Tetrahedron Letters 57 (2016) 4468-4472

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

CuO/Fe₂O₃ NPs: robust and magnetically recoverable nanocatalyst for decarboxylative A3 and KA2 coupling reactions under neat conditions

Upasana Gulati, U. Chinna Rajesh, Diwan S. Rawat*

Department of Chemistry, University of Delhi, Delhi 110007, India

ARTICLE INFO

Article history: Received 13 June 2016 Revised 20 August 2016 Accepted 20 August 2016 Available online 22 August 2016

Keywords: Decarboxylative strategies A3 and KA2 coupling reactions Green and sustainable chemistry Magnetically recoverable Propargylamines

ABSTRACT

CuO/Fe₂O₃ NPs were found to be robust, green and sustainable nanocatalysts for the synthesis of trisubstituted propargylamines by the reaction of propiolic acid, secondary amines and aldehydes via decarboxylative A3 coupling reaction under solvent free conditions. Further, we explored the wide applicability of the present methodology by replacing the more reactive aldehydes with less reactive ketones to afford the tetrasubstituted propargylamines via decarboxylative KA2 reaction. The present method showed several advantages such as usage of magnetically recoverable with six times recyclability of nanocatalyst, follows green chemistry principles including low E-factor and high atom economy for the A3 and KA2 reactions as well as high turnover numbers through easy catalyst recycling.

© 2016 Elsevier Ltd. All rights reserved.

Introduction

Chemical pollution has been the major environmental issue since the time of industrial revolution. In order to solve this problem, green chemistry principles have been introduced in the last decade of twentieth century. These principles mainly deal with the minimization of waste production rather than focusing on waste treatment.¹ Nanocatalysis has been considered to be an efficient approach to achieve sustainable chemistry with various advantages such as high surface area, recovery and reusability of catalyst with minimum waste generation.² Magnetically recoverable nanocatalysts (MRNCs) have attracted great attention due to their intriguing catalytic properties along with rapid and robust magnetic separation by external magnet.³ Recently, we reported green approach for the one-step synthesis of CuO/Fe₂O₃ MRNC to afford heterocycles such as aminoindolizines and pyrrolo[1,2-a] quinolones.⁴ Moreover, our group has reported that Cu(II)/HM as a versatile nanocatalyst for the synthesis of tetrasubstituted propargylamines and pyrrolo[1,2-a]quinolines via KA2, A3 coupling reactions and also included some preliminary results on their decarboxylative coupling strategies.⁵ Decarboxylative coupling reactions have attracted significant attention in organic synthesis due to in-situ formation of organometallic species which eliminates the requirement of expensive and toxic organometallic reagents.^{6–9} The decarboxylative C—C bond formation involves usage of relatively neutral reaction conditions as compared to organometallic reagents.^{7,10–16}

However, there have been very limited reports on the utilization of decarboxylative coupling strategies for the synthesis of heterocycles and value-added chemicals such as imidazo[1,2-a] pyridines, substituted propargylamines, oxazolidin-2-ones, 3amino-1,4-enynes and 1,4-diamino-2-butynes using copper based homogeneous catalysts.^{17–23} To the best of our knowledge there is no report on decarboxylative A3 and KA2 coupling reactions using MRNCs. With this background and in continuation of our interest towards green and sustainable chemistry,^{4,5,24–27} we herein report the catalytic potential of CuO/Fe₂O₃ NPs for decarboxylative A3 and KA2 coupling reactions under solvent free conditions for the first time (Scheme 1).

Results and discussion

CuO/Fe₂O₃ catalyzed decarboxylative A3 coupling reaction

Initially, a model reaction was performed among benzaldehyde (**1a**), morpholine (**2a**) and phenylpropiolic acid (**3a**) using 5 mg of CuO/Fe₂O₃ as catalyst in the presence of various solvents and under neat condition at 110 °C as shown in Table 1. Product (**4aa**) was obtained in 60% yield in the presence of water (entry 1, Table 1),





etrahedro



^{*} Corresponding author. Tel.: +91 11 27662683; fax: +91 11 27667501. *E-mail address:* dsrawat@chemistry.du.ac.in (D.S. Rawat).



Scheme 1. Decarboxyalative A3 and KA2 coupling reactions.

