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Citation	Chemical communications (2011), 47(48): 12876-12878
Issue Date	2011-11-11
URL	http://hdl.handle.net/2433/162559
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Type	Journal Article
Textversion	author

Efficient Synthesis of Biazoles by Aerobic Oxidative Homocoupling of Azoles Catalyzed by Copper(I) / 2-pyridonate Catalytic System

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A highly efficient and convenient CuCl/2-pyridonate catalytic system for oxidative homocoupling of azole affording biazole product has been developed. With this system, a variety of biazoles have been effectively synthesized in good to excellent yields in the presence of very small amount of copper catalyst (1.0 mol%). It was feasible to employ air as a green oxidant.

Synthesis of biazole compounds have attracted great attention because of their important utility as N,N-bidentate ligands in transition metal catalysts[1] and luminescent metal complexes[2] as well as their potential use in pharmaceuticals.[3]

A commonly used method for biazole synthesis is a three-component reaction of ammonium salts, glyoxal and methylation reagent.[1c,1d,2b,4] However, this method can be used only for the synthesis of some very simple biimidazoles such as 1,1'-dimethyl-1*H*,1*H*'-2,2'-biimidazole.

Transition-metal catalyzed C-C bond formation between mono-azoles by direct C-H activation, which is another feasible method for the synthesis of biazoles, have attracted great attention because of its high atom efficiency. With this viewpoint, catalytic homocoupling of azoles catalyzed by Pd[5] and other transition-metal catalysts[6] have been developed. However, the former reaction requires a stoichiometric oxidant such as pyridine N-oxide and suffers from low yields of the products, and the latter one requires a stoichiometric amount of strong base and pure dioxygen as the terminal oxidant. Quite recently, catalytic systems for the synthesis of biazoles via oxidative C-H homocoupling of unfunctionalized azoles using $Cu(OAc)_2/Ag_2CO_3$ or $Cu(OAc)_2$/air as catalysts have been reported.[7] However, relatively high catalyst loadings (10-20 mol%) were required in those systems.

Meanwhile, we have recently reported dehydrogenative oxidation of alcohols and amines catalyzed by a Cp*Ir 2-pyridonate complex,[8] disclosing that the Ir complex bearing a 2-pyridonate ligand have superior dehydrogenative ability. Consequently, we intended to extend its application to other transition-metal catalyzed reactions which include dehydrogenative processes. Here, we report a new and efficient system for biazole synthesis through aerobic oxidative C-H homocoupling of azoles catalyzed by copper(I)/2-pyridonate, in which very small amount of the copper catalyst (1.0 mol%) is required.

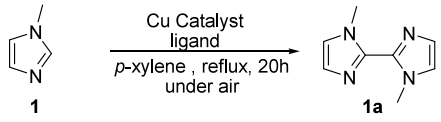
Firstly, we examined the homocoupling reaction of 1-methylimidazole (**1**) to give 1,1'-dimethyl-1*H*,1*H*'-2,2'-biimidazole (**1a**) under various conditions in order to find optimum conditions (Table 1). When the reaction of **1** was carried out in the presence of CuCl (2.0 mol%) in *p*-xylene under reflux in air for 20 hours, no formation of **1a** was observed (entry 1). Addition of sodium 2-pyridonate (**L1**) (4.0 mol%) greatly improved the catalytic activity for the homocoupling reaction, giving **1a** in 95% yield (entry 2). Effect of various copper salts on the present reaction was also investigated. Employment of other copper(I) salts (CuBr, CuI, CuOAc and $[CuOTf]_2$·toluene complex) resulted in lower yields of **1a** (entries 3-6). Addition of $Cu(OAc)_2$, which was reported to be an active catalyst for the same reaction,[7] gave only 7% yield with a low catalyst loading of 2.0 mol% (entry 7). When the reaction was carried out under Ar atmosphere, no formation of the biimidazole product was observed (entry 8), indicating that dioxygen in the air must be served as a terminal oxidant. We have also conducted the reaction in other solvents such as toluene, mesitylene, diglyme, DMF and water. However, the best result was obtained by the reaction in *p*-xylene.

Effect of the additive ligand was also examined. When sodium 3-pyridonate (**L2**) or sodium 4-pyridonate (**L3**) was used instead of sodium 2-pyridonate (**L1**), homocoupling reaction did not proceed at all (entries 9 and 10), suggesting that the copper complex bearing a 2-pyridonate ligand would act as an important catalytic species.[9] Neutral 2-hydroxypyridine (**L4**) was not a good additive ligand (entry 11). The reactions using a series of sodium 2-pyridonates having a substituent on the pyridine ring as an additive ligand were also examined (entries 12-19). As a result, sodium 2-pyridonates with electron-donating substituents (entries 13-17) showed much better activity than those with electron-withdrawing substituents (entries 18 and 19). Finally, the reaction using sodium 5-methyl-2-pyridonate (**L8**) as the additive ligand gave the best yield (entry 16).

