-pot copper-catalyzed N-functionalized pyrazole synthesis from boronic acids[a,22]



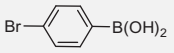
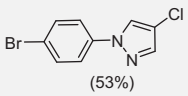
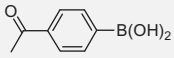
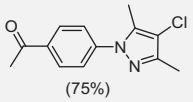
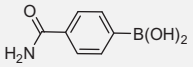
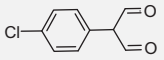
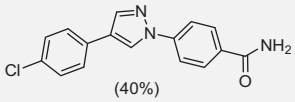
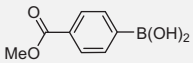
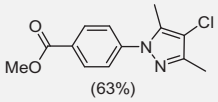
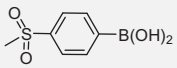
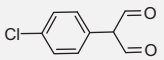
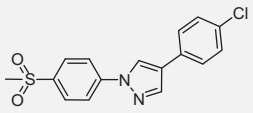
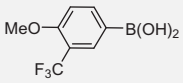
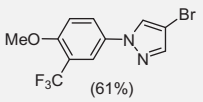
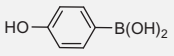
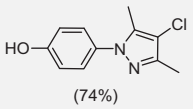
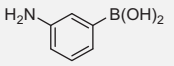
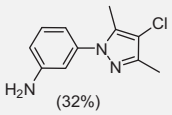
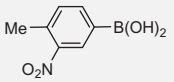
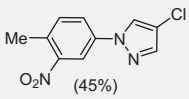
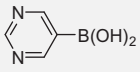
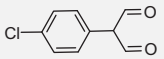
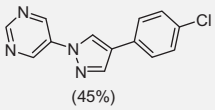
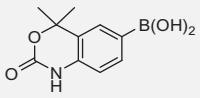
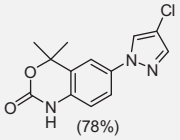
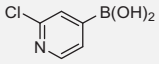
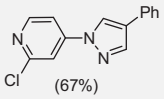
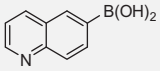
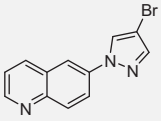
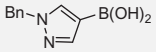
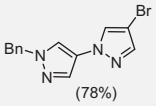
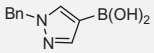
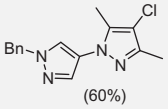
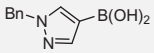
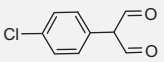
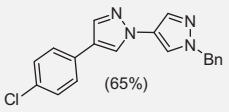
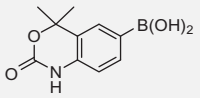
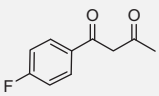
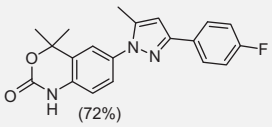
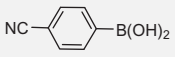
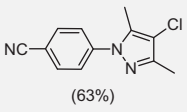

| Entry | Boronic acid | Dicarbonyl | Product[b] (% yield) |
|---|---|---|---|
| **1a** |  |  |  (53%) |
| **1b** |  |  |  (75%) |
| **1c**[c] |  |  |  (40%) |
| **1d** |  |  |  (63%) |
| **1e** |  |  |  (78%) |
| **1f** |  |  |  (61%) |
| **1g** |  |  |  (74%) |
| **1h** |  |  |  (32%) |
| **1i** |  |  |  (45%) |
| **1j** |  |  |  (45%) |

**Table 1** (*continued*)

| Entry | Boronic acid | Dicarbonyl | Product[b] (% yield) |
|---|---|---|---|
| **1k** |  |  |  (78%) |
| **1l** |  |  |  (67%) |
| **1m** |  |  |  (53%) |
| **1n** |  |  |  (78%) |
| **1o** |  |  |  (60%) |
| **1p** |  |  |  (65%) |
| **1q**[d] |  |  |  (72%) |
| **1r** |  |  |  (63%) |

[a] Boronic acid (0.75 mmol), DBAD (115 mg, 0.5 mmol) and $Cu(OAc)_2H_2O$ (5.1 mg, 0.025 mmol) were combined in 3 mL MeOH and placed in a 65 °C heating block for 1 h. Cooled to rt, added the dicarbonyl (0.75 mmol) and 2 mL 4 N HCl in dioxane, stirred at rt for 10 min then heated at 80 °C for 10 min.

[b] Isolated yield.

[c] MeOH removed before addition of 4 N HCl in dioxane.

[d] 72% Combined yield of a 1.4:1 mixture of regio-isomers in favour of the one shown.

