An Efficient *N*-Arylation of Heterocycles with Aryl-, Heteroaryl-, and Vinylboronic Acids Catalyzed by Copper Fluorapatite

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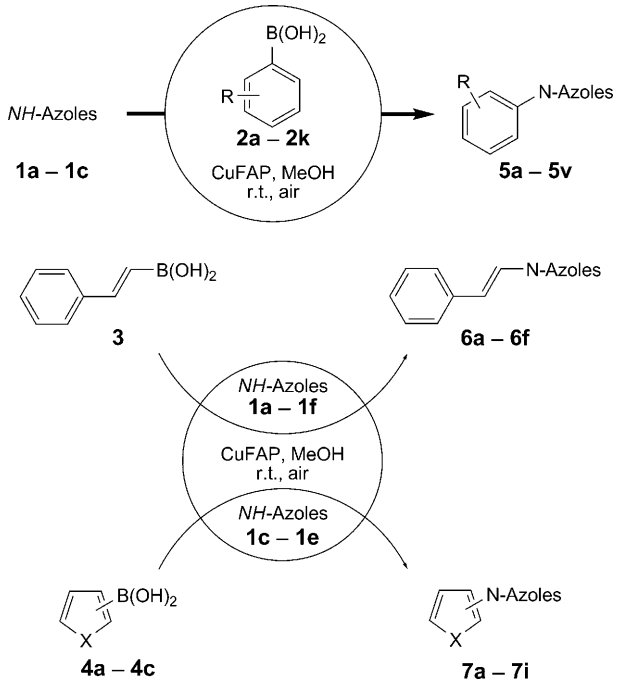
N-Arylation of N-containing heterocycles, such as pyrazoles, imidazoles, and benzimidazoles with aryl-, heteroaryl-, and vinylboronic acids was efficiently carried out by copper fluorapatite (CuFAP) catalyst in MeOH at room temperature under base-free conditions. The *N*-arylated heterocycles were isolated in good-to-excellent yields.

Introduction. – *N*-Arylated heterocycles are found in many biologically active compounds [1–5]. The traditional synthesis of these compounds involves nucleophilic aromatic substitution [6], *Ullmann* reaction [7], and coupling of imidazoles with metalloarenes like aryllead, arylbismuth, arylborane, and arylsilane reagents [8–11]. Previously, an efficient method for *N*-arylation of azoles with arylboronic acids using stoichiometric amounts of $Cu(OAc)_2$ and pyridine as base was reported by the *Chan* and *Lam* groups [12][13]. Later, *Collman* and co-workers demonstrated the use of a diamine-copper complex for the coupling of arylboronic acids with imidazole in CH_2Cl_2 and H_2O at room temperature [14][15]. Very recently, the same coupling reaction was also performed by *Xie* and co-workers using a copper salt in protic solvents under reflux conditions without using any base [16]. Thus, the development of mild and cost-effective catalytic procedures for *N*-arylation of imidazoles and amines still remains an active research area [17].

Heterogeneous catalysis is particularly attractive as it allows production and ready separation of large quantities of products with the use of a small amount of catalyst. Recently, we reported the preparation of recyclable heterogeneous Cu-exchanged fluorapatite (CuFAP) and Cu-exchanged (*tert*-butoxy)apatite catalysts, by incorporating basic species F^-/*t*-BuO^- in apatite *in situ* by co-precipitation and subsequent exchange with Cu^{II} for *N*-arylation of imidazoles and other heterocycles with chloro-, fluoro- (EW), bromo-, and iodoarenes in good-to-excellent yields for the first time [18][19]. Later, we reported *N*-arylation of imidazole, benzimidazole, and amines with arylboronic acids at room temperature under base-free conditions using CuFAP catalyst [20].

