

# Tandem Protocol of Hexahydroquinoline Synthesis Using $[H_2\text{-DABCO}][HSO_4]_2$ Ionic Liquid as a Green Catalyst at Room Temperature

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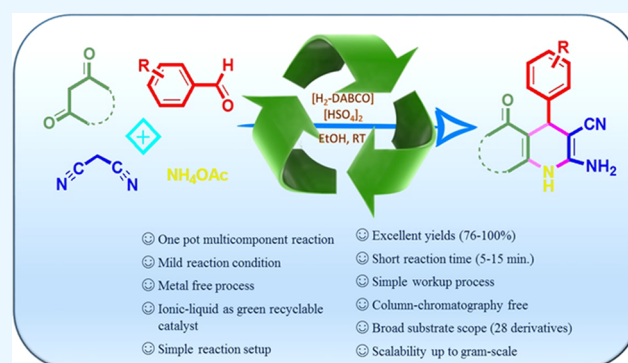
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**ABSTRACT:** Green, eco-benign, and sustainable synthesis is paramount in present chemistry. Here, a facile, efficient, and  $[H_2\text{-DABCO}][HSO_4]_2$  ionic-liquid-catalyzed one-pot multicomponent synthesis of hexahydroquinolines was reported under ambient reaction conditions. The reaction of 1,3-dicarbonyls, malononitrile, and ammonium acetate with various aldehydes in the presence of an ionic liquid catalyst and EtOH solvent at room temperature afforded excellent yields (76–100%) of hexahydroquinolines under a short reaction time (5–15 min). Mild reaction conditions, broad substrate scope (28 derivatives), and column-chromatography-free synthesis with excellent catalytic efficiency and good recyclability rendered this protocol superior and practical. The greenness of the present method was assessed through eco-score and E-factor. The significant results in gram-scale synthetic conditions validate its applicability in industries as well as academia in the near future.



## 1. INTRODUCTION

Nitrogen-based heterocycles possess arguably a rich history with huge applications and a high impact on synthetic, medicinal, and industrial chemistry. Several natural products, drugs, and materials prominently possess a variety of heterocyclic molecules and are very essential for mankind.<sup>1–3</sup> They continue to play an overwhelming role in the advancement of new treatments against life-threatening diseases. 1,4-Dihydropyridine (1,4-DHP) nuclei are key fragments in various natural compounds as well as in synthetic molecules because of their interaction properties with different proteins.<sup>4</sup> Since 1,4-DHP is an analogue of the coenzyme NADH (nicotinamide adenine dinucleotide), biochemists are highly attracted toward its green synthesis with its applications in medicinal chemistry.<sup>5–7</sup> The 1,4-DHP skeleton works as a calcium channel modulator and cardiovascular agent (nicardipine, amlodipine, and nifedipine) and shows antitubercular, antitumor, antiatherosclerotic, vasodilator, neuroprotective, hepatoprotective, and bronchodilator activity.<sup>5–13</sup> Polyhydroquinoline (PHQ) is a derivative of 1,4-DHP, a large family of medicinal and industrially important compounds, and has fascinated researchers.<sup>14</sup>

The Hantzsch one-pot multicomponent synthesis of 1,4-DHP was first reported by Hantzsch in 1881, and after that, several advancements have been made in their synthetic route in the context of economy, environment, and sustainability.<sup>15</sup>

One-pot multicomponent reactions (MCRs)<sup>16–18</sup> are facile, fast, and provide efficient pathways to synthesize diversified

and complex hybrid compounds *via* the formation of several bonds in a single process with high regio- and stereo-selectivity.<sup>19–22</sup> MCRs are valuable in the field of medicinal chemistry and drug design due to their various features such as operational simplicity, atom-economy, simple purification, minimal waste production, and eco-friendliness.<sup>23</sup> All of these features support the green chemistry principles and have prompted intensive research toward more proficient synthetic pathways for diversity-oriented and combinatorial synthesis.

