

Microwave-Promoted Three-Component Coupling of Aldehyde, Alkyne, and Amine via C–H Activation Catalyzed by Copper in Water

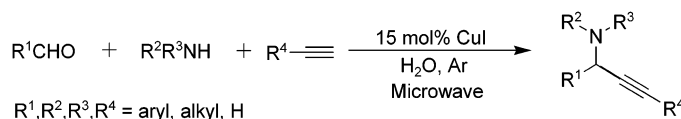
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Received January 12, 2004

ABSTRACT



An efficient three-component coupling of aldehyde, alkyne, and amine to generate propargylamines has been effected under microwave irradiation in water using only CuI catalyst without the noble metal cocatalyst. This method has proved to be applicable to a wide range of substrates. In addition, the preliminary experiment using (S)-proline methyl ester as a chiral source demonstrated that it could be developed to be a direct and highly diastereoselective method for construction of chiral propargylamines.

Microwave (MW)-promoted reactions, especially those run in water, have been attracting increasing research interest from chemists in recent years, not only because these reactions exhibit some particular or unexpected reactivities in some cases but also because they are significantly useful for green chemistry.¹ In our corresponding investigations, we have reported a MW-promoted coupling reaction of two components (aromatic halide and amine).² As a continued interest, we recently have developed another MW-promoted procedure in a water system of three-component coupling of aldehyde, alkyne, and amine (A³ coupling).³ We chose this reaction because it produces important propargylamines,^{3–5} which are major skeletons⁶ or synthetically versatile and key

intermediates⁷ for preparation of many biologically active nitrogen compounds such as conformationally restricted peptide isosteres, oxotremorine analogues, and β -lactams. Although several methods for construction of such units in water were reported,³ some required expensive Au^{3c} or Ag^{3d} as catalyst, while some were limited to only one kind of aldehyde (the aromatic^{3c} or aliphatic^{3d}) or the aromatic

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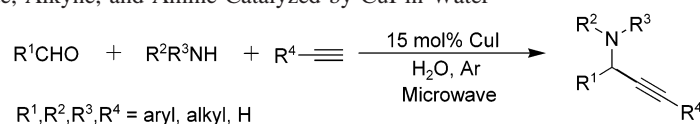
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Table 1. Coupling of Aldehyde, Alkyne, and Amine Catalyzed by CuI in Water^a

entry	R ¹	amine (R ² , R ³)	R ⁴	product	time (min)	yield (%) ^b
1	Ph	morpholine	Ph	1a	20	90
2	2-FC ₆ H ₄	morpholine	Ph	1b	20	89
3	2-ClC ₆ H ₄	morpholine	Ph	1c	20	88
4	3-ClC ₆ H ₄	morpholine	Ph	1d	20	90
5	4-ClC ₆ H ₄	morpholine	Ph	1e	20	91
6	4-BrC ₆ H ₄	morpholine	Ph	1f	20	90
7	4-MeC ₆ H ₄	morpholine	Ph	1g	30	82
8	4-MeOC ₆ H ₄	morpholine	Ph	1h	30	85
9	4-NO ₂ C ₆ H ₄	morpholine	Ph	1i	5	41
10	2-furyl	morpholine	Ph	1j	20	86
11	1-naphthyl	morpholine	Ph	1k	20	88
12	cyclohexyl	morpholine	Ph	1l	20	90
13	<i>n</i> -C ₃ H ₇	morpholine	Ph	1m	20	78
14	Ph	pyrrolidine	Ph	2a	10	93
15	Ph	piperidine	Ph	2b	20	91
16	Ph	R ² = R ³ = Et	Ph	2c	20	90
17	Ph	R ² = R ³ = (Me) ₂ CH	Ph	2d	20	83
18	Ph	R ² = R ³ = <i>c</i> -C ₆ H ₁₁	Ph	2e	20	75
19	Ph	R ² = R ³ = Ph	Ph	2f	10	0 ^c
20	Ph	R ² = Bn, R ³ = Me	Ph	2g	20	83
21	Ph	R ² = Ph, R ³ = H	Ph	2h	10	85
22	Ph	R ² = (Me) ₃ C, R ³ = H	Ph	2i	10	76
23	Ph	morpholine	<i>n</i> -C ₅ H ₁₁	3a	20	83
24	Ph	morpholine	TMS	3b	20	80 ^d
25	Ph	morpholine	CH ₂ OTBS	3c	20	86

