1*H*-imidazol-3-ium tricyanomethanide {[HIM]C(CN)$_3$} as a nanostructured molten salt catalyst: Application to the synthesis of pyrano[4,3-*b*]pyrans

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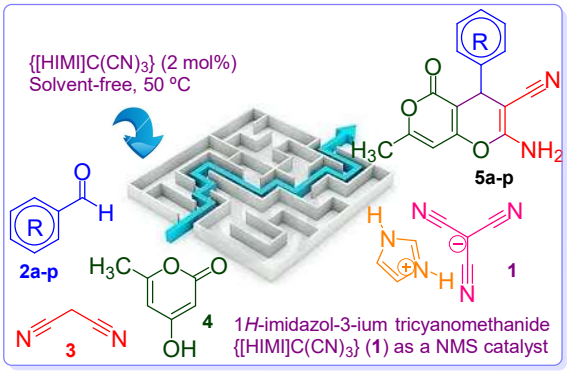

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Abstract In this work, we have synthesized a novel nanostructured molten salt, ^{1}H-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**), as an efficient, and green protocol compatible catalyst. This new molten salt has been fully characterized by different analytical techniques such as, FT-IR, ^{1}HNMR, ^{13}CNMR, thermal gravimetric analysis (TGA), derivative thermogravimetry (DTG), differential thermal analysis (DTA), X-ray diffraction (XRD), scanning-(SEM), and High resolution transmission-(HRTEM) electron microscopy. Additionally, the catalytic activity of {[HIMI]C(CN)$_3$} (**1**, 2 mol%) has been tested in a three component domino Knoevenagel condensation reaction. A range of structurally diverse aromatic aldehydes (**2a-p**), malononitrile (**3**), and 4-hydroxy-6-methyl-2H-pyran-2-one (**4**) are tolerated for the synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-b]pyran-3-carbonitrile derivatives (**5a-p**) under neat conditions at 50 °C. The obtained results have demonstrated that catalyst **1** shows interesting catalytic properties, such as, clean reaction profile, cost effectiveness, and green conditions. Importantly, the aforementioned catalyst is thermally stable with a 171 °C melting point not showing any significant loss in catalytic activity after 7 reaction cycles.

Key words Multicomponent reactions, Knoevnagel condensation, nanostructured molten salt, solvent-free, green chemistry

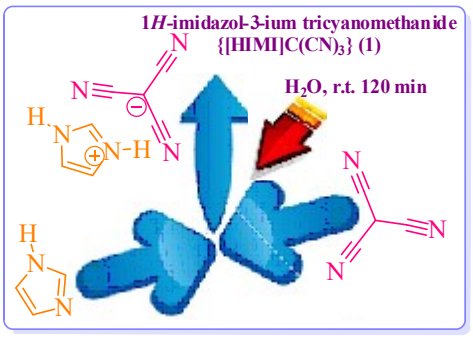
Nowadays, multicomponent reactions (MCRs) have been successfully applied to crop highly functionalized and complex molecules *via* a single procedure.[1] This type of reactions have opened new approaches towards the preparation of combinatorial libraries of varied pharmacologically significant organic molecules and have provided efficient and leading scaffolds towards novel drug discovery. Furthermore, multicomponent reactions involve the one-shot activation of different molecules and bonds providing advantages such as, structural diversity, high selectivity, high atom-economy, and green conditions.

The pyrano[4,3-*b*]pyran scaffold, as non-peptide human immunodeficiency virus inhibitor, shows a noteworthy structural subunit for the discovery of novel drug candidates as fused pyran-2-ones. Additionally, the pyrano[4,3-*b*]pyran skeleton has been found in various natural and biologically active products such as, davallialactone, arisugacins, pyripyropenes, philigridrins, clavilactone, and territrems.[2-4] The synthesis of pyrano[4,3-b]pyranes is usually performed in a three-component reaction of aldehydes, malononitrile and 4-hydroxy-6-methyl-2H-pyran-2-one catalyzed by different systems, such as, KF-Al_2O_3,[5] alum,[6] β-alanine/$CaSO_4$,[7] eggshell (ES) supported $Cu(OH)_2$ nanoribbons,[8] thiourea dioxide,[9] nano-CaO based on eggshell waste,[10] electro-catalysis,[11] ZnO nanoparticles,[12] 4-(succinimido)-1-butane sulfonic acid (SBSA),[13] piperidine,[14] heteropolyacid ($H_6P_2W_{18}O_{62}.18H_2O$),[15] and [BBMIm]$(HSO_4)_2$.[16]

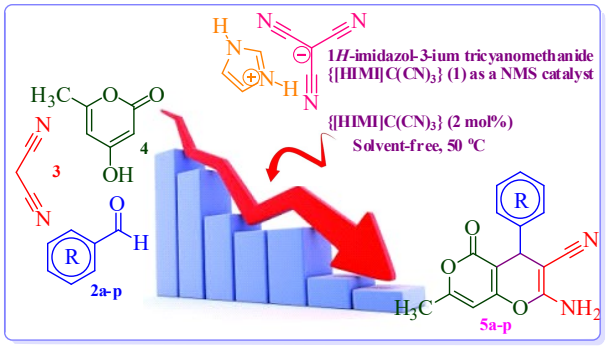
Ionic liquids (ILs) and molten salts (MSs) are liquid or solid materials at room temperature fully composed by ions.[17-20] The attention on these compounds as high-tech and green media of the future has rapidly increased due to their high thermal stability, near-zero vapor pressure, tunable properties as regards hydrophobicity, polarity, and solvent miscibility behavior by suitable modification of the cation and the anion. Generally, on account of their uncommon miscibility behavior, ionic liquids present an increased potential to revolutionize reaction technology. The difference between molten salt (very corrosive medium, high-melting and highly viscous) and ionic liquids (relatively low viscosity and liquid below 100 °C) is determined by melting point pattern.[21]

