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Original article

Tetrazole-1-acetic acid as a ligand for copper-catalyzed *N*-arylation of imidazoles with aryl iodides under mild conditions



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ABSTRACT

Tetrazole-1-acetic acid was found to serve as a superior ligand for CuI-catalyzed *N*-arylation of imidazoles with aryl iodides under a low catalyst loading (5 mol% of CuI). A variety of aryl iodides could be aminated to provide the *N*-arylated products in good to excellent yields without the need of an inert atmosphere.

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1. Introduction

Copper-catalyzed carbon-nitrogen cross-coupling reactions have been established as a powerful strategy for the preparation of *N*-arylation of nitrogen nucleophiles, which play a vital role as intermediates for agrochemicals, pharmaceuticals, energetic materials and fine chemical industries [1]. Traditionally, these reactions were often suffered from harsh reaction conditions involving elevated temperatures and highly polar solvents, and stoichiometric amounts of copper reagents [2]. Recently, pioneered by the Buchwald's and Taillefer's works [3], the process of Cu-based C-N coupling reactions have reinvigorated by the implementation of several classes of mono- and bidentate chelating ligands [4]. However, more work still needs to be done to identify new ligands to widen the scope of substrate tolerance, lower copper loading, milder reaction conditions, enhanced chemoselectivity and enantioselectivity of copper-catalyzed C-N coupling reactions.

On the other hand, it is well-known that carboxylate O atoms and tetrazolyl ring N atoms have good coordination capacities [5], and tetrazole-1-acetic acid (TZA), with both a carboxylate and tetrazolyl ring, is a multifunctional ligand. Therefore, it could bind to several metals *via* N and/or O atoms to form multi-dimensional coordination polymers with various coordination modes [6–9].

However, TZA, to our knowledge, has seldom been used as ligand in copper-mediated cross-coupling reactions. In continuation of our endeavors to develop copper-catalyzed cross couplings [10-12], we report herein TZA as an accelerating ligand for copper-catalyzed *N*-arylation of imidazoles with aryl iodides under mild reaction conditions.

2. Experimental

All reagents were purchased from commercial suppliers and used without further purification. All known products were characterized by GC–MS, and ¹H NMR, which were compared with the previously reported dates. ¹H NMR spectra were recorded at room temperature on a Varian Inova-400 instrument at 400 MHz, 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.

General procedure for the *N*-arylation of imidazoles with aryl halides: Cul (0.05 mmol), **L1** (0.1 mmol), aryl halides (1.0 mmol), imidazoles (1.5 mmol), NaOH (2 mmol), and DMSO (2 mL) were added to a 10 mL of sealed tube. The reaction mixture was reacted at 110 °C in a preheated oil bath for 12 h. The reaction mixture was cooled to r.t., diluted with 10 mL H₂O, and then the mixture was extracted with ethyl acetate (3×20 mL). The combined organic phases was washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 2:1 to pure ethyl acetate) to afford the target products.



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Table 1

Screening of the reaction conditions on the coupling reaction of 4-iodoanisole with imidazole.^a



Entry	[Cu]	Ligand	Solvent	Base	<i>T</i> (°C)	Yield (%) ^b
1	CuI	L1	DMSO	NaOH	110	93
2	CuI	L2	DMSO	NaOH	110	84
3	CuI	L3	DMSO	NaOH	110	77
4	CuI	L4	DMSO	NaOH	110	88
5	CuI	_	DMSO	NaOH	110	75
6	CuO	L1	DMSO	NaOH	110	81
7	CuSO ₄	L1	DMSO	NaOH	110	71
8	$Cu(OAc)_2$	L1	DMSO	NaOH	110	83
9	CuCl	L1	DMSO	NaOH	110	87
10	CuBr	L1	DMSO	NaOH	110	89
11	-	L1	DMSO	NaOH	110	0
12	CuI	L1	DMF	NaOH	110	48
13	CuI	L1	DMAC	NaOH	110	80
14	CuI	L1	1,4-Dioxane	NaOH	110	40
15	CuI	L1	H ₂ O	NaOH	110	Trace
16	CuI	L1	DMSO	КОН	110	79
17	CuI	L1	DMSO	K ₃ PO ₄	110	88
18	CuI	L1	DMSO	Cs ₂ CO ₃	110	81
19	CuI	L1	DMSO	K ₂ CO ₃	110	11
20	CuI	L1	DMSO	NaOH	100	88
21	CuI	L1	DMSO	NaOH	80	16
22	CuI	L1	DMSO	NaOH	110	92 ^c (70 ^d)
23	CuI	L1	DMSO	NaOH	110	80 ^e

^a Reaction conditions: 4-iodoanisole (0.5 mmol), imidazole (0.75 mmol), [Cu] (10 mmol%), L (20 mmol%), base (1.0 mmol), solvent (1 mL), 12 h.