Catalysis is one of the important pillars of green chemistry that improves the reaction process and lowers the negative impact of chemical reactions on the environment. Ionic liquids (ILs) are employed as eco-friendly reaction media and catalysts and sometimes show dual behavior as solvent catalysts in various reactions.<sup>24</sup> ILs possess a wide range of combination of anions and cations and show unique properties such as nonvolatility, low vapor pressure, high chemical and thermal stability, and recyclability with low waste generation.<sup>25</sup> Functionalized ILs are also known as ‘task-specific ionic liquids’ due to their utility in specific reactions. DABCO (1,4-

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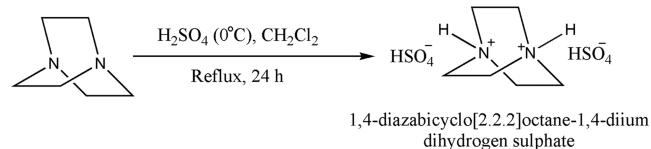


diazabicyclo[2.2.2]octane)-based ionic liquids  $[\text{DABCO}]-(\text{SO}_3\text{H})_2(\text{Cl})_2$ ,<sup>26</sup>  $[\text{DABCO}(\text{C}_4\text{H}_8\text{SO}_3\text{H})_2][\text{HSO}_4]_2$ ,  $[\text{DABCO-PDO}][\text{OAc}]$ , and  $[\text{DABCO}](\text{SO}_3\text{H})_2(\text{HSO}_4)_2$  have been utilized in various chemical transformations like Aza-Michael addition,<sup>27</sup> Knoevenagel condensation,<sup>28</sup> and oxathioacetalization<sup>29</sup> and many more. DABCO is a cage-like tertiary amine having weak alkalinity. This cage-like structure increases the energy barrier of nitrogen inversion so the lone pair is localized and makes DABCO more susceptible toward quaternization and ionic liquid preparation and further applied in organic reactions.<sup>29–32</sup> Regarding the abovementioned notable properties of 1,4-DHP derivatives, their synthetic methods have been investigated in various environmental conditions.<sup>33–37</sup> However, most of the research studies have been done on the synthesis of 3-carboxylate derivatives of 1,4,5,6,7,8-hexahydroquinoline compared to 3-carbonitrile derivatives. 1,4,5,6,7,8-Hexahydroquinoline-3-carbonitrile was previously synthesized using  $\text{NH}_4\text{OAc}$ , sulfonated rice husk, nanosized  $\text{MgO}$ , nano- $\text{Fe}_3\text{O}_4@ \text{TDI}@ \text{TiO}_2$ , citric acid/MCM-48, and  $\text{K}_2\text{CO}_3$  catalyst.<sup>38–43</sup> Despite the undeniable advantages of these processes, some disadvantages are also present, like the involvement of metal catalysts, nonrecyclable catalysts, high catalyst loading, long reaction time, high temperature, and small substrate scope. Therefore, further efforts are needed to present more proficient and eco-benign methods for the synthesis of hexahydroquinoline-3-carbonitriles. In our continuous efforts to utilize eco-friendly catalysts for the green synthesis of nitrogen-based heterocyclic compounds,<sup>44–46</sup> we envisioned that the ionic liquid  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$  efficiently catalyzed the Hantzsch-type synthesis of hexahydroquinolines by employing 1,3-dicarbonyl, malononitrile, and ammonium acetate with substituted aldehydes as a coupling partner. To the best of our knowledge and literature studies, this economical, sustainable, and eco-friendly  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ -catalyzed 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile synthesis is not reported to date. Good productivity, operational simplicity, mild and ambient reaction conditions, use of green catalyst, high catalyst recyclability, high yields in short reaction time, column-chromatography-free synthesis, and diversified substrate scope are notable advantages of the present protocol.

