Copper complex-catalysed C–N coupling reaction of aryl iodides with nitrogen-containing heterocycles

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An efficient method for the copper-catalysed arylation of nitrogen-containing heterocycles is reported using 3-(diphenylphosphino) propanoic acid as a ligand in combination of CuCl. The C–N coupling reactions afford various N-arylated products in good to excellent yields.

Keywords: copper, arylation, heterocycles, 3-(diphenylphosphino)propanoic acid

The construction of *N*-arylated nitrogen compounds efficiently is currently an active area of research in the synthesis of various medicinal and natural products.^{1–10}

The classical approaches to the syntheses of compounds bearing an arylated nitrogen moiety^{11–15} are based on the aromatic nucleophilic substitution reaction (S_NAr) by nitrogen nucleophiles of activated aryl halides or alternatively the classical Ullmann^{16,17} coupling at higher temperature.^{18–20}

However, each of these methods suffer from different drawbacks such as high reaction temperatures (often 150 °C or as high as 200 °C), tedious work-up, the use of very expensive palladium catalysts, or the use of stoichiometric amount of Cu salt. These make scale-up difficult and ecologically unfriendly. Other drawbacks are the use of toxic and air-sensitive aryl coupling reagents that can be difficult to access, whilst excess aryl halide starting materials are required to achieve reasonable product yields.^{16–20} Thus, it is desirable to develop a convenient and simple method for the copper-catalysed arylation of nitrogen-containing heterocycles.

Among various methods for the transition copper-catalysed arylation of nitrogen-containing heterocycles with aryl halides, amino acids, diamines, Schiff-bases, [1,10]-phenanthroline, quinoline, amino-arenethiol, and oxime-phosphine oxide have been investigated as effective ligands.^{21–24} In spite of these methods, there are no reports on the synthesis of *N*-arylated nitrogen compounds *via* arylation of nitrogen-containing heterocycles using 3-(diphenylphosphino)propanoic acid as an efficient ligand.

As part of our ongoing interest in the chemistry of nitrogencontaining compounds and the synthesis of heterocyclics,^{25,26} we now report the copper-catalysed arylation of nitrogencontaining heterocycles with aryl iodides in the presence of 3-(diphenylphosphino)propanoic acid as a new ligand (1) under thermal conditions (Scheme 1).



Results and discussion

Usually the ligands play an important role for a successful copper-catalysed C-N coupling reaction. In order to optimise the reaction conditions, we chose the reaction of 4-methoxyphenyl iodide with imidazole in the presence of various copper catalysts and ligand 1 as the model reaction. The effects of the base and solvents were examined. First, several solvents were screened for the reaction. According to data given in Table 1, DMSO was the most efficient solvent for this reaction (Table 1, entry 5). After choosing DMSO as the solvent, we examined several different Cu source and bases. As shown in Table 1, among the various Cu sources tested in the presence of 1 as ligand, CuCl led to a significant conversion. The reaction was also influenced significantly by the base that was employed. The best result was obtained in the case of NaOH (Table 1, entry 5). The best result was obtained with 1 (20.0 mol%), CuCl (15.0 mol%), 4-methoxyphenyl iodide (1.0 mmol), imidazole (1.4 mmol), NaOH (2.0 mmol) and DMSO (4 mL) which gave the product in a good yield (94%). Increasing the amount of ligand 1 and copper salt gave no substantial improvement in the yield. Next, using the optimised procedure, a series of aryl iodides possessing both electron-releasing and electronwithdrawing groups were employed (Table 2). This newly

Entry	Cu source /mol%	Ligand /mol %	Solvent	Base /mol %	Yield ∕%⁵
1	CuCl (15)	20	Toluene	NaOH	0
2	CuCl (15)	20	Dioxane	NaOH	0
3	CuCl (15)	20	MeOH	NaOH	0
4	CuCl (15)	20	DMF	NaOH	Trace
5	CuCl (15)	20	DMSO	NaOH	94
6	CuCl (15)	20	DMSO	Et ₃ N	10
7	CuCl (15)	20	DMSO	K ₂ CO ₃	20
8	CuCl (15)	20	DMSO	Na ₂ CO ₃	18
9	CuCl (15)	20	DMSO	K ₃ PO ₄	16
10	Cu(OAc),.H,0 (15)	20	DMSO	NaOH	75
11	Cul (15)	20	DMSO	NaOH	65
12	Cu ₂ O (15)	20	DMSO	NaOH	79
13	CuCl (10)	10	DMSO	NaOH	78
14	CuCl (15)	25	DMSO	NaOH	95

^aGeneral reaction conditions: imidazole (1.4 mmol), 4-methoxyphenyl iodide (1.0 mmol), Cu source (15 mol%), Ligand **1** (20.0 mol%), base (2.0 mmol), DMSO (4 mL), 120 °C, 14 h, pressure tube, N_2 atm. ^bYields are after work-up.

