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Three-component synthesis of 4*H*-pyran scaffolds accelerated by a gabapentin-based natural deep eutectic solvent†

Meysam Alipour Khoshdel, Farhad Shirini,* Mohaddeseh Safarpoor Nikoo Langarudi, Mehdi Zabihzadeh and Mohammad Biglari

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The development of environmentally benign synthetic protocols has attracted increasing attention in recent organic syntheses. As a part of this concept, our group synthesized a new natural deep eutectic solvent (NADES) by using gabapentin and choline chloride. After characterization by FTIR, ^{1}H and ^{13}C NMR, and mass spectra, the prepared NADES was utilized as an efficacious catalyst for the synthesis of 4*H*-pyran scaffolds such as tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone(thione) derivatives. The use of inexpensive and bio-compatible reagents for the synthesis of the catalyst, a simple and green procedure for the preparation of the catalyst and products, short reaction times, high yields of the products, and applicability to large-scale synthesis are the prominent features of this protocol. Also, the catalyst could be recovered easily and recycled up to five times without significant loss of its catalytic activity.

Introduction

For up to two decades, ionic liquids (ILs) have been selected as green solvents for the replacement of traditional organic solvents in synthetic methodologies. For years, scientists' attempts have led to less moisture-sensitive ionic liquids and metal-free ones designed for specific tasks. However, the sustainability and greenness of ILs have grown dubiously and chemists struggle to find novel solvent–catalysts to use in organic syntheses. To develop eco-friendly solvents, deep eutectic solvents (DESs) have attracted a great deal of attention because they show ionic character like ILs. However, they are more cost-saving (because of the use of inexpensive raw materials), less toxic, and more biodegradable than ILs. DESs consist of a mixture of compounds possessing lower melting points than their ingredients. This cut in the melting point is due to the formation of hydrogen bonding between H-bond donor and acceptor species used for the preparation of the requested DES.[1]

In recent years, Dai and co-workers focused on natural compounds that can be used as H-bond donors such as organic acids, amino acids, and sugars.[2,3] Use of these compounds along with a natural H-bond acceptor like choline chloride, betaine, glycerol, and lactic and malic acids[3,4] causes the development of a novel category named Natural Deep Eutectic Solvents (NADESs) as very important biodegradable types of DESs. Amino acids are highly abundant molecules which are well-known as the sub-units of proteins. Amino acids hold an acidic (COOH) and a basic (NH_2) functional group in their structures. This special structure causes brilliant properties in these materials. Because of these groups, amino acids can be convenient H-bond donors for the preparation of DESs. Based on the relative position of the COOH and NH_2 groups, amino acids are divided into α, β, γ, and δ ones (Fig. 1). Although α-amino acids are known as protein-building amino acids (proteinogenic), non-proteinogenic amino acids are used as intermediates in metabolic pathways (*e.g.* β-alanin is an intermediate in the synthesis of vitamin B5 in plants and microorganisms)[5] or as medications in the drug industry (gabapentin is *e.g.* used to treat neuropathic pain[6] and pregabalin is a medication for treating epilepsy and fibromyalgia).[7]

Choline is an essential nutrient, commonly grouped with the B complex vitamins, that plays key roles in many biological processes. It is a constituent of sphingomyelin and lecithin and a precursor of acetylcholine. Choline plays a vital role in methyl group metabolism, carcinogenesis, and lipid transport. Its deficiency is associated with a fatty liver.[8] It can be used for bodybuilding and delaying fatigue in endurance sports. On the other hand, researchers showed that taking choline can loosen the symptoms of asthma in people who have this disease.[9] In recent years, the choline chloride reagent as a bi-functional compound containing quaternary ammonium and alcoholic groups is widely used in the synthesis of DESs.[10–13] 4*H*-Pyrans and pyran-annulated heterocyclic scaffolds have attracted great attention due to their diverse useful biological and pharmacological

Department of Chemistry, College of Sciences, University of Guilan, Rasht, 41335-19141, Iran. E-mail: shirini@guilan.ac.ir; Fax: +98 131 3233262; Tel: +98 1313233262

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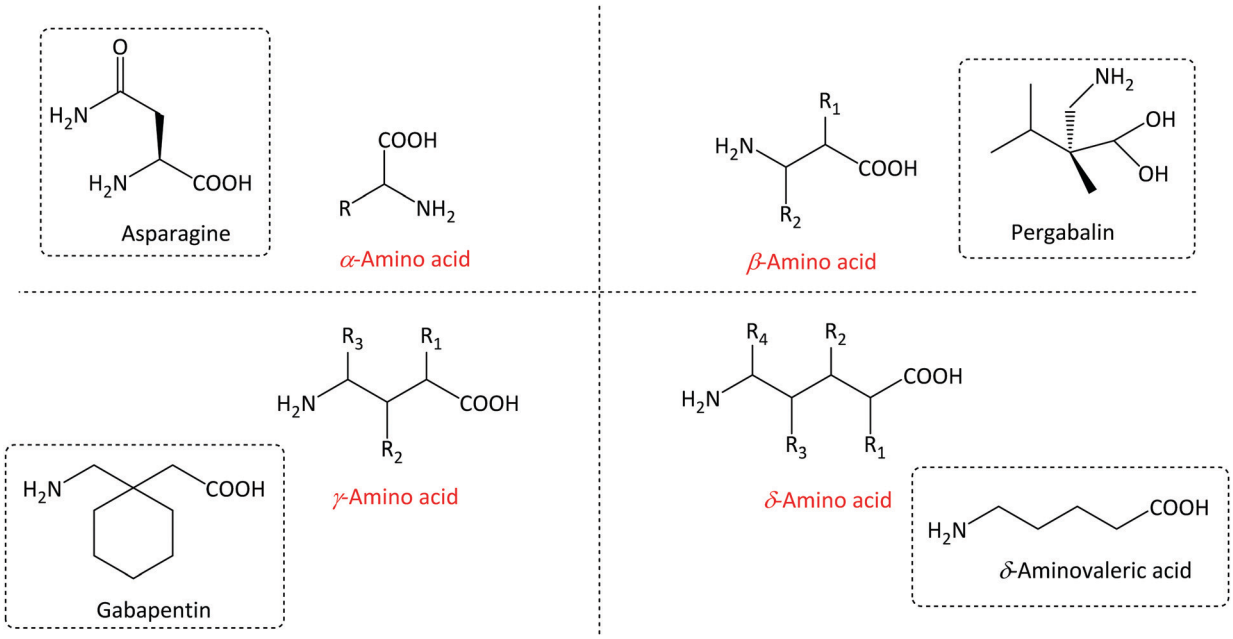


