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Ionic Liquid Catalyzed 4,6-Disubstituted-3-Cyano-2-Pyridone Synthesis Under Solvent-Free Conditions

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Abstract A green protocol for the synthesis of 4,6-disubstituted-3-cyano-2-pyridones from cyanoacetamides and 1,3-dicarbonyl compounds or chalcones using guanidine based ionic liquid as catalyst has been developed. In solvent-free conditions at 30 °C, [TMG][Lac] (1,1,3,3-tetramethylguanidine lactate) was found to have the highest catalytic activity among the ionic liquids including [TMG][Ac] (1,1,3,3-tetramethylguanidine acetate), [TMG][Pr] (1,1,3,3-tetramethylguanidine propionate), [TMG][*n*-Bu] (1,1,3,3-tetramethylguanidine *n*-butyrate) and [TMG][TFA] (1,1,3,3-tetramethylguanidine trifluoroacetate). The catalyst was recovered and recycled several times without significant loss of catalytic activity.

Keywords 3-Cyano-2-pyridone · Ionic liquid · Cyanoacetamides · Acetyl acetone · Guanidine · Solvent-free

1 Introduction

Today, ionic liquids (ILs) are extensively used as reaction media as well as catalyst for organic transformations, due to their physicochemical properties such as negligible vapor pressure, excellent chemical and thermal stability, good solvating ability, ease of recyclability, non-flammability and their potential to enhance reaction rate [1–3]. Moreover, their hydrophilicity or hydrophobicity and solvent miscibility can be tuned by selecting the appropriate cation and anion [4, 5], which renders them useful for facilitating catalyst recovery from reaction mixtures.

Functionalized 2-pyridones have been reported to possess various pharmacological activities such as anticonvulsant [6], sedative [7], anti-atherosclerotic [8], anticancer [9] and phosphodiesterase inhibition [9]. Substituted 3-cyano-2-pyridones are important intermediates in the photo and dye industries [10] as well as for the synthesis of vitamins [11]. They are also used as starting materials for the synthesis of a number of fused heterocycles of biological importance such as isoxazolopyridines, pyrazolopyridines, thienopyridines and pyridoquinazolines [12]. 3-Cyano-2-pyridones can be synthesized by reaction of cyanoacetamides with 1,3-diketones [13–15], acrylonitrile [16, 17] or α,β-unsaturated carbonyl compounds [18] in presence of various basic catalysts. Some studies have been published on synthesis of 3-cyano-2-pyridones using microwave irradiation in presence of strongly basic catalysts [19, 20]. Most of these methods have one or more limitations such as prolonged reaction time [12], harsh refluxing temperatures which leads to more energy consumption [15, 20], use of environmentally hazardous base such as pyridine and piperidine [12, 15], use of volatile organic solvents [14, 15], low product yields [18–20], require acid–base work up and difficult or no recovery of catalysts [12–15, 18–20].

In the quest of developing mild, simple, environmentally friendly and solvent-free synthetic protocols, previously we have reported several reactions including hetero-Michael reaction [21], Knoevenagel condensation [22], Biginelli reaction [23] and Heck reaction [24] using ILs as recyclable catalytic system. As new generation ILs, a wide

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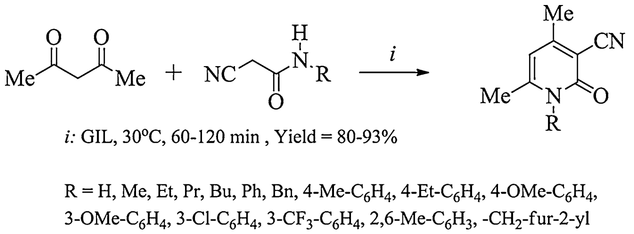
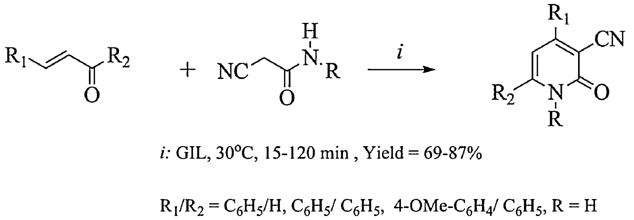


i: GIL, 30°C, 60-120 min , Yield = 80-93%

R = H, Me, Et, Pr, Bu, Ph, Bn, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-OMe-C_6H_4, 3-OMe-C_6H_4, 3-Cl-C_6H_4, 3-CF_3-C_6H_4, 2,6-Me-C_6H_3, -CH_2-fur-2-yl

