## Graphical Abstract

# Design, synthesis and application of 1*H*-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$} as a recyclable nanostructured ionic liquid (NIL) catalyst for the synthesis of imidazo[1,2-*a*]pyrimidine-3-carbonitriles

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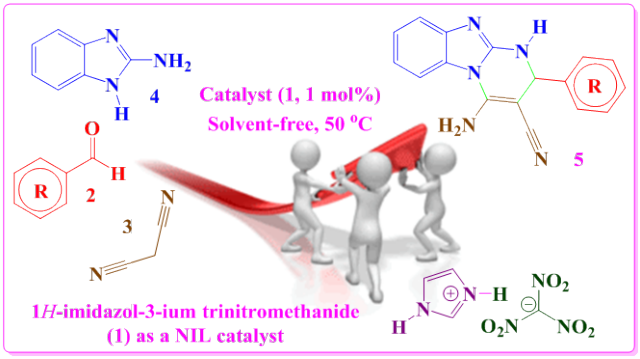


Design, synthesis, and characterization of [1*H*-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$} as an efficient, and recyclable nanostructured ionic liquid catalyst and its application for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles at 50 °C under neat conditions.

# Design, synthesis and application of 1*H*-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$} as a recyclable nanostructured ionic liquid (NIL) catalyst for the synthesis of imidazo[1,2-*a*]pyrimidine-3-carbonitriles

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**Abstract:** In this study, 1*H*-imidazol-3-ium trinitromethanide (**1**) {[HIMI]C($NO_2$)$_3$} as a green and recyclable catalyst based on nanostructure ionic liquid (NIL) was designed, synthesized, fully characterized by various analysis techniques and applied as catalyst for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives *via* one-pot three component condensation reaction. The reaction tolerates a wide range of electron-donating and electron-withdrawing substituents on aldehydes with malononitrile and 2-aminobenzimidazole at 50 $^{o}$C under neat conditions. The described reaction is compatible with the green chemistry disciplines and their main advantages are short reaction time, high yields, simplicity of product isolation, and clean reaction profile. Additionally, the NIL catalyst (**1**) {[HIMI]C($NO_2$)$_3$} can be readily recovered in the reaction vessel by using a mixture of EtOAc/$H_2O$ (1:1) and reused for four consecutive runs without a significant loss in catalytic activity. The present study can open up a new and promising insight in the course of rational design, synthesis and applications of nanostructured task-specific ionic liquids (NTSILs) for numerous green purposes.

**Keywords:** Multicomponent reactions (MCRs), knoevenagel condensation, nanostructured ionic liquid (NIL), solvent-free, 1*H*-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$}.

## 1. Introduction

Fused salts are liquids including unique ions, ionic liquids (ILs). Through careful election of substrates it is feasible to synthesize ionic liquids that are liquid or solid at and below or high room temperature. The development of air and moisture stable ILs has provided improved ionic liquid chemistry, and the emerging use of these ILs will be investigated first [1]. Because of the unique chemical and physical properties of ionic liquids, such as their low vapor pressure, non-volatility, thermal stability, non-flammability, and controlled miscibility, nowadays they have become a very interesting tool for chemists in numerous fields, especially in green chemistry. The reevaluation of classical organic synthesis in these novel medium has led to a superb series of examples where chemical yields, regio-, chemo- and stereoselectivity, as well as the recycling of catalysts have been deeply improved [1,2-7]. While ionic liquids were firstly presented as alternative green reaction media, at the moment they have improved far outside this boundary, displaying their noteworthy role in controlling reactions as solvent or catalysts. Another feature of ILs is their ability to be reused many times [8].

One-pot multicomponent reactions (MCRs) have been explained as a process where more than three reactants are combined in a single reaction to produce a product that contains portions of all the components [9-19]. More specifically, the use of multi-component reactions (MCRs) benefits from various valuable features such as, conventional reaction design and atom economy. Therefore, among all current synthetic tools in organic chemistry, MCRs have particularly appeared as an efficient, inexpensive, and attractive methodology for both academic and industrial purposes. On the other hand, purification of products resulting from MCRs is very simple, since all the organic reagents employed are expended and are combined into the target

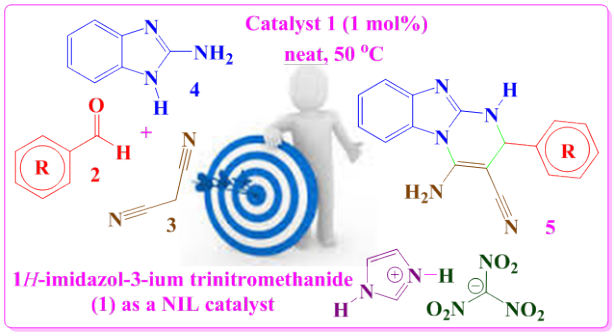
compound. Multi-component reactions, leading to interesting heterocyclic scaffolds, are mainly useful for the production of chemical libraries of 'drug-like' molecules.

Numerous imidazo[1,2-*a*]pyrimidine derivatives are significant as pharmaceuticals since they have been found to have several biological activities, [20-24] being remarkable clinical examples the antiulcerative omeprazole, the antihistaminic astemizole, and the fungicide rabenzazole [25]. Due to the significance of this type of compounds, a number of synthetic procedures and catalysts have been reported for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives such as, EtOH/$NH_4OAc$/reflux, [26] melamine trisulfonic acid (MTSA)/neat/100 $^oC$, [27] *p*-TSA/solvent-free/80 $^oC$, [28] $H_2O$/90 $^oC$, [29] piperidine/60 $^oC$, [30] silica sulfuric acid (SSA)/neat/110 $^oC$, [31] alum/EtOH/ r.t. or 70 $^oC$, [32] EtOH/$Me_3N$/reflux, [33] MeOH/$Me_2NH$/reflux or EtOH/$Et_3N$/reflux or $H_2O$/MW, [34] Schiff bases/MeOH or EtOH/$Et_3N$/reflux [35] and water mediated synthesis [36].

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 important heterocyclic compounds.[37-47] Due to the above mentioned advantages of multicomponent reactions and ionic liquids, an eco-compatible imidazo[1,2-*a*]pyrimidine derivatives synthesis involving both methodologies would be highly desirable.[48] Herein, we report the synthesis of a green, mild, efficient, and reusable nanostructured ionic liquid catalyst, namely 1*H*-imidazol-3-ium trinitromethanide {[HIMI]$C(NO_2)_3$} (**1**) (scheme 1) [49] and its application to the one-pot three component synthesis of 4-amino-1,2-

dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives at 50 $^{o}$C under neat conditions (scheme 2).


**Scheme 1.** Synthesis of 1*H*-imidazol-3-ium trinitromethanide catalyst (**1**) {[HIMI]C($NO_2$)$_3$}.




**Scheme 2.** One-pot three component synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles catalyzed by **1**.

## 2. Experimental

### *2.1. General*

Chemicals and materials were achieved from Merck, Fluka, and Sigma-Aldrich and were applied without any additional purification. All reactions were identified through thin layer chromatography (TLC) on gel F254 plates. $^{1}$H NMR (400 MHz and 300 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in

proton coupled mode. $^{13}C$ NMR (100 MHz, 75.5 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in proton decoupled mode at 20 ºC in DMSO-$d_6$; chemical shifts are given in δ (parts per million) and the coupling constants (*J*) in Hertz. Catalyst **1** was characterized by FT-IR, $^{1}H$ NMR, $^{13}C$ NMR, TGA, DTG, DTA, XRD, SEM, and TEM analysis. X-ray diffraction (XRD) patterns 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 *via* a Perkin–Elmer TGA were synthesized on catalysts. The SEM analyses were prepared with a TESCAN/MIRA with a maximum acceleration voltage of the primary electrons between 10 and 15 kV. Transmission electron microscope, TEM measurements were carried out on a Philips CM10 analyzer (operating at 120 kV). The TEM-200 microscope is from JEOL model JEM-2010 working at 200 kV with a LaB6 filament. It reaches a resolution between layers of 0.14 nm and between points 0.25 nm. It is equipped with a camera from Gatan, model Orius 831.