## 2. RESULTS AND DISCUSSION

The ionic liquid  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$  was synthesized via a previously reported method<sup>47</sup> and characterized on the basis of

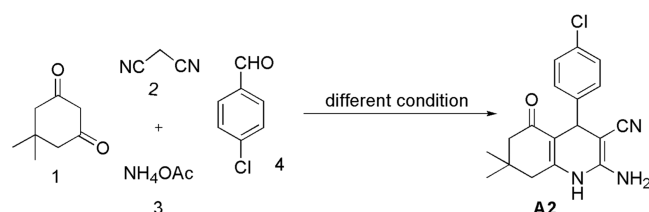
### Scheme 1. Synthesis of $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ Catalyst



melting point, IR,  $^1\text{H}$ ,  $^{13}\text{C}$ , and XRD (Scheme 1, spectral studies are provided in the Supporting Information).

Keeping the Hantzsch strategy in mind, we concentrated on the optimization of reaction conditions using dimedone (**1a**), malononitrile (**2**), and ammonium acetate (**3**) with *p*-Cl benzaldehyde (**4b**) as a model substrate (Table 1). To our delight,  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$  (30 mg) in EtOH worked as an effective catalyst for this protocol at room temperature (Scheme 2).

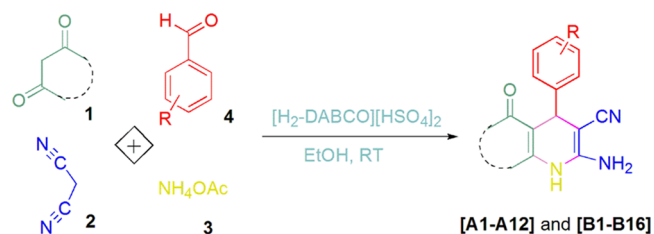
**Table 1. Optimization of Reaction Conditions on Model Reaction for the Synthesis of Compound A2<sup>a</sup>**



sl. no.	catalyst (amount)	solvent	time	yields <sup>b</sup> (%)
1	without catalyst	EtOH	1 h	traces
2	without catalyst	H <sub>2</sub> O	1 h	traces
3	H <sub>2</sub> SO <sub>4</sub> (100%, 0.5 mL)	EtOH	10 min	40 (with lots of mixing)
4	DABCO (30 mg)	EtOH	10 min	80
5	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (20 mg)	EtOH	10 min	88
6	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (20 mg)	H <sub>2</sub> O	10 min	50
7	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (30 mg)	H <sub>2</sub> O	10 min	60
8	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (30 mg)	EtOH	5 min	98
9	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (30 mg)	EtOH + H <sub>2</sub> O	10 min	64
10	$[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ (40 mg)	EtOH	5 min	98

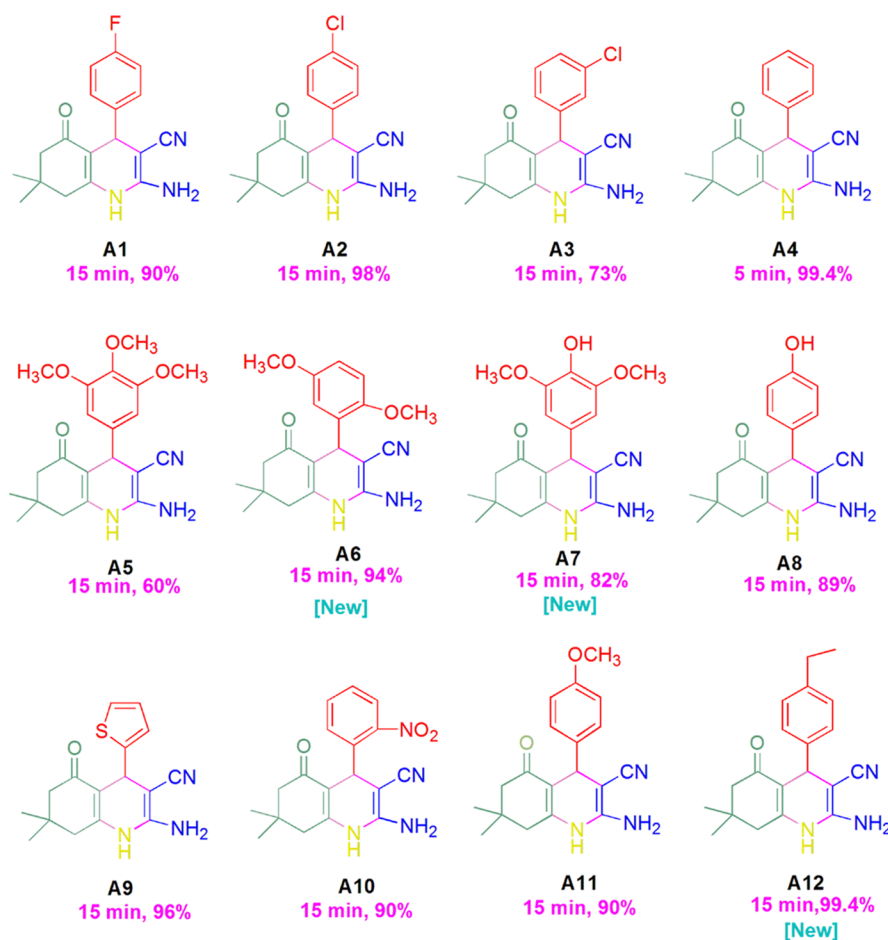
<sup>a</sup>Reaction conditions: 1,3-dicarbonyl (**1a**), malononitrile (**2**), ammonium acetate (**3**), 4-Cl benzaldehyde (**4b**), and stirring at room temperature. <sup>b</sup>Isolated yield.

