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Copper-catalysed *N*-arylation of pyrrole with aryl iodides under ligand-free conditions

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A simple, inexpensive and ligand-free copper-catalysed *N*-arylation of pyrrole with aryl iodides has been developed giving *N*-arylated products in moderate to excellent yields. The catalyst loading is relative low (5 mol%) and the catalyst system was stable in air.

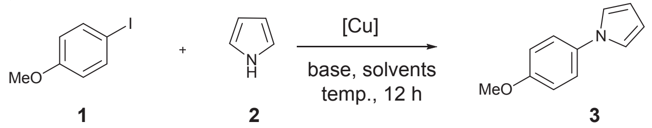
Keywords: copper, ligand-free, *N*-arylation, pyrrole, aryl iodides

Pyrrole-containing heterocycles are ubiquitous in natural and well-represented among the desirable structures of modern medicinal chemistry and polymer materials.[1,2] Consequently, many procedures have been developed for the synthesis of substituted pyrroles including reductive coupling reactions, aza-Witting reactions, Paal–Knorr reaction, and other multi-step reactions.[3] However, transition-metal-catalysed (such as palladium and copper) coupling reactions of aryl halides with pyrroles remains one of the most attractive methods for the synthesis of *N*-aryl pyrroles. Several classes of mono- and bidentate chelating ligands have been employed.[4–8] A few copper-catalysed *N*-arylations of pyrroles under ligand-free conditions have been reported. However, additives (such as $^{n}Bu_4NBr$),[9] moisture-unstable bases (such as NaH),[10] or relative high catalyst loadings[11,12] are often necessary. Following our recent report on Cu-catalysed cross coupling,[13–15] we now describe a new set of reaction conditions, optimised for the Cu-based *N*-arylation of pyrroles with aryl iodides under ligand-free conditions.

Results and discussion

Initially, 4-iodoanisole and pyrrole were selected as the model substrates to optimise the coupling reaction conditions including various copper sources, solvents, bases without ligands and protection by an inert gas. The results are summarised in Table 1. Five copper salts with 5 mol% loading were tested in DMSO at 110 °C using NaOH as the base. Cu^{II} or Cu^{I} salts showed moderate to good activity. $CuSO_4$ gave the highest yield, while copper powder was the worst (entries 1–5). Control experiments conducted in the absence of any catalyst resulted

Table 1 Screening of the reaction conditions[a]



Entry	[Cu]	Solvent	Base	Temp./°C	Yield/%[b]
1	CuI	DMSO	NaOH	110	77
2	$CuSO_4$	DMSO	NaOH	110	80
3	CuCl	DMSO	NaOH	110	66
4	CuBr	DMSO	NaOH	110	68
5	Cu	DMSO	NaOH	110	Trace
6	–	DMSO	NaOH	110	0
7	$CuSO_4$	DMF	NaOH	110	41
8	$CuSO_4$	DMA	NaOH	110	24
9	$CuSO_4$	1,4-Dioxane	NaOH	110	11
10	$CuSO_4$	H_2O	NaOH	110	0
11	$CuSO_4$	DMSO	KOH	110	76
12	$CuSO_4$	DMSO	K_3PO_4	110	9
13	$CuSO_4$	DMSO	Cs_2CO_3	110	43
14	$CuSO_4$	DMSO	K_2CO_3	110	Trace
15	$CuSO_4$	DMSO	NaOH	110	86[c]
16	$CuSO_4$	DMSO	NaOH	110	33[d]
17	$CuSO_4$	DMSO	NaOH	100	62
18	$CuSO_4 \cdot 5H_2O$	DMSO	NaOH	110	84

[a]Reaction conditions: 4-iodoanisole (0.5 mmol), pyrrole (0.75 mmol), [Cu] (5 mmol%), base (1.0 mmol%), solvent (1 mL).
[b]Isolated yield.
[c]10 mol% of $CuSO_4$.
[d]2.5 mol% of $CuSO_4$.

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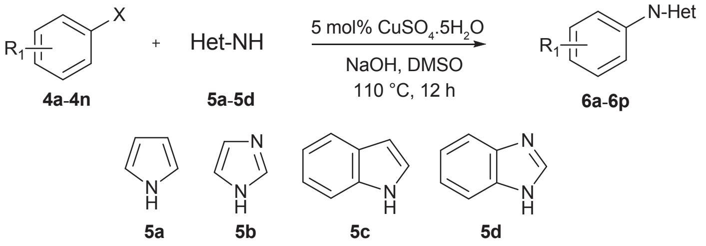
Table 2 Copper-catalysed *N*-arylation of pyrroles with aryl halides under ligand-free conditions[a]



