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Microwave-assisted solvent-free N-arylation of imidazole and pyrazole

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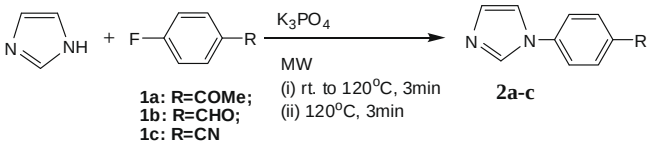
ABSTRACT

Solvent-free coupling reactions between imidazole or pyrazole and aryl bromides were achieved with microwave irradiation using copper salts and L-amino acids as catalysts.

Cross coupling reactions between *N*-heterocycles and aryl halides are important for the preparations of many compounds of interest in biological, pharmaceutical and materials sciences.[1,2] In particular, *N*-arylimidazoles of pharmaceutical interest include thromboxane synthase inhibitors,[3] AMPA receptor antagonists,[4] AMP phosphodiesterase inhibitors,[5] cardiotonic agents,[6] and topical anti glaucoma agents.[7] *N*-Arylpyrazole is a structural element of Celecoxib, a potent and selective COX-2 inhibitor.[8] In general, coupling reactions of this type use palladium-,[9] or copper-,[10] and more recently iron-catalysts.[11] The reaction conditions have in common the use of organic solvents such as DMF, DMSO, nitrobenzene, *N*-methylpyrrolidone (NMP), dioxane or toluene. These solvents are all volatile and contribute to environmental pollution as volatile organic contaminants (VOCs). Some of the solvents are toxic. It is therefore desirable to see if these reactions can be carried out under solvent-free conditions.

We began the preliminary investigation by examining microwave-assisted solvent-free conditions for aromatic nucleophilic substitution[12] of aryl fluorides **1a–c** having electron-withdrawing groups in the *p*-position with imidazole (Scheme 1). Recently, Meciaerova et al. reported that such S_NAr reactions can be carried out efficiently in DMSO with potassium carbonate as the base using microwave irradiation.[13] When the same reactions were conducted without the solvent DMSO, the reactions gave modest yields of the products **2a–c** (Table 1). We then used potassium phosphate tribase (K_3PO_4) instead of potassium carbonate for the reaction as several reports described the use of K_3PO_4 in C–N coupling reactions.[14] The yields were improved considerably especially when 2 equiv of K_3PO_4 was used (Table 1). The reactions were quite convenient as only 6 min of microwave irradiation was required for 1 mmol scale reaction (see Scheme 1).[15]

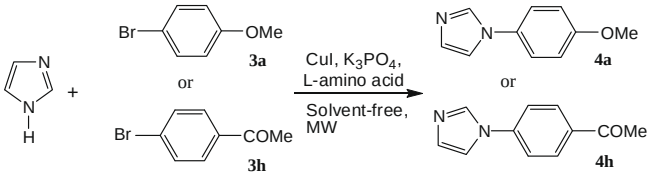
For aryl halides which are not amenable to nucleophilic aromatic substitution, transition metal catalyst is required to promote the coupling reaction. Recently, Ma and his co-workers reported that CuI together with an amino acid can effectively catalyze C–N bond formation between aryl halides and amines in DMSO.[16] Since their reactions required the less expensive CuI as the transition metal catalyst, we decided to explore its use for solvent-free conditions. We began by surveying the reaction using different naturally occurring amino acids and K_3PO_4 to replace K_2CO_3 for both electron-rich aryl bromide **3a** and electron-deficient aryl bromide **3 h** (see Scheme 2). The results are summarized in Figures 1 and 2. The reaction was carried out with aryl bromide (1 mmol), a slight excess of imidazole (1.2 equiv) and CuI (10 mol %), L-amino acid (20 mol %), and K_3PO_4 (2 equiv) in a sealed reaction vessel. A



Scheme 1.

Table 1
Microwave-assisted solvent-free aromatic nucleophilic substitution reactions according to Scheme 1

Entry	Substrate	Yield (^{1}H NMR) of **2**		
		K_2CO_3 (1 equiv)	K_3PO_4 (1 equiv)	K_3PO_4 (2 equiv)
1	**1a**	8%	45%	82%
2	**1b**	33%	57%	74%
3	**1c**	44%	77%	84%



Scheme 2.

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E-mail address: bcchanth@polyu.edu.hk (T.H. Chan).

