



Research Article

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An Efficient Synthesis of Propargylamines via A3 Coupling Catalyzed by Silica-Grafted Imidazolium-Based Ionic Liquids

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ABSTRACT

An efficient method has been developed for the synthesis of propargylamines via A3 coupling reaction of aldehyde, amines and alkynes using silica-grafted immobilized ionic liquid as expeditious reusable catalyst. Three-component coupling (A3 coupling) is done using the terminal alkynes as a carbon nucleophile source via C-H activation. The imine/iminium ion and the copper acetylide intermediates formed in situ reacts to give the propargylamine as final product. In addition to short time requirement, ease of workability and eco-friendliness, other advantages of the method are extremely fast, cleaner than conventional reactions and lead to higher atom economy.

Keywords: C-H activation; Immobilized metal catalyst; Ionic liquids; Three-component (A3) coupling; Propargylamines

INTRODUCTION

Propargylamines are highly versatile building blocks in organic synthesis [1] and their structural unit has been found in various natural products [2] and in compounds of pharmaceutical [3], phytoprotective [4] or biological importance. In addition the propargylamines are high-value synthetic intermediates biologically active compounds such as β -lactams, conformationally restricted peptides, isosteres, natural products and therapeutic drug molecules. One-pot multicomponent coupling reactions (MCR), where several organic moieties are coupled in one step is an attractive synthetic strategy [5,6]. Three-component coupling of an aldehyde, an alkyne and an amine (A3 coupling) using the terminal alkyne as a carbon nucleophile source via C-H activation [7,8], is an excellent example MCRs and also provides an elegant method for the synthesis of propargylamines which are frequent skeletal components and synthetically versatile key intermediates for the preparation of many nitrogen-containing biologically active compounds [9].

Ionic liquids have emerged as a set of green solvents with unique properties such as tuneable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapour pressure and recyclability [10]. Ionic liquids have been exploited as efficient catalysts for many organic reactions, and generally can afford higher yields and selectivity against traditional catalyst [11]. The A3 coupling reaction in the presence of traditional-metal-catalyst like copper, zinc, nickel, gold, silver, iron, cobalt, iridium has already been reported [12-32]. Despite their widespread use in catalysed reactions, a series of drawbacks, such as product isolation, catalyst recovery and the use of large amount of ionic liquids in biphasic systems, which is costly and may cause toxicological concerns, still exist. Immobilized ionic liquids combine the benefits of ionic liquids and heterogeneous catalysts such as high design ability, high solubility of catalytic site, ease of handling, separation and recycling. Thus, in this study some immobilization processes for ionic liquids on solid supports have been designed [33] for the synthesis of propargylamines.

Imidazolium ions commonly used as the cationic moiety are 1-ethyl-3-methylimidazolium (Emim) and 1-butyl-3-methylimidazolium (Bmim) and common counter anions to date are BF_4^{2-} , PF_6^{2-} , halogen anions and haloaluminates

(e.g., AlCl_4^{2-}). AlCl_4^{2-} containing ionic liquids were applied to catalytic reactions [34]. The crystal structures of Emim- and Bmim-salts with transition metal chloride anions such as CoCl_4^{2-} , NiCl_4^{2-} , and PdCl_4^{2-} were also reported, and the PdCl_4^{2-} -containing Bmim-ionic liquid was active in the hydro-dimerization of butadiene [35]. However, no report claims the investigation into the effects of the incorporation of different metal ions into imidazolium-based ionic liquids on the synthesis of propargylamines. In this study, we have incorporated copper chloride ions into silica-grafted imidazolium-based ionic liquids, and used them as heterogeneous catalysts to catalyze the synthesis of propargylamines using microwaves as these reactions are extremely fast, cleaner than conventional reactions, lead to higher atom economy (less chemical waste) and short time requirement. In addition ease of workability and eco-friendliness provide an alternative green approach to environmentally unacceptable procedures using toxic and expensive reagents [36-47].

EXPERIMENTAL SECTION

General Remarks

Microwave oven used was Plazmatronika (RM 2001 PC). ^1H NMR spectra was recorded using Varian EM-360 (60 MHz) and Jeol A1 300 F (300 MHz) spectrophotometers. Chemical shift values are expressed in δ values (ppm) downfield from tetramethylsilane (TMS) used as internal standard. IR was recorded using Perkin Elmer model 1430 spectrometer. ^{13}C NMR was recorded using Jeol A1 300 F (300 MHz) spectrophotometer.