^a For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. ^b Isolated yields based on the aldehyde. ^c No desired product was obtained. ^d Under solvent-free conditions.

aldehyde and primary amine in the presence of RuCl₃ cocatalyst;⁸ all of these reactions often proceeded slowly in water. In comparison to the methods above, our recently developed method showed particular advantages: (i) it required only the cheaper CuI as catalyst without Au, Ag, or other additives; (ii) it was applicable to a broader substrate scope (both aromatic and aliphatic aldehydes and secondary amines); and (iii) it proceeded faster and gave good to high yield, and its experimental process was simple and easy. In this paper, we present our experimental results.

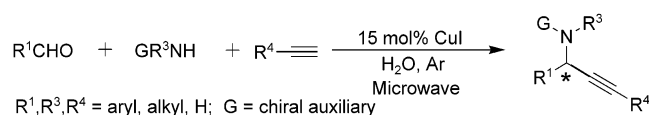
The MW-promoted A³ coupling experiment was performed (for the general procedure, see Supporting Information) by irradiation of the three-component/H₂O system in the presence of 15 mol % CuI (it is necessary to freshly prepare CuI rather than using commercial CuI) in a sealed tube to afford the desired propargylamines within 30 min in good to excellent yields. The results are listed in Table 1. In each example we isolated mostly the propargylamine products, together with a small amount of oligomerization of the excessive alkynes in some cases (entries 1–8, 10–18, and

20–22). Additionally, a sealed tube was necessary for this reaction; otherwise, a low conversion and more byproducts were obtained.

At the beginning of the search for the aldehyde substrate scope, morpholine and phenylacetylene were used as model substrates (entries 1–13), and the results indicated that aromatic aldehydes bearing such functional groups as fluoro, chloro, bromo, methyl, or methoxy were able to effect the A³ coupling. We have also observed delicate electronic effects:³ that is, aryl aldehydes with electron-withdrawing groups (entries 2–6) reacted rapidly, while substitution of electron-rich groups (entries 7 and 8) on the benzene ring decreased the reactivity, requiring longer reaction times. Moreover, a very low yield for 4-nitrobenzaldehyde (entry 9), the substrate with a strong electron-withdrawing group, was observed because of the low conversion. When the reaction time was prolonged, a complicated mixture (not identified) was obtained. In addition, the 2-furaldehyde (entry 10) and 1-naphthaldehyde (entry 11) also gave good yields (86 and 88%, respectively) of products. On the other hand, the aliphatic aldehydes (entries 12 and 13) still displayed high reactivity and clean reactions under this standard condition. While unwanted trimerization of aliphatic alde-

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Table 2. Diastereoselective A³ Coupling Induced with Chiral Amine Substrate^a



entry	R ¹	amine (G, R ³)	R ⁴	product	dr ^b	yield (%) ^c
1	Ph	(S)-proline methyl ester	Ph	4a	95:5	88
2	Ph	G = (S)-Ph(CH ₃)CH, R ³ = H	Ph	4b	67:33	83
3	Ph	G = (S)-Ph(CH ₃)CH, R ³ = Bn	Ph	4c	67:33	81

^a For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. ^b Diastereomeric ratio (dr) was determined by ¹H NMR; the absolute configuration has been not determined. ^c Isolated yields based on the aldehyde.