We have previously investigated on the design, synthesis, applications, and development of green nanostructured, ionic liquids, molten salts, and organocatalysts for organic functional group transformations as well as for eco-friendly multicomponent synthesis of biologically heterocyclic compounds.[22] As a continuation of these studies, herein we report the synthesis of a green mild, efficient and reusable nanostructured molten salt catalyst, namely 1H-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**, Scheme 1) and its

catalytic application in a three component domino Knoevenagel condensation between several structurally diverse aromatic aldehydes, malononitrile, and 4-hydroxy-6-methyl-2H-pyran-2-one to prepare 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3 carbonitrile derivatives (**5**) under neat conditions at 50 °C (Scheme 2).



Scheme 1 Synthesis of 1*H*-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**) as a green, mild, and efficient nanostructured molten salt (NMS) catalyst.



Scheme 2 One-pot three component synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitriles via domino Knoevenagel condensation using {[HIMI]C(CN)$_3$} (**1**) as a new NMS catalyst.

Synthesis and characterization of 1*H*-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**).

Initially, 1*H*-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**) was synthesized by reaction between imidazole and methanetricarbonitrile through a proton transfer mechanism in water for 120 min. The structure of catalyst (**1**) was fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, TGA, DTG, DTA, XRD, SEM, and HRTEM analyses.

The FT-IR spectrum of {[HIMI]C(CN)$_3$} (**1**) (Figure 1) exhibited a broad peak at 3450 cm^{-1} which can be related to the N–H stretching absorption of the imidazolium moiety. Furthermore, the absorption band at 2079 cm^{-1} is related to the C≡N stretching on tricyanomethanide counter ion. By comparing the IR absorptions of catalyst **1** and imidazol (Figure 1), it is clear that not only the intensity of the band related to the stretching absorption of CN groups has decreased, but also its wavelength has very slightly shifted to lower values, which could be related to mesomeric effects.

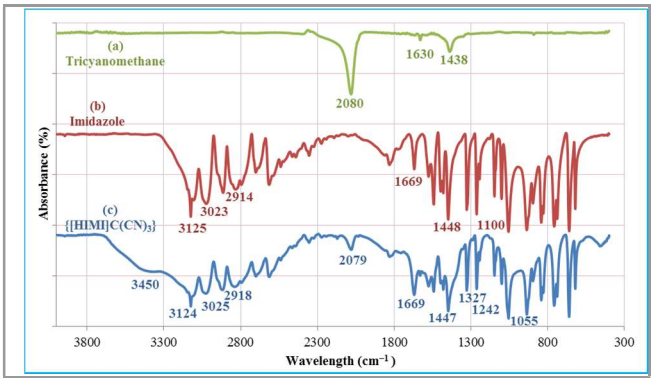


Figure 1 IR spectrum of tricyanomethane (a), imidazole (b) and {[HIMI]C(CN)$_3$} (**1**) (c).

Additionally, we have also studied the structure of {[HIMI]C(CN)$_3$} (**1**) by ^{1}H and ^{13}CNMR spectroscopy (Figures 2 and 3). The experiments were carried out in DMSO-d_6 as solvent and they can be compared with the spectra of starting materials imidazole and methanetricarbonitrile (see SI, Figures S1-S4). Regarding the ^{1}HNMR spectrum (Figure 2), catalyst **1** showed two singlets (7.62 and 7.00 ppm), corresponding to the aromatic protons of the imidazolium ring, and a broad singlet at 11.94 ppm from the most acidic NH protons of the nanostructured molten salt catalyst (Figure 2).

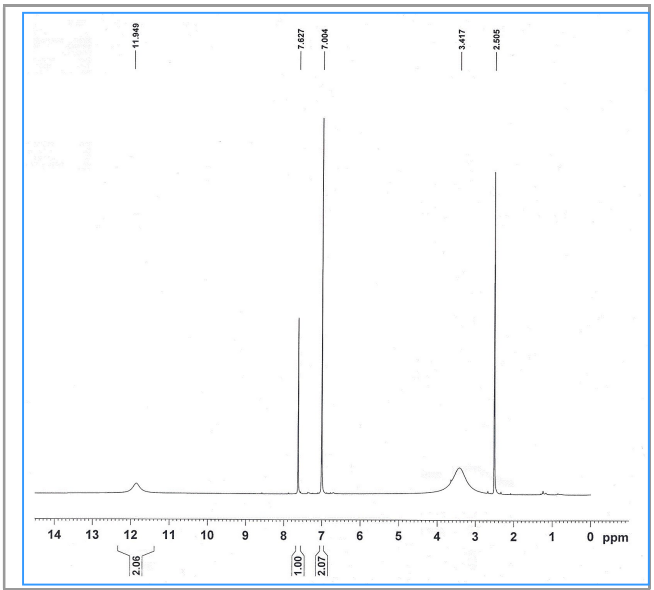


Figure 2 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of {[HIMI]C(CN)$_3$} (**1**).

