ORGANIC LETTERS

2008
Vol. 10, No. 20
4565−4568

Copper-Catalyzed One-Pot Multicomponent Coupling Reaction of Phenols, Amides, and 4-Bromphenyl Iodide

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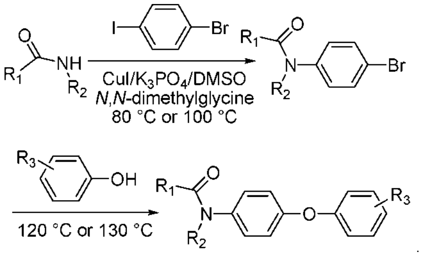
Received July 30, 2008

ABSTRACT



An efficient copper-catalyzed multicomponent reaction of phenols, amides, and 4-bromphenyl iodide was developed that uses commercially available *N*,*N*-dimethylglycine as the ligand. This multicomponent reaction proceeds in moderate to good yields for a range of phenols and amides. The simple experimental procedure and high levels of functional group compatibility make this method attractive for applications on pesticides.

Copper-catalyzed cross-coupling reactions of aryl halides with various nucleophilic compounds are now among the most prominent synthetic methods for the formation of C−N, C−O, and C−S bonds in the preparation of numerous important products in the fields of biological, pharmaceutical, and material sciences.[1] During the past few years, some exciting achievements have already appeared in this field. For instance, Buchwald[2] reported that ligands such as 1-naphthoic acid, 4,7-dimethoxy-1,10-phenanthroline, *N*,*N*-diethylsalicylamide, β-diketones, diamines, and ethylene glycol enabled the Ullmann-type arylation to be performed under milder conditions and in the presence of catalytic amounts of the copper catalyst. At the same time, other groups also reported that the Ullmann-type arylation could be performed under milder conditions by using oxime,[3] amino alcohols,[4] 8-hydroxyquinoline,[5] and 1,1,1-tris(hy-

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(1) For reviews, see:(a) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345. (b) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499. (c) *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: New York, 1998.

(2) (a) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. (b) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779–2782. (c) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190–6199. (d) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796. (e) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8472–8473. (f) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3940–3941. (g) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (h) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845. (i) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.

(3) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695–709.

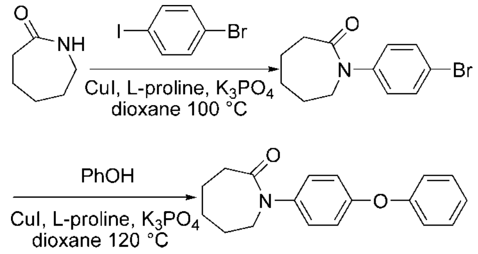
(4) Lu, Z. K.; Twieg, R. J.; Huang, S. P. D. *Tetrahedron Lett.* **2003**, *44*, 6289–6292.

10.1021/ol801730g CCC: $40.75

droxymethyl)ethane[6] as the ligands. Among these reports, Ma's work has attracted our attention. In 1998, Ma[7] reported that the structures of α- and *β*-amino acids could induce acceleration of Ullmann-type arylation which led to the coupling reaction of aryl halides with α- or *β*-amino acids at relatively low temperatures. Soon after these reports, milder Ullmann-type processes for C−N bond formation such as N-arylation of amides,[8] amines,[9] unsaturated heterocycles,[9b] and C−O bond formation such as O-arylation of phenols[10] which use amino acids as supporting ligands have been reported by Ma and co-workers. Because these copper-catalyzed coupling reactions could be carried out at a much lower temperature than the traditional copper-mediated Ullmann coupling protocols, these results represented a major advance in the development of Ullmann-type arylation methodology.

On the other hand, a multicomponent reaction plays an important role in modern organic chemistry since it exhibits generally a higher atom economy and selectivity, as well as lower costs, time, and energy. Furthermore, this methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis. Inspired by the work of Ma and colleagues on the copper-catalyzed cross-coupling reactions and endeavoring us to develop useful organic transformations taking advantage of the multicomponent reaction, we were prompted to construct an aryl C−N bond and a C−O bond in one pot via copper-catalyzed cross-coupling. Thus, a competitive experiment was undertaken (Scheme 1) in which a mixture of CuI catalyst (10 mol %), L-proline (20 mol %), caprolactam (1.2 equiv), 4-bromphenyl iodide (1.0 equiv), and K_3PO_4 (5.0 equiv) was stirred in dioxane at 100 °C for 48 h, and then phenol (1.2 equiv) was added into the mixture and stirred at 120 °C for another 48 h.

