



Cu₂O-catalyzed Ullmann-type reaction of vinyl bromides with imidazole and benzimidazole

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ABSTRACT

Cu₂O was found to be an efficient and economical metal catalyst in the Ullmann cross-coupling reaction of vinyl bromides with imidazole or benzimidazole. The system Cu₂O/ethyl 2-oxocyclohexanecarboxylate showed high catalytic activity in MeCN at 80–90 °C. The reaction gave the corresponding coupling products in good to excellent yields.

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1. Introduction

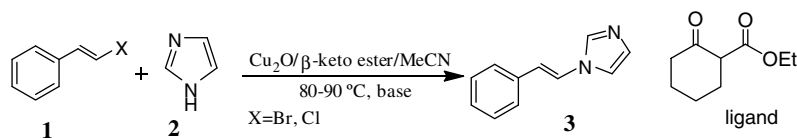
N-Vinylimidazoles are important building blocks and intermediates in the synthesis of polymers,¹ natural product analogues,² pharmaceuticals and agriculture chemicals.³ For instance, poly(1-vinylimidazole)s are involved in the preparation of polymeric dyes, catalysts and ion-exchange resins.⁴ There are several methods to synthesize *N*-vinylimidazoles, including direct addition of imidazole to alkynes,⁵ *N*-vinylation of imidazole with vinyl halides or acetates,⁶ copper-catalyzed C–N bond cross coupling of benzimidazole with vinylboronic acid⁷ and olefination of β -hydroxyimidazoles.⁸ The copper-catalyzed Ullmann-type coupling of vinyl halides with imidazole would be an economic and versatile method. Catalyzed by CuI/*L*-proline in ILs at 90–110 °C, vinyl bromides have been coupled with imidazole and good to excellent yields were obtained.⁹ However, the required amounts of CuI and the corresponding ligands in many Ullmann-type coupling reactions were usually large (often 10–30 mol % for CuI and 20–60 mol % for ligand). Moreover, CuI, which was usually used in the Ullmann condensations in recently published papers, is still expensive to the goal of practical applications in industry.

It was reported that Cu₂O could efficiently catalyze the coupling of nitrogen-nucleophiles with aryl iodides and bromides under mild conditions.¹⁰ In Taillefer's report, imidazole was shown to be less reactive than pyrazole, which could couple with bromobenzene under the catalysis of Cu₂O/salicylaldoxime in CH₃CN at 82 °C. Buchwald reported that coupling of imidazole with aryl iodides and bromides could be realized in high yields under the catalysis of Cu₂O/4,7-dimethoxy-1,10-phenanthroline system in *n*-PrCN at the temperature range of 80–110 °C. It was also proved that Cu₂O could be used in ligand-free cross-coupling protocol.^{10d}

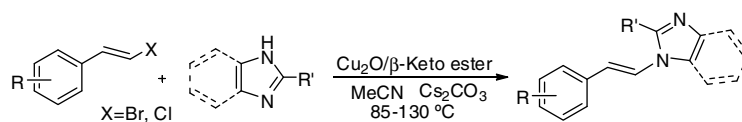
Apparently, Cu₂O was also an efficient catalyst in the Ullmann-type coupling. In the suitable solvents the reaction conditions catalyzed by Cu₂O will not be harsher than that catalyzed by CuI. In the reported coupling reactions, the molar ratio of Cu₂O was usually no more than 5%. Obviously, the use of Cu₂O is more economic than the use of CuI. So, it is particularly interesting to use Cu₂O as a copper source owing to its inexpensiveness and low insensitivity to light and air. Herein, we wish to report a new example of Cu₂O application: the synthesis of *N*-vinylimidazoles by *N*-vinylation of imidazole with vinyl halides catalyzed by Cu₂O/ethyl 2-oxocyclohexanecarboxylate system.