Fig. 1 Amino acids, categorized based on the relative position of the functional groups (NH_2 and COOH).

activities such as antimicrobial,[14] anti-cancer,[15,16] antiviral, and antileishmanial properties.[17]

They are also used as cognition-enhancing drugs for the treatment of neurodegenerative disease, including schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Down's syndrome.[18]

In this study, a new natural deep eutectic solvent was prepared from gabapentin and choline chloride. After identification its catalytic activity was investigated in the synthesis of 4*H*-pyran scaffolds such as tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]-pyrimidinone(thione) derivatives.

Experimental

Materials

All of the aldehydes, malononitrile, C–H activated acidic compounds, gabapentin, and choline chloride were purchased from Sigma-Aldrich (Mumbai) and Merck (Munich) chemical companies and were used without further purification. The purity of the substrates was monitored by thin-layer chromatography (TLC). All solvents were purchased from Merck (Munich) and were kept sealed in airtight bottles as well to minimize the absorption of atmosphere moisture. Moreover, they were distilled before being used.

Characterization techniques

The products were characterized by their physical constants, comparison with authentic samples, and IR and NMR spectroscopies. The purity determination of the substrate and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates. Melting points were measured using an electrothermal IA9100 melting point apparatus in capillary tubes. The starting temperature of the approximate melting range was input *via* the keyboard and the melting point range was spotted visually.

FT-IR spectra were recorded with a PerkinElmer Spectrum BX series and KBr pellets were used for solid samples. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker AV-400 and 500 using TMS (0.00 ppm) as an internal standard and DMSO-d_6 and $CDCl_3$ as solvents. Mass spectra were measured using an Agilent Technologies 5975C spectrometer *via* a mass selective detector operating at an ionization potential of 70 eV.

Preparation of the [Ch]Cl:Gab NADES

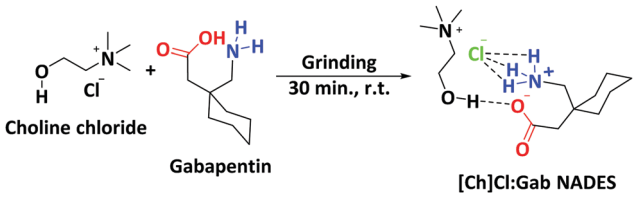
A mixture of choline chloride ([Ch]Cl) (6.98 g, 50 mmol) and gabapentin (Gab) (8.56 g, 50 mmol) was ground in a mortar at room temperature for 30 min until a homogeneous white highly viscous liquid appeared. Then, the reaction was stopped and the prepared NADES was collected without any further purification. The characterization of the obtained NADES was done using FT-IR, mass, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques.

General procedure for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone(thione) derivatives

In a round-bottomed flask (10 mL) a mixture of aldehyde **1** (1 mmol), the requested C–H activated acidic compound **2** (1 mmol), malononitrile **3** (1 mmol), and the prepared NADES (0.031 g, 10 mol%) was stirred and heated in an oil-bath at 75 °C for an appropriate period of time. After completion of the reaction (monitored by TLC [*n*-hexane–EtOAc (10 : 2)]), water was added to separate the catalyst. Then, the precipitated product was filtered, dried, and subsequently recrystallized from ethanol (**4a–y**).

Results and discussion

In recent years the use of organocatalysts in organic transformations has become an important part of our ongoing research program.[19,20] In this line, very recently we have reported the



Scheme 1 Preparation of the [Ch]Cl:Gab NADES.

preparation of a choline chloride, urea, and thiourea based DES and its ability in the promotion of some multi-component reactions.[21] Herein and in continuation of these studies we wish to report the preparation, identification, and application of the [Ch]Cl:Gab NADES as a new, green, and efficient natural deep eutectic solvent in the promotion of the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone(thione) derivatives.

Catalyst characterization

After preparation of the [Ch]Cl:Gab NADES (Scheme 1), various spectroscopic techniques were used to characterize its structure. Here are some elucidations in detail.

FT-IR analysis

The FT-IR spectra of the prepared [Ch]Cl:Gab NADES, choline chloride, and gabapentin are shown in Fig. 2. In the FT-IR spectrum of the [Ch]Cl:Gab NADES, the broad peak in the 2500–3500 cm^{-1} region is related to the vibrations of –OH in choline chloride and gabapentin. Also, the average peak observed at 3020 cm^{-1} is related to the vibrations of the aliphatic CH bonds. Also, the sharp peaks at 955 and 1080 cm^{-1} are related to the C–N and C–O tensile vibrations, respectively.

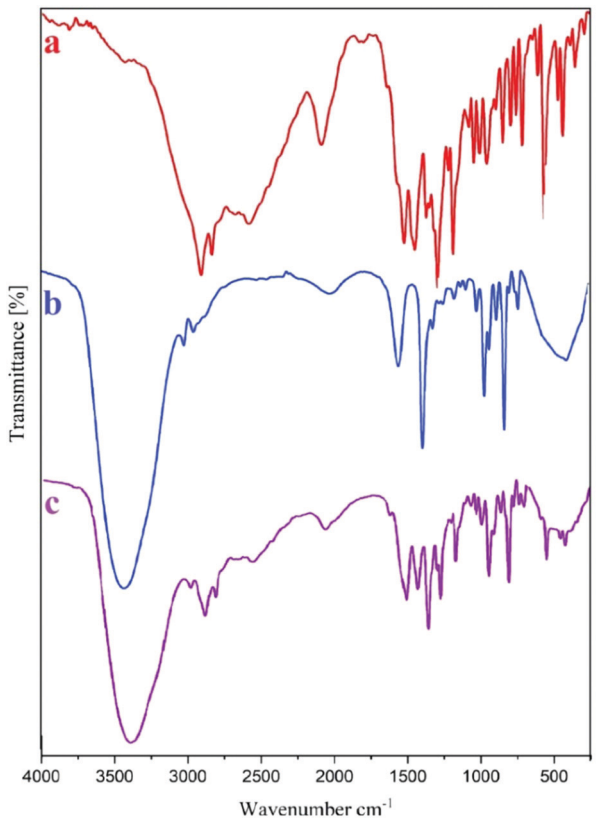


Fig. 2 FT-IR spectra of gabapentin (a), choline chloride (b) and the [Ch]Cl:Gab NADES (c).

