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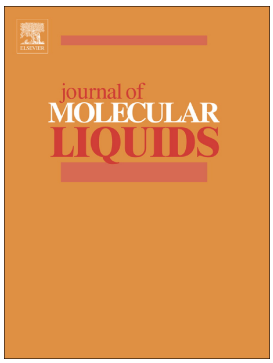

Triphenyl(3-sulfopropyl)phosphonium trinitromethanide as a novel nanosized molten salt: Catalytic activity at the preparation of dihydropyrano[2,3-c]pyrazoles

Meysam Yarie, Mohammad Ali Zolfigol, Saeed Baghery, Diego A. Alonso, Abbas Khoshnood, Yadollah Bayat, Asiye Asgari

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Triphenyl(3-sulfopropyl)phosphonium trinitromethanide as a novel nanosized molten salt: Catalytic activity at the preparation of dihydropyrano[2,3-*c*]pyrazoles

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Abstract

In this paper, designing, preparation and characterization of a unique nanosized molten salt namely triphenyl(3-sulfopropyl)phosphonium trinitromethanide (TPSPPTNM) was reported. The successful formation of nanosized catalyst was verified by using suitable skills like fourier transform infrared spectroscopy (FT-IR), proton, carbon and phosphor NMR, X-ray diffraction patterns (XRD), field emission scanning electron microscopy (FESEM), energy dispersive X-ray analysis (EDX), SEM elemental mapping, high resolution transmission electron microscopy (HRTEM), thermogravimetry (TG) and derivative thermogravimetry (DTG) analysis. The catalytic application of the novel molten salt was explored towards the synthesis of pyrano[3,2-*c*]pyrazole derivatives under mild and green reaction conditions.

Keywords: Triphenyl(3-sulfopropyl)phosphonium trinitromethanide, Nanosized molten salt, Pyrano[3,2-*c*]pyrazole derivatives, Multicomponent reactions.

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1. Introduction

Heterocyclic structural kernels have found their prominent position among the therapeutic active molecules. Heterocyclic compounds play a critical role in molecular form of life for example nucleotides, carbohydrates, hemes and amino acids [1]. Specifically, nitrogen-rich heterocyclic molecules containing pyrazole moieties due to the privilege applications as biological and pharmacological active species, occupy a distinguish location in the domain of medicinal chemistry [2]. Figure 1 depicted some drug structures containing pyrazole moiety [3-4]. Among fused nitrogen-containing heterocyclic molecules, dihydropyrano[2,3-*c*]pyrazole derivatives which established significant precursors for the drug compounds, exhibit a broad scope of vital medicinal and pharmaceutical applications. They can be used as inhibitors of human Chk1 kinase [5], antimicrobial [6] anti-inflammatory [7] and anticancer agents [8-10]. Therefore, because of the high biological importance of these compounds, it is not surprising that several protocols have been reported for their preparation [11-21]. Various methods are reported for the synthesis of target molecules such as sonication in H_2O [12], DIPH in refluxing H_2O [13], nanomagnetic acidid catalyst under solvent free conditions [14], Uncapped SnO_2 QDs [16], ZrO_2, EtOH-H_2O [17], CTACl [18] and [DMDBSI]-$2HSO_4$ [20].

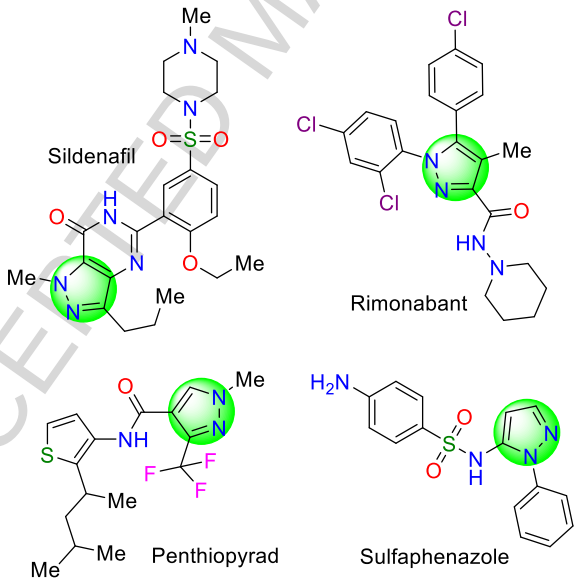

Figure 1: Some therapeutic active molecules bearing pyrazole moiety.