We firstly conducted the coupling of β -bromostyrene and imidazole catalyzed by 5 mol % Cu₂O and 10 mol % ethyl 2-oxocyclohexanecarboxylate. The reaction conditions were systematically evaluated (Table 1). Different solvents were tested initially. In a recent report, it was suggested that less polar solvents will retard the reaction because of the relative insolubility of Cs₂CO₃ or a polar Cu complex. The reactivity of Cu₂O–ligand system in nitrile solvents was in the order of MeCN > EtCN > *n*-PrCN, opposite to the trend of their boiling points in the same series.^{10b} So we chose MeCN from nitrile solvents. It was observed that in MeCN, the coupling of β -bromostyrenes with imidazole gave the best result (Table 1, entry 6). DMSO, DMF and NMP provided much lower yields (Table 1, entries 1, 2 and 4). When the reaction temperature was raised, much higher yields could be obtained (entries 3 and 6). When the dose of metal catalyst and the ligand was reduced to 60%, the yield had only decreased a little (Table 1, entries 6 and 8). Then different bases were tested. Compared with Cs₂CO₃, K₂CO₃ was a bad base (Table 1, entries 5 and 6). From the results in Table 1, it was obvious that ethyl 2-oxocyclohexanecarboxylate was a more efficient ligand (entries 9 and 10) and gave the coupling product in 98% yield. Consistent with our previous experiment, (*Z*)-vinyl bromides were tried to react with imidazole under this condition and the reaction seemed to be much slower and lower yield was obtained, most likely because of their increased level of steric

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Table 1Screening the reaction conditions for Cu₂O-catalyzed coupling of β-bromostyrene **1** with imidazole **2**^a

Entry	X	Solvent	T ^c (°C)	t (h)	Base	Yield ^b (%)
1	Br	NMP	85	28	Cs ₂ CO ₃	33.6
2	Br	DMSO	90	28	Cs ₂ CO ₃	38.5
3	Br	MeCN	75	24	Cs ₂ CO ₃	25.0
4	Br	DMF	85	28	Cs ₂ CO ₃	30.7
5	Br	MeCN	85	24	K ₂ CO ₃	55.6
6	Br	MeCN	85	24	Cs ₂ CO ₃	98.2
7	Cl	MeCN	85	24	Cs ₂ CO ₃	20.1
8	Br	MeCN	85	24	Cs ₂ CO ₃	88.7 ^d
9	Br	MeCN	85	24	Cs ₂ CO ₃	44.7 ^e
10	Br	MeCN	110	24	Cs ₂ CO ₃	85.2 ^f
11	Br	MeCN	120	30	Cs ₂ CO ₃	48.0 ^g
12	Br	MeCN	85	24	Cs ₂ CO ₃	80.0 ^h

^a Reaction conditions: vinyl halide (1.5 mmol), imidazole (1.0 mmol) and Cu₂O (0.05 mmol), ligand (0.10 mmol) and Cs₂CO₃ (2.0 mmol) in 1.5 mL solvent under N₂.^b Isolated yields based on imidazole.^c Oil-bath temperature.^d Reaction conditions: vinyl halide (1.5 mmol), imidazole (1.0 mmol), Cu₂O (0.03 mmol), ligand (0.06 mmol) and Cs₂CO₃ (2 mmol) in 1.5 mL solvent under N₂.^e 1,10-Phenanthroline as the ligand.^f L-proline as the ligand.^g (Z)-1-(2-Bromovinyl)-4-chlorobenzene was used as the substrate, and was performed in a sealed tube at 120 °C.^h Without ligand.**Table 2**Coupling of imidazole and benzimidazole with vinyl bromides^{a,c}

Entry	Vinyl bromide	Imidazole	Product	Yield ^b (%)	E/Z ^d
1				90.8	>99:1
2				92.6	98:2
3				72.3	>99:1
4				99.0	>99:1
5				98.5	>99:1
6				97.7	98:2
7				70.1	97:3

(continued on next page)

Table 2 (continued)

Entry	Vinyl bromide	Imidazole	Product	Yield ^b (%)	<i>E/Z</i> ^d
8		2a		60.3	97:3
9				82.2	>99:1
10		2b		77.6	96:4
11		2b		90.5	>99:1
12		2b		70.8	>99:1
13		2b		53.6	>99:1
14		2b		60.4	98:2
15				61.5	97:3
16		2a		45.6 ^e	>99:1
17		2a		53.2 ^{e,f}	>99:1

^a Reaction conditions: β -bromostyrene (1.5 mmol), imidazole (1.0 mmol), Cu₂O (0.05 mmol), ligand (0.10 mmol) and Cs₂CO₃ (2 mmol) in 1.5 mL suitable solvent at 85 °C under N₂.