### Scheme 2. $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ -Catalyzed Hexahydroquinoline Synthesis



A brief optimization study was performed using different solvents (H<sub>2</sub>O, EtOH, and EtOH + H<sub>2</sub>O) and catalyst loadings. During the course of this study, it has been found that EtOH was an ideal solvent for this synthesis, which remarkably enhanced the reaction rate (Table 1 entry 8). The reaction did not show any incremental effect on the use of H<sub>2</sub>O and the EtOH + H<sub>2</sub>O solvent system (Table 1 entries 6, 7, 9). Reaction yields were increased with increasing the catalyst amount up to 30 mg. Afterward, on increasing catalyst loading, no significant effect was observed (Table 1 entries 5, 8, 10). To study the effect of the catalyst, the model reaction was also performed with H<sub>2</sub>SO<sub>4</sub>, DABCO, and without catalyst conditions in different solvents. In the absence of a catalyst and in H<sub>2</sub>SO<sub>4</sub>, the results were not good, and traces were obtained with lots of impurities. After that, DABCO showed good results; however, these catalytic activities were comparatively low to  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$  IL. So, the reaction was continued with this IL (Table 1 entries 1–4).

Intrigued by this  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$ -catalyzed protocol, the generality of the present strategy was first investigated by



**Figure 1.** Library of synthesized hexahydroquinoline (A series).

reacting a variety of aromatic aldehydes, and the results are summarized in Figure 1. A range of aromatic aldehydes having electron-donating and electron-withdrawing groups worked well and afforded corresponding products (A) in good to excellent yields. A range of functional groups like fluoro, nitro, chloro, methoxy, ethoxy, bromo, and hydroxy at different positions were well tolerated in the present methodology and afforded good yields of expected products (A). Gratifyingly, heteroaromatic and benzylic aldehydes also proved to be suitable in reaction and afforded desired products with high efficiency.

To further check the versatility of the reaction, the scope of 1,3-dicarbonyl compound was next explored using cyclohexane-1,3-dione (**1b**) as a substrate. This dicarbonyl worked as an elegant coupling partner with substituted aldehydes and afforded moderate to good yield of corresponding hexahydroquinoline (Figure 2). Overall, the electronic nature of substituents did not affect the reaction progress significantly. Thus, this facile synthetic method provides an elegant route to synthesize several hexahydroquinolines in one step under eco-benign conditions. The structure, reaction time, and yield of all of the synthesized hexahydroquinoline derivatives are depicted in Figures 1 and 2.

