Research Article

Ultrasound-assisted aqua-mediated synthesis of multi-substituted tetrahydropyridine-3-carboxylates using *N*-carboxymethyl-3-pyridinium hydrogensulfate ([*N*-CH_2CO_2H-3-pic]$^+HSO_4^-$) as a new efficient ionic liquid catalyst

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Abstract
A simple, straightforward, and ultrasound-promoted method for the preparation of some highly functionalized tetrahydropyridines reported via pseudo five-component reaction of (hetero)aromatic aldehydes, different anilines, and alkyl acetoacetates in the presence of [*N*-CH_2CO_2H-3-pic]$^+HSO_4^-$, as a novel ionic liquid, in green aqueous medium. The IL was synthesized utilizing simple and easily-handled substrates and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, GC-MASS, FESEM, EDX, and TGA/DTG techniques. The procedure contains some highlighted aspects which are: (a) performing the MCR in the presence of aqua and sonic waves, as two main important and environmentally benign indexes in green and economic chemistry, (b) high yields of products within short reaction times, (c) convenient work-up procedure, (d) preparing the new IL via simple substrates and procedure.

Keywords Tetrahydropyridine-3-carboxylate · Ionic liquid · Alkyl acetoacetates · Ultrasound · Green chemistry

1 Introduction

Synthesis of various nitrogen-containing heterocyclic compounds widely attracted in organic chemistry [1, 2]. Among different types of *N*-heterocycles, tetrahydropyridines are particularly significant because of their organic and pharmaceutical attractions [3, 4].

Tetrahydropyridine (THP) moiety exists in various alkaloids and natural products [5]. Tetrahydropyridine existence in heterocycles cause to different pharmacological and biological activities such as antimicrobial activity against Escherichia coli [6], antimalarial [7], anti-oxidant (which made them as potent radical scavengers) [8], anti-fungicidal and insecticidal [9], anti-tumor [10], and neuroprotective (Parkinson's disease) [11]. Some compounds hold THP scaffolds also used as corrosion inhibitors for mild steel [12],

Recently a wide range of functionalized tetrahydropyridine-3-carboxylates has been synthesized via the reaction of various aldehydes, amines, and β-keto esters utilizing various catalysts under different conditions such as: bromodimethylsulfonium bromide (BDMS) in acetonitrile at room temperature [13], $FeCl_3/SiO_2$ NPs in refluxing methanol [14], Bi(III) immobilized on triazine magnetized dendrimer (Fe_3O_4@TDSN-Bi(III)) in ethanol at room temperature [15], nano-$Al_2O_3/BF_3/Fe_3O_4$ at 80 °C [16], CAN in

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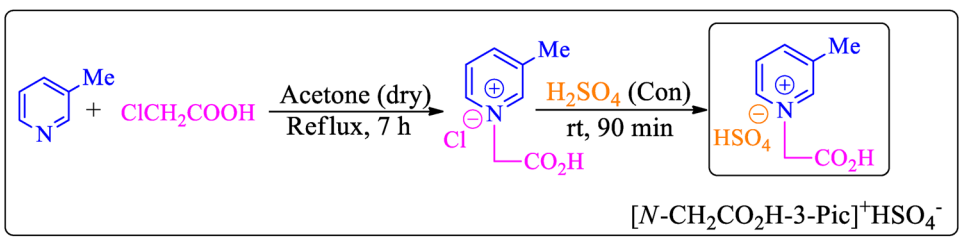
acetonitrile at room temperature [17], nano-spherical silica sulfuric acid (NS-SSA) in acetonitrile at 65 °C [18], Ag, Ni^{2+}, and Fe^{2+} immobilized on the core-shell hydroxyapatite γ-Fe_2O_3 MNPs (γ-Fe_2O_3@-HAp-Ag, γ-Fe_2O_3@HAp-Ni^{2+}, and γ-Fe_2O_3@HAp-Fe^{2+}) in ethanol at room temperature [19], and $[(Et_3N)_2SO][HSO_4]_2$ at 120 °C [20].

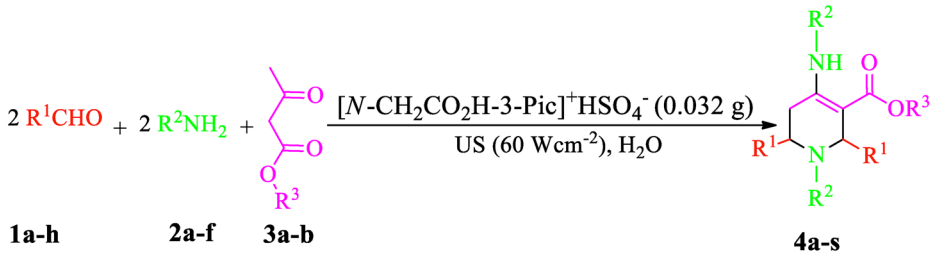
Sonochemistry, utilizing the high-power ultrasound that generate cavitation in a liquid, is a source of energy to accelerate a wide-spread chemical transformation. The hot-spot theory explains the energy release from cavitation as a physical process. The theory explains that each cavity (bubble) acts a localized microreactor that produces thousand degrees temperatures and pressures more than one thousand atmospheres [21]. Recently ultrasound, as one of the useful non-traditional condition, utilized for enhancing diverse organic reactions in heterocyclic preparations [22–25], and multi-component one-step or domino reactions [24, 26, 27], The sonochemistry is also green technique due to enhanced reactivity and acceleration leads to energy savings and cleaner products with formation of little or no by-products [23].

