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Deep Eutectic Solvent Based on Choline Chloride/Urea as an Efficient Catalytic System for the One-Pot Synthesis of Highly Functionalized 1,4-Dihydropyridines and Polysubstituted 4*H*-Chromenes

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Abstract

One-pot four-component synthesis of polyfunctionalized 1,4-dihydropyridine derivatives was developed by a condensation of aldehydes, malononitrile, diethylacetylenedicarboxylate and aniline in the presence of choline chloride/urea as a deep eutectic solvent (DES)at room temperature. Moreover, an efficient method was reported for the synthesis of highly substituted 4*H*-chromenes through one-pot, three-component reactions of cyclohexane-1,3-dione or dimedone, malononitrile and diethylacetylenedicarboxylate, in the presence of the deep eutectic solvent at 60 °C. This method develops by using an environmentally benign synthetic method along with the use of a cost-effective catalyst.

Keywords: *Multicomponent reactions, Deep eutectic solvent, 1,4-Dihydropyridine, 4H-chromene, Diethylacetylenedicarboxylate*.

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Introduction

Deep eutectic solvents are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species [1]. They incorporate a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), which are able to give a eutectic with a melting point much lower than either of the individual components [2]. One of the most significant deep eutectic phenomenons was observed for a mixture of choline chloride and urea in a 1:2 mole ratio. The resulting mixture has a melting point of 12 °C, which makes it liquid at room temperature [3]. 1,4-Dihydropyridines (1,4-DHPs) are one of the most well-known heterocyclic frameworks since a large number of these molecular building block show interesting pharmacological properties such as, antiangin [4], antitumor [5], antitubercular [6], analgesic [7], antithrombotic [8], and muscle relaxant activity [9]. 4*H*-Chromene derivatives are also considered as a venerable pharmacophore and have a wide range of biological applications e.g. inhibitors of excitatory amino acid transporters (EAAT1) [10], an anticancer agent [11] and Bcl-2 inhibitor [12]. There are some methods for the synthesis of functionalized 1,4-dihydropyridines by the four component reaction of aldehydes, malononitrile, dialkylacetylenedicarboxylate and aniline derivatives in the presence of Sm_2O_3/ZrO_2 [13], Et_3N [14], [3,6-DOMDA]OTf [15], KF/Al_2O_3 [16], NaOH [17], pipiridine [18] and L-proline [19]. Also, the synthesis of highly substituted 4*H*-chromenes reported via the three component reaction of dimedone or cyclohexane-1,3-dione, malononitrile and dialkylacetylenedicarboxylate catalyzed by CH_3NH_2 [20], Na_2CO_3 [21], and nano crystalline $CuFe_2O_4$ [22]. However, some drawbacks still exist, such as, hard reaction condition, moderate yields, and non-recyclable catalysts. Thus, a simple, efficient, and green method to synthesize these highly important heterocycles would be attractive.

Experimental

General

All chemicals were purchased from the Merck. Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. NMR spectra were determined in $CDCl_3$ on a Bruker Avance DRX-300 MHz apparatus spectrometer by TMS as internal standard. FT-IR spectra were provided with potassium bromide pellets in the range 400–4000 cm^{-1} with an SP-1100, Shimadzu instrument. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values.

The catalyst preparation

Choline chloride-urea deep eutectic solvent was prepared according to the reported method in the literature [23].

General procedure for the synthesis of functionalized 1,4-dihydropyridines

A mixture of aromatic aldehyde (1mmol), malononitrile (1mmol, 0.066 g), aniline (1 mmol, 0.93 g) and diethylacetylenedicarboxylate (1 mmol, 0.142 g) in the presence of choline chloride/urea (1 mL) was stirred at room temperature in 2 hours. After completion of the reaction by TLC monitoring, the mixture was diluted with ethanol (5 mL), then, the crude solid residue was filtered and recrystallized from ethanol to afford pure crystals of the proper functionalized 1,4-dihydropyridines in 88-96% yields. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and by comparison with authentic samples reported in the literature.

