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Highly efficient and scale-up synthesis of propargylamines catalyzed by graphene oxide-supported CuCl₂ catalyst under microwave condition

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Abstract:

An efficient, green and practical approach was developed to synthesize propargylamines using recyclable GO-CuCl₂ *via* a one-pot multicomponent aldehyde-alkyne-amine (A^3) coupling reaction. The propargylamines are readily obtained in good to excellent yields (85-96%) and on multi-gram scale (88%, 150 mmol) under microwave irradiation. GO-CuCl₂ could be easily recovered through filtration and reused at least five recycles with no significant decreases in the yields. **Keywords:** Propargylamines, A^3 -coupling, GO-CuCl₂, Green chemistry

1. Introduction

Propargylamines not only are important structural elements in natural products and pharmaceutical preparations, but also are versatile synthetic intermediates, which have attracted increasing academic attention [1]. Because of the potent usefulness of propargylamines, several synthetic methods have been developed to synthesize them. Traditionally, the reaction of lithium acetylides or Grignard reagents with imines or their derivatives is applied for the synthesis of propargylamines [2]. However, the use

of stoichiometric amounts of organometallic reagents, and strictly controlled reaction conditions are required. The protecting groups are also needed because of the instability of aldehydes. Thus, the development of the environmentally benign and cost-efficient protocols has been demanded. Recently, the synthesis of propargylamines has been successfully carried out using an atom-economic approach of one-pot three-component A^3 -coupling [3], where water is merely theoretical by-products.

Firstly, homogeneous catalysts such as Zn salts [4], Cu salts [5], Fe salts [6], Ag salts [7], Au salts [8], and etc. are applied for the reaction. Unfortunately, the homogenous catalysts suffer from drawbacks such as the loss of the precious or hazardous catalysts at the end of the reaction. In order to overcome these drawbacks, heterogeneous catalysts have been widely investigated for A³-coupling reaction due to their thermal stability, reusability and high catalytic activities.

Subsequently, a number of methods have been developed to immobilize metal salts on various solid supports, such as zeolite [9], organosilica [10], polymers [11,12] and so on [13-18]. However, most of them have certain drawbacks, such as long reaction time, complex catalyst preparation processes and involvement of expensive reagents. So, most of the above mentioned approaches may cause economic and environmental concerns when large-scale synthesis of propargylamines is considered.

Different from the above solid supports, graphene oxide (GO) has been demonstrated as a promising material for heterogeneous catalysts because of high chemically stability and good accessibility. Furthermore, the abundance of functional

groups on its basal planes and edges of GO is also a key factor for the further chemical mdification [19].

Microwave (MW) technology has gained widespread popularity in organic synthesis, mainly due to its obvious reductions in reaction time and significant enhancements in conversions [20, 21]. It was shown that MW irradiation was very necessary for speeding up synthesis of propargylamines [22-28]. As a part of our continuing interest in the further improvement the practicability and efficiency of MW technology [29-31], herein we report an efficient and green strategy for scale-up synthesis of propargylamines, which catalyzed by GO-CuCl₂ under MW irradiation. GO-CuCl₂ could be separated conveniently and reused at least five times without a significant drop in the yields. The propargylamines can be prepared in 88% yield and on multi-gram scale (150.0 mmol).

[Insert Scheme 1]

2. Experimental section

2.1 Preparation of GO-CuCl₂

GO (0.25 g) was dispersed in toluene (40.0 mL) by sonication for an hour to obtain a light brown dispersion and 3-aminopropyltriethoxysilane (APTS) (1.32 g) was added when the solution was heated to 90 °C. The mixture was stirred overnight at this temperature. Finally, the GO-APTS was filtered, washed with ethanol, and dried under vacuum at 40 °C. GO–APTS (0.2 g) was dispersed in *N*, *N*-dimethylformamide (DMF) (40.0 mL) by sonication for an hour and then CuCl₂ (0.05 g) was added. It was stirred at room temperature for 6 hours. The GO–CuCl₂ catalyst was separated

through filtration, washed with deionized water and ethanol followed by drying under vacuum at 40 $^{\circ}$ C overnight for further use.