Continuing our work on *N*-arylation, herein we report an efficient *N*-arylation of N-containing heterocycles **1** such as pyrazoles, imidazoles, and benzimidazoles with aryl-, heteroaryl-, and vinylboronic acids, **2**–**4**, respectively, using heterogeneous CuFAP catalyst (*Scheme 1*) at room temperature under base-free conditions. To the best of our

Scheme 1. N-*Arylation of N-Containing Heterocycles Using the CuFAP Catalyst*



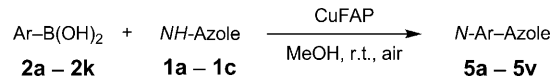
knowledge, *N*-arylation of substituted imidazoles or pyrazoles and the use of heterocyclic boronic acids for such coupling at room temperature has not been explored previously.

To identify the best catalytic system for *N*-arylation of 1*H*-pyrazole (**1a**) with phenylboronic acid (**2a**) to form compound **5a**, a variety of solvents were screened and MeOH was found to be the best solvent. CuFAP was recovered quantitatively by simple centrifugation and reused for four cycles with consistent activity (*Table 1*, *Entry 1*). A control reaction conducted under identical conditions devoid of CuFAP gave no coupled product despite prolonged reaction time.

We chose a variety of arylboronic acids, **2a**–**2k**, possessing a wide range of substituents to evaluate the scope and the generality of the CuFAP-promoted *N*-arylation of N-containing heterocycles to afford the corresponding *N*-arylated heterocycles **5a**–**5v**, and the results are summarized in *Table 1*. Arylboronic acids with electron-donating groups afforded better yields (*Table 1*, *Entries 2*, *3*, *6*, and *7*) than the substrates containing electron-withdrawing groups (*Table 1*, *Entries 4* and *5*). Arylboronic acids with sterically demanding *ortho*-substituents on the phenyl ring (*Table 1*, *Entries 8* and *9*) gave lower yields compared to their *para*-counterparts, which may be attributed to an *ortho* steric effect.

Among the different N-containing heterocycles tested, 3,5-dimethyl-1*H*-pyrazole (**1b**) afforded poor yields compared to 1*H*-pyrazole (**1a**), which may be due to the sterically hindering Me groups on the pyrazole ring (*Table 1*, *Entries 11–13*). 2-Methyl-

Table 1. N-*Arylation of N-Containing Heterocycles* **1** *with Different Arylboronic Acids* **2**[a])



2a – 2k **1a – 1c** **5a – 5v**

Entry	Arylboronic acid	*NH*-Azole	Product	Time [h]	Yield [%][b])
1	**2a** (Ar = Ph)	1*H*-Pyrazole (**1a**)	**5a**	10	92, 88[c])
2	**2b** (Ar = 4-Me–C_6H_4)	**1a**	**5b**	10	88
3	**2c** (Ar = 4-MeO–C_6H_4)	**1a**	**5c**	10	87
4	**2d** (Ar = 2-Br–C_6H_4)	**1a**	**5d**	12	88
5	**2e** (Ar = 4-CHO–C_6H_4)	**1a**	**5e**	13	80
6	**2f** (Ar = 2-Me-4-MeO–C_6H_3)	**1a**	**5f**	10	90
7	**2g** (Ar = 2,4-$(MeO)_2$–C_6H_3)	**1a**	**5g**	15	75
8	**2h** (Ar = 2-Me–C_6H_4)	**1a**	**5h**	22	60
9	**2i** (Ar = 2-MeO–C_6H_4)	**1a**	**5i**	22	65
10	**2j** (Ar = $C_{10}H_9$)	**1a**	**5j**	15	85
11	**2a**	3,5-Dimethyl-1*H*-pyrazole (**1b**)	**5k**	24	58
12	**2b**	**1b**	**5l**	24	50
13	**2c**	**1b**	**5m**	24	53
14	**2a**	2-Methyl-1*H*-imidazole (**1c**)	**5n**	10	95
15	**2b**	**1c**	**5o**	10	92
16	**2c**	**1c**	**5p**	10	94
17	**2d**	**1c**	**5q**	5	96
18	**2k** (Ar = 3-NO_2–C_6H_4)	**1c**	**5r**	8	91
19	**2j**	**1c**	**5s**	12	90
20	**2g**	**1c**	**5t**	10	92
21	**2h**	**1c**	**5u**	12	87
22	**2i**	**1c**	**5v**	12	89