Then, the aerobic oxidative homocoupling of various imidazoles were conducted under the optimized condition. The results are summarized in Table 2. The reaction of 1-

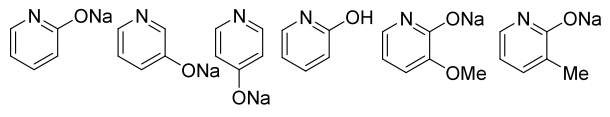
methylimidazole (**1**) under the optimized condition gave the biimidazole product **1a** in 95% yield (entry 1). Increasing the length of the carbon chain of the alkyl group at 1-position (ethyl group or n-butyl group) did not result in decrease of the yields (entries 2 and 3). The reactions of imidazoles bearing vinyl and aromatic groups also proceeded well to give the corresponding biimidazole product **4a** and **5a** in moderate yields (entries 4 and 5). However, the oxidative coupling reaction of 1-acetylimidazole (**6**) failed under the reaction condition, probably due to easy deacetylation of the substrate or acetyl-transfer reaction from the substrate to the pyridonate ligand,[10] which would disable the dehydrogenative ability of the pyridonate ligand.

Table 1. Screening of the reaction conditions on the aerobic oxidative homocoupling of 1-methylimidazole (**1**)[a]

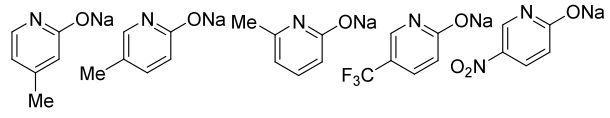


1 **1a**

Entry	Cat. (mol%)	Ligand (mol%)	Yield (%)[b]
1	CuCl (2.0)	---	0
2	CuCl (2.0)	**L1** (4.0)	95[c]
3	CuBr (2.0)	**L1** (4.0)	80
4	CuI (2.0)	**L1** (4.0)	50
5	CuOAc (2.0)	**L1** (4.0)	33
6	$[CuOTf]_2 \cdot$ toluene (1.0)	**L1** (4.0)	4
7	$Cu(OAc)_2$ (2.0)	**L1** (4.0)	7
8[d]	CuCl (2.0)	**L1** (4.0)	0
9	CuCl (2.0)	**L2** (4.0)	0
10	CuCl (2.0)	**L3** (4.0)	0
11	CuCl (2.0)	**L4** (4.0)	4
12	CuCl (1.0)	**L1** (2.0)	73
13	CuCl (1.0)	**L5** (2.0)	70
14	CuCl (1.0)	**L6** (2.0)	72
15	CuCl (1.0)	**L7** (2.0)	92
16	CuCl (1.0)	**L8** (2.0)	95[c]
17	CuCl (1.0)	**L9** (2.0)	80
18	CuCl (1.0)	**L10** (2.0)	30
19	CuCl (1.0)	**L11** (2.0)	2



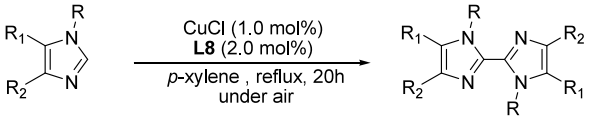
L1 **L2** **L3** **L4** **L5** **L6**



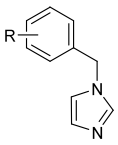
L7 **L8** **L9** **L10** **L11**

[a] The reactions in entries 1-11 were carried out with **1** (1.0 mmol), Cu-catalyst (0.02 mmol, 2.0 mol%) and additive ligand (0.04 mmol, 4.0 mol%) in *p*-xylene (4 mL) at 140 °C for 20 hours. The reactions in entries 12-19 were carried out with **1** (2.0 mmol), CuCl (0.02 mmol, 1.0 mol%) and additive ligand (0.04 mmol, 2.0 mol%) in *p*-xylene (4 mL) at 140 °C for 20 hours. [b] Determined by ^{1}H-NMR. [c] Isolated yield. [d] The reaction was carried out under Ar atmosphere in a sealed reactor.

Table 2. Cu(I)-catalyzed aerobic oxidative homocoupling reaction of various imidazoles[a]



1 - 14 **1a - 14a**

Entry	Substrates		Yield (%)[b]
1		R = methyl (**1**)	95
2		ethyl (**2**)	96
3		n-butyl (**3**)	90
4		vinyl (**4**)	63
5		4-methoxy-phenyl (**5**)	76
6		acetyl (**6**)	0
7		R = H (**7**)	92
8		4- Me (**8**)	86
9		4- CF_3 (**9**)	88
10		4-Br (**10**)	90
11		4-Cl (**11**)	90
12		3-Cl (**12**)	83
13		2-Cl (**13**)	81
14		(**14**)	85

[a] The reaction was carried out with imidazoles (2.0 mmol), CuCl (0.02 mmol, 1.0 mol%) and **L8** (0.04 mmol, 2.0 mol%) in *p*-xylene (4 mL) at 140 °C for 20 hours.[b] Isolated yield.