2.2 A³-Coupling Reaction

GO-CuCl₂ was added to a reaction mixture of aldehyde, alkyne and amine. The combined mixture was refluxed under microwave irradiation. After complete conversion of the aldehyde, let the mixture cool to room temperature and the mixture was filtered, extracted by EtOAc and dried. After the evaporation of the solvent, the crude product was obtained. Purification was performed by flash column chromatography to afford propargylamines in good to excellent yields.

3. Results and discussion

3.1 Catalyst characterization

FTIR spectra of GO, GO-APTS and GO-CuCl₂ are shown in Fig. S1. For GO, the peaks at 3417 and 1722 cm⁻¹ were attributed to the stretching mode of OH and the asymmetric stretching mode of C=O, respectively. For GO-APTS, new peaks at 2923 and 2854 cm⁻¹ were assigned to the asymmetric and symmetric stretching modes of C–H in APTS. The sharp peak at 1384 cm⁻¹ was characteristic stretching band of the C–O–C [32]. The peaks at 1118 and 1037 cm⁻¹ were characteristic bands of the Si–O–Si, indicating that the surface of GO was successfully modified with APTS. After complexation with CuCl₂, the peaks at 1643, 1118 and 1037 cm⁻¹ were shifted to 1631, 1116 and 1041 cm⁻¹, respectively. This is probably caused by the coordination effect of CuCl₂ with the monodentate and bidentate ligands APTS.

The copper contents of GO-CuCl₂ and the reused catalyst after five recycling were found to be 11.28 and 9.25 wt% by AAS, respectively (Table 1). It can be further confirmed that the copper contents of catalyst is not evidently decrease by the following tests.

[Insert Table 1]

The typical TEM images of GO and GO-CuCl₂ were shown in Fig. 1A and 1B, respectively. As can be seen from Fig. 1A, TEM image of the GO exhibited the ordered stacking of multilayer. From Fig. 1B, the TEM image of GO-CuCl₂ confirmed that the silanization and the complexation between CuCl₂ and the amino groups of APTS caused no significant damage to the GO sheet structure. From Fig. 1B, we can also see that CuCl₂ species are well dispersed on the surface of amine modified GO. The results indicated that amine groups on the surface of GO played an important role to improve the dispersibility of CuCl₂ and the nano-sized organic-inorganic hybrid material was obtained.

The typical SEM images of GO-CuCl₂ and the recycled catalyst after 5 consecutive trials were shown in Fig. S2. The surface morphology of the recycled catalyst did not show any significant change even after 5 reaction cycles. Energy dispersive X-ray spectroscopy (EDS) mapping images showed that CuCl₂ were dispersed uniformly onto GO sheet by the complexation (Fig. 2a). However, the copper content of GO-CuCl₂ after five recycling is a slight decrease compared with the fresh catalyst (Fig. 2b), which showed GO-CuCl₂ has good stability during the A³-coupling reaction.

[Insert Figure 1]

[Insert Figure 2]

XRD patterns are showed in Fig. S3. GO shows a sharp peak at 10.9° , corresponding to the (001) reflection. In GO-APTS, the intensity of the peak at 10.9° significantly decreased, and an obvious peak at $20=21.4^{\circ}$ appeared, indicating that APTS was conjugated onto the surface of GO. GO-CuCl₂ showed the characteristic reflections for CuCl₂ at $20=14.7^{\circ}$, 21.4° and 33.2° corresponding to the planes (110), (020) and (201) of cubic CuCl₂ crystal, respectively. The results showed GO–CuCl₂ had been prepared successfully.