*2.2. General procedure for the synthesis of 1H-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$} (**1**) as a green NIL catalyst.*

To a round-bottomed flask (50 mL) containing imidazole (5.0 mmol, 340 mg) and $CH_3CN$ (5 mL, $1_M$), trinitromethane (5.0 mmol, 755 mg) was added drop wise. The resulting mixture was stirred over a period of 120 min at room temperature. Subsequently, the solvent was removed *via* evaporation under reduced pressure and the obtained product was dried under vacuum at 80 ºC for 120 min. The resulting yellow solid was washed with $Et_2O$ three times and

then it was dried under vacuum. Characterization by FT-IR, $^{1}$H NMR, $^{13}$C NMR, TGA, DTG, DTA, XRD, SEM, and TEM analysis as well as melting-point determination were performed.

**1H-imidazol-3-ium trinitromethanide (1) {[HIMI]C($NO_2$)$_3$}:** M.p: 73-75 $^{o}$C ($Et_2O$); Yield: (1062 mg, 97%); Spectral data: FT-IR (KBr): υ 3433, 3153, 2985, 1751, 1634, 1586, 1384, 1049 cm$^{-1}$; $^{1}$H NMR (400 MHz): δ 7.70 (d, 2H, *J* = 1.2), 9.10 (t, 1H, *J* = 2.4), 14.09 (brs, 2H); $^{13}$C NMR (100 MHz): δ 119.8, 134.9, 160.2.

*2.3. General procedure for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile derivatives.*

In a round bottom flask, catalyst **1** {[HIMI]C($NO_2$)$_3$} (1.0 mol%, 2.2 mg) was added to a mixture of the corresponding aromatic aldehyde (1.0 mmol), 2-aminobenzimidazole (1.0 mmol, 133 mg), and malononitrile (1.0 mmol, 66 mg). The obtained mixture was stirred magnetically at 50 $^{o}$C under solvent-free conditions for the appropriate time. After completion of the reaction, as identified by TLC (*n*-hexane/EtOAc: 5/3), EtOAc (10 mL) was added, and the mixture was stirred and refluxed for 10 min. Then, the resulting solution was washed with water (10 mL). Separation of the phases led to the crude product in the EtOAc phase while catalyst **1** was soluble in water. The organic phase was dried ($MgSO_4$) and the solvent evaporated to afford the corresponding crude product which was purified *via* recrystallization from ethanol/water (10:1).

**Spectral data for analysis compounds**

Compounds **5a**,[36] **5c**,[32] **5d**,[33] **5e**,[28] **5g**,[28] **5h**,[28] **5j**,[50] **5k**,[36] and **5l**,[26] are known, being their physical and spectroscopic data in accordance with the reported in the literature. Physical and spectroscopic data for new compounds (**5b**, **5f**, **5i**) or those not fully characterized in the literature, follows:

*Spectral data for analysis compounds*

**4-Amino-2-phenyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5a**):** White solid; M.p: 218-220 $^{o}$C (EtOAc); Yield: (270 mg, 94%); IR (KBr): υ 3443, 3320, 3214, 3058, 2192, 1683, 1640, 1602, 1470, 1442, 1402, 1352 cm$^{-1}$; $^{1}$H NMR (300 MHz) δ 8.62 (s, 1H), 7.63 (d, *J* = 7.8, 1H), 7.39-7.22 (m, 6H), 7.12 (td, *J* = 7.7, 1.0, 1H), 7.00 (td, *J* = 7.9, 1.3, 1H), 6.85 (s, 2H), 5.22 (s, 1H); $^{13}$C NMR (75 MHz) δ 152.3, 149.6, 144.1, 143.4, 129.8, 129.2, 128.3, 126.4, 123.8, 120.3, 119.7, 116.6, 112.9, 62.5, 53.7; GC-MS: m/z = 156 [$M^{+}$-$C_7H_6N_3$, 10%], 155 (100), 127 (69), 103 (49), 76 (11).

**4-Amino-2-(2-methoxyphenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5b**):** White solid; M.p: 219-221 $^{o}$C (EtOAc); Yield: (282 mg, 89%); IR (KBr): υ 3362, 3303, 3135, 3006, 2940, 2182, 1677, 1606, 1493, 1474, 1454, 1407, 1258 cm$^{-1}$; $^{1}$H NMR (300 MHz) δ 8.26 (br.s, 1H), 7.62 (d, *J* = 7.9, 1H), 7.31-7.19 (m, 2H), 7.14-7.05 (m, 2H), 7.00 (t, *J* = 8.6, 2H), 6.87 (t, *J* = 7.4, 1H), 6.72 (s, 2H), 5.38 (s, 1H), 3.69 (s, 3H); $^{13}$C NMR (75 MHz) δ 156.8, 152.8, 149.9, 144.1, 130.7, 129.8, 129.6, 126.9, 123.6, 120.8, 120.2, 119.5, 116.4, 112.7, 111.8, 61.7, 55.8, 49.4; GC-MS: m/z = 185 [$M^{+}$-$C_7H_6N_3$, 10%], 184 (100), 156 (40), 119 (75), 91 (34), 78 (17).

**4-Amino-2-(2,3-dichlorophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5f**):** White solid; M.p: 230-232 $^{o}$C (EtOAc); Yield: (324 mg, 91%); IR (KBr): υ 3428, 3293, 3207, 3176, 2198, 1678, 1629, 1600, 1472, 1447, 1382 cm$^{-1}$; $^{1}$H NMR (300 MHz) δ 8.57 (br.s, 1H), 7.68 (d, *J* = 7.9, 1H), 7.63 (dd, *J* = 7.4, 2.0, 1H), 7.43-7.31 (m, 2H), 7.25 (d, *J* = 7.5, 1H), 7.14 (t, *J* = 7.3, 1H), 7.03 (t, *J* = 8.1, 1H), 6.95 (br.s, 2H), 5.73 (s, 1H); $^{13}$C NMR (75 MHz) δ 206.9, 152.0, 150.1, 144.0, 142.4, 132.7, 130.6, 130.0, 129.7, 129.3, 127.5, 123.9, 120.5,

118.9, 116.6, 113.0, 60.7, 52.1, 31.1; GC-MS: m/z = 227 ($M^+$+4-$C_7H_6N_3$, 0.1%), 225 ($M^+$+2-$C_7H_6N_3$, 0.6), 223 ($M^+$-$C_7H_6N_3$, 1), 226 (7), 224 (42), 222 (62), 187 (100), 152 (13), 124 (14).

**4-Amino-2-(2-fluorophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5i**):** Cream solid; M.p: 219-221 $^oC$ (EtOAc); Yield: (278 mg, 91%); IR (KBr): υ 3405, 3313, 3083, 2194, 2180, 1680, 1634, 1603, 1472, 1444, 1406, 1252 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 8.52 (s, 1H), 7.65 (d, *J* = 7.9, 1H), 7.42-7.31 (m, 1H), 7.31-7.07 (m, 5H), 7.02 (td, *J* = 7.9, 1.2, 1H), 6.86 (br.s, 2H), 5.47 (s, 1H); $^{13}C$ NMR (75 MHz) δ 160.0 (d, *J* = 246.1), 152.2, 149.9, 144.0, 130.5 (d, *J* = 8.2), 129.9 (d, *J* = 13.5), 129.7, 128.4 (d, *J* = 3.8), 125.2 (d, *J* = 2.9), 123.8, 120.4, 119.1, 116.5, 116.3 (d, *J* = 21.3), 112.8, 61.2, 48.9; GC-MS: m/z = 173 ($M^+$-$C_7H_6N_3$, 12%), 172 (100), 145 (82), 121 (30).