Mass spectroscopy

The mass spectrum of the [Ch]Cl:Gab NADES is shown in Fig. 3. The molecular ion peak (M^+) appearing at m/z = 311 with relative intensity up to 0.40 corresponds to the molecular weight of the catalyst. Other ion peaks at m/z = 171 (11.2, gabapentin), m/z = 140 (5.6, [Ch]Cl[OH]), m/z = 128 (1.2, $C_8H_{17}N$), and m/z = 44 (24.8, C_2H_5O) and the base peak at m/z = 81.0 (100, C_6H_{12}) are also observed clearly.

NMR spectroscopy

In the ^{1}H NMR spectrum, of the prepared [Ch]Cl:Gab NADES, the aliphatic hydrogens of the are appeared as multiplet in the range of 1.41 to 1.21 ppm. The H_7 and H_8 peaks are seen at 2.22 ppm and 2.64 ppm, respectively. The peak related to H_{13} appears with coupling constant 4 Hz at 3.44 ppm as a triple and the quadrated H_{14} peak comes up with coupling constant 4 Hz at 3.82 ppm. The weakness of the OH and NH peaks also indicates the formation of hydrogen bonds in this compound (Fig. 4).

In the ^{13}C NMR spectrum of the prepared DES the number of peaks observed is equal to the number of carbons of the compound, and the peak corresponding to the carboxyl group appears at 175.1 ppm (Fig. 5).

Catalytic activity

The obtained data from the structural studies pointed out that the [Ch]Cl:Gab NADES is successfully synthesized. In the next step and in order to show the catalytic ability of this new NADES the promotion of the synthesis of tetrahydrobenzo[*b*]-pyran and pyrano[2,3-*d*]pyrimidinone(thion) derivatives in the presence of this reagent was investigated. The study was started by the optimization of the three-component reaction of 4-chloro-benzaldehyde, dimedone, and malononitrile as a model one. In this regard, the effect of different factors such as the catalyst loading, temperature, and solvent in this reaction was studied. Preliminary experiments revealed that only a trace amount of the desired product can be obtained when the reaction proceeded in aprotic solvents such as CH_3CN and CH_3Cl at reflux temperature. Next, the reaction was tested in protic solvents, water, and EtOH, at room temperature and under reflux conditions.

In these cases, the reactions were not completed after a prolonged time of reaction (60 min). When the reaction was carried out under solvent-free conditions, both the reaction times and yields were drastically improved. Further studies, as shown in Table 1 (entry 7), clarified that the best result can be obtained in the presence of 10 mol% of the [Ch]Cl:Gab NADES at 75 °C in the absence of solvent. It is very important to note

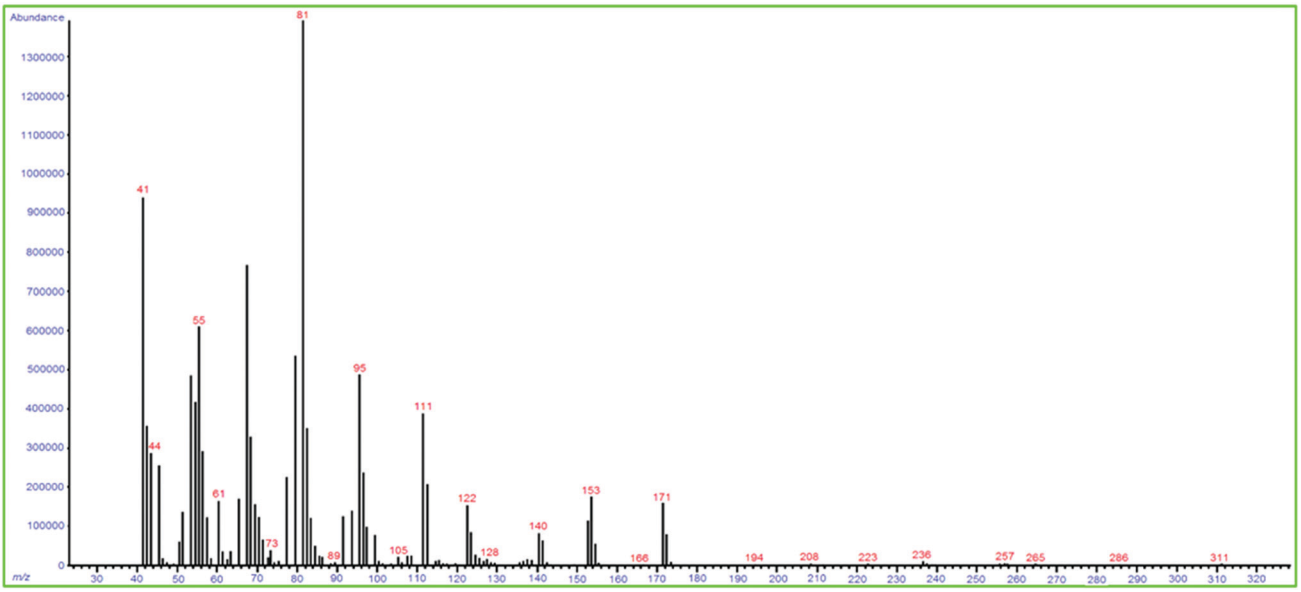


Fig. 3 Mass spectrum of the [Ch]Cl:Gab NADES.