Scheme 1



The sequence of the reaction was based on that phenol exhibits higher activity than amide.[10,11] It was found that in this case not only 50% yield of the product but also *N*-(4-bromphenyl)-proline was isolated. This result clearly indicated that L-proline could couple with 4-bromphenyl iodide during the reaction, thereby reducing the activity of the catalytic system. Encouraged by this result, we examined several amino acids as the ligands. As shown in Table 1, glycine gave a similar result (entry 2), and then we employed *N*,*N*-dimethylglycine as the ligand because this amino acid is unable to process the *N*-aryl amination. As expected, *N*,*N*-dimethylglycine gave better conversion in comparison with L-proline and glycine (compare entries 1 and 3, as well as entries 2 and 3). Besides the above amino acids, other bidentate O,O and O,N ligands such as 1,2-ethanediol and 2-aminoethanol were also tested, but these ligands led to a lower catalytic activity (entries 5 and 4). Using *N*,*N*-dimethylglycine as the ligand, we changed the solvent dioxane to DMSO, DMF. To our delight, the use of DMSO gave excellent yield of the product (entry 7). Base effects were preliminarily surveyed, and K_3PO_4 was found to be effective as base; however, K_2CO_3 and Na_2CO_3 gave inferior results (entries 8 and 9). Further optimization of the reaction conditions revealed that the best ratio between CuI and *N*,*N*-dimethylglycine was 1.5:2 (compare entries 7 and 11, as well as entries 10 and 11). In addition, we evaluated the effect of reaction time. The results showed that lower yields of 1-(4-bromophenyl)azepan-2-one were observed if the time of the first reaction step was reduced to 24 or 36 h, and lower yields of product were obtained if the time of the second reaction step was shortened (entries 12 and 13).

Table 1. Coupling Reaction of Phenol, Caprolactam, and 4-Bromphenyl Iodide under the Catalysis of CuI and Ligands[a]

entry	ligand	solvent	base	yield[b] (%)
1	L-proline	dioxane	K_3PO_4	50
2	glycine	dioxane	K_3PO_4	42
3	*N*,*N*-dimethylglycine	dioxane	K_3PO_4	65
4	2-aminoethanol	dioxane	K_3PO_4	23
5	1,2-ethandiol	dioxane	K_3PO_4	34
6	*N*,*N*-dimethylglycine	DMF	K_3PO_4	55
7	*N*,*N*-dimethylglycine	DMSO	K_3PO_4	78
8	*N*,*N*-dimethylglycine	DMSO	K_2CO_3	43
9	*N*,*N*-dimethylglycine	DMSO	Na_2CO_3	41
10	*N*,*N*-dimethylglycine	DMSO	K_3PO_4	70[c]
11	*N*,*N*-dimethylglycine	DMSO	K_3PO_4	82[d]
12	*N*,*N*-dimethylglycine	DMSO	K_3PO_4	69[e]
13	*N*,*N*-dimethylglycine	DMSO	K_3PO_4	78[f]

[a] Reaction conditions: 4-bromphenyl iodide (1.0 mmol), caprolactam (1.2 mmol), CuI (0.1 mmol, 10 mol %), ligand (0.2 mmol, 20 mol %), and base (5.0 mmol) in 3 mL of solvent were stirred at 100 °C for 48 h. Then phenol (1.2 mmol) was added and stirred at 120 °C for another 48 h. [b] Isolated yield. [c] Using 10 mol % of CuI and 30 mol % of ligand. [d] Using 15 mol % of CuI and 20 mol % of ligand. [e] The time of the second reaction step: 24 h. [f] The time of the second reaction step: 36 h.