**4-Amino-2-(4-nitrophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5m**):** Cream solid; M.p: > 300 $^oC$ (EtOAc); Yield: (299 m, 90%,); IR (KBr): υ 3466, 3425, 3326, 3222, 3081, 2917, 2188, 1678, 1640, 1600, 1519, 1470, 1445, 1405, 1350 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 8.77 (s, 1H), 8.25 (d, *J* = 7.8, 2H), 7.64 (d, *J* = 7.8, 1H), 7.59-7.54 (m, 2H), 7.26 (dd, *J* = 7.8, 0.8, 1H), 7.13 (td, *J* = 7.7, 1.0, 1H), 7.02 (td, *J* = 7.9, 1.2, 1H), 6.97 (s, 2H), 5.45 (s, 1H); $^{13}C$ NMR (75 MHz) δ 151.9, 150.6, 149.9, 147.5, 144.0, 129.7, 127.7, 124.5, 123.9, 120.5, 119.4, 116.7, 113.0, 61.1, 53.0; GC-MS: m/z = 201 ($M^+$-$C_7H_5N_3$, 25%), 136 (100), 106 (37), 89 (33), 78 (29).

**4-Amino-2-(3-nitrophenyl)-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5n**):** Yellow solid; M.p: 228-230 $^oC$ (EtOAc); Yield: (302 mg, 91%); IR (KBr): υ 3302, 3225, 3144, 3075, 2192, 1682, 1630, 1602, 1535, 1475, 1349 $cm^{-1}$; $^1H$ NMR (300 MHz) δ 8.79 (s, 1H), 8.24-8.12 (m, 2H), 7.78 (dd, *J* = 6.6, 1.2, 1H), 7.70 (d, *J* = 7.8, 1H), 7.65 (d, *J* = 7.8, 1H), 7.26

(dd, *J* = 7.8, 0.8, 1H), 7.13 (td, *J* = 7.8, 1.0, 1H), 7.03 (dd, *J* = 7.8, 1.2, 1H), 7.00 (br.s, 2H), 5.50 (s, 1H); $^{13}$C NMR (75 MHz) δ 151.9, 150.1, 148.3, 145.5, 144.0, 133.2, 130.9, 129.7, 123.9, 123.3, 121.3, 120.5, 119.5, 116.7, 113.0, 61.0, 52.8; GC-MS: m/z = 201 ($M^+$-$C_7H_5N_3$, 12%), 136 (100), 128 (11), 90 (17).

## 3. Results and discussion

### *3.1. Synthesis and characterization of 1H-imidazol-3-ium trinitromethanide (**1**) {[HIMI]C(NO$_2$)$_3$} as a green benign NIL catalyst.*

To start the study, 1*H*-imidazol-3-ium tricyanomethanide (**1**) {[HIMI]C(CN)$_3$} was synthesized by reaction between imidazole and methanetricarbonitrile through a proton transfer mechanism in MeCN (1 M) for 120 minutes. Then, the structure of **1** was investigated and fully characterized by FT-IR, $^1$HNMR, $^{13}$CNMR, TGA, DTG, DTA, XRD, SEM, and TEM analyses.

The FT-IR spectrum of catalyst **1** displayed a broad peak at 3433 cm$^{-1}$ which can be assigned to the N–H stretching absorption on imidazolium ring. Additionally, the absorption peaks at 1586 cm$^{-1}$ and 1384 cm$^{-1}$ are related to the asymmetric and symmetric –NO$_2$ stretching absorption bands on trinitromethanide counter ion (Figure 1).

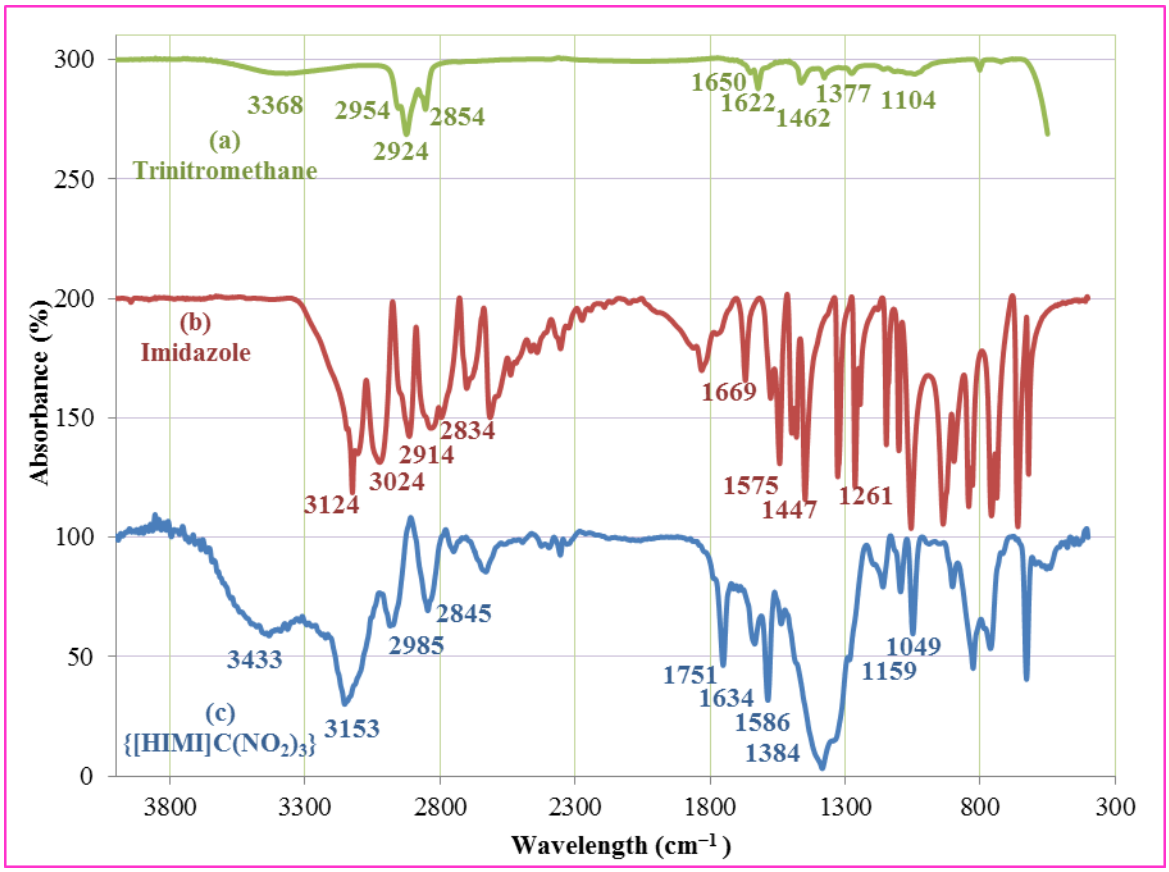



**Figure 1.** IR spectrum of trinitromethane (a), imidazole (b) and catalyst **1** (c).

$^{1}$H- and $^{13}$CNMR spectra of catalyst **1** in DMSO-$d_6$ are showed in Figures 2 and 3. Regarding the $^{1}$HNMR spectrum, it can be clearly distinguished the resonance peak corresponding to the acidic hydrogen (N–H) of the nanostructured ionic liquid catalyst at 14.09 ppm. Also, it can be seen a triplet at 9.10 ppm and a doublet at 7.70 ppm, resonances linked to the aromatic protons of the imidazolium ring (Figure 2).