Spectroscopic data for new compounds as follows:

*Diethyl 6-amino-4-(4-bromophenyl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (**5c**)*

Yellow solid; mp 152-154 °C; FT-IR (KBr): $\bar{\nu}$ = 3448 and 3361 (NH_2 stretch), 2970 (C-H stretch), 2185 (CN stretch.), 1708 (C=O), 1649 (C=O), 1581(C=C stretch), 1222 (C-N stretch), 1070 (C-Br stretch), 698 (aromatic C-H out of plane bending. ^{1}H NMR δ: 0.82 (t, *J* = 7.2 Hz, 3H, CH_3), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3), 3.72-3.87 (m, 2H, CH_2), 3.93-4.01 (q, *J* = 6.9 Hz, 2H, CH_2), 4.7 (s, 1H, CH), 5.79 (s, 2H, NH_2), 7.38-7.42 (m, 2H, Ar-H), 7.52-7.55 (m, 2H, Ar-H), 7.60 (d, *J* = 8.7 Hz, 2H, Ar-H), 8.31 (d, *J* = 8.7 Hz, 2H, Ar-H); ^{13}C NMR δ: 13.6, 14.2, 59.6, 61.0, 61.9, 113.5, 114.5, 120.5, 121.2, 128.8, 129.6, 130.0, 130.5, 130.8, 130.9, 132.1, 132.6, 133.1, 135.7, 142.3, 145.4, 151.3, 160.7, 162.7, 164.8. Anal. Calcd. (%) for $C_{24}H_{21}N_3O_4Br$: C, 58.19, H, 4.27, N, 8.48. Found: C, 58.26, H, 4.30, N, 8.51.

*Diethyl 6-amino-5-cyano-4-(4-fluorophenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (**5d**)*

Yellow solid; mp 157-159 °C; FT-IR (KBr): $\bar{\nu}$ = 3448 and 3359 (NH_2 stretch), 3058 and 2975 (C-H stretch), 2185 (CN stretch.), 1712 and 1649 (C=O stretch), 1518 (C=C stretch), 1222 (C-N stretch), 1159 (C-F stretch), 696 (aromatic C-H out of plane bending); ^{1}H NMR δ: 0.81 (t, *J* = 7.2 Hz, 3H, CH_3), 1.04 (td, *J* = 7.2 Hz, 2.7 Hz, 3H, CH_3), 3.69 -3.88 (m, 2H, CH_2), 3.95 (q, *J* = 14.1 Hz, 2H, CH_2), 4.54 (s, 1H, CH), 5.66 (s, 2H, NH_2), 7.22 (t, *J* = 8.7 Hz, 2H, Ar-H), 7.35 (t, *J* = 5.4 Hz, 4H, Ar-H), 7.52 (t, *J* = 3.3 Hz, 3H, Ar-H); ^{13}C NMR δ:13.6, 14.1, 60.0, 60.9, 61.8,104.8, 115.7, 116.0, 121.3, 129.1, 129.3, 130.0, 130.5, 135.7, 142.1, 142.3, 142.3, 151.2, 162.7, 164.9. Anal. Calcd. %: $C_{24}H_{21}N_3O_4F$: C, 66.35, H, 4.87, N, 9.67. Found: C, 66.38, H, 4.90, N, 9.69.

*Diethyl 6-amino-5-cyano-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (**5e**)*

Yellow solid; mp 172-174 °C, FT-IR (KBr): $\bar{\nu}$ = 3473 and 3375 (NH_2 stretch), 3066 and 2979 (C-H strech), 2181(CN stretch), 1745 and 1695 (C=O stretch), 1647 and 1569 (C=C strech), 1523 and 1344 (NO_2 strech), 1247 (C-N stretch.), 698 (aromatic C-H out of plane bending); ^{1}H NMR δ: 0.82 (t, *J* = 7.2 Hz, 3H, CH_3), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3), 3.74-3.87 (m, 2H, CH_2), 3.94 (q, *J* = 7.2 Hz, 2H, CH_2), 4.7 (s, 1H, CH), 5.80 (s, 2H, NH_2), 7.38-7.42 (m, 2H, Ar-H), 7.52-7.57 (m, 3H, Ar-H), 7.60 (d, *J* = 8.7 Hz,2H, Ar-H), 8.31 (d, *J* = 8.7 Hz, 2H, Ar-H); ^{13}C NMR δ: 13.6, 14.0, 61.8, 63.2, 94.1, 99.7, 114.1, 114.8, 119.5, 123.1,130.7, 131.7, 136.1, 141.6, 150.1, 153.8, 164.7, 165.0.Anal. Calcd. %: $C_{24}H_{21}N_4O_6$: C, 62.47, H, 4.59, N, 12.14. Found: C, 62.51, H, 4.62, N, 12.16.

