Letter

Zn(OTf)₂-Mediated Expeditious and Solvent-Free Synthesis of Propargylamines via C–H Activation of Phenylacetylene

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Received: 23.02.2016 Accepted after revision: 10.04.2016 Published online: 10.05.2016 DOI: 10.1055/s-0035-1562114; Art ID: st-2016-d0127-l

Abstract Zn(OTf)₂-mediated expeditious and solvent-free synthesis of propargylamines via A³ coupling of aldehydes, amines, and phenylacetylene has been described. The described protocol proceeds effectively with variety of substituted benzaldehydes, enolizable aldehyde, and formaldehyde. Recyclability of the catalyst, low catalyst loading, and use of inexpensive catalyst are the key features of the present protocol.

Key words Zn(OTf)₂, solvent-free synthesis, C–H activation, A³ coupling, propargylamine

Increasing environmental concerns demand the development of environmentally benign, efficient, economical, and green synthesis.¹ Multicomponent reactions (MCR) have emerged as a powerful tool to construct complex molecular architecture in a single reaction step with high atom efficiency,² and MCR under solvent-free conditions offers eco-friendly alternatives and unfolds possibilities for conducting rapid organic synthesis in an efficient manner.³ Developments of reactions that afford C-C or C-heteroatom bonds via C-H activation of alkynes using transition-metal catalyst continue to be a key area of research in organic synthesis. Various catalytic systems using late-transition-metal catalysts such as silver(I) salts,⁴ gold(I)/(III) salts,⁵ gold(III)salen complexes,⁶ indium(III),⁷ iron(III),⁸ copper(II),⁹ and copper(I)¹⁰ have been used to increase structural as well as skeletal diversity from simple and readily available alkynes, aldehydes, and amines. However, the loss of an expensive metal catalyst (silver, gold, etc.) at the end of a reaction is a serious concern of such processes. A few processes involving the recycling of these expensive catalysts have also been developed.¹¹ Striving for recyclability, heterogeneous catalysts employing inexpensive metals like copper and iron using metal-organic frameworks, resins, oyster-shell waste, and graphene oxide as supports have also been exemplified recently.¹² Zinc-catalyzed reactions have emerged as a sustainable alternative to use of more expensive or toxic transition metals.¹³

Propargylamines are the useful building blocks for the construction of fused N- and O-heterocycles and B-lactams.¹⁴ In addition, they are important skeletal motifs of biologically active compounds and natural products.^{14b,15} Zinc catalyst mediated synthesis of propargylamines via threecomponent coupling of aldehydes, alkynes, and amines (A³ coupling) is documented in the literature.¹⁶ Zn(OTf)₂ finds a myriad catalytic applications due to high thermal stability, low toxicity, ease of availability, and low cost. Zn(OTf)₂ has been used for in situ generation of reactive acetylides and their subsequent addition to carbonyl groups,¹⁷ nitrones,¹⁸ and enones¹⁹ to construct propargyl derivatives. Herein, we report a simple and efficient protocol for the addition of reactive acetylides to iminium ions to afford propargylamines. Thus, we have achieved A³ coupling using inexpensive and reusable Zn(OTf)₂ under solvent-free conditions (Scheme 1).



Scheme 1 Zn(OTf)₂-catalyzed A³ coupling

In our initial attempts, several zinc salts were screened for effective A³ coupling of benzaldehyde, piperidine, and phenylacetylene (Table 1). To our satisfaction, three-component coupling proceeded smoothly in the presence of 10 mol% of $Zn(OTf)_2$ in toluene to afford propargylamine in

Synlett

P. B. Sarode et al.

Table 1	Screening of Zinc	Catalysts for th	e Synthesis of 4a ª
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Entry	Catalyst (mol%)	Solvent	Temp	Time (h)	Yield (%) ^b
1	ZnCl ₂ (10)	toluene	reflux	6	20
2	ZnBr ₂ (10)	toluene	reflux	6	17
3	ZnSO ₄ (10)	toluene	reflux	6	trace
4	ZnO (10)	toluene	reflux	6	69
5	Zn dust (10)	toluene	reflux	6	38
6	triflic acid (10)	toluene	reflux	6	40
7	Zn(OTf) ₂ (10)	toluene	reflux	8	80
8	Zn(OTf) ₂ (10)	MeCN	reflux	6	55
9	Zn(OTf) ₂ (10)	EtOH	reflux	8	45
10	Zn(OTf) ₂ (10)	THF	reflux	8	50
11	Zn(OTf) ₂ (10)	solvent-free	100 °C	0.5	96
12	$Zn(OTf)_2(5)$	solvent-free	100 °C	0.5	96
13	$Zn(OTf)_2(5)$	solvent-free	90 °C	1	84
14	$Zn(OTf)_2(5)$	solvent-free	80 °C	1.5	78
15	$Zn(OTf)_2(3)$	Solvent-free	100 °C	3	48

^a Reaction conditions: 1.0 mmol benzaldehyde, 1.2 mmol piperidine and 1.5 mmol phenylacetylene.