On the other hand, the ^{13}CNMR (100 MHz, DMSO-d_6) spectrum of **1** (Figure 3), showed two absorption resonances at 166.4 and 69.6 ppm corresponding to the C(CN)$_3$ group. As expected, the absorption resonance peak of the deprotonated carbon had been shifted upfield from the reference value (77.9 ppm) of the starting methanetricarbonitrile (see SI, S2). Finally, two absorption resonances at 135.6 and 122.3 ppm were detected corresponding to the aromatic carbons of the imidazolium ring.

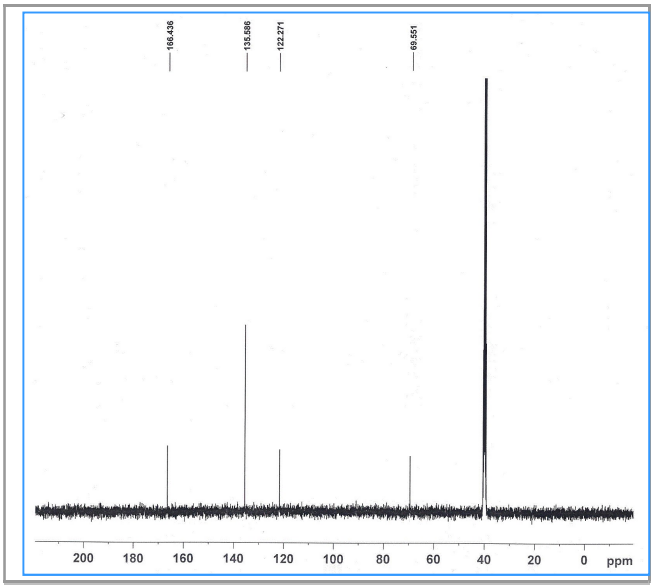


Figure 3 ^{13}C NMR spectrum (100 MHz, DMSO-*d6*) of {[HIMI]C(CN)$_3$} (**1**).

The thermal gravimetric (TG), derivative thermogravimetry (DTG), and differential thermal (DTA) analyses of {[HIMI]C(CN)$_3$} (**1**) showed an strong loss of organic material mass as they are removed from the catalyst or decompose upon heating (Figure 4). Catalyst (**1**) shows a one-step weight loss behaviour. The first 2% weight loss from the {[HIMI]C(CN)$_3$} (**1**) catalyst (room temperature to 120 °C) is due to the removal of physically adsorbed water and organic solvents, which were used during the preparation of **1**. The 50% weight loss between 120 and 185 °C is mainly due to the thermal decomposition of the catalyst. The thermal gravimetric analysis of the NMS catalyst offered significant loss in one-step, and decomposed after 185 °C (The DTA analysis diagram is downward and endothermic).

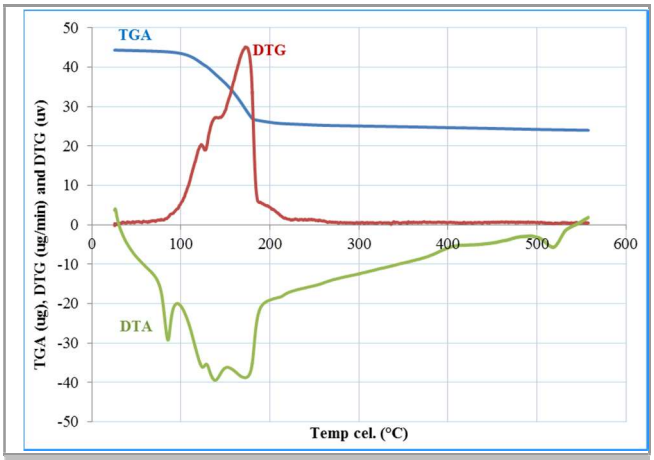


Figure 4 The thermal gravimetric (TGA), derivative thermogravimetry (DTG), and differential thermal (DTA) analysis of {[HIMI]C(CN)$_3$} (**1**).

The structure of {[HIMI]C(CN)$_3$} (**1**) was also investigated by X-ray diffraction (XRD) (Figure 5). Peak width (FWHM), size and inter planer distance related to XRD pattern of {[HIMI]C(CN)$_3$} (**1**) were studied in the 20.40° to 38.60° degree and the attained results are summarized in Table 1. Assignments for the highest diffraction line at 25.50° offered that an FWHM of 0.13, a crystalline size of the NMS catalyst of ca. 62.66 nm via the Scherrer equation [$D = K\lambda/(\beta\cos\theta)$] (Where D is the mean size of the arranged (crystalline) domains, which may be smaller or equal to the grain size. K is a dimensionless shape factor. The shape factor has a model value of about 0.9. λ is the X-ray wavelength. β is the line width at half the maximum intensity (FWHM), after subtracting the instrumental line width, in radians. θ is the Bragg diffraction angle in degree and an inter planer distance of 0.348893 nm (the same highest diffraction line at 25.50°) was investigated using the Bragg equation: $dhkl = \lambda/(2\sin\theta)$, (λ: Cu radiation (0.154178 nm) were achieved. Attaining crystalline sizes from various diffraction lines by the Scherrer equation were found to be in the nanometer range (6.75-62.66 nm), which is in close agreement with the scanning electron microscopy (SEM) and transmission electron microscopy (HRTEM) (Figure 6).