*Diethyl 6-amino-4-(4-chloro-3-nitrophenyl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarbo-xylate (**5l**)*

Yellow solid; mp 194-196 °C; FT-IR (KBr): $\bar{\nu}$ = 3438 and 3328 (NH_2 stretch), 3087 and 2983 (C-H stretch), 2183 (CN stretch), 1745 and 1691 (C=O strech), 1652 (C=C stretch), 1519 and 1371(NO_2 strech), 1251 (C-N stretch.), 702 (aromatic C-H out of plane bending); ^{1}H NMR δ: 0.85 (t, *J* = 7.2 Hz, 3H, CH_3), 0.98-1.05 (m, 3H, CH_3), 3.72-3.88 (m, 2H, CH_2), 3.91-4.02 (m, 2H, CH_2), 5.43 (s, 1H, CH), 5.82 (s, 2H, NH_2), 7.38 -7.45 (m, 2H, Ar-H), 7.57 (t, *J* = 2.1 Hz, 3H, Ar-H), 7.81 (d, *J* = 8.7Hz , 1H), 8.14 (dd, *J* = 8.7, 2.7 Hz, 1H, Ar-H), 8.31 (d, *J* = 2.7 Hz,1H, Ar-H); ^{13}C NMR δ: 13.5, 14.0, 19.0, 56.51, 58.3, 61.1, 62.0, 103.1, 120.6, 123.8, 124.4, 130.2, 130.7, 130.8, 131.6, 135.3, 138.5, 143.9, 145.2, 147.5, 151.8, 162.4, 164.4. Anal. Calcd. %: $C_{24}H_{20}N_4O_6Cl$: C, 58.13, H, 4.07, N, 11.30. Found: C, 58.16, H, 4.05, N, 11.33.

*Ethyl (E)-2-cyano-3-(4-chlorophenyl) acrylate (**3a**)*

Reaction time 1 h; yield 94%;wight solid; mp 81-83 °C; FT-IR (KBr): $\bar{\nu}$ = 2987 (C-H stretch), 2221 (CN stretch),1722 (C=O stretch.), 1610 and 1585 (C=C stretch), 1265 (C-O stretch), 1080 (C-Cl stretch), 829 (aromatic C-H out of plane bending); ^{1}H NMR δ: 1.30 (t, *J* = 7.2 Hz, 3H, CH_3), 4.30 (q, *J* = 6.9 Hz, 2H, CH_2), 7.65 (d, *J* = 8.7 Hz, 2H, Ar-H), 8.04 (d, *J* = 8.7 Hz, 2H, Ar-H), 8.40 (s, 1H, C=CH).

*Ethyl (E)-2-cyano-3-(4-bromophenyl) acrylate (**3b**)*

Reaction time 1 h; yield 92%; wight solid; mp 80-82 °C; FT-IR (KBr): $\bar{\nu}$ = 2985 (C-H stretch), 2219 (CN stretch),1722 (C=O stretch.), 1610 and 1579 (C=C stretch), 1066 (C-Br stretch), 825 (aromatic C-H out of plane bending); ^{1}H NMR δ: 1.30 (t, *J* = 4.8 Hz, 3H, CH_3), 4.30 (q, *J* = 7.9 Hz, 2H, CH_2), 7.82 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.98 (d, *J* = 8.7 Hz, 2H, Ar-H), 8.40 (s, 1H, C=CH).

*Ethyl (E)-2-cyano-3-(4-fluorophenyl)acrylate (**3c**)*

Reaction time1 h; yield 94%; wight solid; mp 94-96 °C; FT-IR (KBr): $\bar{\nu}$ = 2997 (C-H stretch), 2225 (CN stretch),1716 (C=O stretch.), 1608 and 1595 (C=C stretch), 1161 (C-O stretch),1014 (C-F stretch), 838 (aromatic C-H out of plane bending); ^{1}H NMR δ: 1.30 (t, *J* = 6.9 Hz, 3H, CH_3), 4.30 (q, *J* = 7.2 Hz, 2H, CH_2), 7.42 (t, *J* = 8.7 Hz, 2H, Ar-H), 813-8.19 (m, 2H, Ar-H), 8.41 (s, 1H, C=CH).