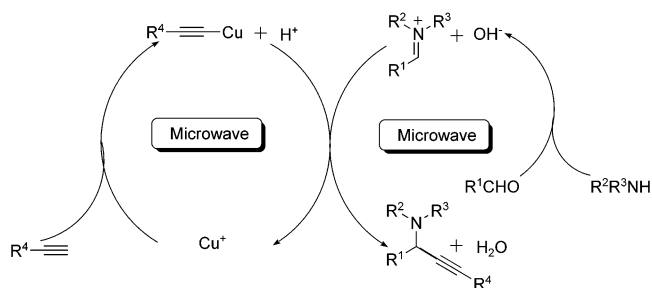
hydrides was a major limitation of the A³ coupling catalyzed by Au and Cu in water,³ no trimer could be isolated in our experiments of entries 12 and 13.

To expand the scope of amine substrates, we used benzaldehyde and phenylacetylene as model substrates and examined various amines, including primary or secondary amines (entries 14–22). The coupling (except for entry 19) proceeded smoothly to afford the corresponding propargylamines in good yields under standard conditions. It was important to notice that N-substitution on amines could affect this reaction. Whereas dialkylamines reacted smoothly under these conditions, the bulky amines (entries 16–19) would lead to the lower yields of products. Particularly, when the two substituents were phenyls (entry 19), no expected product was observed.

Subsequently, a variety of other alkynes were also examined for the coupling using benzaldehyde and morpholine as model substrates (entries 23–25). In these cases, the reactions proceeded smoothly to give the corresponding propargylamines in a yield of 80–86%. It is worthwhile noting that this reaction under solvent-free conditions afforded a higher yield than that in water in entry 24, which may be due to the destabilization of TMS in microwave-assisted water.

Considering that chiral propargylamines are widely present in many important bioactive compounds, we subsequently tried to investigate a novel substrate-controlled asymmetric MW-promoted A³ coupling in water using the same method as above. Therefore, three chiral amines sources, (S)-proline methyl ester, (S)-α-methylbenzylamine, and (S)-N-benzyl-1-phenylethylamine, were selected for examination using benzaldehyde and phenylacetylene as model substrates, and the results are summarized in Table 2. It was interesting to note that (S)-proline methyl ester exhibited high diastereoselectivity (95:5). This preliminary result implied that it was possible for the highly diastereoselective A³ coupling to be achieved for additional substrates. It is also useful that the chiral imines in our experiment were not necessarily pre-made⁹ but simply derived in situ from aldehydes and amines.

Scheme 1



To examine the reaction process of the MW-promoted A³ coupling, further investigations were performed. Without MW irradiation, the A³ coupling under heating required more than 5 days. In a stepwise experiment, the two-component coupling of phenylacetylene and the pre-made imine in the presence of 15 mol % CuI took one more day under conventional heating condition. These reactions proceeded very slowly, and only low conversions and yields were achieved. These facts indicated that MW irradiation was very necessary for speeding up both the A³ coupling and the separate formation of alkynylcopper¹⁰ and imine.¹¹ On the basis of the above experimental results, together with some literature reports,³ a tentative mechanism was proposed as shown in Scheme 1. The MW irradiation first promoted CuI-catalyzed activation of the C–H bond of alkyne to give the copper acetylide as well as the formation of iminium ion. Then, the copper acetylide intermediate added to iminium ion to give the final propargylamine, with the Cu(I) catalyst being released for further cycle of reactions.

In summary, we have successfully developed a facile, economic, and green method for construction of propargylamines. In particular, the information that (S)-proline methyl ester could induce the high diastereoselectivity suggested that a general and useful method to the optically active propargylamines could be established. Investigations of the scope, absolute stereochemistry, and synthetic applications of this chiral reaction are now in progress in our laboratories.

Acknowledgment. We are grateful for the financial support of the NSFC (No. 29925205, 30271488, 20021001, and 203900501).

Supporting Information Available: Experimental details and data on the A³ coupling reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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