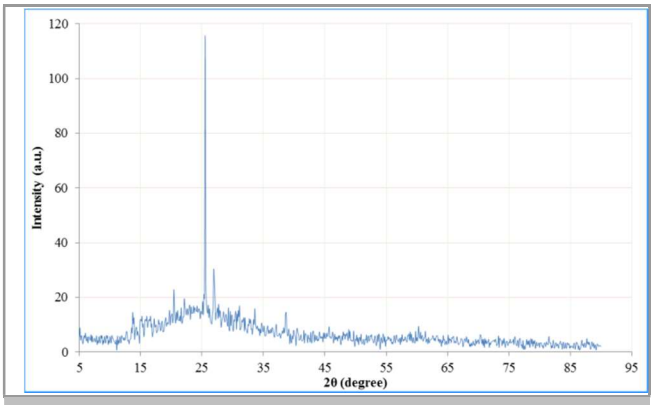


Figure 5 XRD pattern of {[HIMI]C(CN)$_3$} (**1**).

Table 1 XRD data for {[HIMI]C(CN)$_3$} (**1**).

Entry	2θ	Peak width [FWHM] (degree)	Size [nm]	Inter planer distance [nm]
1	20.40	0.36	22.42	0.434819
2	25.50	0.13	62.66	0.348893
3	26.90	0.42	19.45	0.331045
4	33.60	1.23	6.75	0.266406
5	38.60	0.44	19.13	0.232970

To determine the morphology and the size of the nanostructured {[HIMI]C(CN)$_3$} (**1**) catalyst, SEM and HRTEM were studied. This image of the nanostructured {[HIMI]C(CN)$_3$} (**1**) catalyst displays that the average size of these particles is about 63 nm (Figure 6). HRTEM analysis was completed via selected area electron diffraction (SAED) patterns (Figure 6b) to study the materials' crystalline nature. The most distinguished SAED ring pattern is confirmed with XRD results and approved the nano crystalline scale nature of the synthesized NMS catalyst.

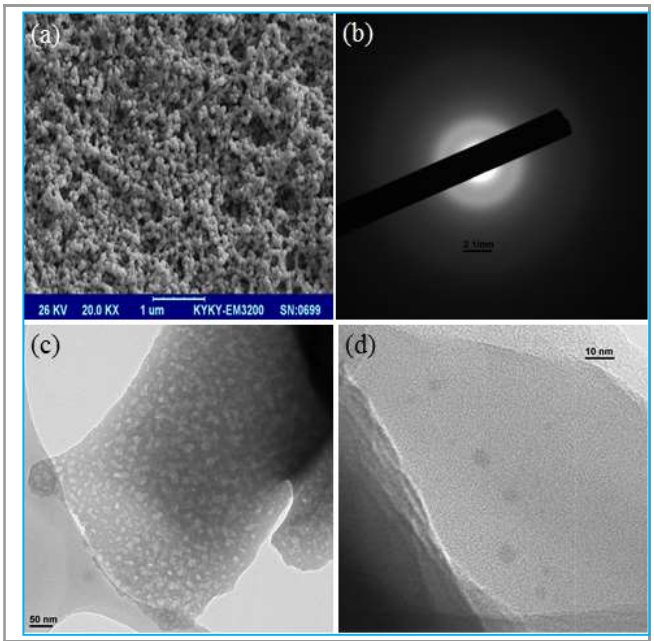
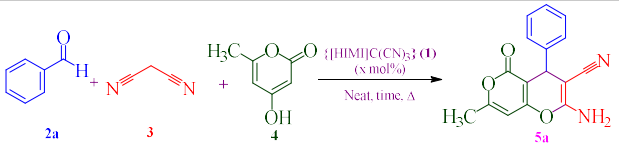


Figure 6 Scanning electron microscopy (SEM) (a), electron diffraction (SAED) patterns (b) and transmission electron microscopy (HRTEM) (c and d) of **1**.

Application of {[HIMI]C(CN)$_3$} (**1**) as a NMS catalyst in the one-pot three component synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitriles (**5**).

To start the study, the condensation of benzaldehyde (**2a**) with malononitrile (**3**) and 4-hydroxy-6-methyl-2H-pyran-2-one (**4**) using {[HIMI]C(CN)$_3$} (**1**) as a NMS catalyst, was examined as the reaction model for the optimization (Table 2). First, as depicted in entry 1, we demonstrated that under neat and catalyst-free conditions, the product was produced in trace amounts at room temperature after 6 h. Interestingly, when increasing the temperature at 50 °C, the reaction preceded smoothly affording (**5a**) in a 43% yield after 6 h. Then, the reaction was performed using 2 mol% of **1** as catalyst (entry 3), conditions that gratifyingly afforded **5a** in a 92% yield after only 10 minutes. No improvements were identified in the yield of the reaction by using lower catalyst loadings (entry 5) or different temperatures (entries 6 and 7). The reaction was also studied in the presence of different solvents in order to compare the effect of this parameter in the process. Thus, the reaction of benzaldehyde, 4-hydroxy-6-methyl-2H-pyran-2-one, and malononitrile in the presence of 2 mol% of NMS, and different solvents (H_2O, EtOH, MeCN, EtOAc, and *n*-hexane) was investigated at 50 °C. The obtained results, which are summarized in Table 2, pointed to the neat conditions as the best choice in this process.