Table 1 Optimization study for CuO/Fe $_2O_3$ catalyzed decarboxylative A3 coupling reaction^a



S. No.	Catal. (mg)	Solvent	Temp. (°C)	Time (h)	Yield of 4aa ^b (%)
1	$CuO/Fe_2O_3(5)$	Water	100	3.5	60
2	$CuO/Fe_2O_3(5)$	EG	110	3.5	78
3	$CuO/Fe_2O_3(5)$	PEG	110	3.5	78
4	$CuO/Fe_2O_3(5)$	DMF	110	3.5	85
5	$CuO/Fe_2O_3(5)$	DMSO	110	3.5	82
6	CuO/Fe_2O_3 (5)	Neat	110	3.5	92
7	CuO/Fe_2O_3 (10)	Neat	110	3.5	92
8	$CuO/Fe_2O_3(3)$	Neat	110	3.5	88
9	$CuO/Fe_2O_3(5)$	Neat	90	5	79
10	$CuO/Fe_2O_3(5)$	Neat	70	8	60
11	$CuO/Fe_2O_3(5)$	Neat	50	21	35
12	$CuO/Fe_2O_3(5)$	Neat	rt	21	_
13	$Fe_2O_3(5)$	Neat	110	8	30
14	CuO NPs (5)	Neat	110	6	81
15	$CuCl_2(5)$	Neat	110	4	76
16	Neat	Neat	110	4	-

Bold value indicate the optimized reaction condition.

^a Reaction conditions: benzaldehyde **1a** (1 mmol), morpholine **2a** (1 mmol), phenylpropiolic acid **3a** (1 mmol), catalyst (5 mg) and solvent (2 mL) were stirred at appropriate temperature.

^b Isolated yield.

whereas in other green solvents such as ethylene glycol and polyethylene glycol, the product was isolated in 78% yield (entries 2 and 3, Table 1). Moreover, polar organic solvents such as DMF and DMSO afforded product (**4aa**) in 85% and 82% yields respectively (entries 4 and 5, Table 1). To our delight, product (**4aa**) was obtained in 92% yield under neat condition (entry 6, Table 1). Next, we studied the effect of catalyst loading under neat condition. Upon increasing the catalyst amount to 10 mg, there was no further improvement in the yield of product (entry 7, Table 1), whereas upon decreasing the catalyst amount to 3 mg the yield was dropped to 88% (entry 8, Table 1). The yield of product (**4aa**) was dropped gradually upon decreasing the temperature to 50 °C (entries 9–11, Table 1). There was no product formation at room temperature even after prolonged reaction time (entry 12, Table 1,).

Next, we screened Fe_2O_3 and CuO NPs alone as catalysts under optimized reaction conditions. The results showed that Fe_2O_3 gave product in 30% yield while CuO NPs gave 81% yield (entries 13 and 14, Table 1). On the other hand, CuCl₂ yielded product in 76% (entry 15, Table 1). There was no product formation in the absence of catalyst under optimized reaction conditions (entry 16, Table 1). Therefore, the optimized condition was found to be usage of 5 mg of CuO/Fe₂O₃ catalyst at 110 °C under neat condition to afford the trisubstituted propargylamines (**4aa**) in 92% yield.

Table 2

CuO/Fe₂O₃ catalyzed synthesis of trisubstituted propargylamine via decarboxylative A3 coupling reaction^a



S No.	Aldehyde (1)	Amine (2)	Product (4)	Yield ^b (%)
1	1a	2a	4aa	92
2	1b	2c	4bc	91
3	1b	2d	4bd	90
4	1c	2c	4cc	92
5	1d	2f	4df	68
6	1e	2d	4ed	90
7	1e	2e	4ee	92
8	1f	2d	4fd	85
9	1f	2e	4fe	88
10	1g	2b	4gb	90
11	1g	2d	4gd	93
12	1h	2a	4ha	94
13	1h	2f	4hf	75
14	1i	2d	4id	89
15	1i	2e	4ie	89
16	1j	2e	4je	90

^a Reaction conditions: aldehydes 1 (1 mmol), secondary amines 2 (1 mmol), phenylpropiolic acid 3a (1 mmol), CuO/Fe₂O₃ (5 mg) were stirred at 110 °C under neat condition.