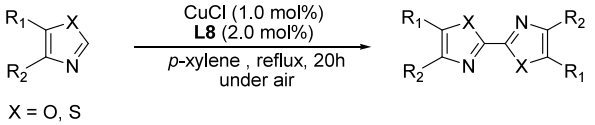
Reactions of 1-benzylimidazole derivatives were also investigated (entries 7-13). As shown in Table 2, electron-donating or electron-withdrawing substituents on the aromatic ring did not retard the coupling reactions, giving the corresponding products **7a**-**13a** in good to excellent yields. Chloro and bromo substituents were tolerant in this catalytic system, indicating the anticipation that the products can be subjected to further transformation (entries 10-13). The reaction of benzimidazole (**14**) also proceeded smoothly to give bibenzimidazole product **14a** in 85% yield (entry 14). The structure of **14a** was confirmed by X-ray analysis (See the Supporting Information).

Next, the scope of this reaction was investigated with respect to oxazoles and thiazoles under the same reaction condition as those shown in Table 3. The reactions of 4-phenyloxazole (**15**) and benzoxazole (**16**) proceeded effectively to give the corresponding bioxazole products in good to excellent yields (entries 1 and 2). The reactions of benzothiazole (**17**) and substituted thiazoles (**18**-**20**) also proceeded smoothly to give corresponding bithiazole products in excellent yields (entry 3-6). It is worth noting that the reaction of thiazole bearing an ester group at the 4-position gave the desired product **20a** in 98% yield (entry 6).

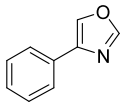
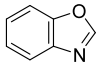
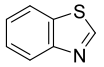
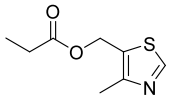
Although the mechanism for the present CuCl/2-pyridonate catalyzed aerobic oxidative homocoupling of azoles is not completely clear so far, our preliminary experiment [11] revealed that the catalytic reaction would start with the formation of a Cu(I) species **A** bearing 2-pyridonate ligand. More detailed explanation of the plausible mechanism involving the ligand-promoted C-H activation[12,13]

through probable Cu(III) species[14] is described in the Supporting Information.

Table 3. Cu(I)-catalyzed aerobic oxidative homocoupling reaction of oxazoles and thiazoles[a]



15 - 20 **15a - 20a**

Entry	Substrates		Yield (%)[b]
1		(**15**)	84
2		(**16**)	91
3		(**17**)	81
4		(**18**)	91
5		(**19**)	92
6		(**20**)	98

[a] The reaction was carried out with oxazoles or thiazoles (2.0 mmol), CuCl (0.02 mmol, 1.0 mol%) and **L8** (0.04 mmol, 2.0 mol%) in *p*-xylene (4 mL) at 140 °C for 20 hours.[b] Isolated yield.

In summary, we have developed an efficient and convenient method for biazole synthesis. With a very low catalyst loading of CuCl (1.0 mol%) and sodium 2-pyridonate ligand (2.0 mol%), a variety of biazoles were synthesized in good to excellent yields using air as a green oxidant.

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9 Reactions using sodium phenoxide, pyridine or potassium t-butoxide as the additive also resulted in no reaction.

10 An example for deacetylation of 1-acetylimidazole, see: W. Langenbeck and R. Mahrwald, *Chem. Ber.*, 1957, **90**, 2423. An example for acetyl transfer of 1-acetylimidazole, see: A. M. Shultz, O. K. Farha, J. T. Hupp and S. T. Nguyen. *J. Am. Soc. Chem.*, 2009, **131**, 4204.

11 By the stoichiometric reaction of CuCl with sodium 5-methyl-2-pyridonate (**L8**) in *p*-xylene under reflux, a copper compound **21** with compositional formula of CuC_6H_6NO (confirmed by element analysis), which was consistent with that of the supposed acitive species **A**, was isolated in 89% yield. Although the structure of **21** has not been completely elucidated so far, we speculate that **21** would be identical to the active species **A**, because catalytic homocoupling reaction of **1** using **21** as a catalyst (1.0 mol%) gave **1a** in 92% yield. For details, see the Supporting Information.

12 For Pd-catalyzed carboxylate-ligand-promoted C-H activation: (a) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.* 2006, **128**, 1066; (b) M. Lafrance, C. N. Rowley, T. K. Woo and K. Fagnou, *J. Am. Chem. Soc.* 2006, **128**, 8754; (c) D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118 and references therein.

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