*(E)-3-(3-Chlorophenyl)-2-cyanacrylamide (**3d**)*

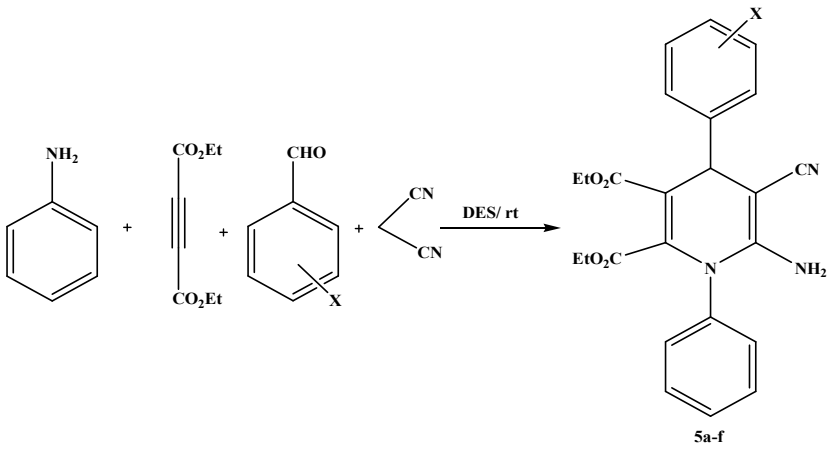
Reaction time1 h; yield 81%;wight solid; mp 92-94 °C; FT-IR (KBr): $\bar{\nu}$ = 3452 and 3303 (NH_2 strech), 3155 (C-H stretch), 2210 (CN stretch),1704 (C=O strech), 1585 (C=C stretch), 1380 (C-N stretch),1089 (C-Cl stretch), 825 (aromatic C-H out of plane bending); ^{1}H NMR δ: 7.66 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 2H, NH_2), 7.95 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (s, 1H, C=CH).

General procedure for the synthesis of highly substituted 4H-chromenes

A mixture of cyclohexane-1,3-dione (1 mmol, 0.112 g) or dimedone (1 mmol, 0.140 g), malononitrile (1 mmol, 0.066 g), and diethylacetylenedicarboxylate (1 mmol, 0.142 g) in the presence of choline chloride/urea (1 mL) was stirred at 60 °C in 2 hours. After completion of the reaction by TLC monitoring, the mixture was diluted with ethanol (5 mL) and cooled in refrigerator. Then, the crude solid residue was recrystallized from ethanol to afford pure crystals of the proper highly substituted 4*H*-chromenes in 94-96% yields. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and by comparison with authentic samples reported in the literature. Yields for known compounds: **4a**:94%, reported: 81% [20], **4b**:96%, reported: 90% [20].

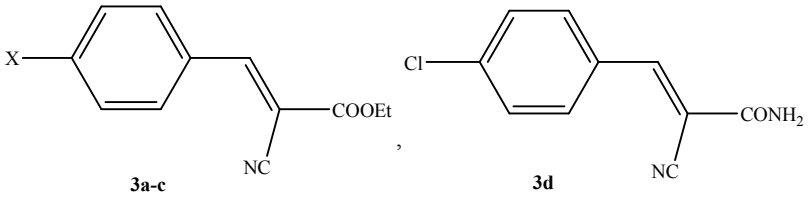
Results and discussion

In this research, polyfunctionalized 1,4-dihydropyridine derivatives synthesized by one-pot four-component condensation of aldehydes, malononitrile, diethylacetylenedicarboxylate and aniline in the presence of choline chloride/urea at room temperature (Scheme 1).



Scheme 1. Synthesis of polyfunctionalized 1,4-dihydropyridines by DES.

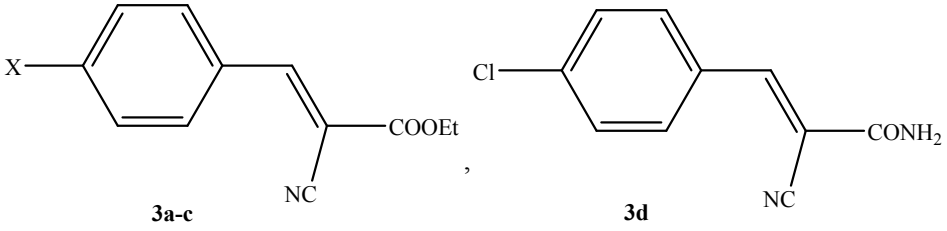
It is notable that replacing malononitrile with ethylcyanoacetate or cyanoacetamide in the above reaction leads to just Knoevenagel products **3a-d** (Scheme 2).