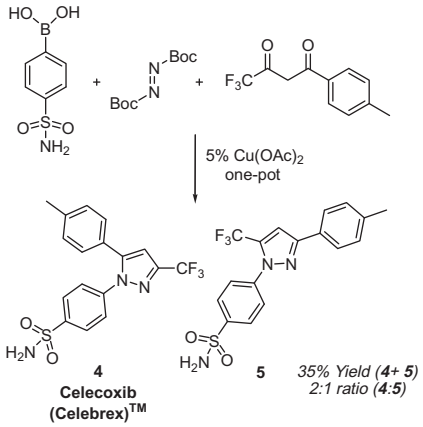
formation of an intermediate hydrazide species, we re-focused our efforts towards the formation of the *N,N*-diBoc hydrazide species **3**.

Recently, aryl-boronic acids have been reported to undergo efficient copper-catalyzed coupling with di-*tert*-butylazodicarboxylate (DBAD) and related diazo-species generating a number of new *N,N*-difunctionalized hydrazide derivatives.[15,16] Subsequently, we considered the potential that readily available pyrimidine 5-boronic acid could be used in an analogous one-pot copper-catalyzed DBAD coupling and condensation towards pyrazoles of type **1**.

While copper-catalyzed boronic acid and diazo-dicarboxylate coupling has been reported to occur using both MeOH[15a] and THF[15b] as solvent, we did not observe the formation of the hydrazide intermediate **3** in THF (Scheme 2). However, we were pleased to observe efficient $Cu(OAc)_2$-catalyzed coupling of this substrate with DBAD in MeOH under the literature conditions resulted in the rapid in situ conversion to the desired *N,N*-di-boced intermediate **3** (vide infra). Direct treatment of **3** with the 1,3-dicarbonyl compound and HCl in dioxane produced the desired pyrimidine-5-pyrazole **1** in good isolated yield in one-pot without pre-isolation of the intermediate hydrazide or hydrazine (Scheme 2).[17] It is interesting to note that copper-mediated Chan-Lam-type conditions of this boronic acid with di-*tert*-butyl hydrazido-formate failed to provide the requisite hydrazide intermediate precursor **3**.

With this result in hand, we sought to explore this method towards the development of a general one-pot method to construct a variety of N-functionalized pyrazoles from readily available boronic acid precursors. Potentially, the commercial availability of a range of boronic acids and their ready synthetic access via mild and functional group tolerant methods[18–21] make these attractive precursors to pyrazoles. As shown in Table 1, a variety of commercially available aryl- and heteroaryl-boronic acid substrates were converted in a simple one-pot protocol in the presence of 5 mol % $Cu(OAc)_2$ to a variety of new N-functionalized pyrazoles.[22]

The mild reaction conditions shown here demonstrate an improvement in scope over our initially developed aryl metallation strategy. For example, boronic acids containing sensitive bromo-, carbonyl, nitrile, amide, nitro, sulfone, amino and hydroxylfunctionalities were all found to generate pyrazole products in good yield. In addition, a variety of heterocyclic boronic acids were found to be compatible including pyrazole, quinoline and sensitive structures such as 2-Cl-pyridine and pyrimidine. Importantly, this reaction can generate species with reactive pyrazole-ring halogen substitutions; a non-trivial transformation via traditional C–N coupling methods, and allows for further modification of these cores




**Scheme 3.** Celecoxib synthesis via copper-catalyzed one-pot pyrazole formation.

towards more complex products. It is particularly interesting to note the compatibility of boronic acids containing hydroxyl, amino, amide and carbamate functionalities since these groups can be reactive towards C–N (or C–O) bond formation with boronic acids in the presence of copper salts.[10]

As an example of the potential utility of this pyrazole N-functionalization strategy, we considered whether the pyrazole-containing drug Celecoxib (Celebrex)™ could be prepared under our one-pot conditions. We were pleased to find that commercially available 4-sulfonamide-phenyl boronic acid, in the presence of 5 mol % $Cu(OAc)_2H_2O$, underwent a clean DBAD coupling and cyclization providing a 35% isolated yield of a 2:1 mixture of regio-isomers in favour of the desired Celecoxib pyrazole material **4** (Scheme 3).

In summary, we have shown that a variety of N-functionalized pyrazoles can be prepared in a simple one-pot copper-catalyzed procedure from readily available boronic acids. The reaction is tolerant to a variety of common functional groups, does not require pre-isolation of the hydrazine and provides ready access to structures containing useful pyrazole-ring halogen substitutions.

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## Supplementary data

Supplementary data (experimental procedures, and $^1H$ and $^{13}C$ NMR data and spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.077.

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