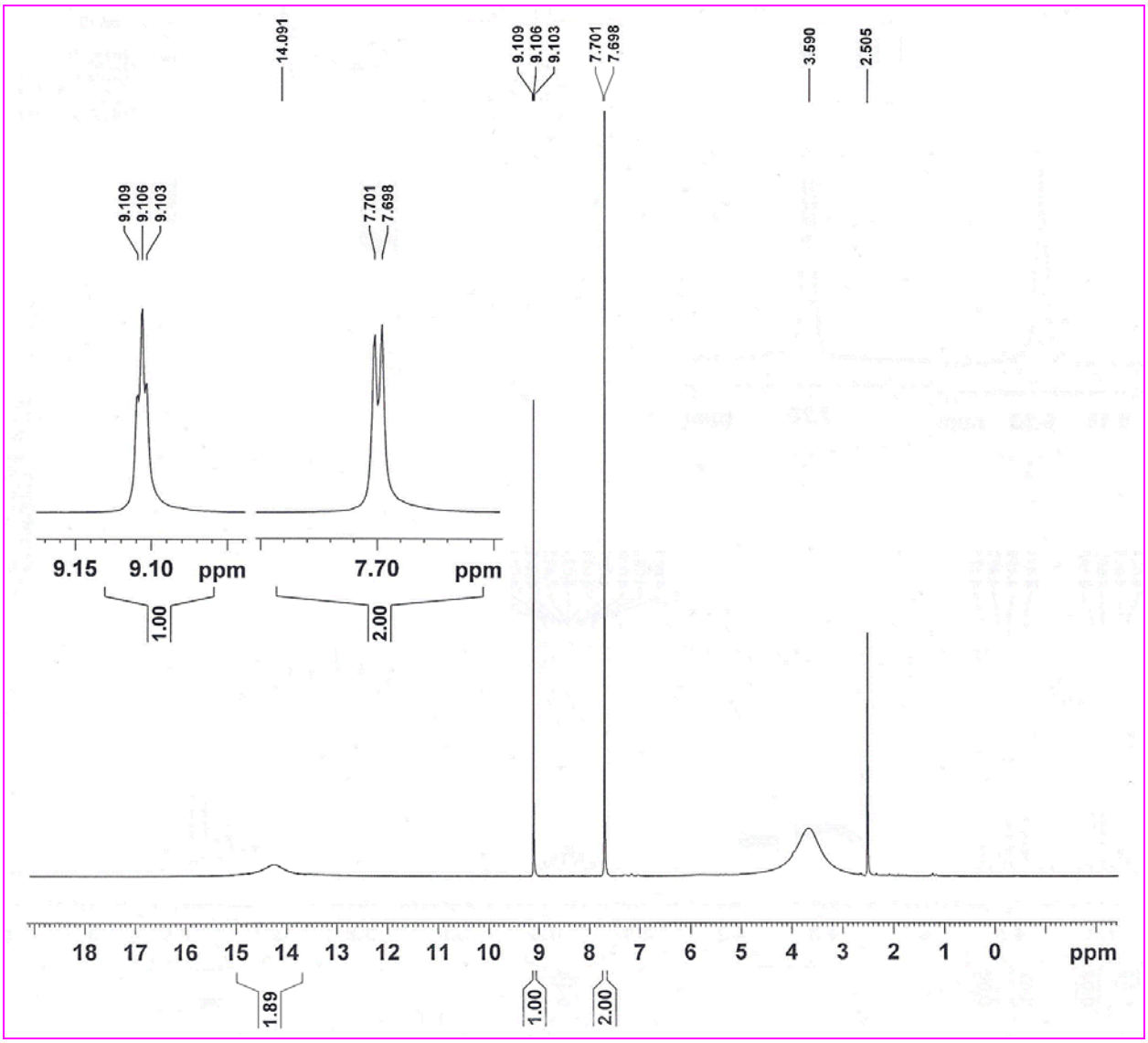



**Figure 2.** $^{1}$H NMR spectrum of catalyst **1**{[HIMI]C($NO_2$)$_3$}.

Furthermore, the $^{13}$C NMR spectrum of **1** confirmed the structure of the synthesized catalyst. Thus, presented peak at 160.1 was related to the carbon of -C($NO_2$)$_3$ group while two peaks at 134.8 and 119.7 ppm were correlated to the aromatic carbons in imidazolium ring (Figure 3).

