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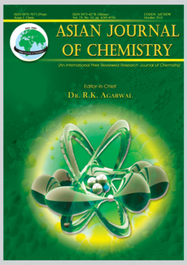

Novel 1-Glycyl-3-Methyl Imidazolium Chloride-Iron(III) Complex for Synthesis of Propargylamines

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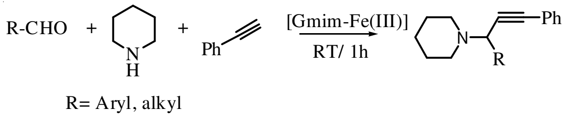
The development of a highly efficient, 1-glycyl-3-methyl imidazolium chloride-iron(III) [Gmim-Fe(III)] complex, catalyst for the three-component coupling reaction of aldehydes, alkyne and amine (A^3-coupling) was described. In the presence of [Gmim-Fe(III)] (0.05 mmol), the A^3-coupling reaction were carried out at room temperature under solvent-free reaction condition and the corresponding propargylamines were generated in good to excellent yields. Both aliphatic and aromatic aldehydes were used in the reaction. Furthermore, the catalyst could be reused several times without a significant loss of its catalytic activity.

Key Words: Iron-ionic liquid, Aldehyde, Amine, Alkyne, Michael addition.

INTRODUCTION

The development of more resourceful and more environmentally benign processes for chemical synthesis has become important day by day[1]. The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C-C bonds in organic synthesis[2]. However, the past ten year one-pot multi-component reactions play an important role in Michael and modern synthetic chemistry since they generally occur in a single pot and exhibit a higher atom economy and selectivity[3]. Propargylamines are important synthetic intermediates for potential therapeutic agents and poly-functional amino derivatives. These compounds are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines or their derivatives[4]. The direct method for the synthesis of propargylamines involves the addition of alkynyl metal reagents to imines[5]. Addition of alkynes to imines, enamines, nitrones and acyl iminium ions using copper salts has been reported to produce propargylamines[6]. Asymmetric versions of enamine-alkyne and imine-alkyne additions have also been reported to produce enantiometrically pure propargylamines[7]. Propargylamines can also be synthesized by one-pot three-component coupling of aldehydes, alkynes and amines *via* C-H activation. Several transition metal salts such as gold, copper, silver and Cu/Ru system have been employed in water as well as in ionic liquids[8a]. Lei Wang reported highly efficient three-component (aldehyde-alkyne-amine) coupling reactions catalyzed by a reusable PS-supported NHC-Ag(I) under solvent-free reaction conditions[8b]. Yadav *et al.*[9a] described In Br_3-catalyzed a facile synthesis of propargylamines. Adapa[9b] successfully evaluated $Zn(OAc)_2.2H_2O$ for the one-pot synthesis of these compounds with moderate to excellent yields. Lakshmi *et al.*[9c] achieved a three component coupling of various aldehydes, alkynes and amines using zinc dust efficiently under mild reaction conditions and in the absence of a co-catalyst. Sreedhar *et al.*[9d] designed a silica gel anchored copper chloride heterogeneous catalyst for the synthesis of propargylamines using both aliphatic and aromatic aldehydes and amines for the reaction. Sreedhar *et al.*[9d] also reported ultrasound-assisted rapid and efficient synthesis of these intermediates. Recently Yong *et al.*[9e] used mesoporous SBA-15 supported silver nano particles as environmentally friendly catalysts for three-component reaction of aldehydes, alkynes and amines with glycol as a green solvent. Chen *et al.*[9f] studied various iron-salts (and complexes) and especially iron(III) chloride catalyzed three-component coupling of aliphatic aldehyde, alkyne and amine with high efficiency under neat conditions in air and in absence of any additional co-catalyst or activator.

Recently, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible favour pressure and recyclability[10]. Their non-volatile character and thermal stability makes them potentially attractive alternatives to environmentally unfavourable organic solvents, notably chlorinated hydrocarbons. They are particularly promising as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes[11]. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis[12]. From the literature survey there is no report of using [Gmim-Fe(III)] complex as catalyst for the synthesis of propargylamines. In view of the emerging importance of imidazolium based ionic liquids as novel catalyst, we wish to explore the use of novel 1-glycyl-3-methyl imidazolium chloride-iron(III) complex as a recyclable catalytic system for the three-component coupling reaction of aldehydes, amines and alkynes to produce propargylic amines in excellent yields (**Scheme-I**).