Performing the reactions in aqueous media achieved attention in recent organic synthesis. The phrase "on-water" that communicates to the situation in which reactants are insoluble in water, firstly expressed by Sharpless [28]. The water has some special characteristics that make it an optional green medium for organic reactions such as non-toxicity, cheapness, non-flammability, readily availability, and some physicochemical properties (polarity, hydrogen bonding, and trans-phase interactions) [29, 30]. Performing the organic transformation in aqueous media included some advantages such as: enhanced reactivity and selectivity of the procedure, work-up and purification improvement, recycling and reusability of the catalyst, milder reaction conditions, and straightforward preparation of natural and bioactive compounds [30].

Ionic liquids (ILs, salts melted without decomposing or vaporizing) are very famous and versatile catalysts and/or solvents in organic transformations. These liquid salts which could own dual catalytic/solvent role are classified as task-specific ionic liquids (TSILs) [31], room temperature ionic liquids (RTILs) [32, 33], chiral ionic liquids [34], basic ionic liquids (BILs) [35], acidic ionic liquids [36], Brønsted acidic ionic liquids (BAILs) [37], and Lewis acidic ionic liquids [38]. They also utilized as part of multi-layered structures which causes to enhance the total efficacy through synergic effects [39–41]. Recently pyridinium-based ILs attached special attention in various kind of organic transformations such as cyclocondensation-Knoevenagel-Michael domino reactions [42], synthesis of bis-naphthodipyrans [43], synthesis of spiropyrans [44], and prepation of pyranopyrazoles [45].

In extending our research group preferences for the synthesis of novel nano promoters to catalyze various MCRs [46–51] here in we report preparation of a new organic IL on the basis of 3-picoline, named *N*-carboxymethyl-3-methylpyridinium hydrogensulfate ($[N\text{-}CH_2CO_2H\text{-}3\text{-}pic]^+HSO_4^-$). Its catalytic activity was examined to obtain multi-substituted tetrahydropyridine-3-carboxylates via a pseudo five-component ultrasound-assisted reaction of (hetero)aromatic aldehydes, different anilines, and alkyl acetoacetates in water (Scheme 1).





$R^1 = C_6H_5$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2-OH-4-$NO_2C_6H_3$, 2-Pyrrolyl

$R^2 = C_6H_5$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4BrC_6H_4

R^3 = Et, Me

Scheme 1. Ultrasound-assisted synthesis of multi-substituted tetrahydropyridine-3-carboxylates in the presence of $[N\text{-}CH_2CO_2H\text{-}3\text{-}pic]^+HSO_4^-$ IL

2 Experimental

2.1 Materials and measurements

The chemicals and reagents purchased from Merck Chemical Company and utilized without any purification. FT-IR spectra were run on a Bruker, Tensor 27 spectrometer. The ^{1}H NMR and ^{13}C NMR were recorder by A Bruker (DRX-300 Avanes) apparatus. Melting points were determined by Electro thermal 9200. Field emission scanning electron microscopy (FESEM) gained by a VEGA//TESCAN-LUM. The mass spectra were recorded on a GC-Mass 5973 Network Mass Selective Detector, GC 6690 and Mass l 5973 Network Mass Selective Detector, Agilent Technology (HP) Agilent. Thermal gravimetric analysis (TGA) done through a "TGA1 METTLER TOLEDO" apparatus. A centrifuge machine UNIVERSAL 320 (capacity of 1000 W) used in the preparation procedure of IL. Homogenization performed in a Wise clean bath with power of 90 W. The ultrasonic device was an HD 3100 ultrasonic homogenizer form Bandelin Company (Germany). The SH 70 G horn, which emits 20 kHz ± 500 Hz ultrasound at intensity levels tunable up to maximum sonic power density of 100 Wcm^{-2}, was used. Sonication carried out at 100% (maximum amplitude 245 μ m). An MS73 probe with the 3 mm diameter was immersed directly to the reaction mixture.