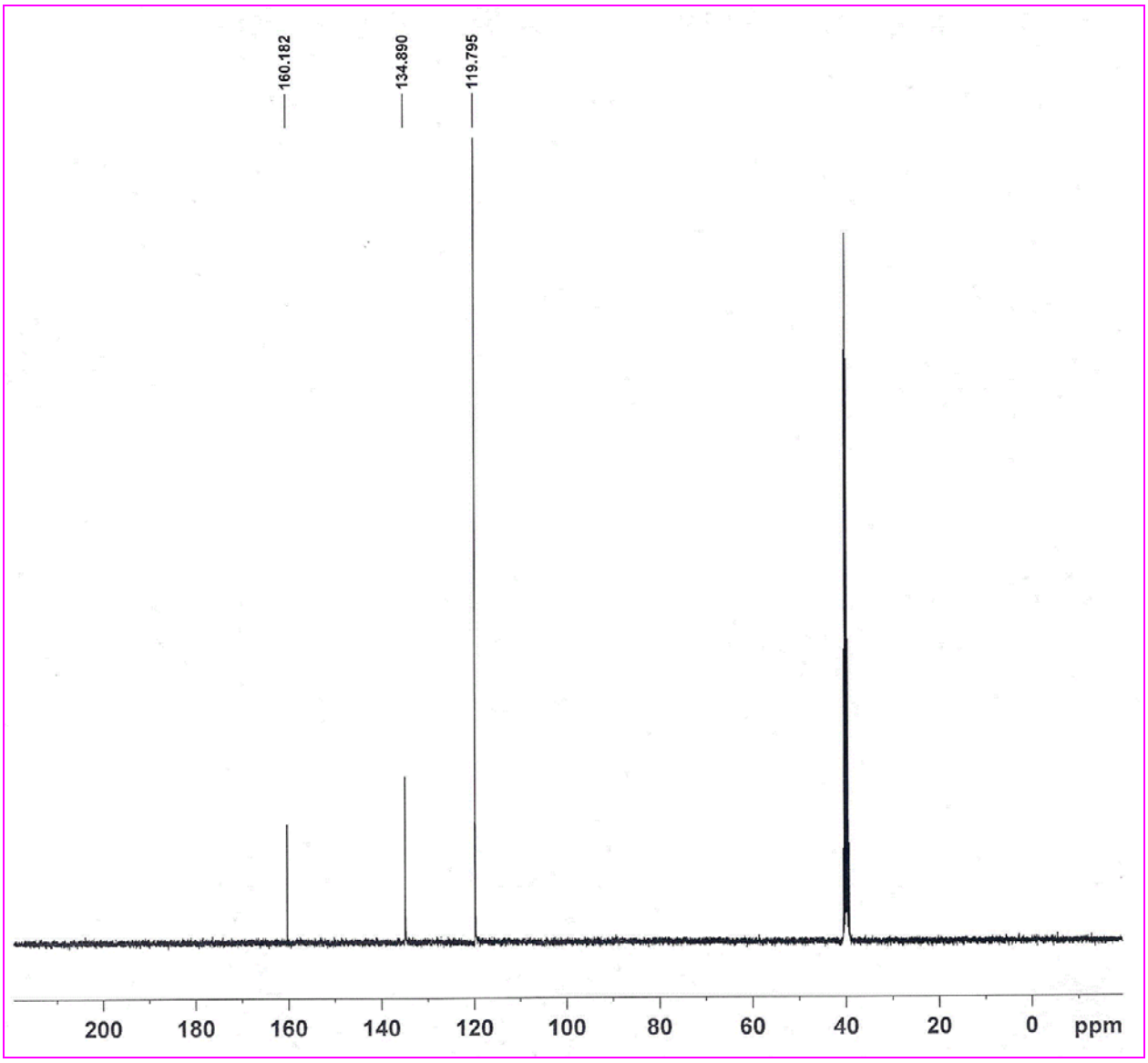



**Figure 3.** $^{13}C$ NMR spectrum of catalyst **1** {[HIMI]C($NO_2$)$_3$}.

The thermal gravimetric (TG), derivative thermal gravimetric (DTG), and differential thermal (DTA) analysis of NIL catalyst **1** display the mass loss of organic materials as they decompose upon heating (Figure 4). The first weight loss (~2%) from the catalyst (room temperature to 110 °C) is due to the removal of physically adsorbed water and organic solvents, which were used in the synthesis of the NIL catalyst. The main weight loss (90 %) between 110 and 175 °C is associated mainly to the thermal decomposition of NIL catalyst. Thus, catalyst **1**

shows a one-step weight loss behavior decomposing after 175 °C. The DTA analysis diagram is upward and exothermic).

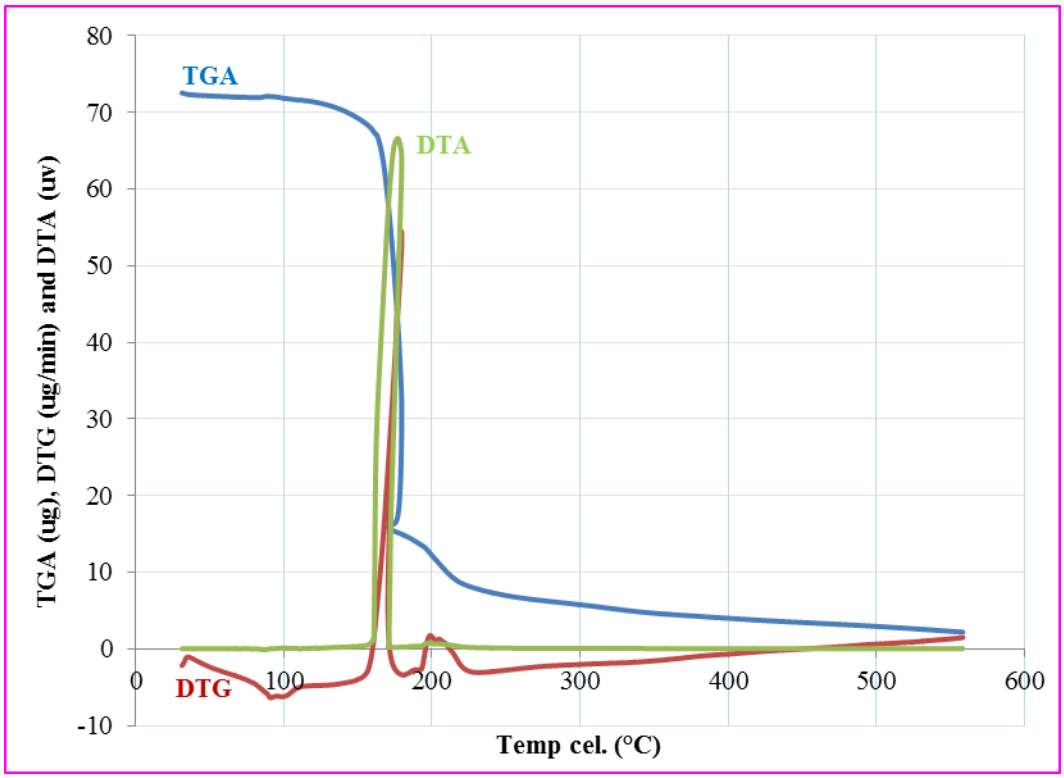



**Figure 4.** The thermal gravimetric (TG), derivative thermal gravimetric (DTG), and differential thermal (DTA) analysis of {[HIMI]C($NO_2$)$_3$}.

The structure of catalyst **1** was further investigated through X-ray diffraction (XRD) pattern (Figure 5), scanning electron microscopy (SEM) (Figure 6) and transmission electron microscopy (TEM) (Figure 6). Peak width (FWHM), size and inter planer distance linked to XRD pattern of **1** were studied in the 16.30$^o$ to 52.00$^o$ degree and the achieved results are summarized in Table 1. For example, assignments for the highest diffraction line 23.50$^o$ presented that an FWHM of 0.22, a crystalline size of the NIL catalyst (**1**) {[HIMI]C($NO_2$)$_3$} of ca. 36.89 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. $\beta$ 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. 378115 nm (the similar highest diffraction line at 23.50$^{o}$) was investigated by the Bragg equation: dhkl = λ/(2sinθ), (λ : Cu radiation (0.154178 nm) were attained. Achieving crystalline sizes from several diffraction lines *via* the Scherrer equation were found to be in the nanometer range (5.87-38.44 nm), which is specially in a close accordance with the scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (Figure 6). To determine the morphology and the size of **1**, SEM and TEM experiments were also performed, showing a particle size for **1** of about 39 nm (Figure 6).