^b Isolated yield.

^c 5 mol% Cul, 10 mol% **L1**.

^d 5 mol% CuI, ligand-free.

^e 2.5 mol% Cul, 5 mol% **L1**.

Table 2

Cul-catalyzed N-arylation of imidazoles with aryl iodides using tetrazole-1-acetic acid as ligand under mild conditions.^a



Entry	ArX	Het-NH	Product	Yield (%) ^b
6	McO		MeO N N	76
7	I OMe	\bigcup_{H}^{N}		75 ^d (50 ^{c,d})
8	I NH2			75 (38°)
9	Ph			84
10			Ph' ~ 9	96 (83 ^c)
11	O ₂ N			82 ^e
12	CI LI	N N H		79 (0 ^c)
13	CI	N N H		74 (28 ^c)
14	Br			35 (15 ^c)
		**	MeO 1	

^a Reaction conditions: aryl halides (1.0 mmol), imidazoles (1.5 mmol), Cul (0.05 mmol), L1 (0.1 mmol), NaOH (2.0 mmol), DMSO (2 mL), 12 h.

^b Isolated yields.

Table 2 (Continued)

^c Ligand-free.

^d Reaction time: 18 h.

^e 90 °C, 6 h.

3. Results and discussion

Initially, 4-iodoanisole and imidazole were selected as the model substrates to optimize the coupling reaction conditions including copper source, ligand, solvent, bases and temperature without the protection by an inert gas. The results are shown in Table 1. Among the ligands used, TZA was more beneficial to the catalysis than other N-heterocyclic-1-acetic acid, which gave the desired product in 93% isolated yield (entries 1-4). This could be attributed to the excellent coordination capacity of L1. In contrast, the reaction was also carried out in the absence of ligand, and the *N*-arylation product was obtained in moderate yield (entry 5). Nevertheless, the effect of the ligands is obvious (entry 1 vs entry 5, and entry 22). By using L1 as the ligand, different copper source have then been examined, and Cu^{II} or Cu^I were more or less active, and CuI demonstrated the highest yields (entries 6-10). Observation of the solvent indicated that DMSO is the most favorable solvent for the model reaction (entries 1, 12–15). The bases, including NaOH, KOH, K₃PO₄, Cs₂CO₃, and K₂CO₃ were explored, and NaOH gave the best yields (entries 1, 16–19). Lowering the reaction temperature can markedly decelerate the reaction rate and led to lower yields (entries 1, 20 and 21). In addition, when the loading of Cul was reduced from 10 mol% to 5 mol%, the excellent yield was also afforded. However, when 2.5 mol% of Cul was employed, the reaction yield decreased to 80% (entries 1, 22 and 23). In summary, the optimal conditions for the *N*-arylation of imidazole with 4-iodoanisole involves the use of 5 mol% of Cul, 10 mol% of **L1**, and 2 equiv. of NaOH in DMSO at 110 °C for 12 h.

The scope of the Cul/**L1** catalytic system was probed by using a wide range of aryl iodides and *N*-heterocyclic substrates under the optimized conditions, and the results are listed in Table 2. In general, the *N*-arylation of imidazoles with most of electron-rich, electron-neutral, and electron-poor aryl iodides afforded the desired products in yield ranging from 74% to 96%. It is worth noting that the sterically hindered *o*-iodoanisole reacted smoothly only with prolonging the reaction time to 18 h (entry 7). In addition, when other potentially reactive functional groups (*e.g.*, amino) are present, high level of chemoselectivity was observed

(entry 8). The *N*-arylation of imidazole with 4-nitroiodobenzene gave the corresponding coupling product in 82% yield, which just needed lower reaction temperature and shorter reaction time (entry 11). We were pleased to find that the arylation reactions also proceed with other nitrogen-containing heterocycles such as benzimidazole and indole in good yields under standard conditions (entries 12 and 13). Unfortunately, the *N*-arylation product was obtained only in 35% yield, when 4-bromoanisole was used as the substrate (entry 14). Furthermore, in comparison to ligand-free condition, several blank experiments without any ligand of typical substrates were carried out in the same conditions, and the results confirmed that the ligand played an important role in this process (entries 1, 4, 5, 7–8, 10, 12–14).

4. Conclusion

In conclusion, we established tetrazole-1-acetic acid as a novel ligand for copper-catalyzed *N*-arylation of various nitrogen nucleophiles with differently substituted aryl iodides under mild conditions. The low catalyst loading (5 mol% of CuI), the commercial availability of the ligand and without the protection of an inert gas are expected to be useful for a variety of synthetic chemists.

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