Table 1 Optimization of reaction conditions.[a]



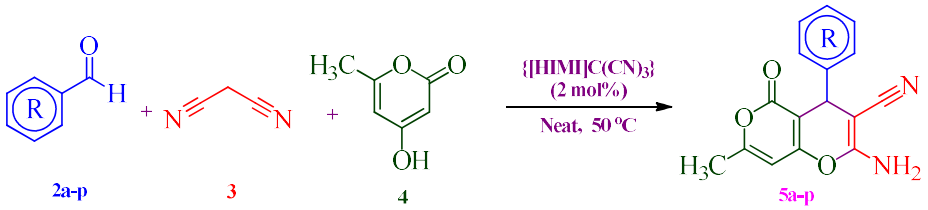
Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (min.)	Isolated Yield of **5a** (%)
1	-	-	r.t.	360	Trace
2	-	-	50	360	43
3	**-**	**2**	**50**	**10**	**92**
4	-	1	50	20	87
5	-	0.5	50	60	83
6	-	2	r.t.	60	Trace
7	-	2	70	10	92
8	H_2O	2	50	20	91
9	EtOH	2	50	20	87
10	MeCN	2	50	30	87
11	EtOAc	2	50	60	81
12	*n*-Hexane	2	50	120	63

[a] Reaction conditions: benzaldehyde (**2a**, 1.0 mmol, 106 mg), malononitrile (**3**, 1.0 mmol, 66 mg), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**4**, 1.0 mmol, 126 mg).

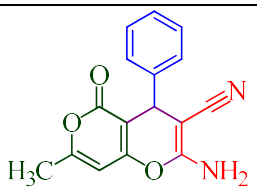
After identifying the optimized reaction conditions [**1** (2 mol%), neat conditions at 50 °C], we investigated the scope of the process by performing the reaction of several aldehydes, (**2b-p**) with malononitrile and 4-hydroxy-6-methyl-2H-pyran-2-one (Table 3). Structurally different aromatic aldehydes with various electron-donating and electron-withdrawing substituents efficiently reacted with 4-hydroxy-6-methyl-2H-pyran-2-one and malononitrile under the optimized conditions. As shown in Table 3, a series of aromatic aldehydes underwent electrophilic substitution with malononitrile and 4-hydroxy-6-methyl-2H-pyran-2-one to give a wide range of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitriles (**5**) in good to excellent yields. As shown, the nature and electronic properties of the substituents on the aromatic ring of the aldehydes did not affect the reaction yield, although electron-poor aromatic aldehydes reacted faster than electron-rich electrophiles.

A suggested mechanism for the synthesis of the 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-b]pyran-3-carbonitriles via one-pot three component domino Knoevenagel condensation/6π-electron is shown in Scheme 3.[5-16] Initially, {[HIMI]C(CN)$_3$} (**1**), as a NMS catalyst, activates the carbonyl group of the aromatic aldehyde (**2**) to give intermediate (**6**) and tautomerizes malononitrile. The Knoevenagel condensation between intermediates **6** and **7** forms the arylidene malononitrile **8**. Next, 4-hydroxy-6-methyl-2H-pyran-2-one (**4**) performs a conjugate addition over **8** providing adduct **9**, which is further tautomerized by **1** to produce intermediate **10**. Intramolecular cyclization of this compound affords **11**, which suffers a tautomerization process promoted by **1** to provide the corresponding fully aromatized 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (**5**).

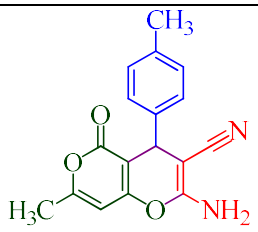
Table 2 Scope of domino Knoevenagel condensation.[a,b,c]



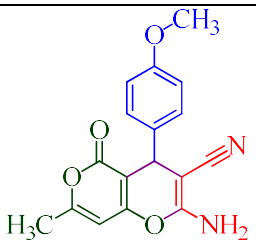
2a-p 3 4 5a-p



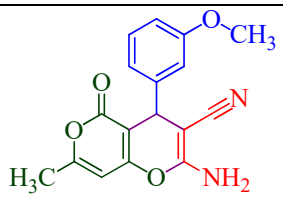
5a
10 min., 92%
White solid
M.p: 250-252, [234-236][6]



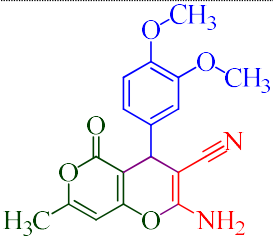
5b
20 min., 87%
White solid
M.p: 207-209 [224-225][6]



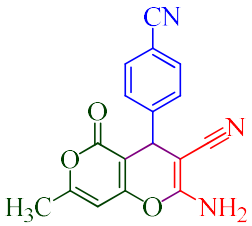
5c
16 min., 90%
White solid
M.p: 212-214, [202-205][6]



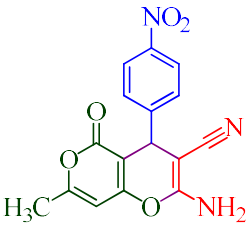
5d
15 min., 90%
White solid
M.p: 233-235



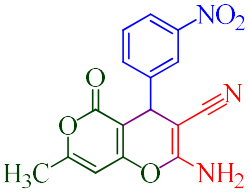
5e
25 min., 80%
Yellow solid
M.p: 144-146 [202-204][6]



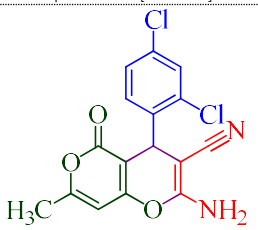
5f
10 min., 92%
White solid
M.p: 230-232



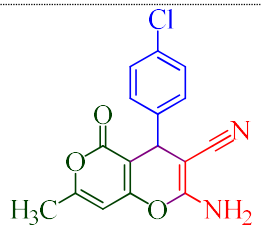
5g
12 min., 90%
Cream solid
M.p: 217-219, [215-218][6]