Nano ionic liquids and molten salts are fast developing fields across many areas of chemistry as they can offer a broad range of encouraging versatilities in catalysis and as excellent alternative for unsafe and/or volatile organic solvents and reagents. Using nano ionic liquids and molten salts can trigger positive improvements regarding to efficiency, selectivity, yield, time and recycling capability in a typical reaction [22]. Also, currently ionic liquids and

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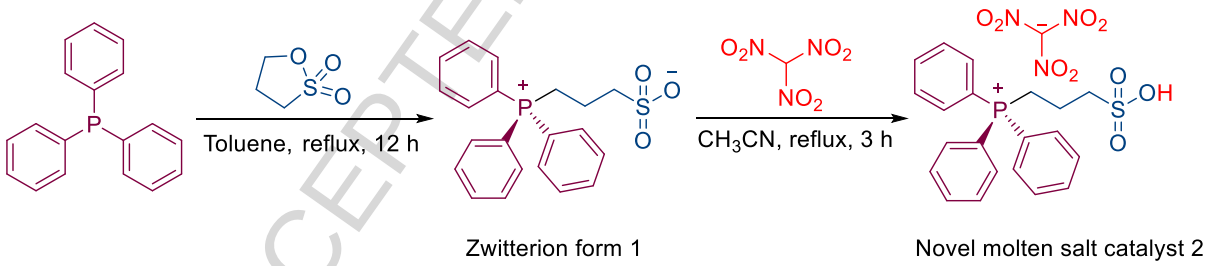
molten salts have found diverse utilities in modern technologies including synthesis, processes, electrochemistry, materials and transporting things [23]. Duo to these versatilities of ionic liquids and molten salts, the synthesis, chemistry and application of them is well reviewed [24-31].

On the other hands, multicomponent reactions (MCRs) as a dominant protocol for the construction of highly valuable complex molecules represent a number of superior synthetic merits over conventional stepwise consecutive methods. The tangible benefits of MCRs protocol are reduce energy consumption, accelerating the reaction while increasing the efficiency, atom and step economy and prevention of time consuming product isolation and purification procedures [32-37]. MCRs can be divided into three distinguished classes including domino-type, sequential and consecutive ones based on reactivity concept [38].

In continuation of our investigation on the knowledge-based development of phosphonium based ionic liquids, molten salts and presentation of eco-compatible catalytic methods for the construction of biologically significant heterocyclic structures [39-41], we encouraged to study the design, synthesis and catalytic activity of a novel nanosized phosphonium based molten salt namely triphenyl(3-sulfopropyl)phosphonium trinitromethanide (TPSPPTNM) (Scheme 1) at the preparation of dihydropyrano[2,3-c]pyrazole through an eco-compatible manner (Scheme 2).



Scheme 1: Synthetic route to TPSPPTNM.

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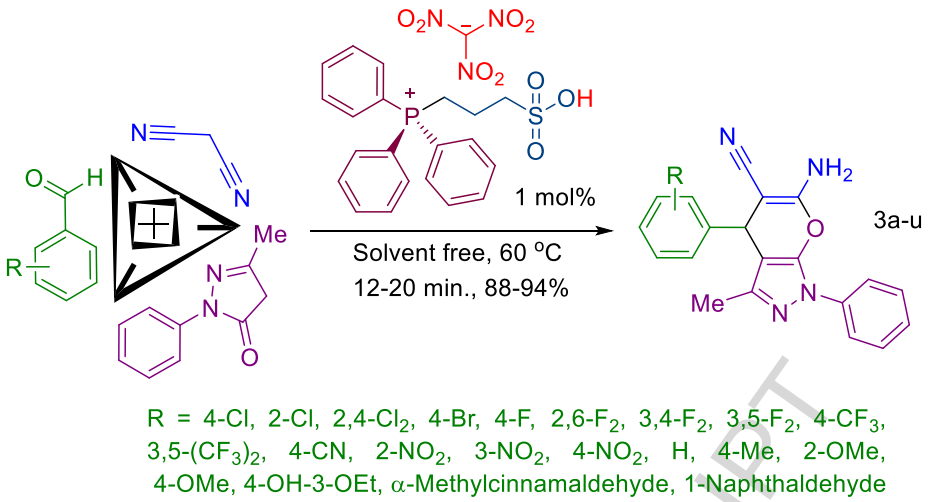

Scheme 2: Preparation of dihydropyrano[2,3-c]pyrazole in the presence of TPSPPTNM.