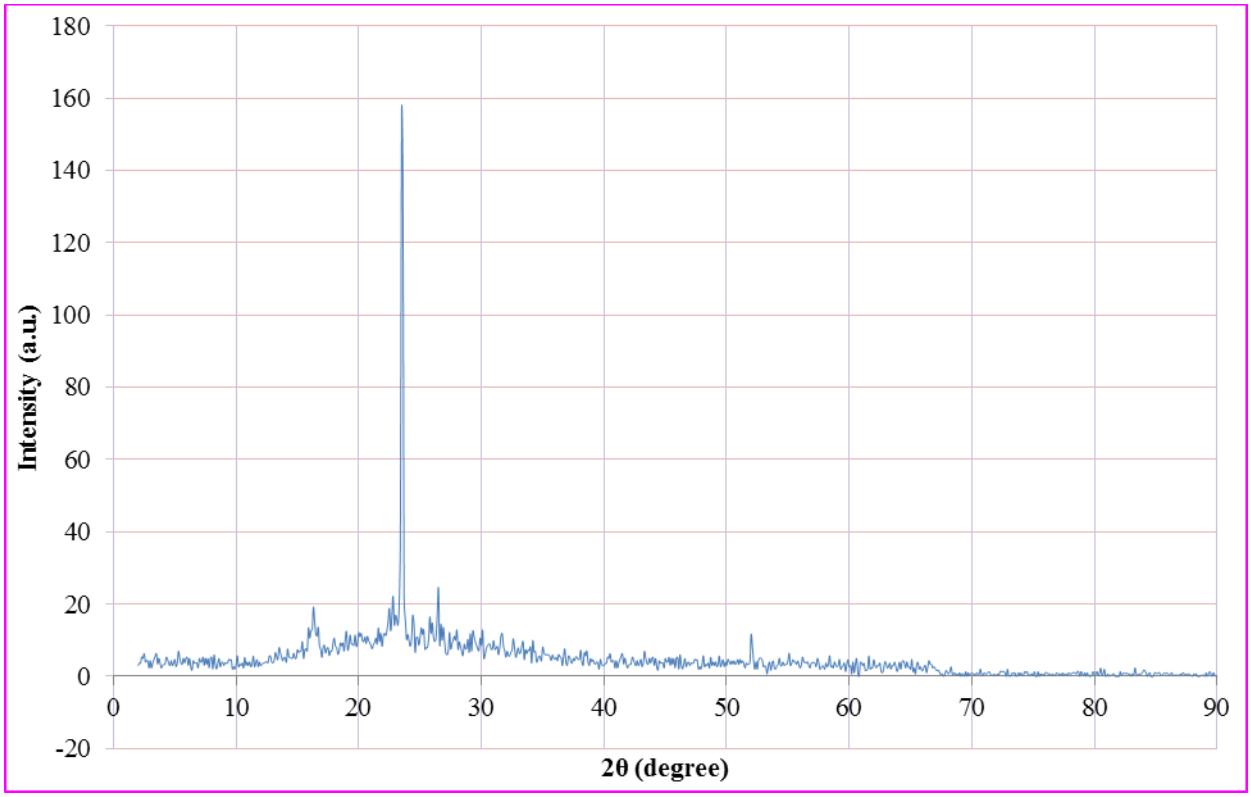



**Figure 5.** XRD pattern of catalyst **1**.

**Table 1.** XRD data for catalyst **1**.

| Entry | 2θ | Peak width [FWHM] (degree) | Size [nm] | Inter planer distance [nm] |
|---|---|---|---|---|
| 1 | 16.30 | 0.99 | 8.11 | 0.274346 |
| 2 | 22.80 | 1.38 | 5.87 | 0.389564 |
| 3 | 23.50 | 0.22 | 36.89 | 0.378115 |
| 4 | 26.50 | 0.24 | 34.01 | 0.335951 |
| 5 | 52.00 | 0.23 | 38.44 | 0.175650 |

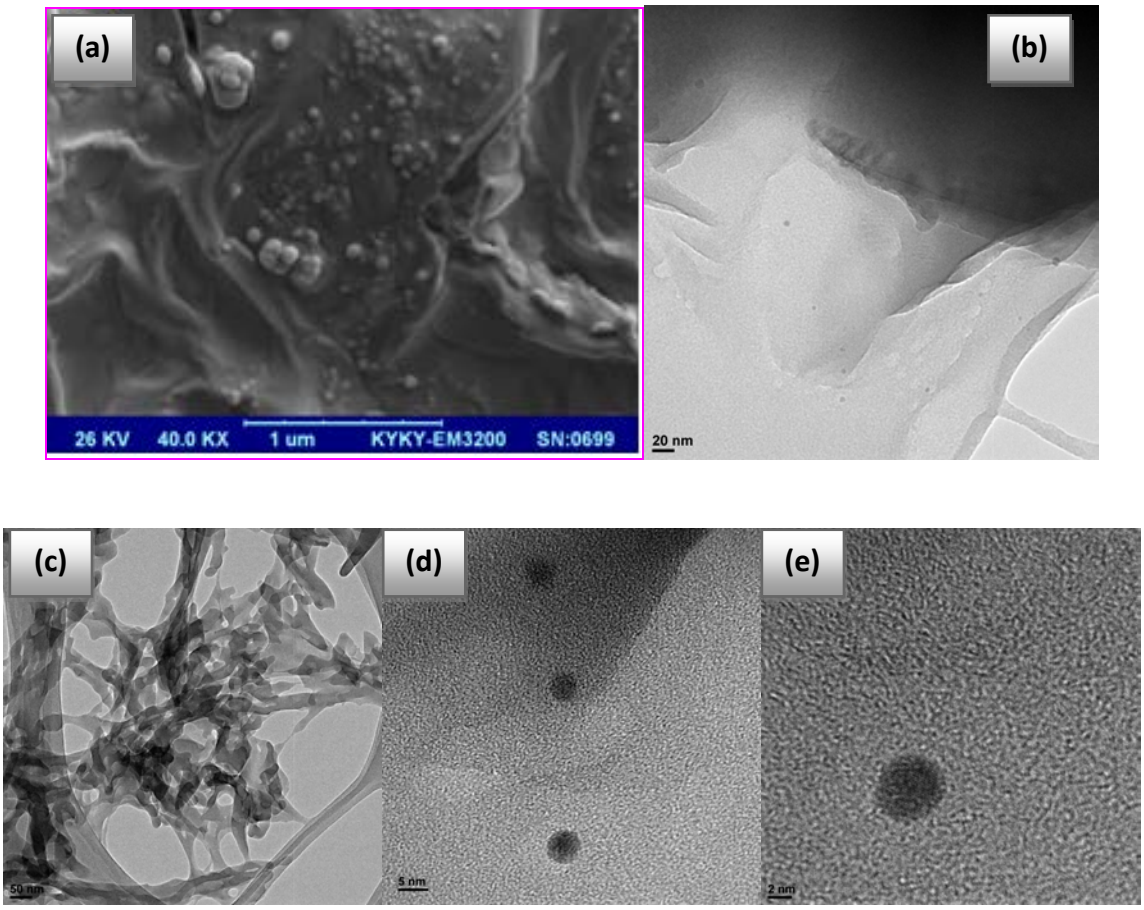
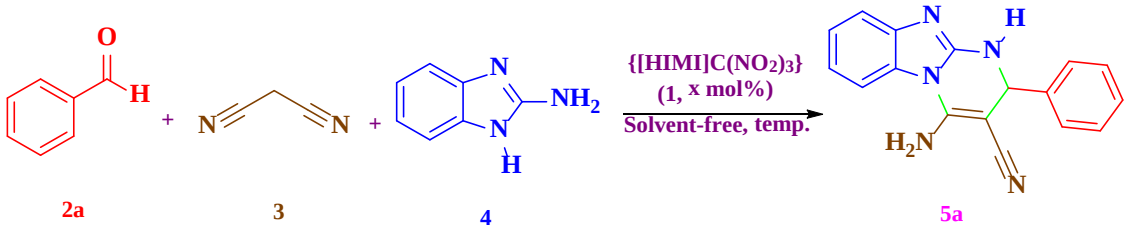



**Figure 6.** Scanning electron microscopy (SEM) (a) and transmission electron microscopy (TEM) (b-e) of catalyst **1**.

*3.2. Application of catalyst (***1***) {[HIMI]C(NO$_2$)$_3$} in the one-pot three component synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile.*

First, the condensation reaction of benzaldehyde (**2a**), with malononitrile (**3**) and 2-aminobenzimidazole (**4**) was examined in the presence of a catalytic amount of catalyst **1** as the standard model reaction for the optimization of conditions (Table 2). As depicted in entry 1, under neat and catalyst-free conditions, the reaction proceeded slowly at 50 $^{o}$C affording 4-amino-2-phenyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**5a**) in a low yield 35% yield after 90 minutes. Importantly, when 0.5 mol% of **1** was employed, the reaction proceeded efficiently yielding **5a** in 90% isolated yield after only 20 minutes (Table 2, entry 2). Subsequently, the reaction was performed using 1.0 mol% of catalyst **1** at room temperature and at 50 $^{o}$C (Table 2, entries 3-4). Interestingly, the increased reaction efficiency afforded **5a** in a 94% yield at 50 $^{o}$C after only 10 minutes. Additionally, a temperature and catalyst loading study was also carried out. As shown in Table 2, entries 5-8, no improvement was detected in the yield of reaction by increasing the temperature or the catalyst loading. Next, the influence in the efficiency of the process of different solvents, such as, EtOH, $H_2O$, $CH_3CN$, EtOAc, and *n*-hexane was investigated in the presence of 1 mol% of NIL catalyst **1** at 50 $^{o}$C. The obtained results, which are summarized in Table 2, entries 9-13 clearly pointed to the solvent-free conditions as the best choice in this model reaction.