2.2 General procedure for the preparation of [*N*-CH$_2$CO$_2$H-3-Pic]$^{+}$HSO$_4^{-}$

A solution of 3-methylpyridine (10 mmol) and chloroacetic acid (10 mmol) in dry acetone (40 ml), in a two necked round bottomed flask, was refluxed within 7 h. The reaction completing-time monitored by TLC (eluent: *n*-hexane:EtOAc, 5:3). After that the flask put into ice-bath and a solution of concentrated sulfuric acid in dried acetone (20 ml) poured into the balloon through a dropping funnel drop by drop and stirred for 90 min at room temperature. The resulting mixture centrifuged (10,000 rpm) and the solid residue washed with further dried acetone (3 × 10 ml). The obtained solid was dissolved in 20 ml acetone and sonicated in a bath for 30 min to be homogenized. After air-drying and oven-drying at 50 °C for 2 h, the obtained white solid is [*N*-CH$_2$CO$_2$H-3-pic]$^{+}$HSO$_4^{-}$ IL (M.P. = 80–82 °C). FT-IR (KBr): 3386, 3171, 3063, 2930, 2809, 1631, 1475, 1313, 1231, 119, 1054 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 2.45 (s, 3H, CH$_3$), 3.85 (s, 2H, CH$_2$), 7.99 (dd, 1H, *J* = 7.8, 5.7 Hz, Ar), 8.46 (d, 1H, *J* = 7.8 Hz, Ar), 8.73–8.78 (br s, 2H, Ar), 12.67 (br s, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): 17.9, 127.0, 138.2, 139.3, 141.5, 147.1. MS (EI) (*m/z*): 248 [M^{+}-1], 234 [M^{+}]–Me, 186 [M^{+}]–CO$_2$H, –H$_2$O, 175 [M^{+}]–CH$_2$CO$_2$H, –Me, 152 [M^{+}]–HSO$_4$, 138 [M^{+}]–HSO$_4^{-}$, –Me, 93 [3-methylpyridine]$^{+}$, 80 [pyridine]$^{+}$, 60 [MeCO$_2$H]$^{+}$.

2.3 General procedure for synthesis of alkyl 1,2,6-triaryl-4-(arylamino)-1,2,5,6-tetrahydropyridine-3-carboxylates (4a-s)

A mixture of aromatic aldehydes **1a-h** (2 mmol), aromatic amines **2a-f** (2 mmol), alkyl acetoacetate **3a-b** (1 mmol), and [*N*-CH$_2$CO$_2$H-3-Pic]$^{+}$HSO$_4^{-}$ IL (0.032 g, 12.8 mol%) in water (5 ml), sonicated by a probe (60 Wcm^{-2}) for the appropriate time monitored by TLC (eluent: *n*-hexane:EtOAc, 5:3). After completion of the reaction, the mixture was dissolved in hot methanol to obtain the desired products **4a-s**.

2.4 Ethyl 2,6-bis(2-hydroxy-4-nitrophenyl)-1-(4-nitrophenyl)-4-((4-nitrophenyl)amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4 l)

Yellow solid; M.P. 194–195 °C; FT-IR (KBr): 3348 (NH), 3368 (OH), 2923 (CH), 1623 (CO), 1588 (C=C), 1515 (N–O), 1345 (N–O), 1291(C–O, ester), 1223 (CO, phenol) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 1.86 (m, 3H, CH$_3$), 3.15–3.27(m, 2H, CH$_2$), 3.27–3.28 (m, 2H, CH$_2$), 6.56–6.59 (m, 1H, CH), 6.71 (d, 1H, *J* = 8.9 Hz, Ar), 7.11–7.14 (m, 2H, Ar), 7.40 (d, 2H, *J* = 8.8 Hz, Ar), 7.49 (d, 1H, *J* = 9.0 Hz, Ar), 7.55 (d, 2H, *J* = 8.8 Hz, Ar), 8.13–8.37 (m, 5H, Ar), 8.57–8.58 (m, 1H, Ar), 10.25 (s, 1H, NH), 11.78 (br s, 1H, OH), 12.93 (br s, 1H, OH).

Ethyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di(1*H*-pyrrol-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate **(4m).**

Black solid; M.P. 288–289 °C; FT-IR (KBr): 3444 (NH), 2922 (C–H), 1648 (CO), 1558 (C=C), 1462 (C=C), 1263 (C–O), 777 (C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-$_{d6}$) δ/ppm: 1.99–2.48 (m, 3H, CH$_3$), 3.16–3.46 (m, 1H, CH), 3.57–3.62 (m, 4H, 2CH$_2$), 6.27–6.57 (m, 5H, Ar), 6.77–7.02 (m, 6H, Ar), 7.20 (m, 1H, Ar), 7.40 (br s, 1H, NH), 7.55 (br s, 1H, NH), 8.19–8.57 (M, 2H, Ar), 11.46–12.18 (br s, 1H, NH).