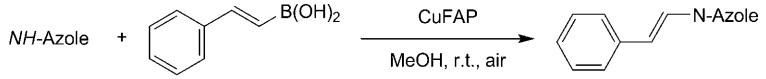
[a]) Reaction conditions: N-containing heterocycle (1.2 mmol), arylboronic acid (1 mmol), CuFAP (0.1 g, 0.073 mmol, 7.3 mol-%), MeOH (4 ml), r.t., under air. All products showed correct spectral data and elemental analyses. [b]) Yield of isolated product. [c]) Yield after fourth cycle.

1*H*-imidazole (**1c**) reacted with arylboronic acids to give similar yields as imidazole [10], which confirms that a substituent on the heterocyclic ring has no effect on the reaction rate (*Table 1*, *Entries 14–22*).

To extend the scope of the methodology, vinylboronic acid **3** was successfully coupled with various N-containing heterocycles, such as pyrazoles **1a** and **1b**, imidazoles **1c** and **1d**, 1*H*-benzimidazole (**1e**), and 2-methyl-1*H*-benzimidazole (**1f**), to give the corresponding *N*-arylated heterocycles **6a – 6f** in moderate-to-good yields (*Table 2*). It is noteworthy that when the reaction was conducted in the absence of air, no coupled product was obtained.

Later, we explored the utility of heteroarylboronic acids **4a – 4c** as arylating agents in the CuFAP catalyzed *N*-arylation of imidazoles **1c** and **1d** and 1*H*-benzimidazole (**1e**) to give the corresponding *N*-arylated products **7a – 7i** in good yields. The results are shown in *Table 3*. We observed that a 2-substituted heteroarylboronic acid such as thiophen-2-ylboronic acid (**4b**; *Table 3*, *Entry 2*) afforded lower yields compared to the 3-substituted heteroarylboronic acids **4a** and **4c** (*Table 3*, *Entries 1* and *3*).

Table 2. N-*Arylation of N-Containing Heterocycles* **1** *with Vinyl Boronic Acids* **3**[a])

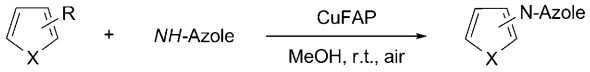


1a – 1f **3** **6a – 6f**

Entry	*NH*-Azole	Time [h]	Product	Yield [%][b])
1	1*H*-Imidazole (**1d**)	10	**6d**	95
2	**1c**	10	**6c**	92
3	1*H*-Benzimidazole (**1e**)	10	**6e**	90
4	**1a**	13	**6a**	88
5	**1b**	20	**6b**	70
6	2-Methyl-1*H*-benzimidazole (**1f**)	24	**6f**	30

[a]) Reaction conditions: N-containing heterocycle (1.2 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), MeOH (4 ml), r.t., under air. All products showed correct spectral data and elemental analyses. [b]) Yield of isolated products.

Table 3. N-*Arylation of N-Containing Heterocycles* **1** *with Heteroarylboronic Acids* **4**[a])