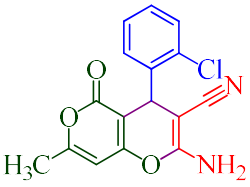
5h
12 min., 93%
White solid
M.p: 232-234 [238-240][5]



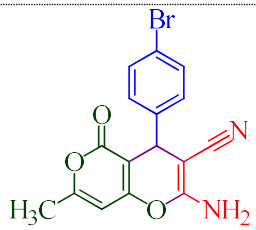
5i
12 min., 90%
White solid
M.p: 229-231, [234-235]5



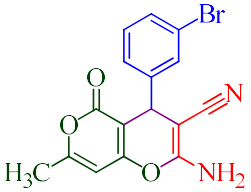
5j
10 min, 94%
White solid
M.p: 220-222, [231-232]5



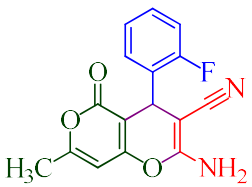
5k
14 min., 91%
White solid
M.p: 262-264 [270-271]5



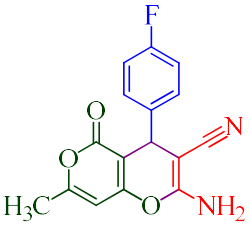
5l
11 min., 94%
White solid
M.p: 212-215 [223-225]5



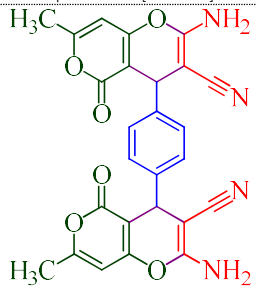
5m
15 min., 92%
White solid
M.p: 258-260 [217-219][13]



5n
12 min., 92%
White solid
238-240

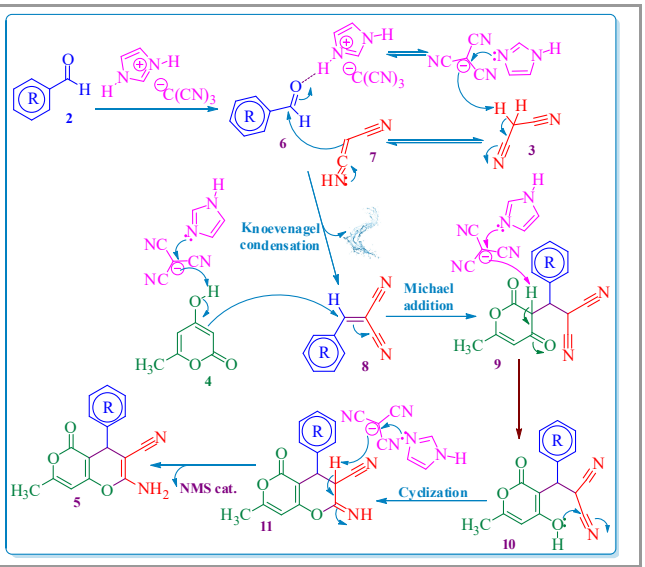


5o
11 min., 91%
White solid
M.p: 231-233 [221-223][13]



5p
20 min., 91%
Cream solid
M.p: >300 [256-258][13]

[a] Reaction conditions: ArCHO (1.0 mmol), malononitrile (1.0 mmol, 66 mg), 4-hydroxy-6-methyl-2H-pyran-2-one (1.0 mmol, 126 mg), **1** (2 mol%, 3.2 mg). [b] Isolated yield after column chromatography. [c] M.p reported in SI unit (°C).



Scheme 3 Proposed mechanism for the synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-b]pyran-3-carbonitriles (**5**) by {[HIMI]C(CN)$_3$} (**1**) as a NMS catalyst.

Reusability of {[HIMI]C(CN)$_3$} (**1**) as a NMS catalyst was confirmed in the condensation of 4-chlorobenzaldehyde (**2j**), malononitrile (**3**), and 4-hydroxy-6-methyl-2H-pyran-2-one (**4**). Thus, once the reaction was finished, ethyl acetate was added to the reaction and the resulting mixture was heated. Extraction with water of the hot crude mixture afforded the corresponding product and unreactive starting materials in the organic phase, while the catalyst remained in the aqueous phase. The recovered catalyst could be reused, within the limits of the experimental errors, for seven continuous runs (Figure 7). Furthermore, the reaction could be scaled up to 10.0 mmol of 4-chlorobenzaldehyde (**2j**), malononitrile, (**3**) and 4-hydroxy-6-methyl-2H-pyran-2-one (**4**), and in the presence of 20 mol% of {[HIMI]C(CN)$_3$} (**1**) catalyst at 50°C to afford compound (**5j**) in a 94% yield after 10 min.

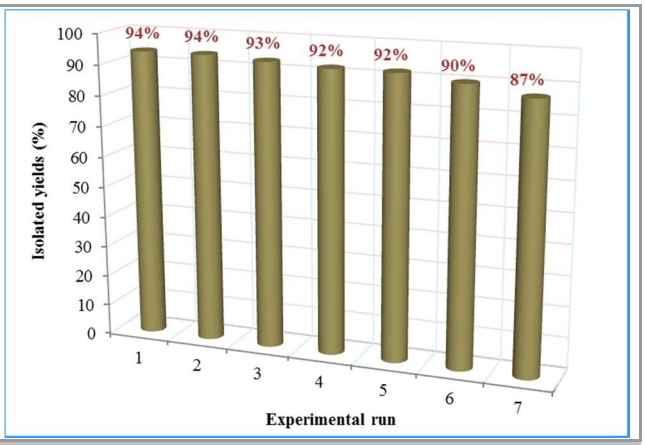


Figure 7 Reusability study of **1** in the reaction of 4-chlorobenzaldehyde (**2j**), malononitrile (**3**), and 4-hydroxy-6-methyl-2H-pyran-2-one (**4**).