TGA curves are showed in Fig. 3. GO was thermally unstable and the whole weight loss of GO is ca. 63% at 210°C, which is presumably due to the removal of adsorbed water and pyrolysis of the thermally unstable oxygen-containing groups. For GO-CuCl₂, a better thermal stability than GO, a much slower and lower mass loss was observed, which might be assigned to the decreased decomposition of oxygen-containing groups.

[Insert Figure 3]

3.2 Effect of the copper source

In order to investigate the optimized conditions, the catalytic activities of homogeneous and heterogeneous catalysts were examined in a model reaction using benzaldehyde, phenylacetylene and morpholine as starting materials under solvent-free conditions at 90°C. The results are summarized in Table 2.

When the reaction were catalyzed by CuCl₂ and CuBr under MW and conventional heating, 4-(1,3-diphenylprop-2-ynyl)morpholine could be obtained in 95, 83 and 87% yield, respectively. However, these catalysts cannot be reused. To ensure the reusability of catalyst, C-CuCl₂, SiO₂-CuCl₂, and GO-FeCl₃ were employed as heterogeneous catalysts. Unfortunately, these heterogeneous catalytic systems resulted in poor to moderate yields yields (40-70%). To our delight, after screening experiments with GO-CuCl₂, the product could be obtained in excellent yields of 95 and 96% under MW and conventional heating, respectively. Comparing with the traditional heating (8 hours), the use of MW could dramatically reduce reaction time (20 min).

The copper metal contamination in the final products is a major concern because of the use of homogeneous copper salts catalytic system. These drawbacks counteract their applications in the fields of biomedicine and pharmaceuticals. So the copper content in the obtained product was detected by AAS. In homogeneous catalytic system, such as CuCl₂, the copper content in the product was 3.26 (wt%), which was far more than 0.006 (wt%) in GO-CuCl₂ catalytic system. Clearly, the copper content of the obtained product in the heterogeneous reaction is ignorable.

[Insert Table 2]

3.3 Synthesis of propargylamines

To extend the scope of the reaction, various aldehydes, amines and alkynes were tested (Table 3). All the A^3 -coupling reactions proceeded smoothly to give the propargylamines in high yields, which clearly reveal the efficiency and generality of

the developed protocol. The reactivity of 4-methoxybenzaldehyde was found to be less reactive than that of benzaldehyde or 4-chlorobenzaldehyde. It was lower yield when 4-methoxybenzaldehyde was treated with corresponding terminal alkynes and secondary amines. Unfortunately, primary aromatic and arylalkyl amines, such as n-Butylamine, benzylamine and aniline, did not yield the coupled products even after long reaction times.

Various alkynes with electron withdrawing and donating groups were also studied. It was observed that there was no significant difference in reactivity for the examined reactants with varied electronic properties. Both electron-poor and electron-rich alkynes as reactants generated good to excellent yields (Entries 8–11, 85-94%).

It is worth noting that when compared with other similar heterogeneous catalysts (such as 4Å molecular sieve-supported copper(II) catalyst [33]), GO–CuCl₂ showed higher catalytic activity (20 min, 85-98%) under MW irradiation. Although under traditional heating conditions, the reaction also could proceed smoothly to completion in 96% yield within 8 h. The semi-heterogeneous and good accessible properties of the GO-CuCl₂ catalyst might cause the extremely high catalytic activity.

[Insert Table 3]

3.4 Reuse test of GO–CuCl₂

In order to enhance the efficiency and reduce waste, the reuse of $GO-CuCl_2$ in the model reaction was investigated. $GO-CuCl_2$ could be easily recovered through by filtration and washed, then new substrates were added for the next cycle. Fig. 4 showed a summary of the obtained results, which indicated no significant decreases in

yields after 5 cycles (96-88%), suggesting that $CuCl_2$ leaching is not significant for GO-CuCl₂.