Catalyst Preparation: $[\text{SiO}_2\text{-PimSO}_3\text{H}]_{1/2}\text{CuCl}_4^{2-}$

Sodium hydride (0.528 g, 22 mmol) was suspended in 20 mL of dry THF at 0°C under inert atmosphere. To this suspension imidazole (0.748 g, 11 mmol) in 10 mL dry THF was added drop wise over 30 min while maintaining the temperature at 0°C and the mixture was stirred for 30 min more at room temperature. Freshly distilled trimethoxysilane propyl iodide (2.90 g, 10 mmol) was then added drop wise over 30 min at 0°C . The reaction mixture was allowed to warm to room temperature and stirred under reflux for further 24 h. After completion of reaction, THF was evaporated under reduced pressure; dry chloroform was added to the residue and then filtered under nitrogen. After removal of CHCl_3 from the filtrate, the crude N-3-propyl imidazole trimethoxysilane was purified under vacuum distillation to give pure product in 65% yield.

The pre-treated silica gel (3.30 g, 55 mmol) and N-3-propyl imidazole trimethoxysilane (1.13 g, 5 mmol) prepared above were dispersed in dry toluene (100 mL) in a round bottom flask. The mixture was refluxed for 24 h under nitrogen atmosphere. The resultant product was filtered and washed with a 1:1 mixture of $\text{Et}_2\text{O}:\text{DCM}$ and dried under nitrogen stream to obtain $\text{SiO}_2\text{-Pim}$ as light yellow powder. To a suspension of $\text{SiO}_2\text{-Pim}$ in dry DCM (100 mL), solution of ClSO_3H (0.70 g, 6 mmol) in DCM (5 mL) was added drop wise at room temperature. The mixture was refluxed for 30 min. Then the resulting product was filtered, washed with DCM , acetone and dried under vacuum to give $[\text{SiO}_2\text{-PimSO}_3\text{H}]\text{Cl}^-$ as light yellow powder.

In the following step above formed immobilized IL having chloride counter ion, was added to 100 mL MeCN solution of anhydrous CuCl_2 and the mixture was refluxed for further 24 h. Solid was then filtered and washed with MeCN and acetone to remove excess salt to give final copper ion containing immobilized IL i.e. $[\text{SiO}_2\text{-PimSO}_3\text{H}]_{1/2}\text{CuCl}_4^{2-}$ as dark brown powder. Its formation was characterized via IR and CHN analysis.

General Procedure for The Synthesis of Propargylamines

A) Conventional heating

A mixture of aldehyde (1 mmol), amine (1 mmol), alkyne (1 mmol) and $[\text{SiO}_2\text{-PimSO}_3\text{H}]_{1/2}\text{CuCl}_4^{2-}$ (0.100 g, 0.15 mmol, ~5 mol%) in 2 mL of THF solvent (Table 1 and 3) was taken in a round bottom flask (10 mL) fitted with a condenser and a guard tube. It was then stirred at refluxing temperature. After completion of the reaction (monitored by TLC), the mixture was cooled and extracted with ether (3×10 mL). The organic layer was separated, washed with saturated NaHCO_3 (20 mL) and water (15 mL) and dried over anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure gave the crude product, which was separated through short column chromatography to get the pure product.

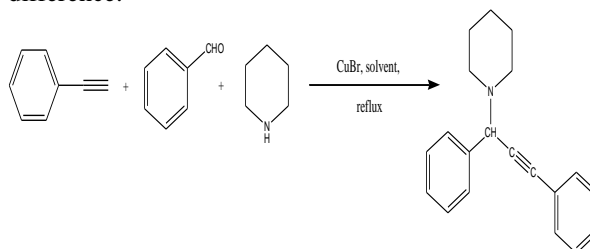
B) Microwave irradiation

A mixture of aldehyde (1 mmol), amine (1 mmol), alkyne (1 mmol) and $[\text{SiO}_2\text{-PimSO}_3\text{H}]_{1/2}\text{CuCl}_4^{2-}$ (0.100 g, 0.15 mmol, ~5 mol%) in 2 mL of THF solvent were taken in a conical flask (50 mL), covered with clinching foil, stirred well and exposed to microwave radiations in commercial microwave oven at $60\text{-}65^\circ\text{C}$. The reaction mixture was cooled and extracted with ether (3×10 mL) and worked up as per given procedure. The ^1H and ^{13}C NMR data of the known compounds are in good agreement with those given in

the literature. Spectroscopic data for the compounds and scanned files are provided as supporting information file 1.