In summary, an efficient, green, and recyclable nanostructured molten salt catalyst namely 1H-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (**1**) was designed, synthesized, characterized, and its catalytic application was investigated in the one-pot three component synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran 3-carbonitriles via domino Knoevenagel condensation under neat conditions at 50 °C. Compound **1**, as a NMS catalyst, was fully characterized analyzed by FT-IR, ^{1}HNMR, ^{13}CNMR, mass spectrometry, thermal gravimetric analysis (TGA), derivative thermogravimetry (DTG), differential thermal analysis (DTA), X-ray diffraction (XRD), scanning electron microscopy (SEM), and transmission electron microscopy (HRTEM). The proposed mechanism exposed that the buffer ability of {[HIMI]C(CN)$_3$}, possibly plays an important and dual catalytic role in the defined reaction. Finally, main advantages of the offered procedure and/or study are the reasonably low cost, high yield, short reaction time, simple work up, recoverability, and reusability of the catalyst, and cleaner reaction profile being in consequence in close agreement with the green chemistry disciplines.

The experimental section has no title; please leave this line here.

All the materials were purchased from Merck, Fluka, Sigma-Aldrich and Across Organic and were used without any additional purification. All reactions were detected by thin layer chromatography (TLC) on gel F254 plates. Proton coupled mode NMR (400 MHz or 300 MHz) spectra were recorded on Bruker Avance 400 or Bruker Avance 300 NMR spectrometers, respectively at 20 °C in DMSO-d_6. Proton decoupled 13CNMR (100 MHz or 75.5 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, at 20°C in DMSO-d_6; chemical shifts are given in δ (parts per million) and the coupling constants (*J*) in Hertz. X-ray diffraction (XRD) pattern of catalyst **1** was attained on a APD 2000, Ital structure with Cu K_ radiation (k = 0.1542 nm) operating at 50 kV and 20 mA in a 2 h range of 10 – 70° with step size 0.01° and time step 1.0 s to assess the crystallinity of the catalyst. Fourier transform-infrared spectra of the samples were recorded on a Perkin–Elmer FT-IR spectrometer 17259 using KBr disks. Thermo gravimetric analyses were carried out using a Perkin–Elmer TGA apparatus. The SEM analyses were prepared with a TESCAN/MIRA with a maximum acceleration voltage of the primary electrons between 10 and 15 kV. The HRTEM-200 microscope from JEOL model JEM-2010 working at 200 kV with a LaB6 filament was used for the corresponding studies, with a resolution between layers of 0.14 nm and between points of 0.25 nm. It is equipped with a camera from Gatan, model Orius 831.

General procedure for the synthesis of 1H-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (1).

To an aqueous solution of tricyanomethane (5.0 mmol, 455.0 mg) in deionized water (10 mL) imidazole (5.0 mmol, 340.0 mg) was added and the resulting mixture was stirred at room temperature for 120 minutes. The solvent was then removed under reduced pressure and the obtained white residue was dried under vacuum at 100 °C during 120 minutes in a standard glassware oven. The white solid formed was suspended in Et_2O and, after filtration with generous washings with Et_2O, it was dried in vacuo. Then, catalyst **1** was characterized by various techniques, including: FT-IR, ^{1}HNMR, ^{13}CNMR, TGA, DTG, DTA, XRD, SEM, HRTEM, and melting-point determination.

1H-imidazol-3-ium tricyanomethanide {[HIMI]C(CN)$_3$} (1):

M.p: 171-173°C; Yield: (95% , 756.0 mg).

FT-IR (KBr): υ 3125, 3023, 2914, 1662, 1549, 1448, 1327, 1100 cm^{-1}.

^{1}HNMR (400 MHz): δ 11.94 (br.s, 2H), 7.62 (s, 1H), 7.00 (s, 2H).

^{13}CNMR (100 MHz): δ 166.4, 135.6, 122.3, 69.6.

General procedure for the synthesis of 2-amino-7-methyl-5-oxo-4-aryl-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile derivatives 5.

To a previously prepared mixture in a round bottom flask of the corresponding aromatic aldehyde (1.0 mmol), 4-hydroxy-6-methyl-2H-pyran-2-one (1.0 mmol, 126.0 mg), and malononitrile (1.0 mmol, 66 mg), catalyst 1 (2.0 mol%, 3.2 mg) was added, and the consequent mixture was magnetically stirred under neat conditions at 50°C. After completion of the reaction, as detected by TLC (n-hexane/ethyl acetate: 5/2), 10 mL of ethyl acetate were added to the mixture, stirred and refluxed for 10 min. The obtained mixture was then washed with water (10 mL) and decanted to separate NMS catalyst from the reaction mixture. Noticeable, the reaction mixture was soluble in hot ethyl acetate and NMS catalyst was soluble in water. Then, the organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent and the crude product was purified via recrystallization from a mixture of ethanol/water: 10/1.