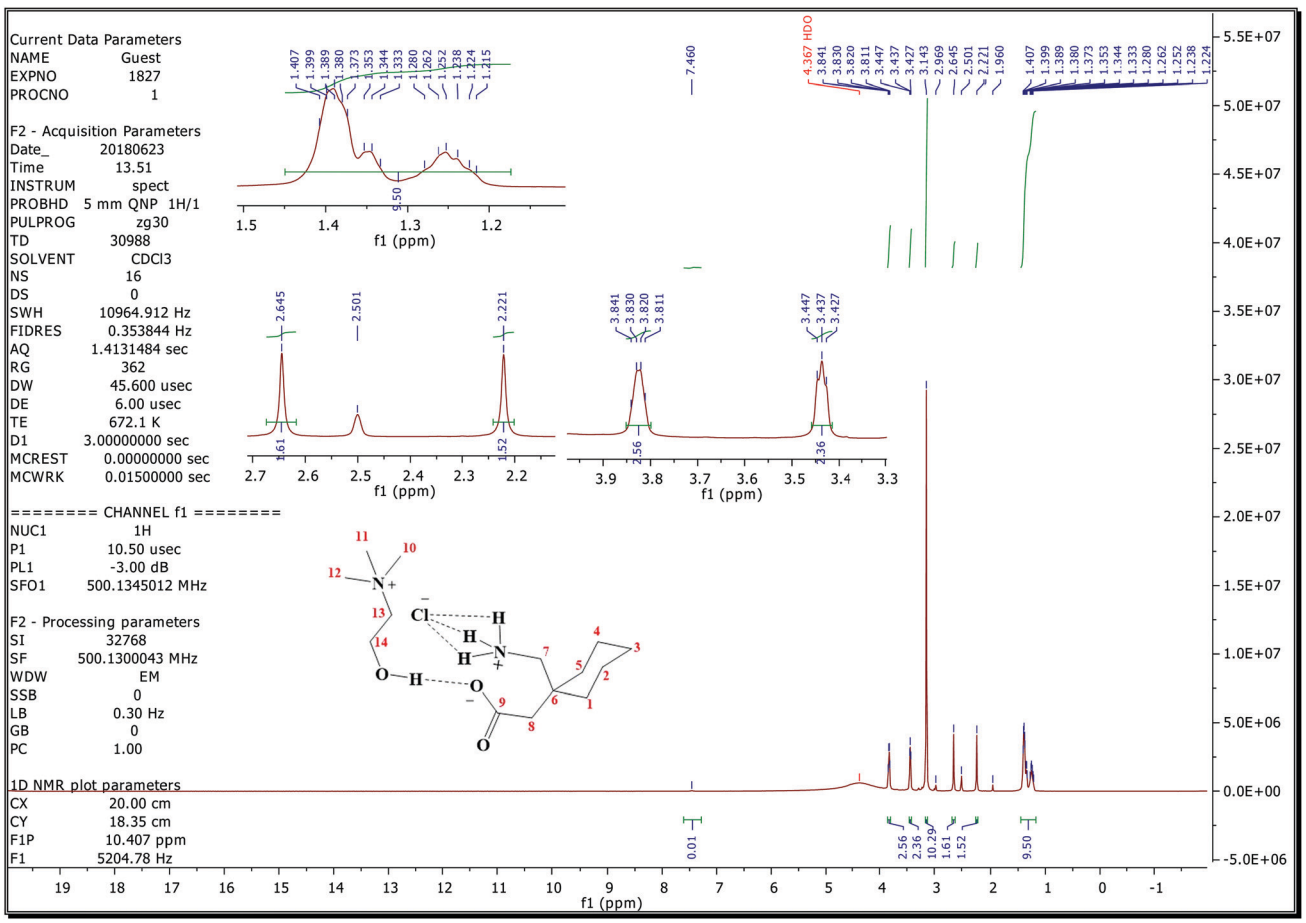


Fig. 4 ^{1}H NMR spectrum of the [Ch]Cl:Gab NADES.

that when the reaction proceeded in the presence of choline chloride or gabapantine, it was not completed even after long reaction times (Table 1, entries 11 and 12). To demonstrate the scope and generality of this protocol, different types of aromatic aldehydes containing electron-withdrawing or electron-donating groups in the *ortho*, *meta*, and *para* positions of the

