Full Paper

Applied
Organometallic
Chemistry

Received: 22 June 2010 Revised: 9 July 2010 Accepted: 10 July 2010

(wileyonlinelibrary.com) DOI 10.1002/aoc.1707

Copper-catalyzed one-pot synthesis of propargylamines via C–H activation in PEG

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An efficient and convenient three-component A^3 coupling reaction of aldehyde, amine and alkyne via C–H activation with CuI alone as the catalyst in PEG is developed, providing a wide range of propargylamines with yields ranging from moderate to excellent. Additionally, the catalyst system was recovered and reused several times without evident loss in activity. Copyright © 2010 John Wiley & Sons, Ltd.

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Keywords: three-component A^3 coupling; propargylamine; C–H activation; CuI; PEG

Introduction

Propargylamines are versatile building blocks for organic synthesis and are generally used as precursors for the synthesis of *N*-containing heterocyclic compounds such as quinolines,[1] pyrroles,[2] pyrrolidines,[3] indolizines[4] and oxazoles,[5] and as well as key intermediates for the synthesis of natural product.[6–9] Traditionally, similar to the addition of carbanions to the carbonyl group of aldehydes and ketones, the addition of organometallic reagents such as lithium acetylides or Grignard reagents to the C EQBOND N bonds of imines or their derivatives is an important and efficient process to afford propargylamine derivatives.[10–12] However, these reagents must be used in stoichiometric amounts, are highly moisture sensitive, and require harsh reaction conditions. An alternative atom-economical approach to their synthesis is to perform this type of reaction by coupling of aldehydes, amines and alkynes (A^3 coupling) via C–H activation, where water is the only theoretical by-product.[13–17] Recent progress in this area has been reported in order to expand the scope of this A^3 coupling using homogeneous catalysts and heterogenous catalysts.[18–32] However, it is a considerable drawback that an expensive metal catalyst (silver, gold, iridium and indium, etc.) is often lost at the end of the reaction. Hence, a process for recycling the catalyst system is of importance. To achieve the recyclability of the metal catalyst, Li[33] and Alper[34] used room-temperature ionic liquid-immobilized catalysts. However, ionic liquids, especially imidazolium-based systems containing BF_4 or PF_6 anions, are toxic in nature because they liberate hazardous HF, and their high cost and disposability make their utility limited.[35] Recently, Yun and co-workers also reviewed the environmental fate and toxicity of ionic liquids.[36] However, many of these methodologies are associated with one or more disadvantages such as prolonged reaction time, unsatisfactory yield, harsh reaction conditions, use of hazardous organic solvents and excess costly reagents.

In recent years, PEG has become prominent as an alternative green reaction media with unique properties such as thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents and recyclability in synthetic chemistry. In general, PEG is non-toxic, being used in food products and cosmetics, is potentially recyclable and is water-miscible, which facilitates its removal from reaction products.[37–39] On the other hand, PEG is inexpensive, completely non-halogenated and easily degradable. The use of PEG as a reaction solvent has received considerable attention in synthetic organic chemistry. Its potential as reaction media and promoter for organic reactions has attracted the attention of organic chemists in recent years.[40–44] However, it is surprising that the A^3 coupling reaction in PEG is still unexplored so far.

Recent studies in our group have focused on metal-catalyzed organic reactions,[45–54] and herein we report an efficient recyclable one-pot synthesis of propargylamines via C–H activation catalyzed by CuI in PEG.

Results and Discussion

The model reaction of benzaldehyde (**1a**), morpholine (**2a**) and phenylacetylene (**3a**) was conducted to screen the optimal reaction conditions and the results are listed in Table 1. Initially, we examined a series of copper salts such as CuCl, Cu_2O, CuBr, $CuSO_4$, $CuCl_2$, $Cu(OAc)_2 \cdot H_2O$ and CuI (Table 1, entries 1–7). The three-component coupling reaction proceeded smoothly and generated the desired product 4-(1,3-diphenylprop-2-ynyl)morpholine (**4a**) in 92% yield, representing one of the best results when 10 mol% of CuI was used as catalyst without any cocatalyst or activator than other copper salts tested [such as CuCl (87%), Cu_2O (40%), CuBr (88%), $CuSO_4$ (53%), $CuCl_2$ (64%), $Cu(OAc)_2 \cdot H_2O$ (42%)] in PEG under nitrogen atmosphere (Table 1, entry 7). In contrast, only