2. Experimental

2.1. General

All chemicals were obtained from Alfa Aesar, Sigma Aldrich and used without further purification. The known products have been identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. R_f values were measured using EtOAc: n-Hexane (3:10) as elution solvents. Fourier transformed infrared (FT-IR) spectra of the catalyst and the synthesized products were performed on a FTIR spectrometer JEOL spectrum 4100 typeA. High resolution mass spectra (GC/QTOF, Chemical Ionization (CI) mode with 20% CH_4 and 300 °C source temperature) were obtained using an Agilent 7200 Network spectrometer. Each sample was dissolved in DMSO and directly injected to the instrument by using standard Agilent glass capillary. ^{1}H NMR (300 MHz) spectra were obtained on a Bruker Avance 300 spectrometers under proton coupled mode using $CDCl_3$ as solvent. ^{13}C NMR (101 MHz) spectra were acquired on a Bruker Avance 400 NMR spectrometer in the proton decoupled mode at 20 °C in DMSO-d_6 as solvent. ^{31}P NMR (400MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). Chemical shifts are given in δ (parts per million) and the coupling constants (J) in Hertz. ^{19}F NMR (282 MHz) spectra were recorded on a Bruker Avance 300 NMR spectrometer, in proton coupled mode. Data for ^{1}H NMR spectra is reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br., broad), coupling constant (Hz), and integration. Simultaneous thermal gravimetry analysis TG-DTG, were carried out on a Mettler Toledo

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equipment (model TGA/SDTA851and/LF/1600), capable of working between room temperature and 1600 °C under inert Argon atmosphere and is equipped with a 34 position autosampler. The experiment was carried out at 25°C and using a heating rate of 25 °C min^{-1} up to 800 °C. Powder X-ray diffraction (XRD) pattern was recorded with a Bruker D8-Advance with mirror Goebel (non-planar samples), high temperature Chamber (up to 900°C), generator of x-ray KRISTALLOFLEX K 760-80F (power: 3000W, voltage: 20-60KV and current: 5-80 mA) and with a tube of RX with copper anode Kα (λ = 0.154 nm) in the range $10° < 2\theta < 90°$. Field emission scanning electron microscopy (FESEM) studies were performed using a Merlin VP Compact from Zeiss, equipped with an EDS microanalysis system Quantax 400 from Bruker. Scanning electron microscopy (SEM) studies were performed using a Hitachi S3000 N, equipped with an X-ray detector (Bruker XFlash 3001) for microanalysis (energy-dispersive X-ray, EDX) and mapping (wavelength-dispersive X-ray, WDX). High-resolution transmission electron microscopy (HRTEM) images were obtained using a JEOL JEM-2010 microscope operating at an accelerating voltage of 200 kv. This microscope is equipped with an X-ray detector OXFORD INCA Energy TEM 100 for microanalysis (EDS) and acquisition of the images is made by means of a digital camera GATAN ORIUS SC600 mounted on-axis, integrated with the program GATAN DigitalMicrograph 1.80.70 for GMS 1.8.0. Sample was prepared by drop casting the dispersed particles in absolute ethanol onto a 300-mesh copper grid from TED PELLA, INC. model 01883-F, coated with a lacey formvar film enforced by a heavy coating of carbon. Holes are completely open.

2.2. General method for the synthesis of TPSPPTNM

In the first step, a mixture of triphenylphosphine (3 mmol, 0.787 g) and 1,3-propane sultone (3 mmol, 0.367 g) dissolved in toluene (30 mL), stirred at reflux condition for 12 h. Then, the obtained white zwitterion form 1, was filtered off, washed with diethyl ether and dried in a vacuum [42]. In next step, to a round bottom flask containing zwitterionic form 1 (2 mmol, 0.769 g) dissolved in acetonitrile, trinitromethane (2 mmol, 0.302 g) was added. Then the mixture was stirred under reflux condition for 3 h. Finally, solvent was removed under vacuum to provide desired catalyst in a quantitative yield (Scheme 1).

2.3. General method for the catalytic synthesis of dihydropyrano[2,3-c]pyrazoles

To a reaction vessel containing a mixture of aromatic aldehydes (1 mmol), malononitrile (1 mmol, 0.066 g) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol, 0.174 g),

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TPSPPTNM (1 mol%, 5 mg) was added. The obtained reaction mixture was stirred at 60 ^{o}C for adequate period of times as indexed in table 3. The progress of the reaction was monitored via TLC (*n*-hexane/EtOAc as eluant). Finally, purification process using hot ethanol provides desired molecules in high yields (Scheme 2).

2.4. Spectral data

Triphenyl(3-sulfopropyl)phosphonium trinitromethanide (TPSPPTNM)

Melting point: >300 °C,

FT-IR: υ (cm^{-1}) = 3434, 3018, 2908, 1587, 1384, 1213, 1113, 1033.