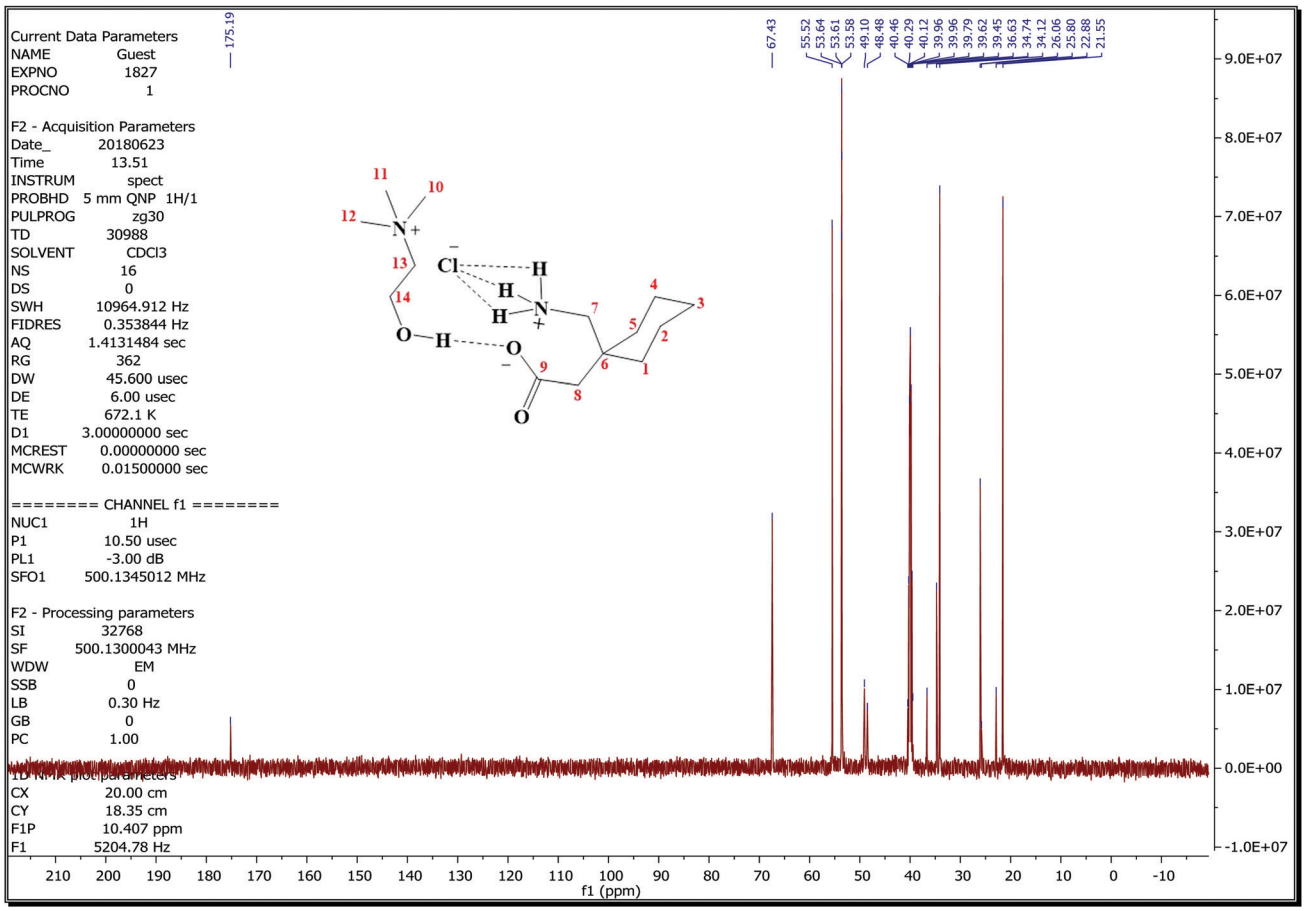


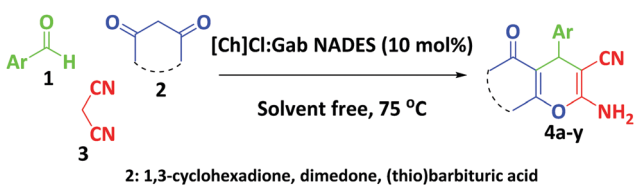
Fig. 5 ^{13}C NMR spectrum of the [Ch]Cl:Gab NADES.

Table 1 Optimization of the amounts of the catalyst, temperature and solvent in the synthesis of the tetrahydrobenzo[*b*]pyran derivative of 4-chlorobenzaldehyde

Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (min)	Conversion (%)
1	[Ch]Cl:Gab NADES (10)	H_2O	r.t.	60	Trace
2	[Ch]Cl:Gab NADES (10)	H_2O	Reflux	60	Not completed
3	[Ch]Cl:Gab NADES (10)	C_2H_5OH	Reflux	60	Not completed
4	[Ch]Cl:Gab NADES (10)	CH_3CN	Reflux	60	Trace
5	[Ch]Cl:Gab NADES (10)	CH_3Cl	Reflux	60	Trace
6	[Ch]Cl:Gab NADES (5)	—	75	11	100 (87)[a]
7	[Ch]Cl:Gab NADES (10)	—	75	7	100 (95)[a]
8	[Ch]Cl:Gab NADES (20)	—	75	10	100 (90)[a]
9	[Ch]Cl:Gab NADES (30)	—	75	15	100 (85)[a]
10	[Ch]Cl:Gab:H_2O (30)	—	75	20	100 (85)[a]
11	Gabapentin (10)	—	100	60	Not completed
12	[Ch]Cl (10)	—	100	60	Not completed
13	—	—	100	60	Trace

[a] The yields are related to the isolated products.

aromatic ring and other C–H activated acidic compounds such as 1,3-cyclohexanedione and (thio)barbituric acid were reacted with malononitrile under the same reaction conditions in the presence of the prepared DES to obtain tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]-pyrimidinone(thione) derivatives, respectively (Scheme 2 and Table 2). As indicated in Table 2, all of the selected starting materials reacted smoothly during acceptable reaction times with high yields. Furthermore, pyridine-4-carbaldehyde



Scheme 2 Synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone derivatives catalyzed by the [Ch]Cl:Gab NADES.

Table 2 Preparation of tetrahydrobenzo[*b*]pyran (entries **4a–l**) and pyrano[2,3-*d*]pyrimidinone(thione) (entries **4m–y**) derivatives using [Ch]Cl:Gab NADES as the catalyst

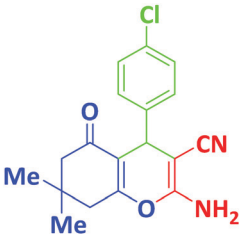
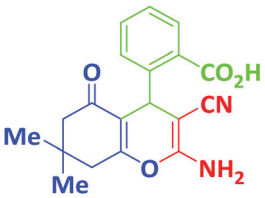
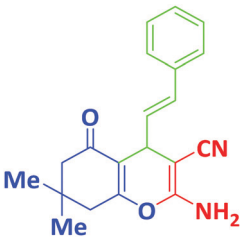
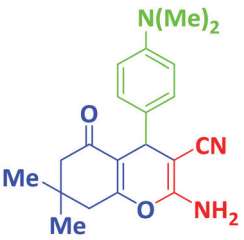
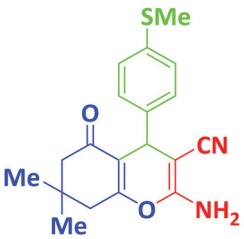
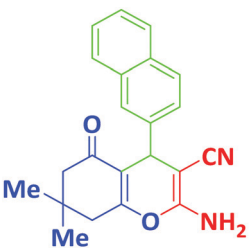
Entry	Aldehyde	Product		Time (min)	Yield[a] (%)	TOF (min^{-1})/100	Melting point (°C) Obs.	Lit. [ref.]
1	4-ClC_6H_4CHO		**(4a)**	7	95	1.357	208–210	208–210[24]
2	2-Carboxy benzaldehyde		**(4b)**	18	86	0.478	189–192	New
3	Cinamaldehyde		**(4c)**	28	91	0.325	198–200	189–191[25]
4	4-$NMe_2C_6H_4CHO$		**(4d)**	27	89	0.333	198–200	199–203[26]
5	4-$SMeC_6H_4CHO$		**(4e)**	14	88	0.628	210–212	211–212[19]
6	2-Naphthaldehyde		**(4f)**	16	92	0.575	260–262	255–257[26]