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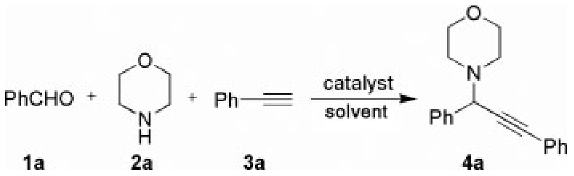
Table 1. Conditions screening[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	CuCl	PEG-400	87
2	Cu_2O	PEG-400	40
3	CuBr	PEG-400	88
4	$CuSO_4$	PEG-400	53
5	$CuCl_2$	PEG-400	64
6	$Cu(OAc)_2 \cdot H_2O$	PEG-400	42
7	CuI	PEG-400	92
8	CuI	[Bmim]PF_6	81
9	CuI	H_2O	27
10	CuI	THF	38
11	CuI	CH_3CN	42
12	–	PEG-400	No reaction

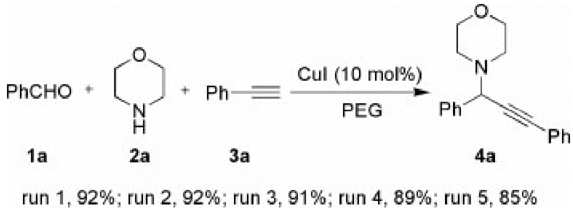
[a] All reactions were run with benzaldehyde **1a** (1 mmol), morpholine **2a** (1.2 mmol), phenylacetylene **3a** (1.5 mmol) and catalyst (10 mol%) in 1 ml of solvent at 100 °C for 12 h under N_2 atmosphere.
[b] Isolated yields.

a trace of **4a** was obtained in the absence of CuI (Table 1, entry 8). On the other hand, the effect of solvents was tested. Among all the solvents screened (H_2O, THF, CH_3CN, PEG and ionic liquid [Bmim]PF_6), PEG was determined to be the most effective medium for the generation the desired product (Table 1, entries 8–12).

With the optimal conditions in hand, we chose a variety of diverse aldehydes, amines and alkynes possessing the of functional groups to understand the scope and generality of copper-catalyzed A^3 coupling reaction in PEG and the results are summarized in Table 2.

As shown in Table 2, aromatic aldehydes bearing either electron-donating or electron-withdrawing groups on the aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield under the optimal conditions. Various aldehydes **1a**–**1h** reacted effectively with morpholine and phenyl acetylene to produce the corresponding propargylic amines in good yields (Table 2, entries 1–8). It should be noted that the products of **4e** and **4f** had the bromo group untouched (Table 2, entries 5 and 6). Similarly, aromatic heterocyclic aldehydes such as furan-2-carboxaldehyde (**1i**) and thiophene-2-carboxaldehyde (**1j**) were also equally effective for this conversion and the desired products of**4i** and **4j** were obtained in 87 and 85% yields, respectively (Table 2, entries 9 and 10). Reactions involving aliphatic aldehydes such as *n*-butyl aldehyde (**1k**) gave higher yields (Table 2, entry 11). While unwanted trimerization of aliphatic aldehydes is a major limitation of the A^3 coupling reactions catalyzed by homogeneous catalysts,[18–34] almost no trimer could be detected with aliphatic aldehydes when using CuI as the catalyst in PEG.

On the other hand, several terminal alkynes were examined for the coupling using benzaldehyde and morpholine as the model substrates. Alkynes with electron-donating groups on the aromatic ring such as 1-ethynyl-4-methylbenzene (**3b**) and 1-ethynyl-4-methoxybenzene (**3c**) gave good yields (Table 2, entries 12 and 13).



Scheme 1. Reuse of the catalyst.

Furthermore, this method was also successful with various amines such as piperidine and pyrrolidine to afford the corresponding propargylamines **4n** and **4o** in good yields under standard conditions (Table 2, entries 14 and 15). In all cases, no propargylic alcohol (an adduct between the aldehyde and alkyne) was obtained under similar reaction conditions, which might be attributed to a rapid formation of the carbon–nitrogen bond from aldehydes and amines.

Finally, we investigated the recycling of PEG in a subsequent reaction, for example, the synthesis of **4a** from the reaction of benzaldehyde, morpholine and phenylacetylene (Scheme 1). The remaining PEG containing CuI could be recycled and reused for five runs without noticeably decreasing the productivity. In the next run there was no need for further additions of copper salt.