^b Isolated yields.

good yield (Table 1, entry 7). We next studied the effect of solvents on the outcome of the reaction. When we em-

ployed acetonitrile, ethanol, or THF as the solvents, product **4a** was generated in slightly lower yields (Table 1, entries 8–10). Interestingly, the solvent-free reaction at 100 °C proceeded rapidly in excellent yields (Table 1, entries 11–12). Lowering the catalyst loading to 5 mol% did not affect the outcome. However, yields were decreased when the reaction temperature and catalyst loading were further lowered (Table 1, entries 13–15).

We speculate that Zn(OTf)₂ facilitates the generation of a reactive acetylide from alkynes and its subsequent nucleophilic addition to the in situ generated iminium ion to afford the A³-coupled product. The complexation of alkynes with zinc(II) yields a π -complex that further activates the terminal C-H. With this expeditious and efficient protocol in hand, its scope and generality were examined (Scheme 2).²⁰ A variety of substituted aldehydes was investigated, and we found this protocol to be very general for substituted benzaldehvdes. Benzaldehvdes with electron-rich or electron-poor groups reacted smoothly and furnished the desired propargylamines in excellent yields. Enolizable aldehydes and formaldehyde also reacted smoothly giving propargylamines in excellent yields (Scheme 2, 4p, 4q, and 4s). We also observed that aldehydes with electron-withdrawing groups reacted rapidly, while those with electronrich groups required longer reaction times. However, heteroaromatic aldehydes such as furfuraldehyde and pyridine-2-carbaldehyde did not furnish the desired product.



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Five- and six-membered cyclic secondary amines reacted smoothly, affording the desired products. Trimethylsilyl-acetylene also underwent the reaction smoothly.

The ease of product isolation prompted us to consider the recyclability of the catalyst (see Supporting Information for details of recyclability). The catalytic efficacy of $Zn(OTf)_2$ was tested in up to five runs for the synthesis of **4a** (Figure 1), and it was found that there was no appreciable loss of catalytic activity of the catalyst.



In conclusion, we have developed a $Zn(OTf)_2$ -catalyzed three-component coupling of aldehydes, terminal alkynes, and amines via C–H activation. Use of economical and readily available $Zn(OTf)_2$ offers a sustainable alternative to other expensive metal catalysts. Recyclability of the catalyst, low catalyst loading, solvent-free conditions, and easy workup are attributes of this protocol. The catalytic generation of zinc acetylides under solvent-free and sustainable conditions provides avenues for further development of efficient C–C bond formation in this area.

Acknowledgment

The authors are grateful to UGC New Delhi, India (F. No. 41-335 /2012 (SR) dt.13.07.2012) for the financial support and SIF, VIT University, Vellore for NMR analysis.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562114.

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P. B. Sarode et al.

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- (20) Typical Experimental Procedure: Preparation of 1-(1,3-Diphenylprop-2-yn-1-yl)piperidine (4a)

To a 25 mL flask were added aldehyde **1a** (0.110 mL, 1.0 mmol), amine **2a** (0.130 mL, 1.2 mmol), alkyne **3a** (0.165 mL, 1.5 mmol), and $Zn(OTf)_2$ (0.02 g, 0.05 mmol). The reaction mixture was stirred at 100 °C until complete consumption of starting aldehyde (TLC monitoring). The reaction mixture was cooled to room temperature, diluted with EtOAc, and then washed with cold H₂O (2 × 5 mL). The organic phase was separated, and the aqueous layer was extracted further with EtOAc (2 × 5 mL). Concentration of the combined organic layers afforded the crude product, which was further purified by column chromatography on 100–200 silica gel (hexane–EtOAc, 20:1) to afford propargylamine **4a** as a pale yellow oil; yield 0.284g, 96%; R_f = 0.8 (5% EtOAc–hexane). ¹H NMR (500 MHz, CDCl₃): δ = 7.65–7.63 (m, 2 H), 7.55–7.51 (m, 2 H), 7.38–7.29 (m, 6 H), 4.81 (s, 1 H), 2.62–2.55 (m, 4 H), 1.63–1.57 (m, 4 H), 1.47–1.45 (m, 2 H). The catalyst was recovered from the aqueous layer via evaporation under reduced pressure and dried at 120 °C for 2 h to obtain pure Zn(OTf)₂. The recovered catalyst was reused for the next reaction in the same way.