Table 2 (*continued*)

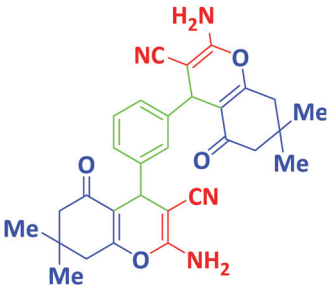
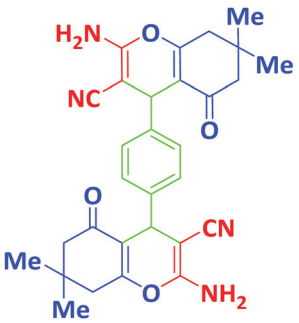
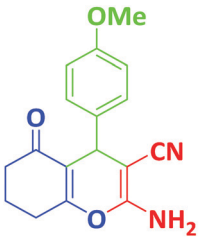
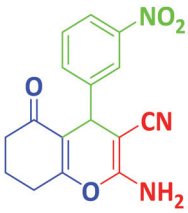
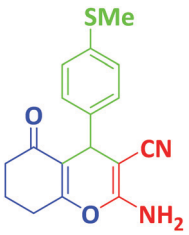
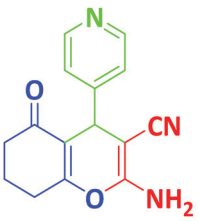
Entry	Aldehyde	Product		Time (min)	Yield[a] (%)	TOF (min^{-1})/100	Melting point (°C) Obs.	Lit. [ref.]
7	3-$CHOC_6H_4CHO$[b]		(4g)	19	90	0.473	243–245	243–244[26]
8	4-$CHOC_6H_4CHO$[b]		(4h)	18	91	0.506	267–268	264–266[26]
9	4-$OMeC_6H_4CHO$		(4i)	16	92	0.575	203–205	202–204[19]
10	3-$NO_2C_6H_4CHO$		(4j)	11	94	0.855	214–216	212–214[25]
11	4-$SMeC_6H_4CHO$		(4k)	27	90	0.333	216–218	217–219[19]
12	Pyridine-4-carbaldehyde		(4l)	23	88	0.382	228–231	New

Table 2 (*continued*)

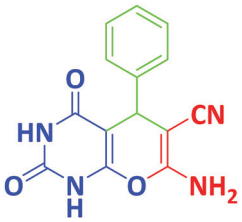
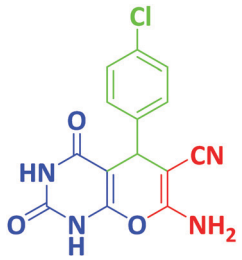
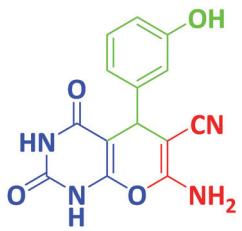
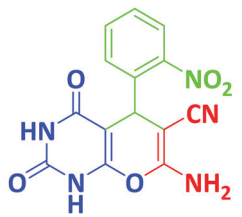
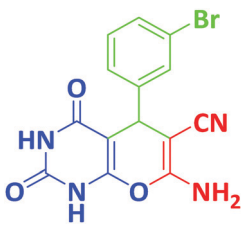
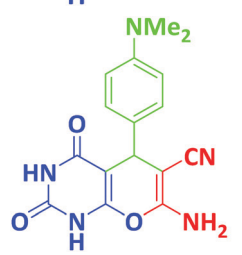
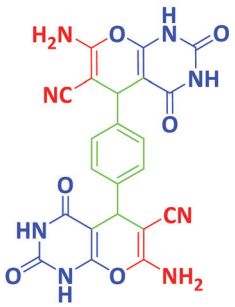
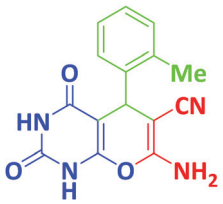
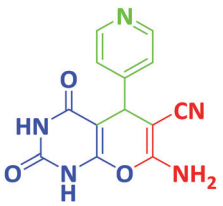
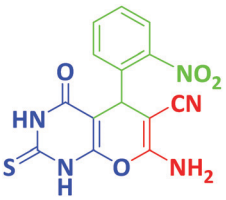
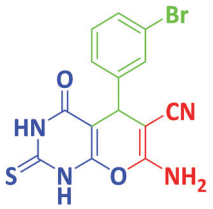
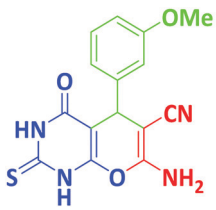
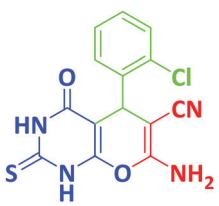
Entry	Aldehyde	Product		Time (min)	Yield[a] (%)	TOF (min^{-1})/100	Melting point (°C) Obs.	Lit. [ref.]
13	C_6H_5CHO		**(4m)**	14	90	0.643	224–226	224–225[24]
14	4-ClC_6H_4CHO		**(4n)**	8	94	1.175	237–240	237–240[24]
15	3-OHC_6H_4CHO		**(4o)**	12	91	0.758	160–161	160–162[27]
16	2-$NO_2C_6H_4CHO$		**(4p)**	13	92	0.708	248–250	249–251[27]
17	3-BrC_6H_4CHO		**(4q)**	13	92	0.708	245–247	254–256[28]
18	4-$NMe_2OC_6H_4CHO$		**(4r)**	16	90	0.563	230–232	231–233[29]