Scheme-I: [Gmim-Fe(III)]-catalyzed A^3 coupling

EXPERIMENTAL

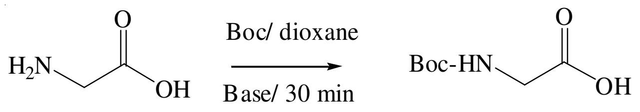
Preparation of ionic liquid: In this study, several ionic liquids including [Cemim]Br, [Aemim]Br were synthesized according to reported method[13].

Spectroscopic data for 1-carboxyethyl-3-methylimidazolium bromide [Cemim]Br: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.87 (s, 1H), 7.05 (s, 1H), 7.71 (s, 1H), 1.63 [sextet (overlapped qt $3J_{H-H}$ = 4.125 Hz), 2H, 2.73 (quintet (overlapped tt, $3J_{H-H}$ = 4.516 Hz)], 2H, 10.98 (s, 1H). The EI (electron impact) mass spectrum of compound molecular ion peak at *m/z* = 234.00, which was consistent with the molecular formula of [Cemim][Br] $[C_7H_{11}N_2O_2Br]^+$. The molecular formula of the product was further confirmed by high-resolution mass spectrometry. The measurement gave a molecular ion peak at *m/z* = 234.000, which was consistent with the calculated formula mass of $[C_7H_{11}N_2O_2Br]^+$. (Theoretical: 235.078).

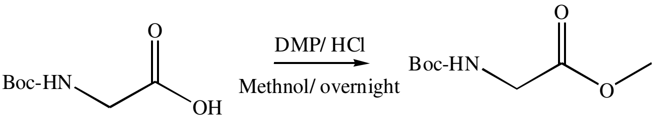
Spectroscopic data for 3-aminoethyl-1-methylimidazolium bromide [Aemim]Br: ^{1}H NMR (500 MHz, DMSO): δ 3.88 (s, 3H), 6.87 (s, 1H), 7.05 (s, 1H), 7.71 (s, 1H), 1.6 (m, 2H), 2.2 (s, 2H), 2.7 (m, 2H). The EI (electron impact) mass spectrum of compound molecular ion peak at *m/z* = 205.021, which was consistent with the molecular formula of [Cemim][Br] $[C_6H_{12}N_3Br]^+$. The molecular formula of the product was further confirmed by high-resolution mass spectrometry. The measurement gave a molecular ion peak at *m/z* = 205.021, which was consistent with the calculated formula mass of $[C_6H_{12}N_3Br]^+$. (Theoretical: 206.083).

Preparation of chloroglycine[14,15]

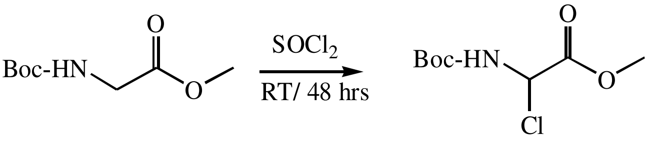
Protection of amine group using *tert*-butyl pyrocarbonate: A solution of the amino acid (10 mmol) in a mixture of dioxane (10 mL), water (5 mL) and 0.5 N NaOH (5 mL) was stirred and cooled in an ice-water bath. Boc (2 g, 8 mmol) was added and stirred continued at ambient temperature for 30 to 45 min. The resulting solution was concentrated *in vacuo* to about 15 mL, cooled in an ice-water bath, covered with a layer of ethyl acetate (15 mL), the reaction mixture was acidified to 2-3 using $KHSO_4$. The aqueous phase is extracted with ethyl acetate (10 mL × 3). The ethyl acetate extracts washed with water, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized using ethanol.



Protection of acid group using methyl ester[16]: Boc-amino acid (10 mmol) was suspended in 2,2-dimethoxypropane (DMP) (50 mL) and concentrated HCl (5 mL) was added. The mixture was allowed to stand at ambient temperature over night. The volatile reactants were removed *in vacuo* at a water bath temperature not exceeding 60 ºC, the residue dissolved in a minimum amount of dry methanol and the solution diluted with dry ether (50 mL). The crystalline methyl ester hydrochloride was collected on a filter, washed with ether and in vacuo over NaOH. Recrystallization from menthol-ether (9:1) affords the analytically pure ester.



Chlorination of protected glycine: In 100 mL round bottom flask, thionyl chloride (6 mmol) was added and cooled in an ice-water bath. The protected glycine (4 mmol) was dissolved in ethanol and added to round bottom flask drop wise at (0 ºC) and stirred at ambient temperature for 48 h. The resulting solution was concentrated under *vacuo*, cooled in an ice -water bath to get the desired precipitate. Recrystallization of the product using ethanol-ether affords the analytically pure chloroglycine.