[Insert Figure 4]

3.5 Scale-up experiment

To further investigate the feasibility of applying this method in a preparative scale, the scale-up experiment was carried out in the presence of formaldehyde, phenylacetylene and diethylamine under the optimum conditions. The detailed results were summarized in the Table 4.

We conducted a series of amplification experiments and increased the scale of the reaction to 3.0, 30.0, 60.0 and 150.0 mmol, keeping the reaction stoichiometry unchanged. These reactions were found to proceed smoothly and the product was obtained in 88-96% yields. When the scale of the reaction was increased to 150.0 mmol, *N*,*N*-diethyl-3-phenylprop-2-yn-1-amine could be obtained in 88% yield. Furthermore, when the scale was 30.0 mmol, GO-CuCl₂ could be reused at least five times and still maintained a moderate yield.

[Insert Table 4]

3.6 Tentative reaction mechanism

On the basis of the obtained results, a proposed reaction mechanism for the A^3 coupling reaction catalyzed by GO-CuCl₂ under microwave-assisted conditions was illustrated in Scheme 2. At first, Cu(II) catalyzed A^3 coupling reaction could be promoted under microwave-assisted conditions by activation of the C-H bond of

terminal alkyne to afford the desired copper–alkylidine complex on the surface of GO support. Similarly, the formation of iminium ion could also be promoted under the same conditions. Subsequently, the copper–alkylidine complex added to iminium ion to give the corresponding propargylamine.

[Insert Scheme 2]

4. Conclusions

A series of propargylamines were synthesized using GO-CuCl₂ as catalyst *via* multicomponent A³-coupling reaction. The reactions were carried out at a relatively lower temperature, in shorter reaction time under solvent-free condition, which gave good to excellent yields. The results showed that GO-CuCl₂ not only has the very high catalytic activity but also could be recovered and reused 5 recycles without significant loss of catalytic activity. Meanwhile the further investigation of the scale-up reaction has been done successfully, which is performed in 150.0 mmol scale and achieved 88% yield.

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References

- [1] L. Zani, C. Bolm, Chem. Commun. 2006, 4263-4275.
- [2] M.E. Jung, A. Huang, Org. Lett. 2 (2000) 2659-2661.
- [3] A.P. Vsevolod, P.P. Olga, VVan der Eycken Erik, Chem. Soc. Rev. 41 (2012) 3790–3807.
- [4] E. Ramu, R. Varala, N. Sreelatha, S.R. Adapa, Tetrahedron Lett. 48 (2007) 7184–7190.
- [5] O. Russo, S. Messaoudi, A. Hamze, N. Olivi, J.F. Peyrat, J.D. Brion, S. Sicsic, I. Berque-Bestel, M. Alami, Tetrahedron 63 (2007) 10671–10683.
- [6] W.W. Chen, R.V. Nguyen, C.J. Li, Tetrahedron Lett. 50 (2009) 2895–2898.
- [7] R. Maggi, A. Bello, C. Oro, G. Sartori, L. Soldi, Tetrahedron 64 (2008)1435–1439
- [8] K. Layek, R. Chakravarti, M.L. Kantam, H. Maheswaran, A. Vinu, Green Chem. 13 (2011) 2878–2887.
- [9] M.K. Patil, M. Keller, B.M. Reddy, P. Pale, J. Sommer, Eur. J. Org. Chem. 2008 (2008) 4440–4445.
- [10] B. Karimi, M. Gholinejad, M. Khorasani, Chem. Commun. 48 (2012) 8961–8963.
- [11] Y. He, M.F. Lv, C, Cai. Dalton Trans. 41 (2012) 12428–12433.
- [12] N. Salam, S. K. Kundu, A.S. Roy, P. Mondal, S. Roy, A. Bhaumik, S. M. Islam, Catal. Sci. Technol. 3 (2013) 3303–3316.
- [13] J. Yang, P.H. Li, L. Wang, Catal. Commun. 27 (2012) 58-62.