Table 2 (*continued*)

Entry	Aldehyde	Product		Time (min)	Yield[a] (%)	TOF (min^{-1})/100	Melting point (°C) Obs.	Lit. [ref.]
19	4-$CHOC_6H_4CHO$[b]		**(4s)**	16	90	0.563	>300	>300[26]
20	2-MeC_6H_4CHO		**(4t)**	12	90	0.750	222–224	223–225[29]
21	Pyridine-4-carbaldehyde		**(4u)**	15	87	0.580	210–213	211–212[29]
22	2-$NO_2C_6H_4CHO$		**(4v)**	19	91	0.479	242–244	242–245[26]
23	3-BrC_6H_4CHO		**(4w)**	23	89	0.387	243–245	245–247[30]
24	3-$OMeC_6H_4CHO$		**(4x)**	21	89	0.424	235–238	New
25	2-ClC_6H_4CHO		**(4y)**	22	88	0.400	240 (dec.)	New

[a] Isolated yield. [b] In this case 2 mmol of malononitrile and 2 mmol dimedone were used.

was used as a heterocyclic aldehyde under the same conditions, and the related derivatives were successfully obtained in high yields during short reaction times (Table 2, entries 12 and 21).

In order to show the reusability potential of the catalyst, the syntheses of 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **4a** (Table 2, entry 1) and 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano-[2,3-*d*]pyrimidine-6-carbonitrile **4n** (Table 2, entry 14) were studied again. For this purpose, after completion of the reaction, the solid product was washed with water to separate the catalyst ([Ch]Cl:Gab NADES is soluble in water). Then, the filtrate was evaporated under reduced pressure. The obtained catalyst was washed with diethyl ether and dried. No appreciable change in the color and the physical properties of the recovered [Ch]Cl:Gab NADES was observed. The FT-IR spectrum of the recycled catalyst was the same as the freshly prepared one, showing the stability of this reagent in the reaction media. The recovered catalyst was reused for at least five runs without appreciable loss of its catalytic activity (Fig. 6 and 7).

The mechanism of the reaction passes through two distinct routes as soon as the carbonyl group of aldehyde **1** gets H-bonded by the NADES (intermediate a). What makes a difference between routes 1 and 2 is the difference between the attack speed of b or d to a. So, the rate of formation of intermediates b and d from 1,3-diketone **2** and malononitrile **3**, respectively, affects the reaction rate. Two factors can impact the formation of b and d in acidic media, provided by DES. First, in malononitrile **3**, acidic hydrogens (–CH_2–) are bonded with two sp carbons (–CN), whereas, in 1,3-diketone **2**, these hydrogens are in correlation with two sp^2 carbons (–C═O). The higher s-character in an orbital, the more electronegative it will be. Therefore, because of the two more electron-withdrawing functional groups (–CN) in malononitrile **3**, it shows more acidic character than 1,3-diketone **2**. Losing an acidic hydrogen, malononitrile 3 changes to a weak base (b), which is reversed by retrieving a hydrogen. In a more acidic medium, this reaction

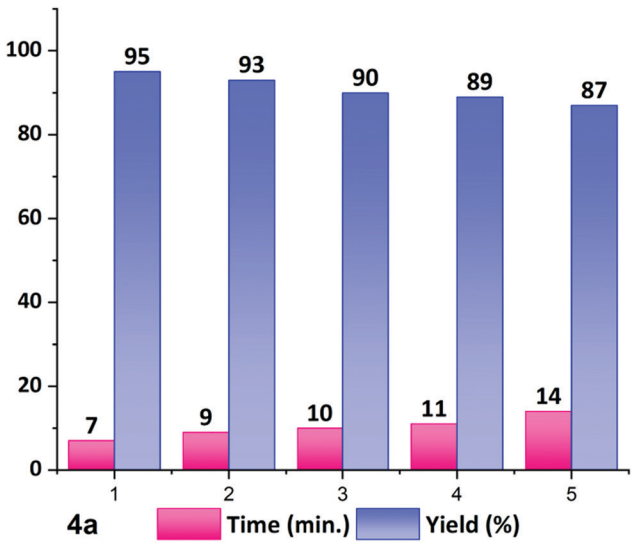


Fig. 6 Reusability of [Ch]Cl:Gab NADES in the synthesis of **4a**.

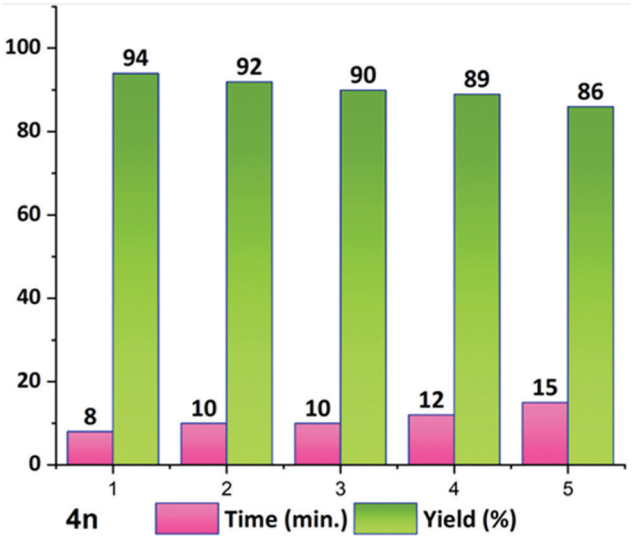


Fig. 7 Reusability of [Ch]Cl:Gab NADES in the synthesis of **4n**.

increasingly undergoes a reverse. Second, the sp orbital in nitrogen decreases the energy level of its lone pairs to bond with hydrogen, so oxygen is H-bonded more rapidly.