The structure of all of the synthesized derivatives was confirmed by melting point and FT-IR,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra. In the IR spectrum, the absorption band in the range of  $3200\text{--}3440\text{ cm}^{-1}$  was seen due to the presence of  $>\text{NH}_2$  and  $-\text{NH}$  groups.  $^1\text{H}$  NMR showed a significant CH proton

peak as a singlet in the range of  $\delta$  3–5 ppm, which validated the formation of desired compound. The  $-\text{NH}_2$  proton peak appeared as a singlet in the range of  $\delta$  4–6 ppm. However, the  $-\text{NH}$  peak sometimes appeared broad and sometimes disappeared due to exchangeable proton. The singlet at  $\delta$  30–35 ppm in  $^{13}\text{C}$  NMR exhibited the presence of methine carbon in molecule (Figure 3).

The postulated mechanism for the synthesis of hexahydroquinoline is depicted in Scheme 3 based on previous literature studies.<sup>38,39,47,48</sup> Here, IL activated all of the reactants *via* hydrogen bonding, and this interaction was displayed by dashed lines. Initially, the carbonyl group of aldehyde was activated from IL and showed Knoevenagel condensation with activated malononitrile and changed into intermediate (III). And in the other part, IL activated 1,3-dicarbonyls, which further reacted with  $\text{NH}_4\text{OAc}$  and afforded enamine (V). Intermediate (III) and (V) showed Michael addition and formed adduct (VI), which further cyclized, displayed tautomerization, and afforded final hexahydroquinolines.

**2.1. Recyclability of the Ionic Liquid.** The ionic liquid is soluble in water, so it can be easily recovered from filtration and then dried under reduced pressure to further utilize for the next reaction (Table 2). The recovered IL was reused for up to five cycles and showed a minimal loss in catalytic activity in the context of decreasing product yield in the same reaction time (Figure 4). The IR spectrum of the IL reused for the fifth time is shown in Figure 5.