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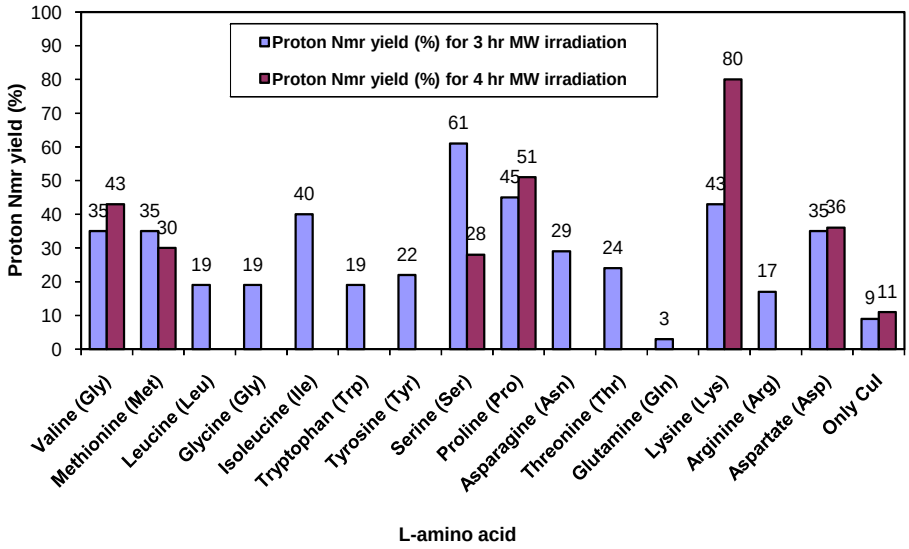


Figure 1. Coupling between 4-bromoanisole **3a** and imidazole with 15 standard L-amino acids under solvent-free conditions.

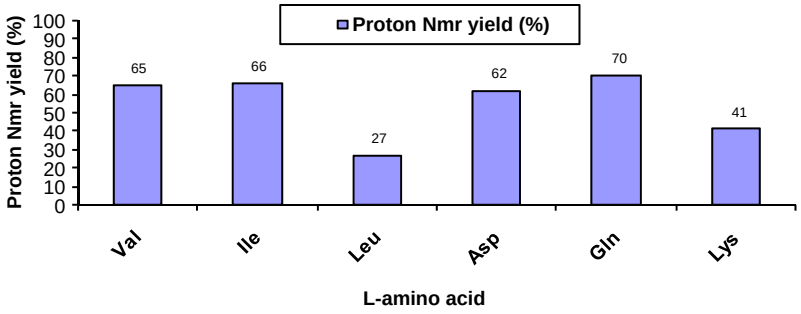
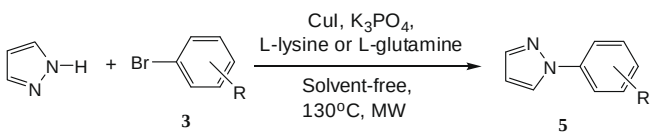


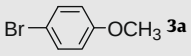
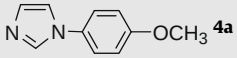
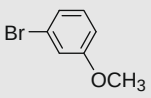
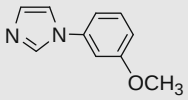
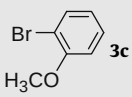
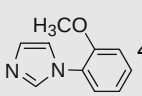
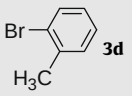
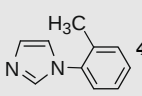
Figure 2. Coupling between 4-bromoacetophenone **3 h** and imidazole with L-amino acids under solvent-free conditions at 130 °C for 3 h.



Scheme 3.

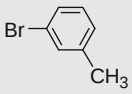
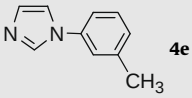
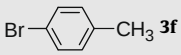
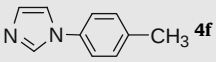
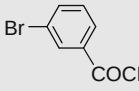
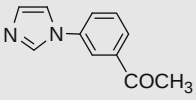
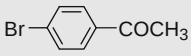
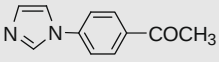
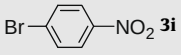
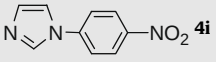
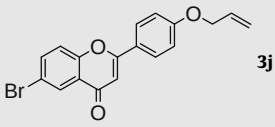
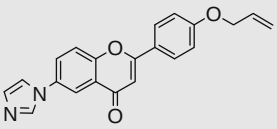
Milestone MicroSYNTH microwave organic synthesis labstation was used for the reaction. The mixture was irradiated for 3 min to allow the temperature rise from room temperature to 130 °C and then further irradiated at that temperature for 3–4 h. The reaction mixture was cooled to room temperature and the product was extracted by ethyl acetate and the crude yield determined by ^{1}H NMR. It was clear that in the absence of amino acid, the reaction gave a poor yield. Some amino acids were more efficient than oth-