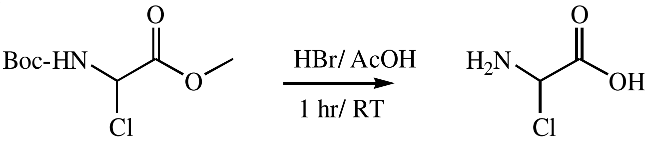
Spectral studies for chloroglycine: FTIR data for chloroglycine (Cl-gly): 610, 1110, 1632, 1700 and 3500 cm^{-1}.

HRMS: The EI (electron impact) mass spectrum of compound molecular ion peak at *m/z* = 191, which was consistent with the molecular formula of [Cemim][Br] $[C_6H_{10}N_3O_2Cl]^+$. The molecular formula of the product was further confirmed by high-resolution mass spectrometry. The measurement gave a molecular ion peak at *m/z* = 191.1062 (M^+), which was consistent with the calculated formula mass of $[C_6H_{10}N_3O_2Cl]^+$. (Theoretical: 192. 6155).

^{1}H NMR of chloroglycine (500 MHz, DMSO): δ 3.63 (s, 3H), 2.2 (s, 2H), 5.7 (m, 1H), 7.2-7.4 (m, 3H), 10.9 (s, 1H).

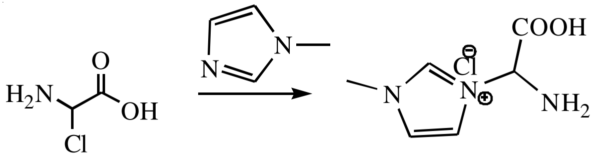
Removal of protecting group using hydrobromic acid in acetic acid[17-19]: An about 33 % (10 mL) solution of HBr in acetic acid is placed in a 100 mL round bottom flask flack and protected chloroglycine (5 mmol) was added with stirring. The flask was closed with a cotton filled drying tube and swirled to effect complete dissolution of the protected chloroglycine. The deprotection occurred with evolution of CO_2 and heat.

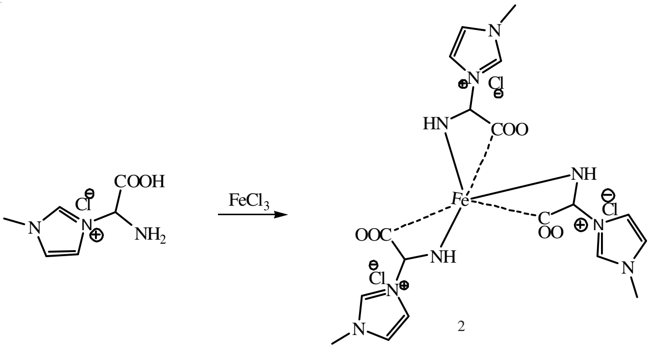
When the gas evolution ceases, dry ether (50 mL) was added with swirling and the reaction mixture was stored in an ice-bath. The precipitate chloroglycine was collected on a filter, washed with ether and dried over NaOH *in vacuo*.



Preparation of 1-glycyl-3-methyl imidazolium chloride-iron(III) complex

Synthesis: The [Gmim-Fe(III)] complex was prepared using the procedure described by Hu *et al.*[20].

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Spectral studies for 1-glycyl-3-methyl imidazolium chloride-iron(III) complex [Gmim-Fe(III)]: FTIR data for 1-glycyl-3-methyl imidazolium chloride-iron(III) complex [Gmim-Fe(III)]: 550, 637, 710, 1260, 1640, 1650 and 1735 cm^{-1}.

HR-MS: The EI (electron impact) mass spectrum of compound molecular ion peak at *m/z* = 623.026, which was consistent with the molecular formula of [Gmim-Fe(III)] $[C_{18}H_{24}C_{l3}N_9O_6Fe]^+$. The molecular formula of the product was further confirmed by high-resolution mass spectrometry. The measurement gave a molecular ion peak at *m/z* = 623.026 (M+1), which was consistent with the calculated formula mass of $[C_{18}H_{24}N_9O_6FeCl_3]^+$. (Theoretical: 624.64).