^b Isolated yield.

Furthermore, the substrate scope for present method was studied from various aromatic aldehydes having electron donating as well as electron withdrawing substituents (Table 2). Secondary amines were also varied in order to study the versatility of the present method and 7-chloro-4-(piperazin-1-yl)quinolone (**2f**) was used as a novel secondary amine to generate the biologically potent framework for the first time as shown in Table 2. The results showed that the reactions proceeded smoothly with almost all screened substrates to afford corresponding products in 68–94% yields (Table 2).

CuO/Fe₂O₃ catalyzed decarboxylative KA2 coupling reaction

Next, we studied the versatile catalytic potential of CuO/Fe₂O₃ NPs for decarboxylative KA2 coupling among cyclohexanone (**5a**), morpholine (**2a**) and phenylpropiolic acid (**3a**) under optimized conditions. The optimization study revealed that the usage of 5 mg of catalyst at 110 °C under solvent free condition was best to afford product in 85% yield (see SI for details on optimization table S1). The generality and substrate scope was studied for decarboxylative KA2 reaction using various cyclic ketones (**5**), secondary

Table 3

CuO/Fe₂O₃ catalyzed synthesis of tetrasubstituted propargylamine via decarboxylative KA2 coupling reaction^a



S No.	Ketone (5)	Amine (2)	Phenylpropiolic acid (3)	Product (6)	Yield ^b (%)
1	5a	2a	3a	6a	85
2	5d	2a	3b	6b	82
3	5b	2a	3a	6c	84
4	5b	2g	3a	6d	85
5	5a	2c	3a	6e	87
6	5d	2c	3b	6f	88
7	5b	2c	3a	6g	85
8	5d	2c	3a	6h	84
9	5c	2c	3a	6i	87
10	5d	2h	3a	6j	85
11	5d	2e	3a	6k	86
12	5a	2d	3a	61	89

^a Reaction conditions: Ketones **5** (1 mmol), secondary amines **2** (1 mmol), phenylpropiolic acids **3** (1 mmol), CuO/Fe₂O₃ (5 mg) were stirred at 110 °C under neat condition. ^b Isolated yield.

amines (**2**) and phenylpropiolic acids (**3**). The results showed that almost all screened substrates underwent KA2 coupling smoothly to afford corresponding propargylamines in 82–89% yields as shown in Table 3.

On the basis of experimental observation, we proposed the plausible mechanism for CuO/Fe_2O_3 catalyzed decarboxylative coupling reactions as shown in Figure 1. The first step involves the formation of copper carboxylate species (I) by the reaction of CuO/Fe_2O_3 with aryl propiolic acid (3). The copper carboxylate intermediate (I) undergo decarboxylation to afford reactive alkynyl intermediate (II), which further reacts with preformed imine (III) to afford the propargylamines (4 or 6).

The recyclability of CuO/Fe₂O₃ nanocatalyst was checked for decarboxylative A3 coupling for the synthesis of **4aa** under optimized reaction conditions. After carrying out the reaction, the catalyst was magnetically recovered, washed with ethanol

and dried in oven at 90 °C for 8 h. The recovered catalyst was reused up to five more cycles for carrying out the decarboxylative A3 reaction. The results showed that there was no significant loss in its catalytic activity as shown in Figure 2.

Conclusion

We have studied the utilization of decarboxylative strategy for the synthesis of trisubstituted and tetrasubstituted propargylamines for A3 and KA2 coupling reactions respectively using CuO/Fe₂O₃ MRNCs for the first time. The results revealed that synergistic effect of Fe₂O₃ and CuO is responsible for excellent yields of propargylamines. Furthermore, involvement of neat reaction condition and magnetic recoverability of nanocatalysts make this method economically profitable and environment friendly with easy handling without work up procedures, recyclable for six



Figure 1. Plausible mechanism of CuO/Fe₂O₃ catalyzed syntheses of propargylamines.



Figure 2. Recyclability of CuO/Fe₂O₃ nanocatalyst for the synthesis of 4aa.

times. The present methodology offers low E-factor and high atom economy for the A3 and KA2 reactions as well as high turnover numbers through easy catalyst recycling.