**Table 2.** Optimization of the reaction conditions.[a]



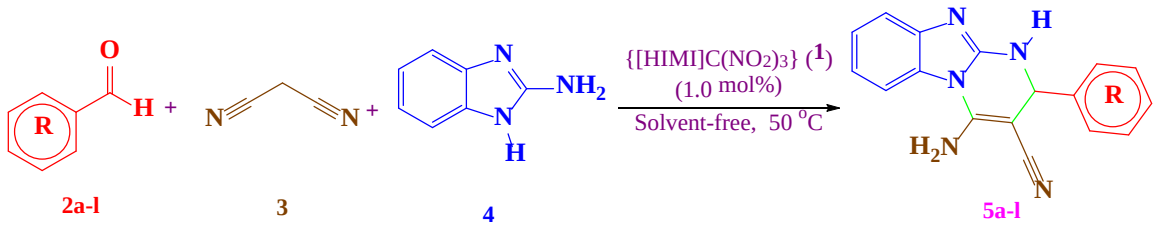

| Entry | Solvent[c] | Catalyst (**1**) (x mol%) | Temperature ($^{o}$C) | Time (min) | Yield %(**5a**)[b] |
|---|---|---|---|---|---|
| 1 | - | - | 50 | 90 | 35 |

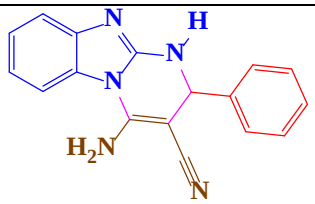
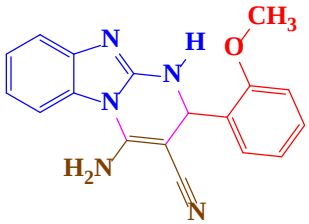
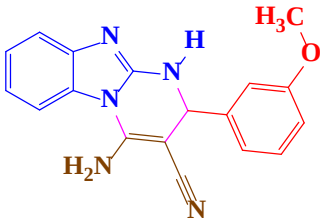
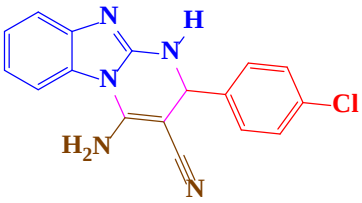
| | | | | | |
|---|---|---|---|---|---|
| 2 | - | 0.5 | 50 | 20 | 90 |
| 3 | - | 1.0 | r.t. | 60 | 50 |
| **4** | **-** | **1.0** | **50** | **10** | **94** |
| 5 | - | 1.0 | 70 | 10 | 94 |
| 6 | - | 1.0 | 90 | 10 | 93 |
| 7 | - | 1.5 | 50 | 10 | 94 |
| 8 | - | 2.0 | 50 | 10 | 94 |
| 9 | EtOH[c] | 1.0 | 50 | 25 | 89 |
| 10 | $H_2O$[c] | 1.0 | 50 | 14 | 91 |
| 11 | $CH_3CN$[c] | 1.0 | 50 | 30 | 77 |
| 12 | *n*-Hexane[c] | 1.0 | 50 | 40 | 65 |
| 13 | EtOAc[c] | 1.0 | 50 | 30 | 70 |

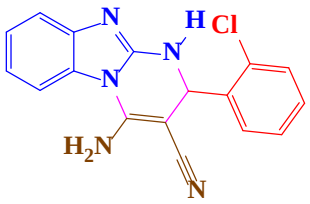
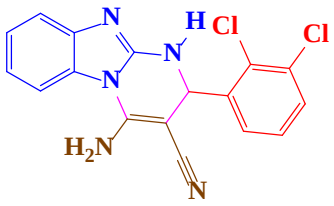
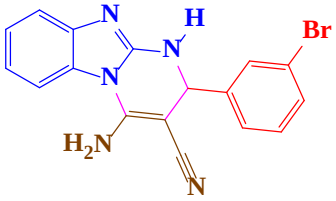
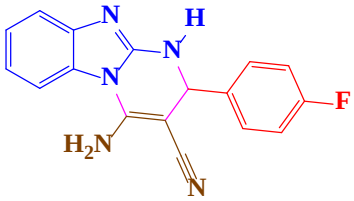
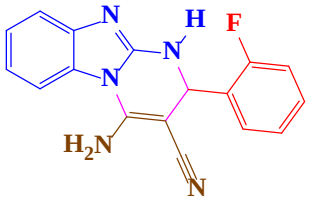
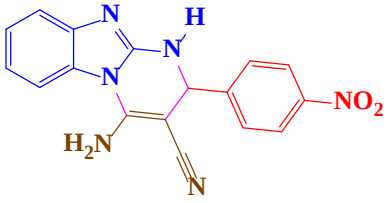
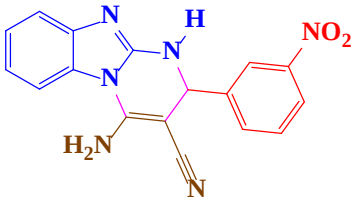
Reaction conditions: [a]**2a** (1.0 mmol, 106 mg), **3** (1.0 mmol, 66 mg), **4** (1.0 mmol, 133 mg), [b]Isolated yield. [c]X ml of solvent were used.

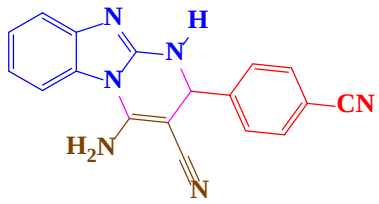
With the optimized conditions in hand (Table 2, entry 4), we set out to investigate the scope of the reaction with a range of aldehydes (**2a-o**), malononitrile (**3**), and 2-aminobenzimidazole (**4**) (Table 3). As exhibited in Table 3, the scope of the reaction is broad and tolerates a series of aromatic aldehydes which react with 2-aminobenzimidazole and malononitrile to provide the corresponding 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles **5a-o** in high to excellent yields. In general, the nature and electronic properties of the substituents on the aromatic ring did not affect neither the reaction rate nor the yield of the process.

**Table 3.** Scope of one-pot three component synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles.[a]




| Entry | R | Time (min) | Product | No, Yield (%)[b] | M.p. (°C) [Lit][ref] | Color |
|---|---|---|---|---|---|---|
| 1 | H | 10 |  | **5a**, 94 (xx)[c] | 218-220 [208-209][36] | White |
| 2 | 2-MeO | 19 |  | **5b**, 89 | 219-221 | White |
| 3 | 3-MeO | 15 |  | **5c**, 88 | 212-214 [216][32] | White |
| 4 | 4-Cl | 10 |  | **5d**, 93 | 235-237 [238][33] | Yellow |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | 2-Cl | 10 |  | **5e**, 91 | 221-223 [236-238][28] | White |
| 6 | 2,3-$Cl_2$ | 13 |  | **5f**, 91 | 230-232 | White |
| 7 | 3-Br | 11 |  | **5g**, 94 | 240-242 [238-240][28] | Cream |
| 8 | 4-F | 13 |  | **5h**, 90 | 225-227 [266-268][28] | White |
| 9 | 2-F | 11 |  | **5i**, 91 | 219-221 [224-226][28] | Cream |
| 10 | 4-$NO_2$ | 13 |  | **5j**, 90 | > 300 [239-241][50] | Cream |
| 11 | 3-$NO_2$ | 14 |  | **5k**, 91 | 228-230 [242-243][36] | Yellow |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12 | 4-CN | 12 |  | **5l**, 89 | 226-228 [215][26] | Yellow |

[a] Reaction conditions: catalyst **1** (1.0 mol%, 2.2 mg), RCHO **2a-o** (1.0 mmol), **3** (1.0 mmol, 66 mg), **4** (1.0 mmol, 133 mg). [b] Isolated yield. [c] Reaction performed at 10 mmol scale.