^b Isolated yields based on imidazole or benzimidazole.

^c Reaction time 24 h.

^d The ratio was based on ¹H NMR spectrum.

^e Conducted in a sealed tube and the oil-bath temperature is 130 °C.

^f Reaction time 45 h.

hindrance (entry 11). Interestingly, if the reaction was run without ligand, 80% yield was obtained (entry 12)! Actually, we already have found that the imidazole was a ligand in the Cu(I)-catalyzed couplings, though it was inferior to ethyl 2-oxocyclohexanecarboxylate.

After reaction condition was optimized, the scope was explored with various vinyl halides and imidazoles. The results are listed in Table 2.¹¹ It was found that the β -bromostyrenes bearing both electron-donating and electron-withdrawing groups were suitable for this reaction and the desired *N*-vinylimidazoles were obtained in excellent yields under the above reaction condition (entries 1, 2, 4, 5 and 6). The hetero-aryl vinyl bromides can also give the product preferably (entry 7). The reaction seemed sensitive to the sterical hindrance on the substrate. Compared with the coupling of vinyl bromides with imidazole, the yields were relatively lower when benzimidazole was used (entries 9–14). We also employed 2-methylimidazole as a nucleophilic substrate, it only gave a mod-

erate yield (entry 15). Vinyl chloride was also successfully coupled under our reaction conditions, whereas higher reaction temperature and longer reaction time were required (entries 16 and 17). The reaction was also stereoselective for the (*E*)-vinyl halide involved coupling. The double bond geometry of the *N*-vinylimidazoles from the (*E*)-vinyl halide was retained, and the *E*- to -*Z* ratio was up to 99:1.

2. Conclusions

In summary, we have developed a mild, economic and efficient method for the Cu₂O-catalyzed coupling of imidazole or benzimidazole with vinyl bromides. Versatile new vinyl imidazoles could be successfully synthesized by using ethyl 2-oxocyclohexanecarboxylate as ligand with low loading of catalyst Cu₂O under relatively mild conditions. The yields were from good to excellent, and the

stereoselectivity for the coupling of (*E*)-vinyl halide with imidazole was satisfactory.

Acknowledgement

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- General experimental procedure. All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. All *E*-vinyl bromides were prepared according to the known literature.¹ All melting points are uncorrected. The NMR spectra were recorded in CDCl₃ on a 400 MHz instrument with TMS as internal standard. IR spectra were taken at KBr plates. TLC was carried out with 0.2 mm thick silica gel plates (GF254). The columns were hand packed with silica gel 60 (200–300). All reactions were carried out in an over-dried Schlenk tube equipped with a magnetic stir bar under N₂ atmosphere. Unknown compound was additionally confirmed by ¹³C NMR and Elemental analysis. An over-dried Schlenk tube was charged with Cu₂O (0.05 mmol), base (2.0 mmol, Cs₂CO₃), imidazole or benzimidazole (1 mmol). The tube was placed under vacuum for twenty minutes and backfilled with N₂. Then vinyl halide (1.5 mmol), the ligand ethyl 2-oxocyclohexanecarboxylate (0.1 mmol) and MeCN (1.5 mL) were added under N₂. The reaction mixture was stirred for 24 h at 85 °C. The resulting suspension was cooled to room temperature and filtered through a pad of filter paper with the help of 10 mL of ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography to afford the products (petroleum ether/AcOEt v/v 1/2 for the products of imidazole and v/v 1:1 for the products of benzimidazole).