Scheme 1 GIL 1 catalyzed reaction of cyanoacetamides with acetyl acetone



i: GIL, 30°C, 15-120 min , Yield = 69-87%

$R_1/R_2 = C_6H_5/H$, C_6H_5/C_6H_5, 4-OMe-C_6H_4/C_6H_5, R = H

Scheme 2 GIL 1 catalyzed reaction of cyanoacetamide with chalcones

range of guanidine ionic liquids (GILs) have been synthesized and used as solvent as well as catalyst in the Henry reaction, aldol reaction, Heck reaction and for the synthesis of polysubstituted benzene [25–30].

In continuation of our endeavour in green synthesis and using ILs as a recyclable and ecofriendly catalytic media, herein, we report for the first time, a facile protocol for the synthesis of 3-cyano-2-pyridones not only from cyanoacetamides and 1,3-dicarbonyl compounds (Scheme 1) but also from cyanoacetamide and chalcones (Scheme 2) using 1,1,3,3-tetramethylguanidine lactate [TMG][Lac] (GIL 1) as an efficient and recyclable catalyst at 30 °C, which is superior to previous base catalyzed thermal methods and overcomes the problems encountered with them.

2 Experimental

2.1 General Information

The ILs were prepared by previously reported method without any modifications and characterized by FTIR and ^1H NMR spectroscopy [31]. The reagents and solvents were commercially available. Cyanoacetamide is commercially available (Spectrochem Pvt. Ltd.). All synthesized compounds were identified by spectroscopic data. FTIR spectra were obtained on a Perkin-Elmer infrared spectrometer with KBr discs and $\nu_{\max}$ was expressed as cm^{-1}. ^1H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-D_6 on a JEOL AL 300 (300 MHz) spectrometer with TMS as internal standard and the chemical shifts were expressed in ppm. Mass spectral data were obtained with micromass-Q—Tof (YA105) spectrometer. TLC was run on silica gel coated aluminium sheets (silica gel 60 F254, E. Merck, Germany) and visualized in UV light at 254 nm.

2.2 General Procedure for 4,6-Dimethyl-2-Oxo-1, 2-Dihydropyridine-3-Carbonitrile in Catalyst GIL 1

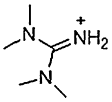
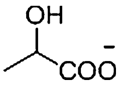
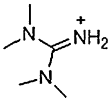
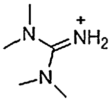
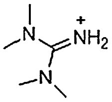
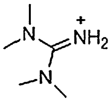
In a typical experiment, cyanoacetamide (3.5 mmol), acetyl acetone (3.5 mmol) and catalyst GIL 1 (1.4 mmol) were charged into a 50 mL round-bottom flask with a magnetic stirring bar. The reaction mixture was stirred at 30 °C for 60 min as mentioned in Table 1 during which time a white solid precipitated. The progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was extracted thrice with hexane–ethyl acetate mixture [(1:2 v/v) 3 mL] and passed over anhydrous sodium sulphate. Evaporating the solvent under reduced pressure gave the product. The recovered ionic liquid was kept under vacuum for 2 h to remove volatiles and stored in a desiccator for its reuse in subsequent catalytic runs. The desired pure products were characterized by comparison of their physical and spectral data with those of known compounds [15, 18–20].