3 Results and discussion

The FESEM images of the [*N*-CH$_2$CO$_2$H-3-Pic]$^{+}$HSO$_4^{-}$ IL has been obtained in order to recognize the structure and size of the particles. As it is illustrated in Fig. 1, there is moderate uniformity in the structure of the IL in μm scale. There are some IL nanoparticles with the average diameter of 35–55 nm on the surface of the [*N*-CH$_2$CO$_2$H-3-Pic]$^{+}$HSO$_4^{-}$.

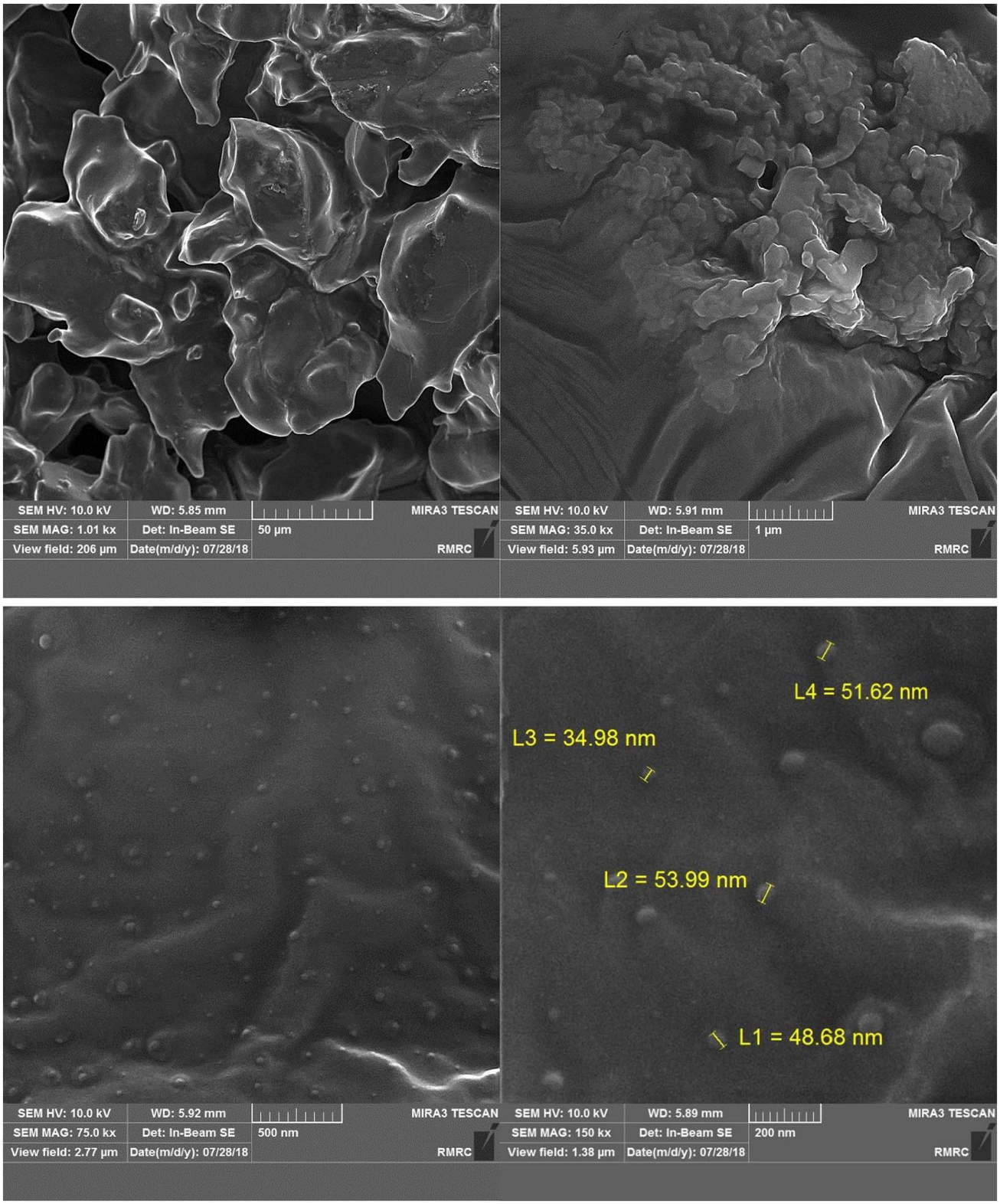


Fig. 1 FESEM images of $[N\text{-}CH_2CO_2H\text{-}3\text{-}Pic]^+HSO_4^-$ IL

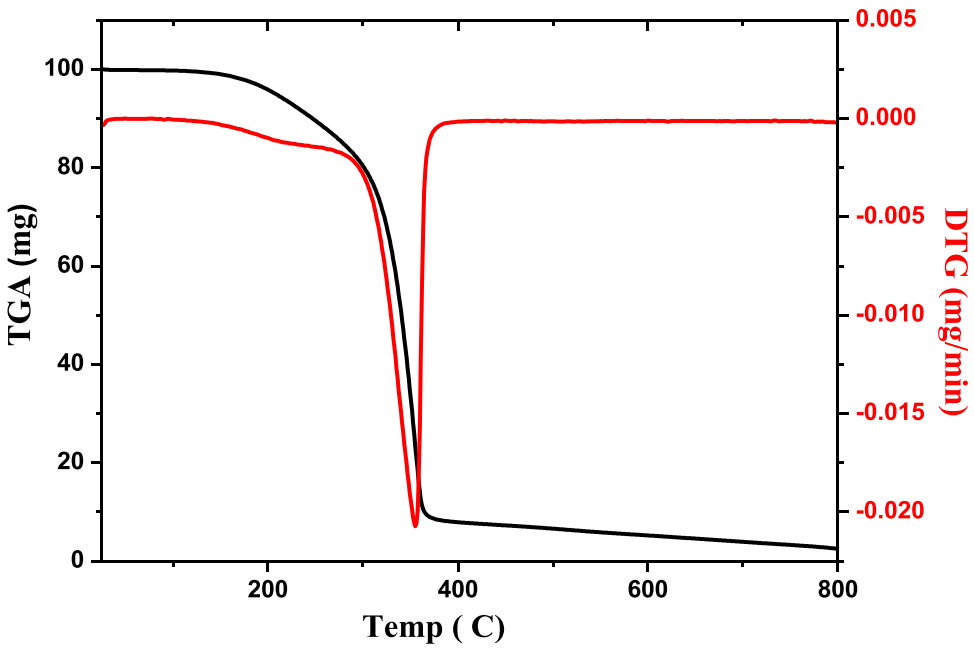


Fig. 2 TGA/DTG analysis of $[N\text{-}CH_2CO_2H\text{-}3\text{-}Pic]^+HSO_4^-$ IL

TGA/DTG analysis of $[N\text{-}CH_2CO_2H\text{-}3\text{-}Pic]^+HSO_4^-$ IL in Fig. 2 showed that the nanostructure decomposes through an endothermic one-step process. It is thermally stable up to about 300 °C and total decomposition occurred at 360 °C.