General procedure for the synthesis of different substituted propargylamines: Typical procedure for the A^3-coupling reaction: in a 100 mL round bottom flask, aldehydes (1.0 mmol), secondary amine (1.2 mmol) and alkyne (1.5 mmol) were mixed and stirred under a nitrogen atmosphere. To this, [Gmim-Fe(III)] catalyst (0.05 mmol) was added. The resulting solution was stirred for 1 h. The progress of reaction was monitored by TLC. The reaction mixture was extracted with ether for three times and the ether layer was dried over anhydrous Na_2SO_4 and the ether was removed under reduced pressure to afford the crude product. The crude product was subjected to purification by silica gel column chromatography using hexane-ethyl acetate (4.5:0.5) as an eluent to yield the propargylamines. All synthesized propargylamines are known compounds. Their characterization is done by a comparison with authentic samples.

RESULTS AND DISCUSSION

The optimization of the coupling of benzaldehyde, phenyl acetylene and piperidine was carried out at ambient temperature and the results are summarized in Table-1. The initial investigation was carried out for 24 h using L-glycine and chloroglycine catalyst. The reaction provided only trace amount of propargylamines (Table-1, entry 1-2). When we replaced the amino acid with ionic liquids such as 1-carboxy ethyl-3-methyl imidazoliumbromide,[Cemim]Br,1-amino-ethyl-3-methylimidazoliumbromide, [Aemim] Br, in presence of molecular solvent, it is worth noting that these ionic liquids can also catalyze the reaction (Table-1, entries 3-4). The reaction could also proceed smoothly in the presence of iron(III) chloride with ionic liquids, that led to significant difference of yields in the presence of molecular solvent (Table-1, entries 5-6). However, desired product was obtained in the presence of 1-glycyl-3-methyl imidazolium chloride-iron(III) complex, which resulted in a higher yield (Table-1, entry 7). The complex iron-catalyzed reaction could also give result with other molecular solvents (Table-1, entries 8-10). The complex iron-catalyzed reaction could not proceed smoothly in the presence of water (Table-1, entry 11). Surprisingly the A^3 coupling could be successfully obtained without solvent by using the novel [Gmim-Fe(III)] catalyst (Table-1, entry 12). Almost similar yield was obtained when slightly increasing the catalyst loading or time duration of the reaction (Table-1, entries 13-15).

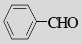
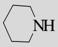
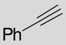
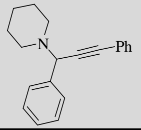
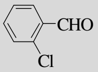
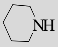
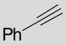
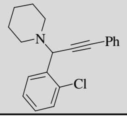
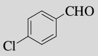
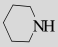
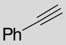
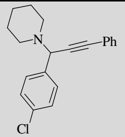
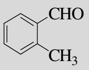
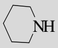
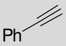
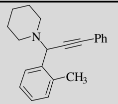
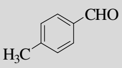
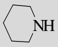
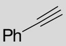
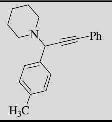
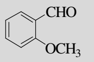
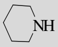
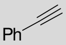
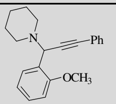
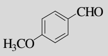
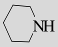
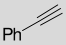
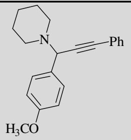
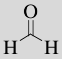
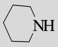
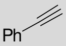
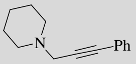
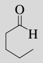
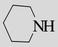
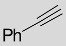
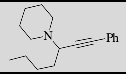
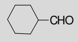
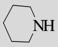
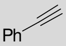
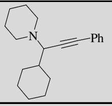
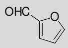
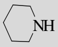
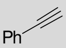
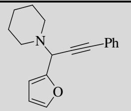
TABLE-1
OPTIMIZATION REACTION OF THREE-COMPONENT COUPLING OF ALDEHYDES, AMINE AND ALKYNE CATALYZED BY [Gmim-Fe(III)] COMPLEX[a]

Entry	Catalyst	Solvent (mol %)	Time (h)	Conversion (%)	Yield[b] (%)
1	L-glycine	Water	24	05	Trace
2	Chloroglycine [Cl-gly]	DMF	24	10	06
3	[Cemim]Br	Acetonitrile	24	37	35
4	[Aemim]Br	Acetonitrile	24	41	40
5	$FeCl_3$/[Cemim]Br	Acetonitrile	24	70	68
6	$FeCl_3$/[Aemim]Br	Acetonitrile	24	67	65
7	[Gmim-Fe(III)]	Acetonitrile	1	86	82
8	[Gmim-Fe(III)]	Toluene	1	86	82
9	[Gmim-Fe(III)]	DMF	1	83	80
10	[Gmim-Fe(III)]	THF	1	85	82
11	[Gmim-Fe(III)]	Water	1	68	66
12	[Gmim-Fe(III)]	--	1	100	93
13	[Gmim-Fe(III)][c]	--	1	100	93
14	[Gmim-Fe(III)]	--	1.5	100	93
15	[Gmim-Fe(III)]	--	2	100	93