- [14] G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, ACS Catal. 2 (2012) 399-406.
- [15] X. Huo, J. Liu, B.D. Wang, H.L. Zhang, Z.Y. Yang, X.G. She, P.X. Xi, J. Mater. Chem. A 1 (2013) 651–656.
- [16] B. Sreedhar, A. S. Kumar, P.S. Reddy, Tetrahedron Lett. 51 (2010) 1891–1895.
- [17] N. Salam, A. Sinha, A.S. Roy, P. Mondal, N.R. Jana, S. M. Islam, RSC Advances 4 (2014) 10001–10012.
- [18] S. Wang, X. He, L. Song, Z. Wang, Synlett. (2009) 447–450.
- [19] B. F. Machadoab, P. Serp, Catal. Sci. Technol. 2 (2012) 54-75.
- [20] P. Lidstrom, J. Tierney, B. Wathey, J. Westman, Tetrahedron 57 (2001) 9225–9283.
- [21] X.Q. Xiong, L. Cai, Z.K. Tang, Chin. J. Org. Chem. 32 (2012) 1410–1428.
- [22] Y.H. Ju, C.J. Li, R.S. Varma, QSAR Comb. Sci. 23 (2004) 891-894.
- [23] L. Shi, Y.Q. Tu, M. Wang, F.M. Zhang, C.A. Fan, Org. Lett. 6 (2004) 1001–1003.
- [24] T.T. He, Z.G. Zha, C.F. Pan, Z.Y. Wang, Synth. Commun. 37 (2007) 849–858.
- [25] J.V. Madhav, B.S. Kuarm, P. Someshwar, B. Rajitha, Y.T. Reddy, P.A. Crooks, Synth. Commun. 38 (2008) 3215–3223.
- [26] J.B. Bariwal, D.S. Ermolat'ev, E.V. Van der Eycken, Chem. Eur. J. 16 (2010) 3281–3284.
- [27] O.P. Pereshivko, V.A. Peshkov, E.V. Van der Eycken, Org. Lett. 12 (2010)2638–2641.
- [28] D.S. Raghuvanshi, K.N. Singh, Synlett 3 (2011), 373–377.

- [29] X.Q. Xiong, L. Cai, Catal. Sci. Technol. 3 (2013) 1301–1307.
- [30] X.Q. Xiong, H.X. Chen, Z.K. Tang, Y.B. Jiang, RSC Advances 4 (2014) 9830–9837.
- [31] X.Q. Xiong, L. Cai, Y.B. Jiang, Q. Han, ACS Sustainable Chem. Eng. 2 (2014) 765–771.
- [32] P.H. Shi, R.J. Su, S.B. Zhu, M.C. Zhu, D.X. Li, S.H. Xu, J. Hazard. Mater. 229–230 (2012) 331–339.
- [33] A. Fodor, Á. Kiss, N. Debreczeni, Z. Hell, I. Gresits, Org. Biomol. Chem. 8 (2010) 4575–4581.

Captions

Scheme 1. Multicomponent synthesis of propargylamines catalyzed by GO–CuCl₂.

- Scheme 2. Tentative mechanism for the synthesis of propargylamine catalyzed by $GO-CuCl_2$ under MW irradiation.
- Figure 1. TEM images of GO (a) and GO-CuCl₂ (b)
- Figure 2. SEM/EDX images of GO-CuCl₂ (a) and GO-CuCl₂ after 5 recycling (b)
- Figure 3. TGA curves of graphite, GO and GO-CuCl_{2.}
- Figure 4. Recyclability results of GO-CuCl₂.
- Table 1. FTIR and microanalysis results.
- **Table 2.** Effect of the catalysts on the A³-coupling.^a
- Table 3. A³-coupling reaction catalyzed by GO-CuCl₂.^a
- **Table 4.** Scale-up synthesis of *N*,*N*-diethyl-3-phenylprop-2-yn-1-amine.