RESULTS AND DISCUSSION

In a preliminary reaction we were interested in studying the effect of various solvents over the conventional reaction for preparing propargylamines. In literature various solvents have been used to carry out this reaction under refluxing conditions or using microwaves. Propargylamine synthesis involving benzaldehyde, piperidine and phenyl acetylene has been chosen as the model reaction using CuBr as the metal catalyst to study this effect. Best conversion was achieved using THF as the solvent as shown in Scheme 1 and Table 1. Variation in the polarity of solvents could be creating this difference.



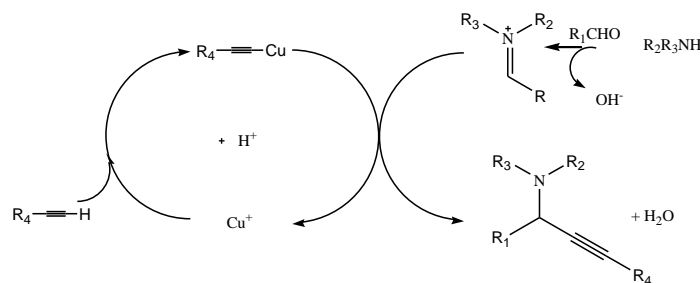
Scheme 1: Propargylamine synthesis

Table 1: Screening of various solvents in the conventional reaction for propargylamine synthesis

S. No.	Solvent	Time (h)	Yield (%)
1	Toluene	12	60
2	THF	5	79
3	MeCN	12	56
4	EtOH	12	50
5	H ₂ O	24	69

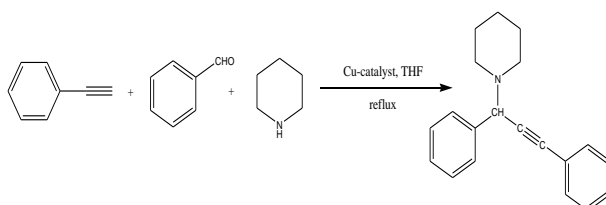
This model reaction has been further used to study the catalytic behaviour of various copper salts. The reactions were carried out in toluene under refluxing conditions taking different salts (Scheme 2, Table 2). It was found that although CuBr, CuCl gave fairly good yields (Table 2, Entry 1-3), CuSO₄, Cu(OAc)₂ could not carry out any reaction even by refluxing for 12 h (Table 2, Entry 4-5). Use of Cu salts as catalyst resulted into good conversion. But there are limitations of using metal catalysts as they are not recoverable under such reaction conditions and their waste thus created is harmful for environment.

The other way of using metal catalysts is immobilizing them over some polymer supports (as discussed in the introduction) which gives a chance to reuse the supported catalyst and leads to lesser waste creation. Here we made use of a few such catalysts which have been supported over neutral alumina, acidic cation exchange resin and silica gel. These were prepared through known procedures. Al₂O₃-Cu(II): a mixture of activated Al₂O₃ with CuCl₂ was refluxed in MeCN for 12 h, resin-Cu(II): clean Amberlyst 15 resin beads were immersed in aqueous 5 mL of 0.5 M CuSO₄ solution overnight, SiO₂-Cu(II): a mixture of activated SiO₂ with CuCl₂ was refluxed in MeCN for 12 h. The reactions carried out with resin-Cu(II) and SiO₂-Cu(II) showed enhanced reactivity whereas that with Al₂O₃-Cu(II) resulted into almost no conversion (Table 2). Because the metal catalyst in all these three is same i.e. Cu(II), only difference is of the support which is of acidic nature in former two (as both the surfaces contain acidic hydroxyl groups) and is neutral in the latter. This leads to a conclusion that incorporation of the acidic character in the catalyst increases the reaction rate. Explanation for this observation comes from the mechanism (Scheme 3) of reaction as:



Scheme 2: General mechanism

Here aldehyde reacts with the amine to form an imine/iminium ion which is otherwise an acid catalysed reaction. This imine/iminium ion then reacts with the copper acetylide intermediate to give the propargyl amine as final product. So, the acidic nature of the support triggers the fast formation of the imine/iminium ion leading to overall increase in the reaction rate.