Spectral data for analyzed compounds

Compounds **5b**,[6] **5e**,[6] **5g**,[6] **5h**,[5] **5i**,[5] **5k**,[5] **5l**,[5] **5m**,[13] **5o**,[13] and **5p**[13] are known, and they were characterized by comparison of their physical and spectroscopic data with those described in the literature. Data for the new compounds or those not fully characterized in the literature follows:

2-Amino-7-methyl-5-oxo-4-phenyl-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (5a).

White solid; M.p: 250-252°C; Yield: (92%, 258 mg).

IR (KBr): υ 3400, 3324, 3207, 3084, 2199, 1711, 1674, 1614, 1385, 1261, 1138 cm^{-1}.

^{1}HNMR (400 MHz) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 6.28 (s, 2H), 4.28 (s, 1H), 2.26 (s, 3H).

^{13}CNMR (100 MHz) δ 162.9, 161.3, 158.1, 158.03, 157.99, 157.95, 143.6, 128.4, 127.5, 127.0, 119.3, 100.7, 97.9, 57.8, 36.2, 19.3.

2-Amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (5c).

White solid; M.p: 212-214°C; Yield: (90%, 279 mg).

IR (KBr): υ 3454, 3313, 3227, 3009, 2185, 1731, 1676, 1646, 1606, 1510, 1380, 1257 cm^{-1}.

^{1}HNMR (400 MHz) δ 7.27 (br.s, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 2H), 4.31 (s, 1H), 3.82 (s, 3H), 2.31 (s, 3H).

^{13}CNMR (100 MHz) δ 162.7, 161.3, 158.2, 157.94, 157.90, 157.8, 135.6, 128.6, 119.4, 113.7, 101.0, 97.9, 58.1, 55.0, 35.4, 19.3.

2-Amino-4-(3-methoxyphenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-b]pyran-3-carbonitrile (5d).

White solid; M.p: 233-235 °C; Yield: (90%, 279 mg).

IR (KBr): υ 3411, 3322, 3296, 3185, 3095, 2960, 2208, 1704, 1675, 1644, 1615, 1587, 1383, 1269, 1047 cm^{-1}.

^{1}HNMR (300 MHz) δ 7.26-7.20 (m, 3H), 6.85-6.78 (m, 1H), 6.76-6.72 (m, 2H), 6.28 (d, *J* = 0.7 Hz, 1H), 4.26 (s, 1H), 3.73 (s, 3H), 2.23 (s, 3H).

^{13}CNMR (75 MHz) δ 163.4, 161.8, 159.6, 158.6, 145.6, 130.0, 120.0, 119.7, 114.2, 112.3, 101.1, 98.4, 58.3, 55.4, 36.6, 31.1, 19.8.

MS (EI, 70 eV): *m/z* = 282 (M^+-CO, 2%), 184 (100), 156 (25), 141 (20), 127 (30), 114 (34).

2-Amino-4-(4-cyanophenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-b]pyran-3-carbonitrile (5f).

White solid; M.p: 230-232°C; Yield: (92%, 281 mg).

IR (KBr): υ 3443, 3339, 3230, 3184, 3113, 2226, 2193, 1697, 1669, 1633, 1603, 1584, 1382, 1263, 1139 cm^{-1}.

^{1}HNMR (300 MHz) δ 7.84-7.80 (m, 1H), 7.80-7.75 (m, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.42-7.39 (m, 1H), 7.34 (s, 2H), 6.31 (d, *J* = 0.9 Hz, 1H), 4.43 (s, 1H), 2.23 (s, 3H).

^{13}CNMR (75 MHz) δ 163.9, 161.8, 159.1, 158.6, 149.5, 132.9, 129.2, 119.5, 119.2, 110.3, 100.1, 98.5, 57.3, 36.8, 19.8; MS: m/z = 279 (M^+-CN), 179 (100), 152 (80), 128 (30).

2-Amino-4-(4-chlorophenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (5j).

White solid; M.p: 220-222°C; Yield: 94%, 295 mg).

IR (KBr): υ 3383, 3328, 3195, 3098, 2202, 1710, 1674, 1613, 1383, 1261, 1141 cm^{-1}.

^{1}HNMR (400 MHz) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.35 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 2H), 4.41 (s, 1H), 2.32 (s, 3H).

^{13}CNMR (100 MHz) δ 163.1, 161.3, 160.1, 158.2, 142.6, 132.1, 131.5, 129.7, 129.5, 128.3, 119.2, 100.2, 97.9, 57.3, 35.7, 19.3.

2-Amino-4-(2-fluorophenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-b]pyran-3-carbonitrile (5n).

White solid; M.p: 238-240°C; Yield: (92%, 274 mg).

IR (KBr): υ 3414, 3328, 3305, 3222, 3092, 2198, 1707, 1674, 1644, 1613, 1384, 1260, 1138 cm^{-1}.

^{1}HNMR (300 MHz) δ 7.40-6.96 (m, 6H), 6.30 (d, *J* = 0.9 Hz, 1H), 4.54 (s, 1H), 2.23 (s, 3H).

^{13}CNMR (75 MHz) δ 163.6, 162.6 (d, *J* = 187 Hz) , 162.4, 159.1, 158.8, 130.53 (d, *J* = 16 Hz), 130.51 (d, *J* = 12 Hz), 129.6 (d, *J* = 11 Hz), 125.0 (d, *J* = 4 Hz), 119.6, 116.0 (d, *J* = 28 Hz), 99.9, 98.4, 56.9, 31.3, 19.8.

MS (EI, 70 eV): *m/z* = 253 (M^+-45, 2%), 172 (100), 145 (90), 121(30).

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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