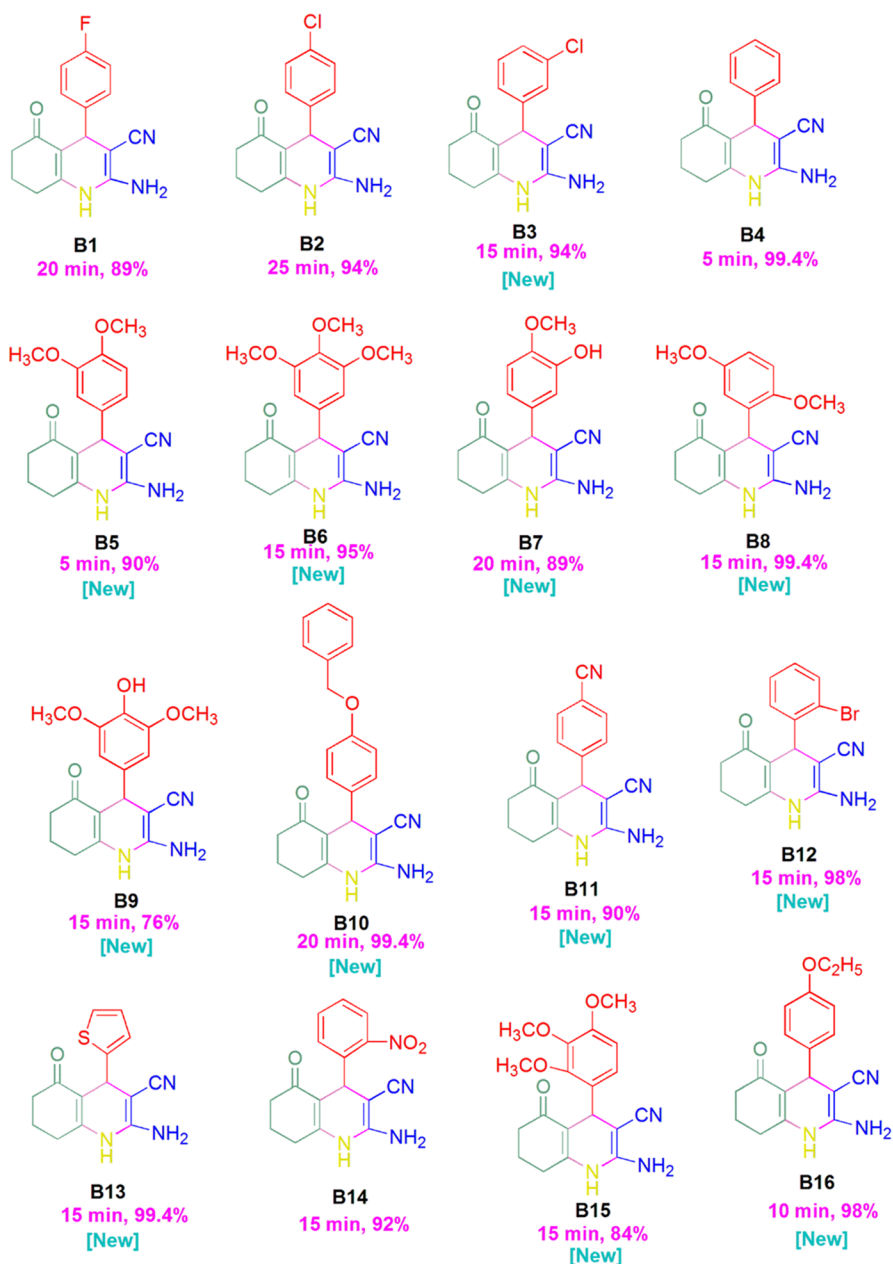


Figure 2. Library of synthesized hexahydroquinoline (B series).

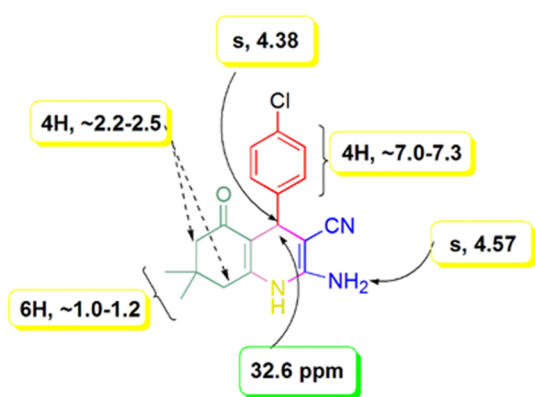


Figure 3. Significant  $^1\text{H}$  and  $^{13}\text{C}$  NMR peaks of 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile.

**2.2. Gram-Scale Synthesis.** For the study of the applicability of the present methodology at the industrial level, gram-scale synthesis was performed. Here, dimedone (**1a**, 1.40 g, 10 mmol), malononitrile (**2**, 0.66 g), ammonium acetate (**3**, 0.848 g), and 4-Cl benzaldehyde (**4b**, 1.40 g, 10 mmol) were stirred for 15 min with  $[\text{H}_2\text{-DABCO}][\text{HSO}_4]_2$  catalyst in ethanol at room temperature and afforded good yields (92%) of the desired product (**A2**).

**2.3. Green Chemistry Matrix.**<sup>49–52</sup> The green chemistry matrix represents the eco-friendliness of any method. As per the above green score calculation, it was concluded that the reaction has a low Environmental factor (E-factor = 0.32), high atom economy (AE = 77.34%), high process mass intensity (PMI = 1.32), and high reaction mass efficiency (RME = 75.76%), with excellent eco-score (78%) (calculation is given in the Supporting Information). These values validate the greenness of the present methodology.