Table 2
Solvent-free route for microwave-assisted coupling between aryl bromides and imidazole

Entry	Substrate	Reaction condition [a]			Product	Isolated yield (%)
		Temperature (°C)	Time (h)	MW power W)		
1[b]	 **3a**	130	5.0	200	 **4a**	99
2[b]	 **3b**	130	5.0	200	 **4b**	99
3[b]	 **3c**	130	6.5	200	 **4c**	95
4[b]	 **3d**	130	5.0	200	 **4d**	30

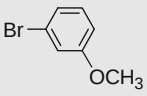
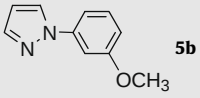
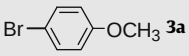
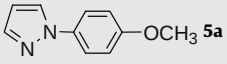
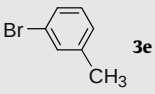
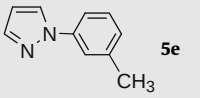
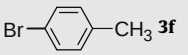
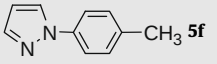
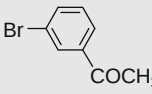
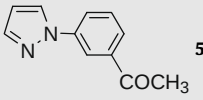
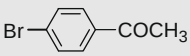
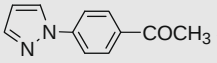
(*continued on next page*)

Table 2 (*continued*)

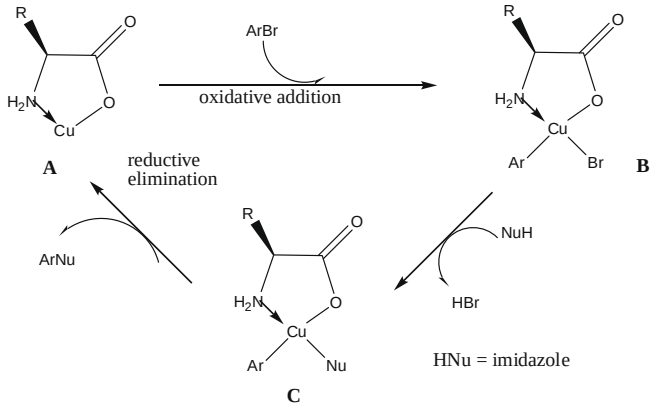
Entry	Substrate	Reaction condition [a]			Product	Isolated yield (%)
		Temperature (°C)	Time (h)	MW power W)		
5[b]	 **3e**	130	3.0	200	 **4e**	79
6[b]	 **3f**	130	2.5	200	 **4f**	49
7[b]	 **3g**	130	5.0	200	 **4g**	73
8[b,c]	 **3h**	130	6.5	200	 **4h**	43[b], 69[c]
9[b,c]	 **3i**	130	7.0	200	 **4i**	48[b], 51[c]
10[d]	 **3j**	140	10	200	 **4j**	15 (64)[e]

[a] The reaction mixture was heated up from room temperature to desired reaction temperature by 500 W microwave irradiation within 3 min.
[b] L-Lysine was used as additive.
[c] L-Glutamine was used as additive.
[d] Flavone **3j** (0.5 mmol), CuI (20 mol %), L-lysine (40 mol%), K_3PO_4 (4 equiv), and imidazole (10 equiv) were used.
[e] Crude yield by ^1H NMR.