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 Table 2
 Formation of N-arylated nitrogen compounds via Cu-catalysed arylation of nitrogen-containing heterocycles^a

Entry	Substrate	Het-NH	Yield ∕%⁵	M.p. /°C	Lit. m.p. /°C ^{Ref.}
1	C ₆ H₅I	1 <i>H</i> -Imidazole	77	Oil	Oil ²⁷
2	<i>p</i> -MeOC ₆ H ₄ I	1 <i>H</i> -Imidazole	94	122–124	121-12228
3	o-MeC ₆ H ₄ I	1 <i>H</i> -Imidazole	81	Oil	Oil ²⁸
4	<i>p</i> -MeC ₆ H ₄ I	1 <i>H</i> -Imidazole	95	Oil	Oil ²⁹
5	$p-NH_2C_6H_4I$	1 <i>H</i> -Imidazole	75	138–140	138-13928
6	<i>p</i> -BrC ₆ H ₄ I	1 <i>H</i> -Imidazole	92	118–120	118-12027
7	p-CHOC ₆ H ₄ I	1 <i>H</i> -Imidazole	93	153–155	153-15530
8	<i>p</i> -FC ₆ H ₄ I	1 <i>H</i> -Imidazole	88	124–129	124-12930
9	$p-NO_2C_6H_4I$	1 <i>H</i> -Imidazole	80	198–203	198-20330
10	<i>p</i> -CF ₃ C ₆ H ₄ I	1 <i>H</i> -Imidazole	92	71–73	7130
12	$p-NO_2C_6H_4I$	1 <i>H</i> -1,2,4-Triazole	84	171–173	170–173 ³¹
13	p-MeC ₆ H ₄ I	1 <i>H</i> -Benzo[<i>d</i>]imidazole	88	Oil	Oil ³¹

^aGeneral reaction conditions: nitrogen-containing heterocycle (1.4 mmol), aryl iodide (1.0 mmol), Cu source (15 mol%), Ligand **1** (20.0 mol%), NaOH (2.0 mmol), DMSO (4 mL), 120 °C, 14 h, pressure tube, N_2 atm. ^bYields are after work-up.

developed Cu-catalysed N-arylation protocol was also applied to various nitrogen-containing heterocycles (Table 2). In all cases, this afforded the desired products in good to excellent yields. Due to its electronic and steric nature, we also tested the *N*-arylation of imidazole with 2-iodotoluene. As shown in Table 2, reaction of 2-iodotoluene with imidazole afforded good yield (Table 2, entry 3). The arylations of 1*H*-benzimidazole and 1*H*-1,2,4-triazole with aryl iodides afforded the corresponding *N*-arylated products in reasonable yields (Table 2, entries 12 and 13).

Several similar mechanisms have been reported for the palladium or copper-catalysed arylation of nitrogen-containing heterocycles using various ligands. Ligand 1 can coordinate with copper *via* the oxygen and phosphorus atoms in a similar manner to other ligands.

In summary, a simple method has been developed for the copper-catalysed arylation of nitrogen-containing heterocycles using 3-(diphenylphosphino)propanoic acid as an efficient ligand under thermal conditions. The significant advantages of this methodology are high yields and a simple work-up procedure. Further investigations on the application of this system in other catalytic reactions are in progress.

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. 3-(Diphenylphosphino)propanoic acid as ligand was purchased from Aldrich. Products were characterised by comparison of their physical and spectral data with authentic samples. The NMR spectra were recorded in DMSO. ¹H NMR spectra were recorded on a Bruker Avance DRX 250 MHz instruments. The chemical shifts () are reported in ppm relative to the TMS as an internal standard and *J* values are given in Hz. ¹³C NMR spectra were recorded at 62.5 Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. TLC was performed on silica gel polygram SIL G/UV 254 plates.

Copper-catalysed arylation of nitrogen-containing heterocycles with aryl iodides; general procedure

NH-containing heterocycle (1.4 mmol) and DMF (2.0 mL) were added to a mixture of CuCl (15.0 mol%) and ligand 1 (20.0 mol%) in DMF (2.0 mL), aryl iodide (1.0 mmol), NaOH (2.0 mmol). The mixture was

vigorously stirred at 120 °C for 14 h under a dry nitrogen atmosphere. After completion of the reaction (as monitored by TLC), H_2O was added and the organic layer was extracted with EtOAc, washed with brine and dried over MgSO₄. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography. The purity of the compounds was checked by ¹H NMR and yields are based on aryl iodide. All the products are known and the spectroscopic data (FT-IR and NMR) and melting points were consistent with those reported in the literature.²⁷⁻³¹

We gratefully acknowledge Soran University for support of this work.

Received 15 November 2013; accepted 7 January 2014 Paper 1302287 doi: 10.3184/174751914X13897958624063 Published online: 5 February 2014

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