## Scheme 3. Plausible Mechanism of Ionic-Liquid-Assisted Hexahydroquinoline Synthesis

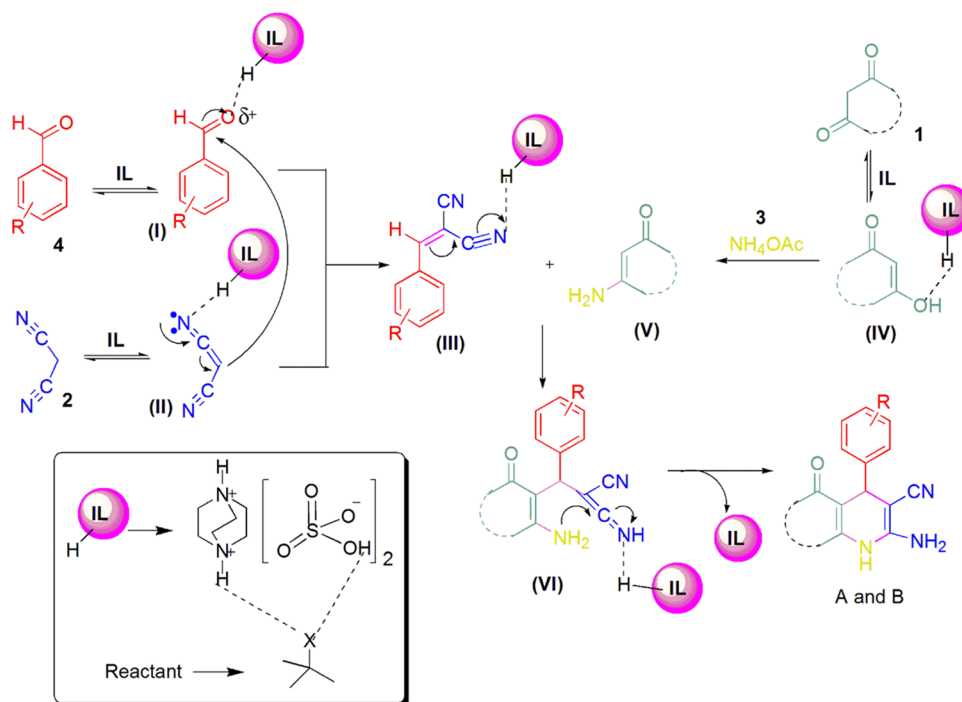
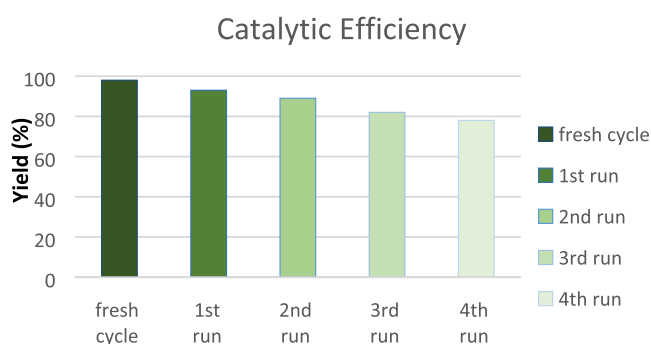


Table 2. Comparative Study of the Efficiency of Present Catalyst and Other Reported Catalysts for A2 Synthesis

sl. no.	catalyst	conditions	time (min)	yield (%)	derivative	catalyst recycle-ability	ref
1	NH <sub>4</sub> OAc (2 mmol)	H <sub>2</sub> O, reflux	57–81	80–90	17		38
2	sulfonated rice husk (60 mg)	solvent-free, 60–80 °C	60	90–98	17	7	39
4	nanosized MgO [65 mol %]	EtOH, reflux	18–29	88–91	6		40
5	<i>n</i> -Fe <sub>3</sub> O <sub>4</sub> @TDI@TiO <sub>2</sub> [0.028 g]	solvent-free, 70 °C	14–40	82–95	22	6	41
6	citric acid/MCM-48 [50 mg]	EtOH, RT	15	92–98	11	7	42
7	K <sub>2</sub> CO <sub>3</sub> [5 mol %]	H <sub>2</sub> O, ultrasound	12–15	85–92	7		43
8	[H <sub>2</sub> -DABCO][HSO <sub>4</sub> ] <sub>2</sub> (30 mg)	EtOH, stirring, room temperature	5–15	76–99	28	5	present work

Figure 4. Graphical representation of [H<sub>2</sub>-DABCO][HSO<sub>4</sub>]<sub>2</sub> reusability.