The EDX analysis of the IL illustrated in Fig. 3. The results show the existence of the elements such as C (40.12%), N (6.98%), O (42.02%), and S (10.87%). The impurities related to the solvents and materials used in the catalyst manufacturing process didn't observe.

In the next step, in order to examine the catalytic activity of newly-prepared IL, the reaction of benzaldehyde **1a** (2 mmol), 4-chloroaniline **2d** (2 mmol), and ethyl acetoacetate **3a** (1 mmol) was chosen as the model. To achieve the optimized conditions different exams performed that are presented in Table 1. As it observed, in the solvent-free conditions the best amount of the catalyst is 0.032 g (12.8 mol%) (Entries 1 & 2). The temperature investigations showed that 60 °C is the best choice (entries 3 & 4). Implementation of the reaction in ethanol (entry 5) and water

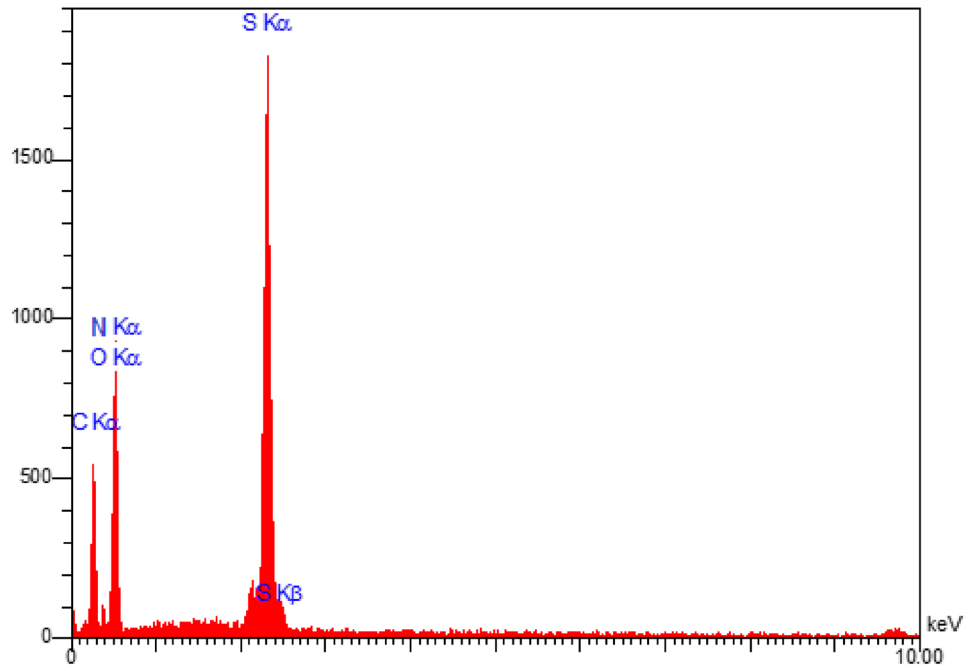
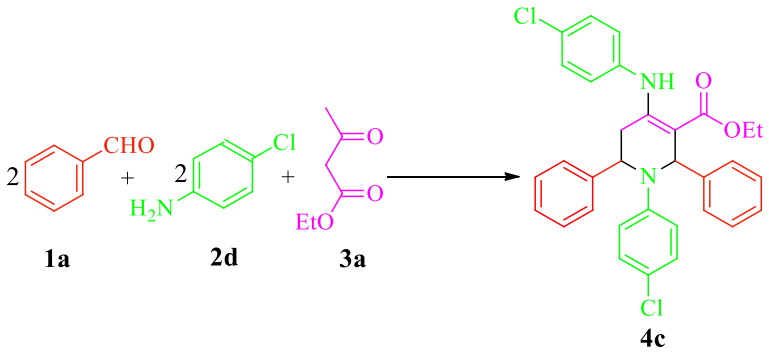