The optimized reaction conditions, CuI (15 mol %), *N*,*N*-dimethylglycine (20 mol %), and 5.0 equiv of K_3PO_4 in DMSO under nitrogen, were tested by a number of different amides and phenols. The results were summarized in Table 2. As can be seen, for most cases, the desired products were

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(5) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135–10138.

(6) Chen, Y. J.; Chen, H. H. *Org. Lett.* **2006**, *8*, 5609–5612.

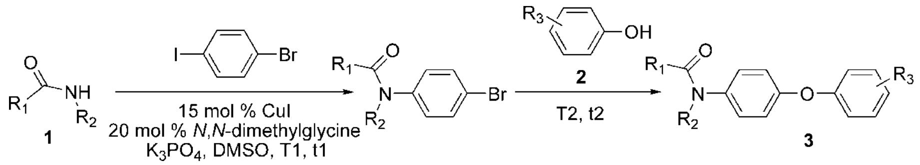
(7) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583–2586.

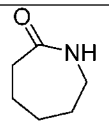
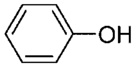
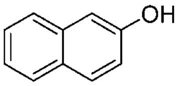
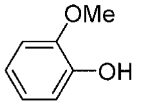
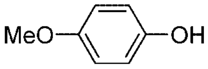
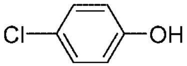
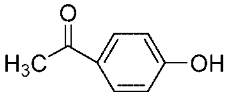
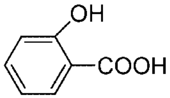
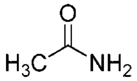
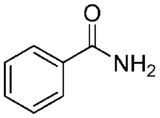
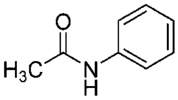
(8) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812.

(9) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.

(10) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799–3802.

Table 2. Coupling Reaction of Phenols and Amides with 4-Bromphenyl Iodide under the Catalysis of CuI and *N*,*N*-Dimethylglycine[a]



entry	amide	phenol	T1 (°C)	t1 (h)	T2 (°C)	t2 (h)	product	yield (%)[b]
1	 1a	 2a	100	48	120	48	**3a**	82[c]
2	1a	 2b	100	48	120	48	**3b**	85[c]
3	1a	 2c	100	48	120	48	**3c**	80[c]
4	1a	 2d	100	48	120	48	**3d**	87[c]
5	1a	 2e	100	48	120	48	**3e**	75[c]
6	1a	 2f	100	48	130	48	**3f**	45[c,e]
7	1a	 2g	100	48	130	48	No product	0[c,d,e]
8	 1b	2a	80	24	120	48	**3g**	65
9	1b	2b	80	24	120	48	**3h**	66
10	1b	2c	80	24	120	48	**3i**	65
11	1b	2d	80	24	120	48	**3j**	70
12	1b	2e	80	24	120	48	**3k**	60
13	 1c	2a	80	24	120	48	**3l**	60 (73[e])
14	1c	2b	80	24	130	48	**3m**	77[e]
15	1c	2c	80	24	130	48	**3n**	75[e]
16	1c	2d	80	24	130	48	**3o**	81[e]
17	1c	2e	80	24	130	48	**3p**	70[e]
18	 1d	2a	80	24	120	24	**3q**	71[f]
19	1d	2b	80	24	120	24	**3r**	77[f]
20	1d	2c	80	24	120	24	**3s**	80[f]
21	1d	2d	80	24	120	24	**3t**	81[f]
22	1d	2e	80	24	120	24	**3u**	70[f]

[a] Reaction conditions: 4-bromphenyl iodide (1.0 mmol), amide (1.2 mmol), CuI (0.15 mmol), *N*,*N*-dimethylglycine (0.2 mmol), and K_3PO_4 (5.0 mmol) in 3 mL of DMSO were stirred at 80 °C for the indicated time. Then phenol (1.2 mmol) was added and stirred at 120 °C for the indicated time. [b] Isolated yield. [c] The first step was carried out at 100 °C. [d] No product was determined. [e] The second step was carried out at 130 °C. [f] Using 2.5 mmol of K_3PO_4.