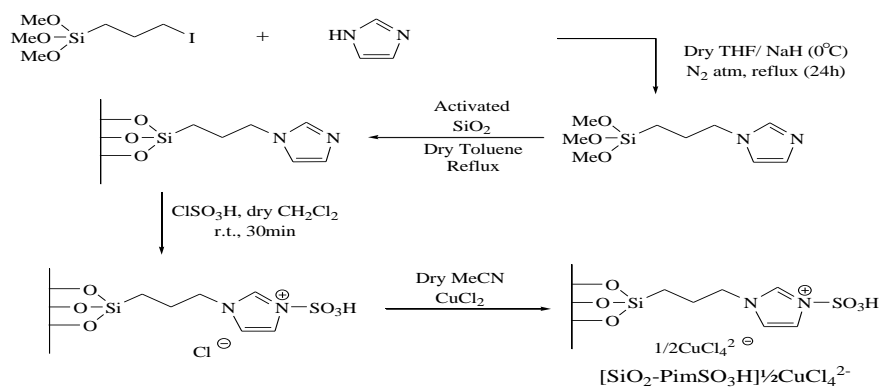


Scheme 3: Synthesis of propargyl amines

Table 2: Scanning of different Cu catalyst for the synthesis of propargyl amines

S. No.	Cu Catalyst	Time(h)	C (%)
1	CuBr	5	75
2	CuCl ₂	6	68
3	CuCl	5	70
4	Cu(OAc) ₂	12	-----
5	CuSO ₄	12	-----
6	Resin-Cu(II)	5	81
7	SiO ₂ -Cu(II)	5	80
8	Al ₂ O ₃ -Cu(II)	12	-----
9	[SiO ₂ -Pmim] ⁺ ½CuCl ₄ ²⁻	4	87
10	[SiO ₂ -PmimSO ₃ H] ⁺ ½CuCl ₄ ²⁻	2	96

Although these supported catalysts are easily recoverable by simple filtration but were not reusable, as the metal ions leached out of the supports just after a single use. This happened because the metal ions were bound to support only via physical adsorption, agitation due to stirring and heating lead to desorption. Solution to this problem is the chemical immobilization of the metal catalysts over supports. In this study, we have incorporated copper chloride ions into imidazolium-based ionic liquids which has been chemically immobilized over activated SiO₂, and used it as heterogeneous catalysts for the synthesis of propargyl amines. First catalyst prepared under this category is [SiO₂⁻Pmim]⁺½CuCl₄²⁻ which gave very good conversion without any leaching of the metal ions. To study any more scope of further increasing the reaction conversion we thought of preparing a silica-grafted imidazolium-based IL having an additional acidic functional group which may further speed up the imine formation and thus the overall reaction. A new silica-grafted imidazolium-based ionic liquid containing CuCl₄²⁻ counter ion and -SO₃H group i.e. [SiO₂-PimSO₃H]⁺½CuCl₄²⁻ has been prepared (Scheme 4) and investigated for further reactions.



$[\text{SiO}_2\text{-PimSO}_3\text{H}]\frac{1}{2}\text{CuCl}_4^{2-}$ catalyst incorporates both the properties of a heterogeneous acidic ionic liquid, and metal catalyst. This also worked very well under the microwave irradiation conditions and gave 89% conversion in 20 min at 60-65°C. As the reaction was better under refluxing conditions so rest of the substrates were reacted under thermal heating conditions (Scheme 5 and Table 3).

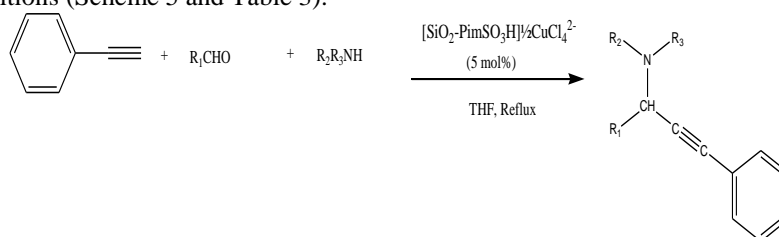
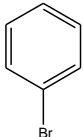

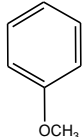

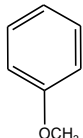





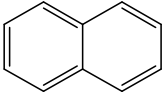



Table 3: Reactions of various substrates using $[\text{SiO}_2\text{-PimSO}_3\text{H}]\frac{1}{2}\text{CuCl}_4^{2-}$ as a heterogeneous catalyst for synthesising propargylamines

S. No.	R ₁	R ₂ R ₃	Time (min)	Yield (%)
1.			10	93
2.			10	92
3.			15	93
4.			15	91
5.			15	89

6.			15	90
7.			15	91
8.			20	93
9.			15	94
10.			15	93
11.			10	94

CONCLUSION

In conclusion, Here we have incorporated copper chloride ions into silica-grafted imidazolium-based ionic liquids, and used them as heterogeneous catalysts to catalyse the synthesis of propargylamines via three-component (A3) reaction of terminal alkynes, amines, and aldehydes. The advantages of this conversion are ease of workability and eco-friendliness and in addition it also provides an alternative green approach to environmentally unacceptable procedures using toxic and expensive reagents.

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