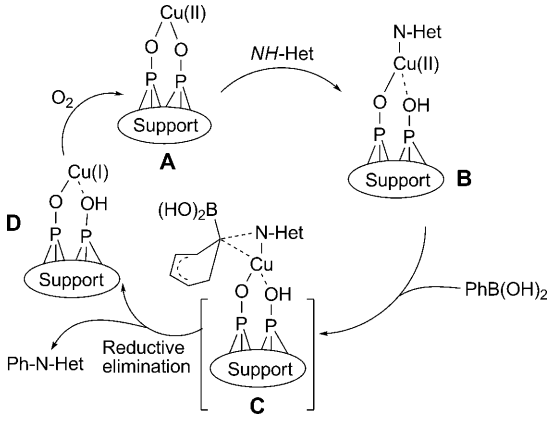
4a – 4c **1c – 1e** **7a – 7i**

Entry	Boronic acid	*NH*-Azole	Time [h]	Product	Yield [%][b])
1	**4a** (X = S, R = 3-$(OH)_2$B)	**1d**	13	**7a**	90
2	**4b** (X = S, R = 2-$(OH)_2$B)	**1d**	16	**7b**	60
3	**4c** (X = O, R = 3-$(OH)_2$B)	**1d**	13	**7c**	90
4	**4a**	**1c**	13	**7d**	92
5	**4b**	**1c**	15	**7e**	65
6	**4c**	**1c**	13	**7f**	92
7	**4a**	**1e**	18	**7g**	88
8	**4b**	**1e**	20	**7h**	69
9	**4c**	**1e**	18	**7i**	89

[a]) Reaction conditions: N-containing heterocycle (1.2 mmol), heteroarylboronic acid (1 mmol), CuFAP (100 mg), MeOH (4 ml), r.t., under air. All products showed correct spectral data and elemental analyses. [b]) Yield of isolated products.

A possible mechanism for the *N*-arylation of heterocycles is depicted in *Scheme 2*. The Cu(II) in the CuFAP catalyst (shown as **A**) forms a complex with pyrazole *via* deprotonation of the *NH*-azoles to form the Cu^{II} intermediate shown as **B** in *Scheme 2* [18]. An FT-IR spectrum of **B** indicates P−OH stretching frequency, which is in consonance to the analogous Ru-enolate intermediate of a ruthenium(II) apatite complex reported earlier [21]. Reductive elimination of 1-phenyl-1*H*-pyrazole (as an example for *NH*-Het) takes place by the addition of phenylboronic acid *via* transition stage **C** to give a Cu^{I} species, depicted as **D**. Oxidation of Cu^{I} to Cu^{II} takes place in presence of O_2, thereby continuing the catalytic cycle. The reaction devoid of O_2 or air

Scheme 2. *Possible Mechanism for the* N-*Arylation of Heterocycles*



does not proceed, which confirms that Cu^I species are formed during the reaction, but they are not active for the progress of the reaction.

Conclusions. – In conclusion, we have developed a simple and efficient method for the *N*-arylation of N-containing heterocycles using the CuFAP catalyst. Various aryl, heteroaryl, and vinylboronic acids were coupled with different N-containing heterocycles to yield the corresponding *N*-arylated heterocycles in good to excellent yields. The catalyst can be readily recovered and reused. This methodology may find widespread use for the preparation of *N*-arylated heterocycles.

Experimental Part

All chemicals were purchased from *Aldrich* and were used as received. All solvents were of analytical grade from *Merck India Pvt. Ltd.* and used as such. ^{1}H-NMR Spectra: *Varian-Gemini-200* MHz and *Bruker-Avance-300* MHz spectrometer, with TMS as an internal standard in $CDCl_3$.

Typical Procedure for N-*Arylation of Azoles with Arylboronic Acids at Ambient Temperature.* In a typical experiment, CuFAP (100 mg) [20] was added to a mixture of N-containing heterocycle (1.2 mmol) and arylboronic acid (1 mmol) in MeOH (4 ml) at r.t., and the mixture was stirred for 5 – 24 h under an atmosphere of air. The progress of the reaction was monitored by TLC, and on completion of the reaction, the mixture was centrifuged to remove the catalyst, and the centrifugate was concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography using silica gel to afford the *N*-arylated heterocycles.

Spectral data of the *N*-arylated heterocycles are available on demand.

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