Fig. 3 EDX analysis of $[N\text{-}CH_2CO_2H\text{-}3\text{-}Pic]^+HSO_4^-$ IL

Table 1 Screening the reaction conditions in the synthesis of **4c**[a]



Entry	Conditions IL (g)/solvent (5 ml)/Temp (°C)	Time (min)	Yield (%)[b]
1	0.032/–/60	50	91
2	0.024/–/60	60	85
3	0.032/–/50	60	85
4	0.032/–/70	30	90
5	0.032/EtOH/60	65	73
6	0.032/H_2O/60	45	84
7	0.032/H_2O/US (60 W cm^{-2})	10	93
8	0.032/EtOH/US (60 W cm^{-2})	15	87
9	0.032/H_2O/US (80 W cm^{-2})	10	92
10	0.032/H_2O /US (40 W cm^{-2})	25	75
11	Con. H_2SO_4 (5 drops)/H_2O/US (60 W cm^{-2})	25	40
12	$ClCH_2COOH$ (0.032)/H_2O/US (60 W cm^{-2})	25	30
13	-/H_2O/US (60 Wcm^{-2})	40	–

[a]Benzaldehyde **1a** (2 mmol), 4-chloroaniline **2d** (2 mmol), and ethyl acetoacetate **3a** (1 mmol)

[b]Isolated yields

(entry 6) defined that the reaction progressed better in the absence of solvent (compare the results of entries 1, 5, and 6). In the best try, the reaction investigated under the sonic waves with various power density (entries 7–10). The results affirmed that utilizing sonic waves with the power of 60 Wcm^{-2} in aqueous medium is the best choice (entry 7). Eventually due to results, performing the reaction in the presence of 0.032 g (12.8 mol%) of the [*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$ IL in aqueous medium under sonic waves (60 Wcm^{-2}) is the best choice. In order to check the IL efficacy and necessity to accelerate the reaction, the model reaction also examined in the absence of [*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$ through addition of 5 drops of concentrated sulfuric acid as protic inorganic acid catalyst (entry 11). According to the result the reaction progress is not satisfactory in comparison to the entry 7, which confirmed the crucial role of IL to perform the reaction. This phenomena could be due to the amphipathic (hydrophilic and lipophilic) characteristics of the CH_2CO_2H-3-Pic]$^+HSO_4^-$ that could be dissolved better than mineral acid (H_2SO_4) in the micelles of the organic reactants suspended in water [52]. The model reaction also repeated in the presence of chloroacetic acid, as an organic acid which is one of the staring materials to prepare the IL (entry 12). The model reaction accomplishment in the absence of IL (entry 13) didn't generate the corresponding product. The results summarized in entries 11–13, affirmed the importance catalytic role of IL for the reaction progress. It seems that the optimized

Table 2 Ultrasound-assisted synthesis of multi-substituted THP-3-carboxylates in aqueous media[a]