3a: X = 4-Cl, 3b: X = 4-Br, 3c: X = 4-F

Scheme 2. Synthesis of Knoevenagel product.

Moreover, an efficient method was developed for the synthesis of highly functionalized 4*H*-chromenes by three-component reactions of cyclohexane-1,3-dione or dimedone, diethylacetylenedicarboxylate, and malononitrile in the presence of choline chloride/urea as deep eutectic solvent at 60 °C (Scheme 3).



3a: X = 4-Cl, 3b: X = 4-Br, 3c: X = 4-F

Scheme 3. Synthesis of highly functionalized 4*H*-chromenes by DES.

To optimize the reaction conditions and get the best catalytic activity, the four-component reaction of 4-Cl-benzaldehyde, dimedone, diethylacetylenedicarboxylate and aniline was examined as a sample reaction in different amounts of DES. It was considered that the variation of the catalyst had

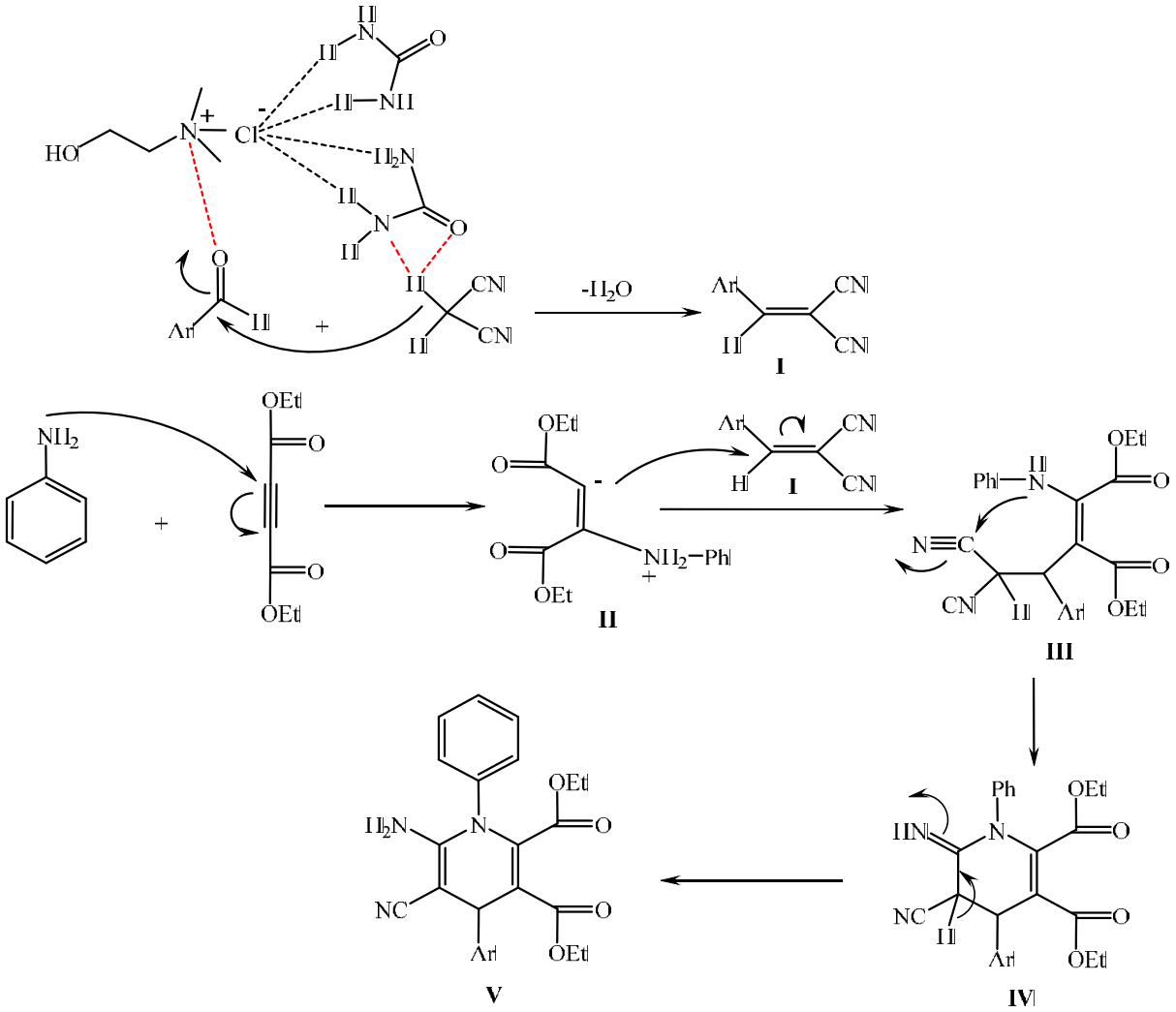
an effective influence on the reaction yields. The results showed the best amount of DES is 1 mL, which afforded the required product in high yields. By these optimized reaction conditions, a diversity of polyfunctionalized 1,4-dihydropyridines were prepared using DES at room temperature (Table 1). All synthesized products were characterized by using FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy and elemental analysis.