Entry	Aryl halides (R, X)	Het-NH	Product	Yield/%[b]	M.p./°C	
					Found	Reported
1	4-OMe, I (**4a**)	**5a**	**6a**	84	110–111	111–112[16]
2	3-OMe, I (**4b**)	**5a**	**6b**	65	57–58	56–57[17]
3	4-OEt, I (**4c**)	**5a**	**6c**	88	69–70	70–71[16]
4	3,5-di-Me, I (**4d**)	**5a**	**6d**	90	Colourless oil	Colourless oil[18]
5	4-Me, I (**4e**)	**5a**	**6e**	80	82–83	82–84[16]
6	H, I (**4f**)	**5a**	**6f**	75	60–62	60–61[16]
7	4-OH, I (**4g**)	**5a**	**6g**	58	111–113	113–115[19]
8	2-Me, I (**4h**)	**5a**	**6h**	37	Yellow oil	Oil[16]
9	2-OMe, I (**4i**)	**5a**	**6i**	66	Yellow oil	Oil[16]
10	4-Ph, I (**4j**)	**5a**	**6j**	86	186–188	183–188[20]
11	4-F, I (**4k**)	**5a**	**6k**	40	50–51	51–52[16]
12	4-Cl, I (**4l**)	**5a**	**6l**	60	87–88	87–88[16]
13	4-Br, I (**4m**)	**5a**	**6m**	47	92–93	93–94[16]
14	4-Cl, Br (**4n**)	**5a**	**6l**	10	86–87	87–88[16]
15	3,5-di-Me, I (**4d**)	**5b**	**6n**	66	Viscous oil	Viscous oil[18]
16	3,5-di-Me, I (**4d**)	**5c**	**6o**	32	Colourless oil	Colourless oil[18]
17	3,5-di-Me, I (**4d**)	**5d**	**6p**	17	Yellow oil	Yellow oil[21]

[a]Reaction conditions: aryl halides (1.0 mmol), Het-NH (1.5 mmol), $CuSO_4·5H_2O$ (0.05 mmol), NaOH (2.0 mmol), DMSO (2 mL), 110 °C, 12 h.
[b]Isolated yield.

in no product (entry 6). The results of the effect of the solvent indicated that DMSO was superior to other solvents (entries 7–10). The target product was obtained by 80% yield in DMSO, and low yields were generated in DMF, DMA and 1,4-dioxane, and no product was detected in water. Investigation into the bases with different basicities revealed that NaOH showed the highest efficiency, KOH was fair, Cs_2CO_3 gave moderate activity, and K_3PO_4 and K_2CO_3 were not suitable as the bases (entries 11–14). Increasing the catalyst loading from 5 mol% to 10 mol% only led to a slight improvement of the yield (entry 15). However, decreasing the copper loading from 5 to 2.5 mol% or lowering the temperature from 110 °C to 100 °C gave markedly lower yields (entries 16 and 17). It must be noted that the hydrate of $CuSO_4$ can accelerate the arylation of pyrrole, possibly because of the hydrate increased the solubility of the catalyst in DMSO (entry 18). Considering the efficiency and the price, $CuSO_4·5H_2O$ was finally chosen as the copper source.

After optimising the reaction conditions, we attempted the coupling reactions with various aryl halides and nitrogen-containing heterocycles under our standard conditions. The substrates which were examined gave the corresponding products in moderate to excellent yields (see Table 2). In general, aryl iodides, containing electron-donating groups possessed a higher activity than those containing electron-withdrawing groups. It was noteworthy that the reaction exhibited high selectivity in the amination of 4-iodophenol, and no diaryl ether products were found (entry 7). More interesting, the system tolerated *ortho*-substituted halides, which afforded the target product in moderate yields (entries 8 and 9). We found that the arylation of imidazole also gave moderate yield, but the yields of arylation of indole and benzimidazole were not satisfactory (entries 15–17). Unfortunately, the *N*-arylation product was obtained only in 10% yield, when 4-bromo-1-chlorobenzene was used as the substrate (entry 14).

Conclusion

In summary, we have developed a new catalyst system for the *N*-arylation of pyrrole with different substituted aryl iodides under ligand-free conditions without the protection of an inert atmosphere. The low loading (5 mol%), cheap and commercial available copper catalyst ($CuSO_4·5H_2O$) is expected to be useful in a variety of synthesis.

Experimental

All reagents were purchased from commercial suppliers and used without further purification. ^1H NMR spectra were recorded at room temperature on a Varian Inova-400 instrument at 400 MHz for ^1H NMR, and the chemical shifts were recorded in ppm (δ) with TMS as internal standard. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model.

N-arylation of pyrrole; general procedure

$CuSO_4·5H_2O$ (12.50 mg, 0.05 mmol), the aryl iodide or bromide (1.0 mmol), pyrrole (1.5 mmol), NaOH (80 mg, 2 mmol), and DMSO (2 mL) were placed in a 10 mL sealed tube. The mixture was heated at 110 °C in a preheated oil bath for 12 h. It was then cooled to room temperature, diluted with 20 mL H_2O, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1 : 100) to afford the target products. All C–N coupling products reported here are known products and were characterised by GC-MS and ^1H NMR, which were compared with the previously reported dates.

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