Entry	R_1	R_2	R_3		Time (min)	Yield[b] (%)	M.P. (°C) Found (reported)
1	Ph	4-MeC_6H_4	Et	**4a**	25	89	190–191 (192–194) [16]
2	Ph	4-$MeOC_6H_4$	Et	**4b**	25	90	199–200 (196–197) [53]
3	Ph	4-ClC_6H_4	Et	**4c**	10	93	203–205 (202–204) [16]
4	Ph	4-BrC_6H_4	Et	**4d**	25	92	225–227 (230–231) [53]
5	4-MeC_6H_4	Ph	Et	**4e**	10	86	219–221 (227–229) [16]
6	4-MeC_6H_4	4-MeC_6H_4	Et	**4f**	25	84	172–173 (170–172) [16]
7	4-$MeOC_6H_4$	4-BrC_6H_4	Et	**4g**	25	91	214–215 (217–219) [16]
8	4-ClC_6H_4	4-ClC_6H_4	Et	**4h**	30	85	210–212 (214–215) [16]
9	4-$NO_2C_6H_4$	Ph	Et	**4i**	20	89	242–244 (247–250) [17]
10	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	Et	**4j**	25	92	195–196 (197–199) [14]
11	3-$NO_2C_6H_4$	Ph	Et	**4k**	25	87	227–229 (229–231) [14]
12	2-OH-4-$NO_2C_6H_3$	4-$NO_2C_6H_4$	Et	**4l**	15	91	194–195
13	2-Pyrrolyl	4-ClC_6H_4	Et	**4m**	30	89	288–289
14	4-MeC_6H_4	Ph	Me	**4n**	25	92	211–213 (215–216) [17]
15	4-MeC_6H_4	4-$MeOC_6H_4$	Me	**4o**	25	91	224–225 (226–227) [14]
16	4-MeC_6H_4	4-BrC_6H_4	Me	**4p**	15	92	248–250 (253–254) [17]
17	4-$MeOC_6H_4$	4-BrC_6H_4	Me	**4q**	20	86	178–179 (177–178) [17]
18	4-ClC_6H_4	4-ClC_6H_4	Me	**4r**	30	94	190–191 (188–190) [17]
19	4-$NO_2C_6H_4$	Ph	Me	**4s**	15	87	238–240 (240–241) [17]

[a]Aldehydes:anilines:alkyl acetoacetate molar ratio is 2:2:1. 0.032 g (12.8 mol%) of the ionic liquid, [*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$, was used

[b]Isolated yields

reaction conditions which consist of ultrasound/ionic liquid/water media could enhanced the reaction progress through generation of hot-spots and cavitation in addition with the catalytic aid of the IL.

Afterwards, the synthesis of various multi-substituted THP-3-carboxylates surveyed under the optimized conditions. Based on the data summarized in Table 2 and Scheme 1, benzaldehydes, various anilines, and ethyl acetoacetate gained their corresponding THPs in good yields (entries 1–13). In order to extend the efficacy of the method methyl acetoacetate also performed the pseudo-five component condensation well (entries 14–19). No significant substituent effect on the time and/or yield of the reactions didn't observe.

Although no mechanistic verification examined, the proposed mechanism illustrated in Scheme 2. According to suggested plan, the synthesis of THPs **4** could be proceeded through two pathways (I & II). In the pathway I, the ionic liquid ([*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$) activates the C = O group of aldehyde **1** which condensed to aniline **2** to obtain imine **A.** Activation the carbonyl group of alkyl acetoacetate **3** by IL followed by condensation with aniline **2** generates *β*-enaminone **B.** The intermolecular Mannich addition of A and B affords the intermediate **C**. Subsequently, the condensation of activated aldehyde with the intermediate **C** generates intermediate **D** that follows by tautomerization to intermediate **E**. The intramolecular ring closure follows by tautomerization obtains the final product **4**. The pathway II, the Knoevenagel condensation of *β*-enaminone **B** with aldehyde **1**, yields intermediate **G** that tautomerizes respectively to **H**. the [4 + 2] Aza Diels–Alder reaction of **H** with imine **A** obtained the desired product **4**.

Finally, to clarify the efficacy of the protocol, a comparison performed for the synthesis of with the previously reported methods illustrated in Table 3. According to data, presence of [*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$ IL, in addition with sonic waves in aqueous medium, elevated the reaction progress.

Scheme 2. The proposed mechanism for the synthesis of multi-substituted THP-3-carboxylates