On the other hand, oxygen can form a bifurcated H-bond[22,23] (depicted in red dashed lines) which causes intermediate d to become more stable. As a result, the formation of intermediate d takes place in a shorter time. According to the reaction rate equation (eqn (1)), where A and B represent the concentration of the reactants, exponents x and y are the partial reaction orders for reactants A and B, respectively, and k is the reaction rate constant for a reaction, the rate of the reaction is correlated with the concentration of the reactants. So when the concentration of intermediate d is increased, the Knoevenagel condensation of aldehyde **1** and 1,3-diketone **2** occurred at a rapid rate.

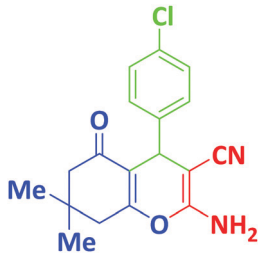
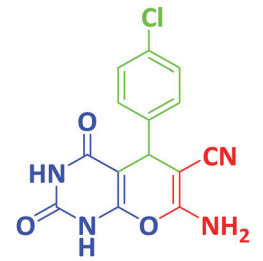
$$r = k[A]x[B]y \quad (1)$$

This fact that oxygen forms a stronger and more rapid H-bond impacts the mechanism till the product (**4a–y**) produces. In the Michael-addition, oxygen H-bonding in intermediate **5** causes the Michael-addition product (intermediate e) to generate d more quickly. In this step, b and d have already been produced and the rate of H-bonding in them is not effective. All outcomes result in route 2 being a shorter and faster pathway to produce the products (**4a–y**) in acidic media (S-17).

To highlight the efficiency of the presented method, we compared some of the results obtained in the presence of the [Ch]Cl:Gab NADES with the same ones obtained in the presence of other catalysts as reported in the literature. As shown in Table 3 the [Ch]Cl:Gab NADES can be proposed as a useful catalyst in terms of the reaction times, amounts of the catalyst and yields. Moreover, the preparation of this reagent is straightforward, and does not require further purification steps which is very worthwhile from the viewpoint of economic and environmental issues (green chemistry).

We also examined the possibility of the present method for large-scale performance *via* the reaction of 4-chlorobenzaldehyde

Table 3 Comparison of the catalytic activity of the [Ch]Cl:Gab NADES with some reported catalysts in the synthesis of 4-chlorophenyl derivatives of tetrahydrobenzo[*b*]pyran (entries 1–9) and pyrano[2,3,*d*] pyrimidinone (entries 10–17)

Entry		Catalyst[ref.]	Amount	Conditions	Time (min)	Yield (%)	TOF (min^{-1})/100
1		Urea[31]	10 mol%	EtOH : H_2O (1 : 1)/r.t.	180	87	0.048
2		Fructose[32]	20 mol%	H_2O : EtOH (2 : 1)/40 °C	80	78	0.049
3		Glutamic acid[33]	20 mol%	EtOH/reflux	40	91	0.114
4		SO_4^{2-}/MCM-41[34]	25 mg	EtOH/reflux	60	80	—
5		2,2,2-Trifluoroethanol[35]	2 mL	Reflux	300	95	0.122
6		DABCO[36]	10 mol%	H_2O/reflux	120	94	0.078
7		Fe_3O_4@MCM-41@Zr-piperazine[37]	30 mg	H_2O : EtOH (7 : 3)/reflux	10	90	—
8		[Ch]Cl/urea[38]	2 mL	80 °C	120	92	0.837
9		[Ch]Cl:Gab NADES[a]	10 mol%	Solvent free/75 °C	7	95	1.357
10		Urea[31]	10 mol%	EtOH : H_2O (1 : 1)/r.t.	840	86	0.010
11		Boric acid[39]	10 mol%	THF : H_2O (8 : 2)/reflux	110	85	0.077
12		Al-HMS-20[40]	30 mg	EtOH/r.t.	720	92	—
13		Fe_3O_4@SiO_2-Propyl-Pip-SO_3H·HSO_4[41]	30 mg	H_2O/80 °C	20	95	—
14		Nano-titania sulfuric acid[39]	20 mg	EtOH : H_2O (19 : 1)/reflux	60	89	—
15		$CaHPO_4$[42]	10 mol%	H_2O : EtOH (4 : 1)/80 °C	120	92	0.077
16		[Ch]Cl/$ZnCl_2$[43]	50 mol%	EtOH/75 °C	2	82	0.820
17		Taurine/ChCl DES[44]	20 mol%	H_2O/90 °C	19	93	0.245
18		ChCl/urea/thiourea DES[21]	36 mol%	H_2O/reflux	17	93	0.152
19		[Ch]Cl:Gab NADES[a]	10 mol%	Solvent free/75 °C	20	92	0.460

[a] This work.

(10 mmol), malononitrile (10 mmol), and dimedone or barbituric acid (10 mmol) using 10 mol% [Ch]Cl:Gab NADES in an oil-bath at 75 °C. The reactions were found to proceed smoothly in both cases affording the desired products, 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **4a** (10 min, 95%) and 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile **4n** (25 min, 94%), almost similar in all respects to the 1 mmol scale (Table 2, entries 1 and 14). The above results indicate that a large-scale reaction is achievable using the [Ch]Cl:Gab NADES as the catalyst.

Conclusions

In this study, a novel natural deep eutectic solvent made from choline chloride and gabapentin was prepared and characterized by FT-IR, ^{1}H and ^{13}C NMR, and mass spectra. Next, the catalytic activity of the prepared NADES was investigated in the three-component reaction of diverse aromatic aldehydes, malononitrile, and C–H activated acidic compounds leading to 4*H*-pyran scaffolds. The current protocol has advantages such as the use of readily available and biocompatible reagents for the synthesis of the catalyst, simple experimental procedures both for the preparation of the catalyst and products, simple separation and recovery of the catalyst from the reaction mixture, an easy and straightforward procedure for work-up and applicability to large-scale synthesis. Further research is currently on-going in our laboratory to explore additional reactions that can be mediated by this eutectic mixture.

Conflicts of interest

There are no conflicts to declare.

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