readily obtained in moderate to good yields. Functional groups such as methoxy, chloro, and keto were found to be compatible in these reaction conditions (Table 2, entries 3−6). Caprolactam, acetamide, benzamide, and acetanilide were suitable substrates, while with acetamide, benzamide, and acetanilide the temperature of the first step could be reduced to 80 °C and the reaction time could be reduced to 24 h (entries 8−22). Benzamide gave only moderate yields under the action of the second step at 120 °C (entry 13), while good yields were obtained by carrying out the second step at higher temperature to overcome their lack of reactivity (entries 13−17). The reaction of acetanilide was inefficient in the condition using 5.0 equiv of K_3PO_4, but it also could be more efficient in the condition by using 2.5 equiv of K_3PO_4 and the reaction time of the second step could be reduced to 24 h (entries 18−22).

For phenols, electron-neutral, -rich, (entries 1, 3, and 4), and -deficient (entry 5) substrates were efficiently transformed to the desired products in good yields. Naphthalene-2-ol also worked well. It is noteworthy that the hindered 2-methoxyphenol gave a slightly lower yield in comparison with that of less-hindered phenol (compare entries 3 and 4). On the contrary, substrates bearing strong electron-withdrawing groups behaved poorly. For example, 4′-hydroxyacetophenone delivered a lower yield (entry 6), and 2-hydroxybenzoic acid even yielded no coupling product at all (entry 7). This phenomenon may be due to the lower activity of the substrates or their related byproducts formed during the coupling reaction. These poor results are however quite general in the literature.[10,12] All previous unknown compounds were fully identified by their ^1H NMR, ^{13}C NMR, IR, and HRMS spectra. Moreover, the structure of **3s** (entry 20) was unambiguously confirmed by X-ray diffraction analysis (Figure 1).[13]

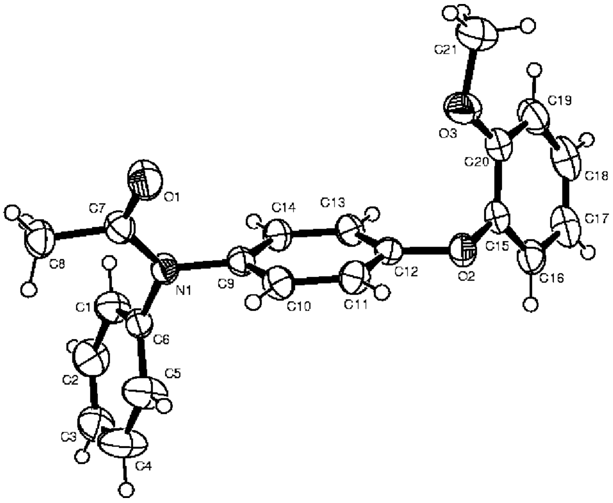


Figure 1. ORTEP diagram of the single-crystal X-ray structure of compound **3s**.

In summary, a facile, economic, and green protocol for a one-pot multicomponent coupling reaction of phenols, amides, and 4-bromphenyl iodide has been described. The catalyst is easily formed in situ by combining air-stable CuI with *N*,*N*-dimethylglycine. With the exception of phenols bearing strong electron-withdrawing groups, the catalyst allows for a number of substrates to be transformed into the desired products in moderate to good yields. A simple experimental procedure, satisfactory atom economy, and tolerance with diverse functional groups make the present methodology very attractive. The application of this method to the synthesis of pesticides is in progress.

Acknowledgment. The authors are grateful to the Natural Science Foundation of Sichuan Province (Grant 2006J13−002−2) and the Scientific Research Fund of Sichuan Provincial Education Department (Grant 2006A070) for financial support.

Supporting Information Available: Detailed experimental procedures and characterization data for the reaction products, as well as X-ray crystallographic data for **3s** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Deng, W.; Wang, Y. F.; Zou, Y.; Liu, L.; Guo, Q. X. *Tetrahedron. Lett.* **2004**, *45*, 2311–2315.

(12) (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623–1626. (b) Quali, A.; Spindler, J. F.; Cristau, H. J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499–505.

(13) Crystallographic data (including structure factors) for compound **3s** (CCDC694124) reported in this paper have been deposited with the Cambridge Crystallographic Data Center. See Supporting Information for details.