3 Results and Discussion

A series of GILs such as 1,1,3,3-tetramethylguanidine lactate [TMG][Lac], 1,1,3,3-tetramethylguanidine acetate [TMG][Ac], 1,1,3,3-tetramethylguanidine propionate [TMG][Pr], 1,1,3,3-tetramethylguanidine *n*-butyrate [TMG][*n*-Bu] and 1,1,3,3-tetramethylguanidine trifluoroacetate [TMG][TFA] were synthesized from 1,1,3,3-tetramethylguanidine and organic acids with varied chemical structures as shown in Table 1. We selected GIL-1 as a catalyst to investigate the optimum reaction condition for the reaction between cyanoacetamide and acetyl acetone at 30 °C as it has low viscosity and more basicity than the other GILs. The effect of the varying concentration of catalyst on the yield of product and time required for the completion of reaction at 30 °C was explored as shown in Table 2. It was observed that 0.4 equivalents of catalyst GIL 1 and reaction time of 60 min gave optimum yield (Table 2, entry 6) at 30 °C.

The reactions of cyanoacetamide and acetyl acetone in different GILs were also examined. It was observed that the reactions of cyanoacetamide with acetyl acetone proceeded slowly in GIL-2–4, with low to moderate yields even after prolonged reaction time (Table 1, entries 2–4) and in GIL-5 no reaction occurred (Table 1, entry 5). The above results suggest that the chemical structures of GILs, including both the anion and cation parts, played a crucial role in product formation. From the data listed in Table 1,

Table 1 : Reactions of cyanoacetamide with acetyl acetone in different GILs

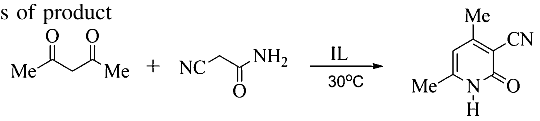
Entry	GIL	Cation	Anion	pH[a]	Time (min.)	Yield[b] (%)
1	GIL 1			10.93	60	93
2	GIL 2		CH_3COO^-	8.15	180	62
3	GIL 3			8.36	180	67
4	GIL 4			8.28	180	64
5	GIL 5		CF_3COO^-	5.17	360	NR[c]

[a] Measured with 0.1 M aqueous solution of GIL [30]

[b] Yield of isolated product

[c] No reaction

Table 2 Effect of varying concentration of catalyst GIL 1 on the yields of product



Entry	GIL-1 (equi)	Time (min)	Yield (%)[a]
1	–	120	NR
2	0.10	40	42
3	0.20	40	64
4	0.30	40	80
5	0.40	40	88
6	0.40	60	93
7	0.40	120	93
8	0.60	120	94
9	0.80	150	94

Reaction conditions: Cyanoacetamide (1 equi), acetyl acetone (1 equi) and catalyst GIL-1, at 30 °C

[a] Yield of isolated product

it seems that the GIL 1 is more basic may be due to reduction in acidity because of intramolecular hydrogen bonding in lactic acid. In addition, low viscosity [30] of GIL 1 could also have a positive impact.

To explore the general validity of this process, a series of 4, 6-disubstituted-3-cyano-2-pyridones were prepared under the optimized reaction conditions. Various types of aliphatic and aromatic cyanoacetamides can be successfully reacted with acetyl acetone to give the products in moderate to high yields. It was also observed that the electronic nature of substituents on the aromatic ring has some impact on the rate of reaction. Substrates with electron donating groups are comparatively less reactive than the substrates with electron withdrawing groups on the aromatic ring and yields obtained with substrates having electron donating groups were slightly lower than substrates having electron withdrawing groups on aromatic ring.

GIL-1 can be applied as an efficient catalyst not only for the synthesis of 3-cyano-2-pyridones from 1,3-dicarbonyl compounds and cyanoacetamide but also from chalcones and cyanoacetamide (Scheme 2). We have used different chalcones and cycanoacetamide for the synthesis of 3-cyano-2-pyridone derivatives under these reaction conditions.