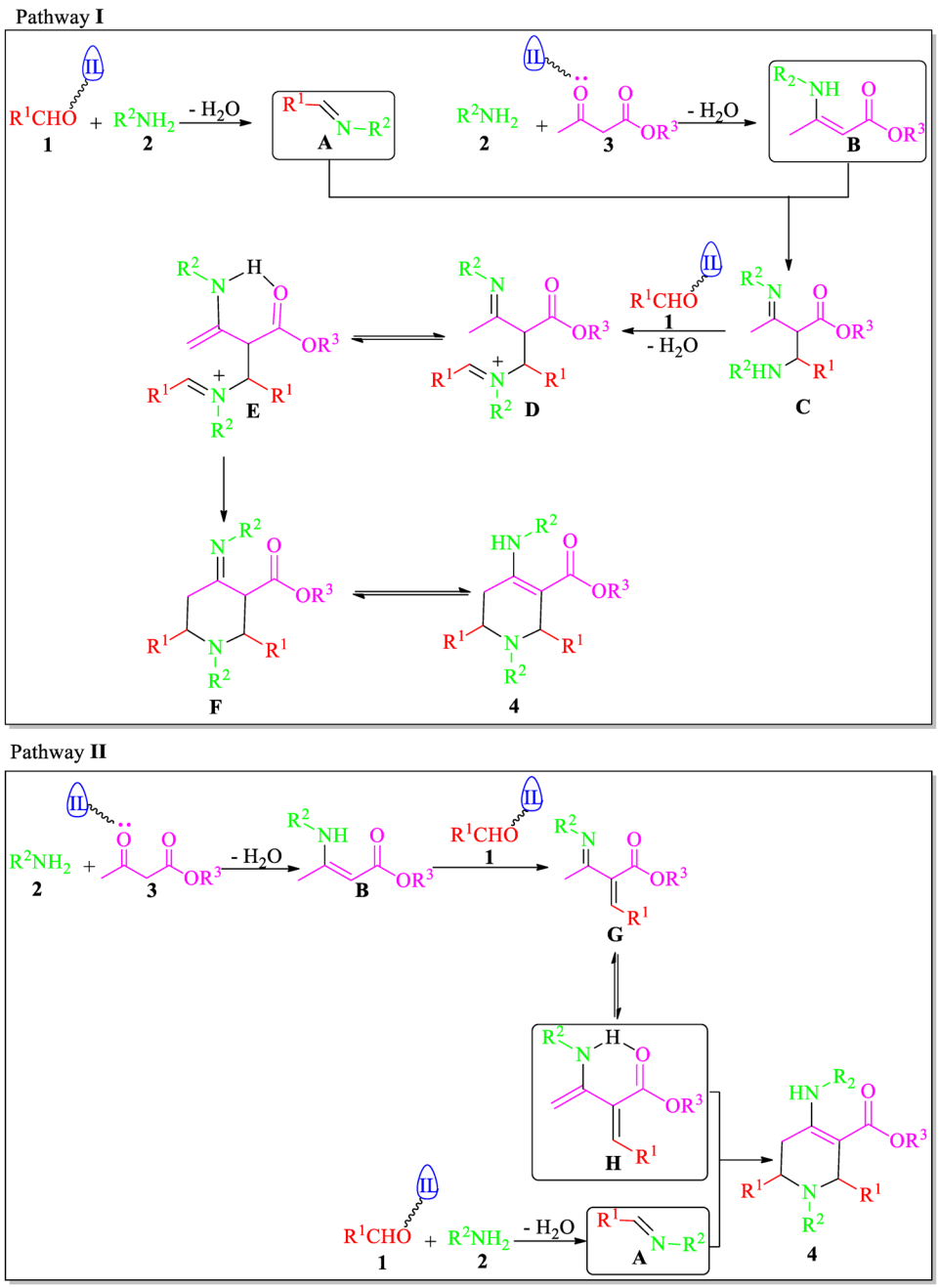


Table 3 Comparison of the methods in the synthesis of **4d**

Entry	Conditions	Time (min)	Yield (%)[b]	References
1	$FeCl_3$–SiO_2 NPs (0.8%)/MeOH/Reflux	300	91	[14]
	Fe_3O_4@TDSN-Bi(III) (0.133 g)/EtOH/RT	60	96	[15]
2	Nano-Al_2O_3/BF_3/Fe_3O_4 (0.03 g)/80 °C	180	84	[16]
3	NS-SSA (0.05 g)/CH_3CN/65 °C	330	89	[18]
4	$[Bmim\text{-}G\text{-}(SO_3H)_4]^+[HSO_4]^-$ (10 mol%)/EtOH/40 °C	300	76	[53]
5	Lactic acid (5 mol%)/EtOH/RT	30	92	[54]
7	$[N\text{-}CH_2CO_2H\text{-}3\text{-}Pic]^+HSO_4^-$ (0.032 g)/H_2O/US (60 W cm^{-2})	25	92	This work

4 Conclusions

In summary, an efficient MCR protocol to obtain multi-substituted tetrahydropyridine-3-carboxylates catalyzed by novel ionic liquid [*N*-CH_2CO_2H-3-Pic]$^+HSO_4^-$ was developed. These compounds were prepared from the ultrasound-assisted pseudo five-component condensation of anilines, (hetero)aromatic aldehydes and alkyl acetoacetates in a one-pot one-step aqueous-mediated process. Utilizing aqua as green solvent in the presence of sonic waves, as powerful microreactors which prepare hot-spots and cavitation, and the catalytic efficacy of the newly prepared organo-based ionic liquid, clean synthesis, and high yields of products, are some advantages of this methodology.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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