[a]Reaction condition: aldehydes (1.0 mmol), secondary amine (1.2 mmol), alkyne (1.5 mmol and catalyst (0.05mmol) at ambient temperature (25 °C)), stirring for 1 h; [b] Based on HPLC and aldehydes; [c]About 0.1 mmol of [Gmim-Fe(III)] was used

Having an optimized conditions, various aldehydes, alkyne and amine were coupled similarly and the results are summarized in Table-2. Both aromatic and aliphatic aldehydes underwent the addition reaction to afford the corresponding three-component propargylic amines effectively.

TABLE-2
THREE-COMPONENT COUPLING OF ALDEHYDES, AMINE AND ALKYNE IN [Gmim-Fe(III)][a]

Entry	Aldehyde	Amine	Alkyne	Product	Yield (%)[b]
1					93
2					90
3					89
4					90
5					92
6					92
7					93
8	 (37 wt % in H_2O)				93*
9					94
10					90
11					93

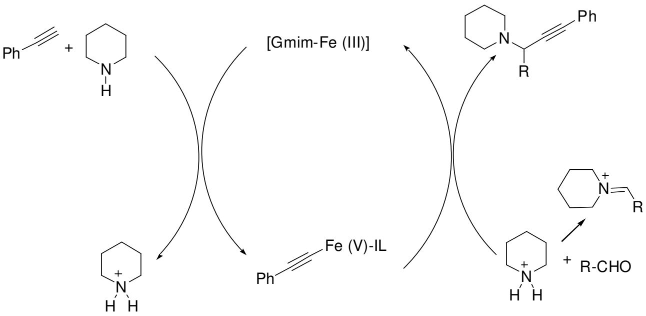
[a]Reaction condition: (aldehydes (1.0 mmol), secondary amine (1.2 mmol), alkyne (1.5 mmol and [Gmim-Fe(III)] (0.05 mmol)) at ambient temperature (25 °C)) stirring for 1 h; [b] Based on HPLC and aldehydes; *Product characterized by spectral analysis

The recyclability of [Gmim-Fe(III)] catalyst was also investigated. After completion of the reaction, the products were easily separated by simple extraction with diethyl ether and the remaining ionic liquid was thoroughly washed with ether and recycled in further reactions without further purification. The recovered catalyst was used in the next run and almost consistent activity was observed for 5 consecutive cycles (Table-3, entries 1-5). The above experiments learn-to some light on the mechanism with the [Gmim-Fe(III)] catalyst. Even though, a detailed mechanistic scheme not yet known, the reaction is catalyzed most likely by Fe^{3+} ion of the ionic liquid complex. Reaction of Fe^{3+} with terminal alkyne in the presence of the amine base generated the terminal iron-acetylide, which undergoes nucleophilic addition to the iminium ion, generated in situ, to give the propargylamine product and regenerates the Fe^{3+}. (**Scheme-II**).

TABLE-3
RECYCLING OF THE CATALYTIC SYSTEM FOR THE A^3 COUPLING OF BENZALDEHYDE, PIPERDINE AND PHENYL ACETYLENE CATALYZED BY [Gmim-Fe(III)] IN SOLVENT FREE CONDITION[a]

Entry	Cycle	Conversion (%)	Yield (%)[b]
1	0	100	92
2	1	100	90
3	2	99	88
4	3	98	87
5	4	98	87

[a]Reaction condition: (aldehydes (1.0 mmol), secondary amine (1.2 mmol), alkyne (1.5 mmol and [Gmim-Fe(III)] (0.05 mmol)) at ambient temperature (25 °C)) stirring for 1 h; [b]Based on HPLC and aldehydes



Scheme-II: Tentative mechanism for the [Gmim-Fe(III)] catalyzed A^3 coupling

Conclusion

In conclusion, we have developed an effective, economical and simple three-component coupling of aldehyde, alkyne and amine (A^3-coupling) with [Gmim-Fe(III)] catalysts to give a diverse range of propargylamines in moderate to high yield under mild conditions. The operation is very simple and can be carried out under solvent free condition at ambient temperature, in air.

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