The recycling performance of catalyst GIL 1 in the same model reaction was also explored. Isolation of product was easier and did not need aqueous work up. Extraction of product with a mixture of suitable solvent under efficient stirring and then recovery of solvent under reduced pressure gave the product. The catalyst was recovered by washing repeatedly with mixture of hexane–ethyl acetate and reused for several times without significant loss of catalytic activity. The reusability of catalyst was quantified by performing a set of experiments (Fig. 1). The catalyst was recovered and reused three times without addition of extra ionic liquid.

The proposed reaction mechanism for GIL 1 catalyzed synthesis of 4,6-disubstituted-3-cyano-2-pyridones is shown in Scheme 3. GIL abstracts the proton from cyanoacetamide. This facilitates the nucleophilic attack of cyanoacetamide on electrophilic carbon of 1,3-dicarbonyl compounds and subsequent dehydration leads to the product formation.

GIL 1 can be used as an efficient and recyclable catalyst for the synthesis of 3-cyano-2-pyridones not only from cyanoacetamides and dicarbonyl compounds but also from cyanoacetamide and chalcones and in most cases it was also superior to earlier reported methods [18–20] for 3-cyano-2-pyridones (Table 3).

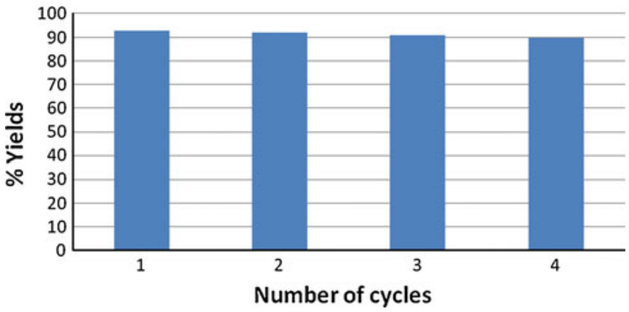
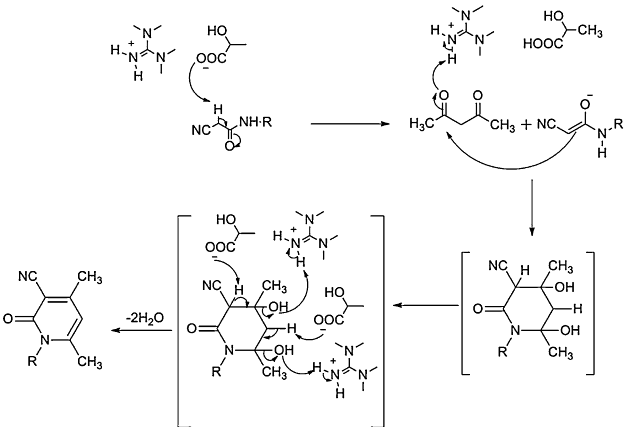


Fig. 1 Recyclability performance of IL



Scheme 3 Proposed reaction mechanism for the synthesis of 3-cyano-2-pyridones in GIL 1

Table 3 Comparison of conventional synthesis with GIL catalyzed synthesis for 3-cyano-2-pyridones

Compound	Conventional synthesis		GIL catalyzed synthesis	
	Time (h)	Yield (%)	Time (h)	Yield (%)
R = H, Me, Et, Pr, Bu, Ph, 4-Et-C_6H_4	4	30–85	1–1.5	80–93
$R_1/R_2 = C_6H_5/C_6H_5$	12	65	2	69
R_1/R_2 = 4-OMe-C_6H_4/C_6H_5	10	68	1.5	75
$R_1/R_2 = C_6H_5$/H	1	65	0.25	87

4 Conclusions

We have developed a simple, mild and efficient protocol for the synthesis of 4,6-disubstituted-3-cyano-2-pyridones from cyanoacetamides and 1,3-dicarbonyl compounds or chalcones at 30 °C using economical and environmentally friendly [TMG][Lac] or GIL 1 as a recyclable catalyst. Most importantly, the catalytic system is very easy to prepare, handle and can be recycled and reused without significant loss of catalytic activity. This method also offers marked improvements with regard to operational simplicity, ease of isolation, high isolated yields of products, greenness of the procedure, no need of aqueous work up, avoiding toxic catalysts and hazardous organic solvents.

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