Scheme 1. Multicomponent synthesis of propargylamines catalyzed by GO–CuCl₂.



Scheme 2. Tentative mechanism for the synthesis of propargylamine catalyzed by

 $GO-CuCl_2$ under MW irradiation.



Figure 1. TEM images of GO (a) and GO-CuCl₂ (b).

Figure 2. SEM/EDX images of GO-CuCl₂ (a) and GO-CuCl₂ after 5 recycling (b).



Figure 3. TGA curves of graphite, GO and GO-CuCl₂.



Figure 4. Recyclability results of GO-CuCl₂.



_		FTIR (KBr, cm^{-1})			AAS results (wt%)	
Sample	$v_{C=0}$	$v_{C=C}$	v _{Si-O-Si}	v _{Si-O-C}	Cu ^a	Cu ^b
GO	1722	1634	_	-	X=	_
GO-APTS	-	1643	1118	1037	<u> </u>	-
GO-CuCl ₂	_	1631	1116	1041	11.28	9.25

Table 1. FTIR and microanalysis results.

[a] AAS result of fresh catalyst. [b] AAS result of GO-CuCl₂ after five consecutive trials.

Entry	catalyst	Yield (%) ^b
1	CuCl ₂	83/95 ^c
2	CuBr	87
3	C-CuCl ₂	60
4	SiO ₂ -CuCl ₂	70
5	GO-FeCl ₃	40
6	GO-CuCl ₂	95/96 ^c

Table 2. Effect of the catalyst on the A³-coupling.^a

[a] Benzaldehyde (3.0 mmol), alkyne (3.6 mmol), amine (3.6 mmol), catalyst (10 mg).

[b] Isolated yields under microwave heating condition, 400W, 90 °C, 20 min.

[c] Isolated yields by using conventional heating, 8 h.

-	.1 —	0	H GO-0	CuCl ₂ R ⁴	N ⁻ R ⁵
F	('	$+ R^2 R^3 + 1$	R ^{4[∠][™] R⁵ 400 W}	/, 90 °C R ^{2/1} R ³	B R ¹
	Entry	——R ₁	0 R ₂ R ₃	$R_4 N R_5$	Yield (%) ^b
	1	————————————————————————————————————	СНО	0 NH	96
	2	<hr/>	Сретено	0 NH	98
	3	<hr/>	сі—————————————————————————————————————	0 NH	92
	4	<hr/>	о-{	0 NH	85
	5		нсно	0NH	88
	6		НСНО	∕_N∕_ H	96
	7		НСНО	HN	97
	8	H ₃ CO-	НСНО	0NH	94
	9	H ₃ CO-{>-0	НСНО	∕_N∕_ H	92
	10		НСНО	0NH	93
	11		НСНО	∕_N∕_ H	85
	12	<hr/>	НСНО	NH ₂	0
	13	<hr/>	НСНО	NH ₂	0
	14		НСНО	NH ₂	0

 Table 3. A³-coupling reaction catalyzed by GO-CuCl₂.^a

[a] Benzaldehyde (3.0 mmol), alkyne (3.6 mmol), amine (3.6 mmol), GO-CuCl₂ (10 mg), 20 min.

[b] Isolated yields.

Entry	Scale (mmol)	Yield (%) ^a
1	3	96
2	30	91
3	60	90
4	150	88
5 ^b	30	89
6 ^c	30	88
7^{d}	30	83
8 ^e	30	70

Table 4. Scale-up synthesis of *N*,*N*-diethyl-3-phenylprop-2-yn-1-amine.

[a] Isolated yields; [b] Catalyst recycled from entry 2 and used for second run; [c] Third run; [d]

Fourth run; [e] Fifth run.

Graphical abstract



Highlights

- GO–CuCl₂ was prepared for on GO support.
- Propargylamines are readily obtained in good to excellent yields and on multi-gram

scale.

• GO-CuCl₂ could be easily recovered and reused at least five recycles.

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