Conclusion

In summary, we have developed a copper-catalyzed method for the one-pot synthesis of propargylamines by three-component A^3 coupling reaction of aldehyde, amine and alkyne via C–H activation in good yields in the presence of CuI in PEG under nitrogen atmosphere. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

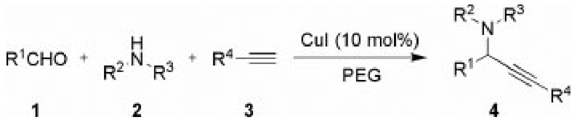
Experimental

All chemicals were either purchased or purified by standard techniques without special mention. IR spectra were recorded on a Bruker-EQUINOX55 spectrometer. The products were identified by NMR on a Bruker-300 spectrometer or a Bruker-500 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Elemental analysis was determined on a Carlo-Erba 1108 instrument. All reactions were conducted using standard Schlenk techniques. Column chromatography was performed using EM Silica gel 60 (300–400 mesh). For analytical data and spectra (^1H and ^{13}C NMR) of all compounds see Supporting Information.

General Synthetic Procedure for One-pot Synthesis of Propargylamines

A mixture of CuI (0.05 mmol), aldehyde (0.5 mmol), amine (0.6 mmol), alkyne (0.75 mmol) and PEG-400 (1 ml) was stirred for 12 h at 100 °C under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate (20 ml), washed with water (20 ml) and the aqueous layer was then extracted with ethyl acetate (3 × 10 ml). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. Further purification was carried out by column chromatography on silica gel eluting with ethyl acetate–petroleum ether. After extraction with ethyl acetate, the catalyst in the aqueous phase was

Table 2. Copper-catalyzed one-pot synthesis of propargylamine derivatives[a]



Entry	R^1	Amine	R^4	Product	Yield (%)[b]
1	Ph (**1a**)	Morpholine (**2a**)	Ph (**3a**)	**4a**	92
2	4-FC_6H_4 (**1b**)	**2a**	**3a**	**4b**	88
3	4-ClC_6H_4 (**1c**)	**2a**	**3a**	**4c**	91
4	$2,4\text{-Cl}_2C_6H_3$ (**1d**)	**2a**	**3a**	**4d**	87
5	4-BrC_6H_4 (**1e**)	**2a**	**3a**	**4e**	91
6	2-BrC_6H_4 (**1f**)	**2a**	**3a**	**4f**	88
7	4-MeC_6H_4 (**1g**)	**2a**	**3a**	**4g**	87
8	4-MeOC_6H_4 (**1h**)	**2a**	**3a**	**4h**	86
9	2-furyl (**1i**)	**2a**	**3a**	**4i**	87
10	2-thienyl (**1j**)	**2a**	**3a**	**4j**	85
11	$CH_3CH_2CH_2$ (**1k**)	**2a**	**3a**	**4k**	96
12	**1a**	**2a**	4-MeC_6H_4 (**3b**)	**4l**	85
13	**1a**	**2a**	4-MeOC_6H_4 (**3c**)	**4m**	88
14	**1a**	Pyrrolidine (**2b**)	**3a**	**4n**	91
15	**1a**	Piperidine (**2e**)	**3a**	**4o**	94

[a] All reactions were run with aldehyde **1** (1 mmol), amine **2** (1.2 mmol), alkyne **3** (1.5 mmol) and CuI (10 mol%) in PEG-400 (1 ml), 100 °C for 12 h under N_2 atmosphere.
[b] Isolated yields.

concentrated in oven at 130 °C for 6 h and the solution of the recovered CuI and PEG-400 could be reused in the next batch reaction.

Analytical Data of New Compound

*4-(3-(4-Methoxyphenyl)-1-phenylprop-2-ynyl)morpholine (**4m**)*

IR (KBr): 2954, 2851, 16.05, 1508, 1450, 1290, 1245, 1171, 1114, 1071, 1030, 1001, 970, 864, 830, 805, 747, 713, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 7.64–7.61 (m, 2H, Ar–H), 7.46–7.43 (m, 2H, Ar–H), 7.37–7.32 (m, 3H, Ar–H), 6.87–6.84 (m, 2H, Ar–H), 4.77 (s, 1H, -CH-), 3.82 (s, 3H, $-OCH_3$), 3.75–3.72 (m, 4H, $-CH_2OCH_2-$), 2.64–2.61 (m, 4H, $-CH_2NCH_2-$); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 159.5, 137.9, 133.2, 128.6, 128.2, 127.7, 115.0, 113.9 (carbon atoms in benzene ring), 88.3, 83.5 (acetylenic carbon atoms), 67.1 (-C–O–C-), 62.0 (-O–C-), 55.3 (-C–N-), 49.8 (-C–N–C-); anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89. Found: C, 78.38; H, 6.72.

Acknowledgments

We are grateful for financial support from the National Key Technology R&D Program (no. 2007BAI34B00), the Natural Science Foundation of Zhejiang Province (no. Y4080107) and the Wenzhou Science and Technology Bureau Program (no. G20090079).

Supporting information

Supporting information may be found in the online version of this article.

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