This synthetic protocol could be scaled up to 10 mmol, as demonstrated for the reaction between benzaldehyde (**2a**), malononitrile (**3**), and 2-aminobenzimidazole (**4**), which afforded **5a** with a xx% yield at 50 $^{o}$C under solvent-free conditions using 10 mol% of catalyst **1**.

Reusability of catalyst **1** was confirmed in the model condensation reaction between benzaldehyde, malononitrile, and 2-aminobenzimidazole. Therefore, once the reaction was completed, ethyl acetate was added 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 NIL catalyst remained in the aqueous phase. After the evaporation of water under vacuum at 80 $^{o}$C for 120 min (see experimental section), the vessel was charged again with a new set of reagents. As depicted in Figure 7, the catalytic activity of catalyst **1** were restored within the limits of the experimental errors for the tested four continuous runs, being product **5a** obtained with a 90% yield after the 4$^{th}$ cycle.

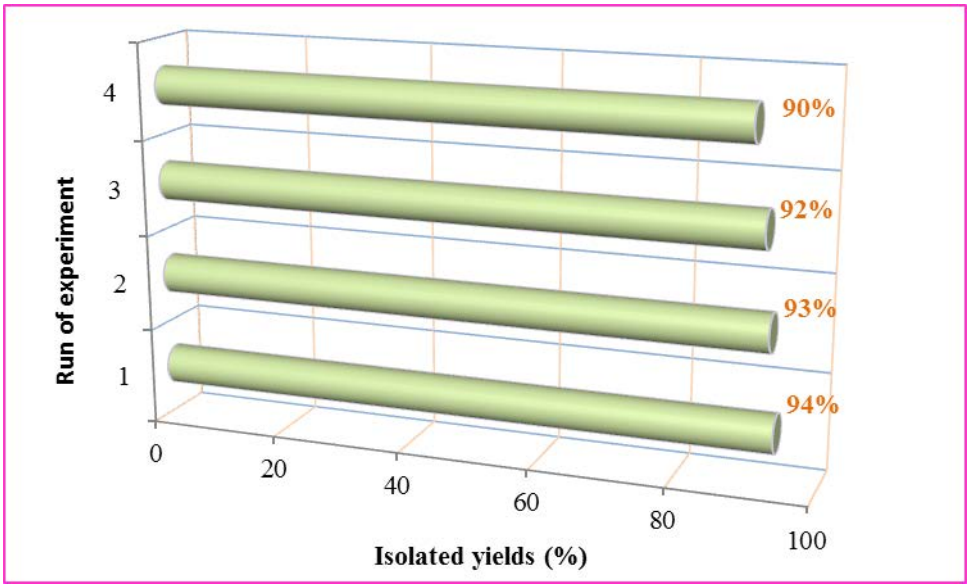
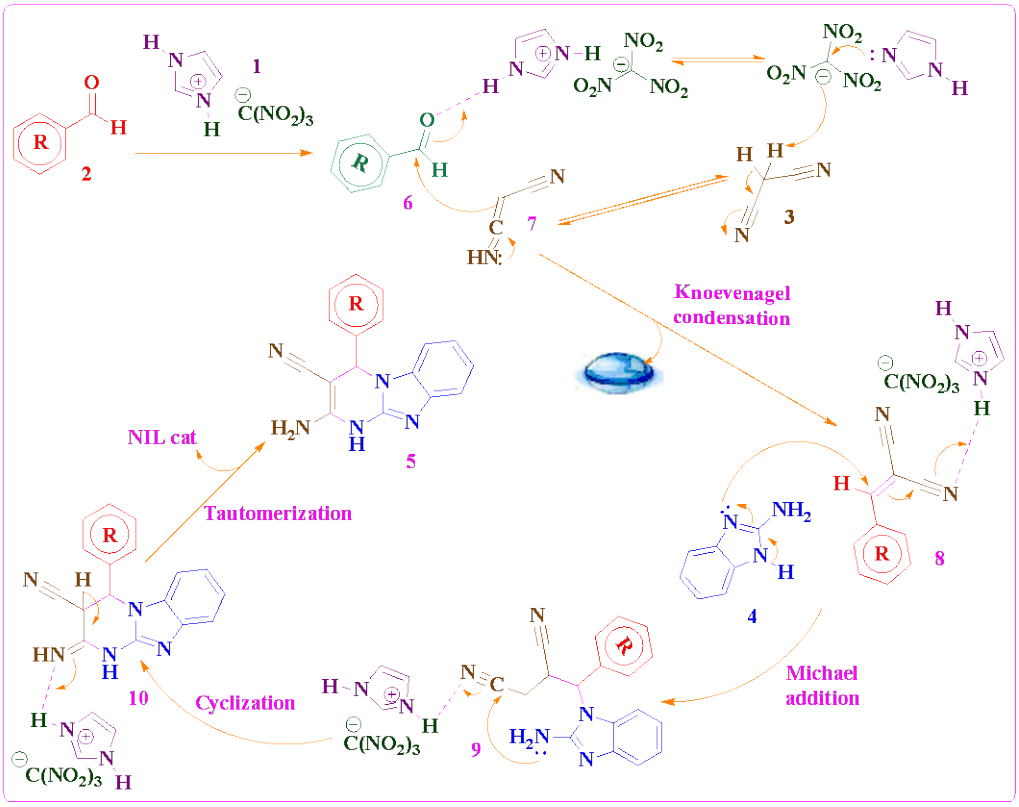



**Figure 7.** Reusability study of catalyst **1** in the 10 minutes reaction between benzaldehyde, 2-aminobenzimidazole and malononitrile.

Based on our previously knowledge[37-47], a probable reaction mechanism for the synthesis of the 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **5** is proposed in Scheme 3. Initially, {[HIMI]C$(NO_2)_3$} activates the carbonyl group of the aromatic aldehyde to afford intermediate **6**, while malononitrile is also tautomerized to **7**. Then, the Knoevenagel condensation of intermediate **6** and **7** occurs to form the arylidene malononitrile **8**. Subsequently, 2-aminobenzimidazole (**4**) performs a nucleophilic attack to **8** providing the corresponding Michael adduct **9**. Finally, a **1**-promoted cyclization of **9** produces intermediate **10**, which then affords the final aromatized 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **5** after tautomerization.




**Scheme 3.** Suggested mechanism for the synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives in the presence of {[HIMI]C($NO_2$)$_3$}.

## 4. Conclusions

In summary, we have designed, synthesized and characterized a green, efficient and recyclable nanostructured ionic liquid catalyst **1**, namely 1*H*-imidazol-3-ium trinitromethanide {[HIMI]C($NO_2$)$_3$}. Catalyst **1** was fully characterized by FT-IR, $^{1}$H NMR, $^{13}$C NMR, thermal gravimetric (TG), derivative thermal gravimetric (DTG), differential thermal analysis (DTA), X-ray diffraction patterns (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis. Then, the catalytic application of the aforementioned NIL catalyst was studied in the one-pot three component synthesis of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives at 50 $^{o}$C under neat conditions. The proposed mechanism exposed that the buffer ability of **1**, possibly plays a

significant and dual catalytic role in the defined reaction. Finally, main advantages of the presented process are practically simple work up, low cost, short reaction time, high yield, recyclability and reusability of the catalyst and cleaner reaction profile which produces it in close accordance with the green chemistry disciplines.

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