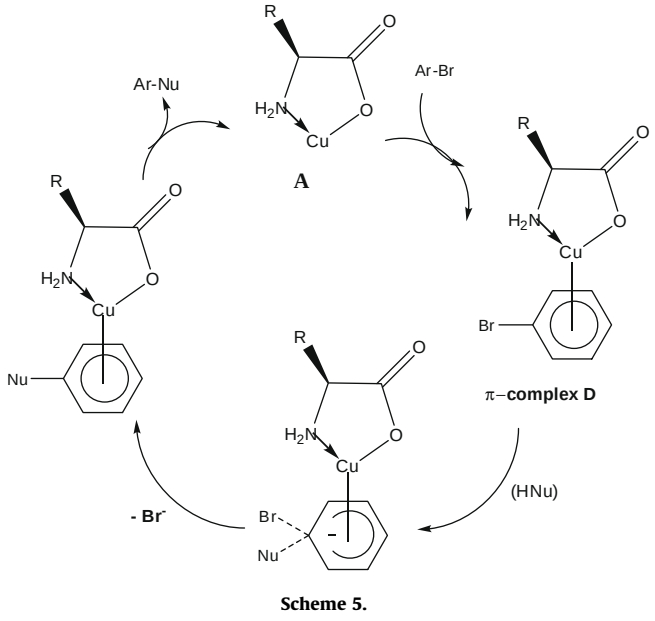
Table 3
Solvent-free route for microwave-assisted coupling between aryl bromides and pyrazole

Entry	Substrate	Reaction condition[a]			Product	Isolated yield (%)
		Temperature (°C)	Time (h)	MW power (W)		
1[b]	 **3b**	150	10	200	 **5b**	32
2[b]	 **3a**	150	10	200	 **5a**	83
3[b]	 **3e**	150	3.0	200	 **5e**	27
4[b]	 **3f**	150	2.0	200	 **5f**	37
5[b]	 **3g**	150	10.0	200	 **5g**	44
6[c]	 **3h**	150	5.0	200	 **5h**	59

[a] The reaction mixture was heated up from room temperature to desired reaction temperature by 500 W microwave irradiation within 3 min.
[b] L-Lysine was used as additive.
[c] L-Glutamine was used as additive.



Scheme 4.



Scheme 5.

ers in promoting this reaction, with L-lysine being the most effective for **3a** (Figure 1) and L-glutamine for **3 h** (Figure 2). We have therefore applied the CuI-promoted cross-coupling of imidazole to a number of aryl bromides under microwave-assisted solvent-free conditions using either L-lysine or L-glutamine (Table 2). The results are summarized in Table 2. As one can see, the reaction worked well for aryl bromides with electron-rich substituents. For bromoanisoles, irrespective of the position of the methoxy group, nearly quantitative yield of the product could be obtained (Table 2, entries 1–3).

We were able to achieve C–N coupling for the complex flavone **3j** with imidazole to give **4j** (Table 2, entry 10), which was required in the study of multidrug resistance.[17,18] When the same reaction was carried out in DMSO, no product was obtained. We have also applied the microwave-assisted solvent-free conditions to the coupling of pyrazole with aryl bromides (Scheme 3). The results are summarized in Table 3. In all cases, the reaction worked and the products were obtained in moderate yields.

It is interesting to compare our observation with that of Ma et al.[16] where they found L-proline and glycine to be the most effective amino acids to promote the CuI catalyzed coupling reaction in DMSO solution. It was suggested that chelation of Cu(I) with the amino acid made the Cu(I) species (**A**, Scheme 4) more reactive toward the oxidative addition step (**B**, Scheme 4), thereby promoting the coupling reaction.[16] We offer the following interpretation of our results. In the reaction of **3a** with imidazole (Figure 1), chelation of the amino acid with Cu(I) facilitates the coupling reaction as nearly all amino acids give a better yield of product **4a** than using CuI alone. However, because the reaction is carried out under solventless conditions and an external base may not be in close proximity, the rate determining step may well be the replacement of the bromide by imidazole to give the intermediate **C** (Scheme 4). If that is the case, the presence of the extra basic amino group in lysine will assist in removing the proton from imidazole thus promoting the substitution. Other factors may play a role as well. Arginine which also has a basic amino group did not show comparable result in this reaction. This may be due to the strong coordination between the guanidine moiety of arginine and copper ion which interferes with the formation of complex **A**.

For the reaction of electron-deficient **3h** (Figure 2), the π-complexed mechanism proposed by Paine may be operative.[19] Under solventless conditions, the formation of the π-complex **D** (Scheme 5) may be the critical step. Hydrogen bonding between the glutamine amide function and the carbonyl function of **3h** may facilitate bringing the Cu(I) species **A** and the aryl bromide together for such complexation formation.

In conclusion, we have shown that microwave-assisted solvent-free reactions can be used for the N-arylation of imidazole and pyrazole.

Acknowledgments

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