## 3. EXPERIMENTAL SECTION

**3.1. General Procedure of Hexahydroquinoline Derivatives (A1–A12) (B1–B16) Synthesis.** To a mixture of 1,3-dicarbonyl (0.5 mmol), substituted benzaldehyde (0.5 mmol), malononitrile (0.5 mmol), and ammonium acetate (0.5 mmol) were added, and the reaction mixture was stirred in the [H<sub>2</sub>-DABCO][HSO<sub>4</sub>]<sub>2</sub> catalyst (30 mg, 0.097 mmol) and EtOH (3–4 mL) solvent at room temperature for up to 5–20 min. After completion of the reaction as confirmed by TLC

(hexane/ethyl acetate), the reaction mixture was dried and cold water was added for catalyst recovery and then filtered to isolate the product. The isolated product was purified using simple crystallization from ethanol.

**3.2. Spectral Data.** The synthesis process of ionic liquid and its characterization data (IR, <sup>1</sup>H, <sup>13</sup>C NMR, and XRD) with FT-IR, <sup>1</sup>H, <sup>13</sup>C NMR, and mass spectra of synthesized compounds are given in the Supporting Information.

## 4. CONCLUSIONS

The catalytic efficiency of [H<sub>2</sub>-DABCO][HSO<sub>4</sub>]<sub>2</sub> ionic liquid for the synthesis of a broad range of substituted hexahydroquinoline-3-carbonitriles has been demonstrated. The synthesized IL is green, inexpensive, readily available, biodegradable,<sup>53</sup> and recyclable. The desired hexahydroquinolines were synthesized in eco-friendly conditions using a mild solvent at room temperature with high purity in a short reaction time. Aldehydes having various key functional groups such as fluoro, chloro, methoxy, ethoxy, nitro, bromo with benzylic, heteroaromatic, and aliphatic groups are well tolerated in this reaction. These superfluous properties of the present protocol make it superior as compared to the previously reported methods.

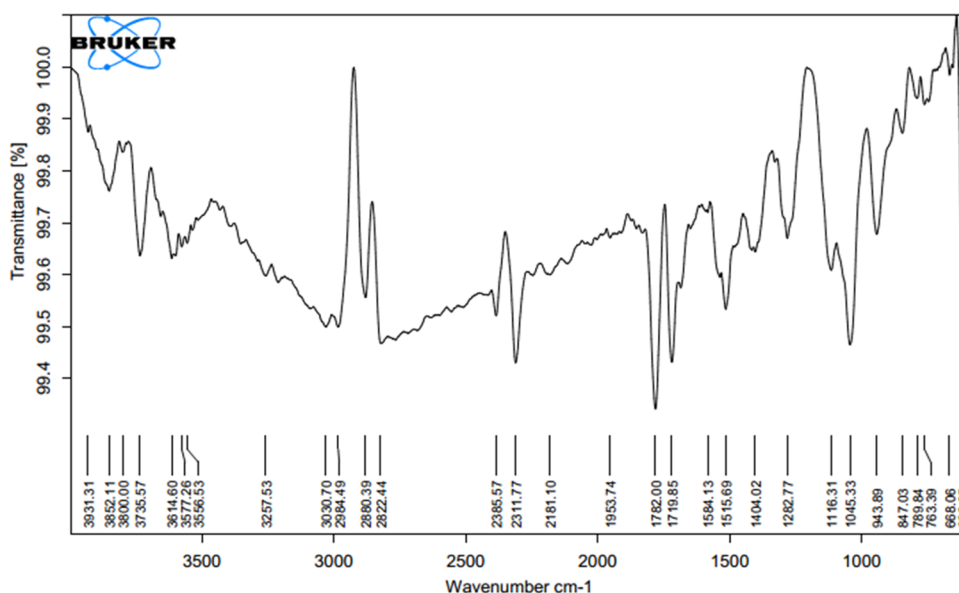


Figure 5. IR spectrum of the catalyst after the fifth cycle.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c07672>.

Catalyst synthesis and characterization data (IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and XRD) with FT-IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and mass data of synthesized compounds. (PDF)

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### Notes

The authors declare no competing financial interest.

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