Acknowledgments

D.S.R. acknowledges DST-JSPS for financial support. U.G and U. C.R thank CSIR and UGC for the award of junior and senior research fellowships respectively. We thank USIC-CIF, University of Delhi, for the analytical data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08. 066.

References and notes

- 1 Sheldon, R. A. Chem. Soc. Rev. 2012, 41, 1437-1451.
- 2. Polshettiwar, V.; Varma, R. S. Green Chem. 2010, 12, 743-754.
- Rossi, L. M.; Costa, N. J. S.; Silva, F. P.; Wojcieszak, R. Green Chem. 2014, 16, 3. 2906-2933.
- 4. Rajesh, U. C.; Pavan, V. S.; Rawat, D. S. RSC Adv. 2016, 6, 2935-2943.
- 5. Rajesh, U. C.; Gulati, U.; Rawat, D. S. ACS Sustainable Chem. Eng. 2016, 4, 3409-3419.
- Rodríguez, N.; Gooßen, L. J. Chem. Soc. Rev. 2011, 40, 5030-5048. 6.
- Weaver, J. D.; RecioIII, A.; Grenning, A. J.; Tunge, J. A. Chem. Rev. 2011, 111, 7. 1846-1913.
- 8. Baudoin, O. Angew. Chem., Int. Ed. 2007, 46, 1373-1375.
- Bonesi, S. M.; Fagnoni, M. Chem. Eur. J. **2010**, 16, 13572–13589. 9
- 10. Goossen, L. J.; Deng, G.; Levy, L. M. Science 2006, 313, 662-664.
- Becht, J. M.; Catala, C.; Drian, C. L.; Wagner, A. Org. Lett. **2007**, 9, 1781–1783. 11.
- Bilodeau, F.; Brochu, M. C.; Guimond, N.; Thesen, K. H.; Forgione, P. J. Org. Chem. 12. 2010, 75, 1550-1560.
- 13. Goossen, L. J.; Rodríguez, N.; Lange, P. P.; Linder, C. Angew. Chem., Int. Ed. 2010, 49.1111-1114.
- Park, A.; Park, K.; Kim, Y.; Sunwoo Lee, S. Org. Lett. 2011, 13, 944–947.
 Zhang, C.; Das, D.; Seidel, D. Chem. Sci. 2011, 2, 233–236.
- Zhang, F.; Greaney, M. F. Org. Lett. 2010, 12, 4745-4747. 16.
- Palani, T.; Park, K.; Kumar, M. R.; Jung, H. M.; Lee, S. Eur. J. Org. Chem. 2012, 17. 2012, 5038-5047.
- Lim, J.; Park, K.; Byeun, A.; Lee, S. Tetrahedron Lett. 2014, 55, 4875–4878. 18.
- Ermolat'ev, D. S.; Feng, H.; Song, G.; Van der Eycken, E. V. Eur. J. Org. Chem. 19. 2014 2014 5346-5350
- 20. Feng, H.; Ermolat'ev, D. S.; Song, G.; Van der Eycken, E. V. J. Org. Chem. 2012, 77, 5149-5154
- Feng, H.; Ermolat'ev, D. S.; Song, G.; Van der Eycken, E. V. Adv. Synth. Catal. 21. 2012, 354, 505-509
- 22. Feng, H.; Ermolat'ev, D. S.; Song, G.; Van der Eycken, E. V. Org. Lett. 2012, 14, 1942-1945.
- 23. Feng, H.; Ermolat'ev, D. S.; Song, G.; Van der Eycken, E. V. J. Org. Chem. 2011, 76, 7608-7613.
- Rajesh, U. C.; Manohar, S.; Rawat, D. S. Adv. Synth. Catal. 2013, 355, 3170-3178. 24
- 25. Rajesh, U. C.; Pavan, V. S.; Rawat, D. S. ACS Sustainable Chem. Eng. 2015, 3, 1536-1543.
- 26. Rajesh, U. C.; Purohit, G. S.; Rawat, D. S. ACS Sustainable Chem. Eng. 2015, 3, 2397-2404.
- 27. Rajesh, U. C.; Wang, J.; Prescott, S.; Tsuzuki, T.; Rawat, D. S. ACS Sustainable Chem. Eng. 2015, 3, 9-18.