Table 1. Synthesis of polyfunctionalized 1,4-dihydropyridines by DES[a].

Entry	X	Product	Time (h)	Yield (%)[b]	m.p. °C	
					Found	Reported
1	H	**5a**	3	88	173-175	174-175 [18]
2	4-Cl	**5b**	2.45	95	187-188	188-189 [18]
3	4-Br	**5c**	2.45	96	152-154	----
4	4-F	**5d**	2.30	96	157-159	----
5	4-NO_2	**5e**	2.30	92	172-174	----
6	4-Cl-3-NO_2	**5f**	2.30	96	194-196	----

[a]Reaction and conditions: aldehyde (1 mmol), aniline (1 mmol), malononitrile (1 mmol), diethylacetylenedicarboxylate (1 mmol), in DES (1 mL) at room temperature.
[b]All yields refer to isolated products.

A reasonable mechanism for the synthesis of polyfunctionalized 1,4-dihydropyridines in the presence of choline chloride/urea is shown in Scheme 4. First, the Knoevenagel intermediate **I** is obtained from the reaction of aldehyde with malononitrile in the presence of choline chloride/urea. Then, reaction of aniline with diethylacetylenedicarboxylate leads to the intermediate **II**. In the next step, the Michael addition of intermediate **II** with intermediate **I**, generate intermediate **III**. Then, with an intra-molecular condensation of the amine group with the cyano group, the intermediate **IV** is formed, which is converted to the final product **V** by the tautomerization.



Scheme 4. Plausible mechanism for the synthesis of polyfunctionalized 1,4-dihydropyridines catalyzed by DES.

In order to study the recyclability of the catalyst, it was utilized in the synthesis of compound **5b**,five runs under the optimized conditions. On completion of the reaction, the crude residue was filtered and the viscous ionic liquid that remains in the reaction flask is thoroughly washed with ether and reused in subsequent reactions without further purifications. It was found that the initial yield of **5b** of 95% decreased only to 90% in the fifth run.

To explore the efficiency of the present method for the synthesis of highly functionalized 1,4-dihydropyridines and polysubstituted 4*H*-chromenes, compounds **5a** and **4b** were compared with some of those reported in the literature (Table 2). As one can see, our results show a very good comparison with previously reported data when all terms, including yields, reaction times, and reaction conditions are taken into account.

Table 2. Comparison of choline chloride/urea with some other catalysts for synthesis of **5a** and **4b**.

Product	Catalyst	Reaction conditions	Time	Yield (%)	Ref.
5a	Piperidin	EtOH/reflux	6 h	78	[18]
5a	[3,6-DOMDA]OTf	50 °C	25 min	89	[15]
5a	DES	Room temperature	2.5 h	92	This work
4b	CH_3NH_2	80 °C	30 min	90	[20]
4b	Na_2CO_3	EtOH/reflux	2.5 h	89	[21]
4b	DES	60 °C	2 h	96	This work

Conclusion

In summary, we have extended a simple, clean, efficient and one-pot procedure for the synthesis of polyfunctionalized 1,4-dihydropyridines, some Knovonagel products and highly functionalized 4*H*-chromenes in choline chloride/urea as deep eutectic solvent. An environmentally friendly conditions, simple performance, and reusability of the catalyst are some of the advantages of this method.

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