^{1}H NMR δ 8.71 (s, 1H, Acidic), 7.97 (d, 6H, *J*= 8.4 Hz, Aromatic), 7.60 (d, 6H, *J*= 8.4 Hz, Aromatic), 7.35 (t, 6H, *J*= 4 Hz, Aromatic), 4.04 (q, 2H, *J*= 7.6 Hz, Aliphatic), 1.94 (t, 2H, *J*= 7.2 Hz, Aliphatic), 0.76-0.68 (m, 2H, Aliphatic).

^{13}C NMR δ 152.7, 134.4, 130.1, 124.5, 123.0, 52.7, 29.5, 23.1.

^{31}P NMR δ 23.5.

6-amino-4-(4-chlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3a):

(340 mg, 94%), R_f: 0.10, Melting point: 193 – 195 °C.

FT-IR: υ (cm^{-1}) = 2205, 1656, 1594, 1517, 1490, 1443, 1388, 1261, 1127, 1063, 1014, 803, 750.

^{1}H NMR δ 7.83 – 7.76 (m, 2H), 7.55 – 7.46 (m, 2H), 7.46 – 7.38 (m, 2H), 7.39 – 7.24 (m, 5H), 4.73 (s, 1H), 1.80 (s, 3H).

^{13}C NMR δ 159.9, 145.6, 144.4, 143.1, 137.9, 130.2, 129. 8, 129.5, 129.2, 129.0, 126.7, 120.5, 98.6, 58.2, 36.5, 13.0.

HRMS calcd. for $C_{17}H_{15}ClN_2O$ ($[M - C_3N_2]+H)^+$ 299.0951, found. 299.0937.

6-amino-4-(2-chlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3b):

(329 mg, 91%), R_f: 0.14, Melting point: 176 – 178 °C.

FT-IR: υ (cm^{-1}) = 2187, 1648, 1583, 1518, 1495, 1445, 1391, 1266, 1127, 1068, 1028, 750, 690.

^{1}H NMR δ 7.82 – 7.76 (m, 2H), 7.54 – 7.43 (m, 3H), 7.37 – 7.28 (m, 6H), 5.16 (s, 1H), 1.76 (s, 3H).

^{13}C NMR δ 160.3, 145.3, 144.7, 140.5, 137.9, 132.6, 131.6, 130.0, 129.8, 129.4, 128.3, 126.7, 120.5, 120.1, 98.2, 57.1, 34.5, 12.8.

HRMS calcd. for $C_{17}H_{15}ClN_2O$ ($[M - C_3N_2]+H)^+$ 299.0951, found. 299.0926.

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6-amino-4-(2,4-dichlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3c):

(364 mg, 92%), R_f: 0.12, Melting point: 196 – 197 °C.

FT-IR: υ (cm^{-1}) = 3457, 3326, 2197, 1655, 1581, 1519, 1388, 1288, 1125, 1064, 1027, 835, 814, 756, 690, 647.

^{1}H NMR δ 7.82 – 7.76 (m, 2H), 7.64 (d, *J* = 2.0, 1H), 7.54 – 7.32 (m, 7H), 5.16 (s, 1H), 1.78 (s, 3H).

^{13}C NMR δ 160.4, 145.3, 144.7, 139.7, 137.9, 133.5, 133.0, 132.9, 129.8, 129.4, 128.6, 126.7, 120.5, 120.0, 97.7, 56.6, 34.0, 12.8.

HRMS calcd. for $C_{17}H_{14}Cl_2N_2O$ ($[M – C_3N_2]+H)^+$ 333.0561, found. 333.0516.

6-amino-4-(4-bromophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3d):

(374 mg, 92%), R_f: 0.12, Melting point: 201 – 203 °C.

FT-IR: υ (cm^{-1}) = 3675, 2986, 2898, 2356, 2325, 2202, 1659, 1514, 1391, 1254, 1063, 896.

^{1}H NMR δ 7.83 – 7.76 (m, 2H), 7.60 – 7.46 (m, 4H), 7.37 – 7.21 (m, 5H), 4.72 (s, 1H), 1.80 (s, 3H).

^{13}C NMR δ 159.9, 145.6, 144.4, 143.5, 137.9, 131.9, 130.5, 129.8, 126.7, 120.6, 120.5, 120.3, 98.6, 58.1, 36.6, 13.0.

HRMS calcd. for $C_{17}H_{15}BrN_2O$ ($[M – C_3N_2]+H)^+$ 343.0446, found. 343.0396.

6-amino-4-(4-fluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3e):

(325 mg, 94%), R_f: 0.13, Melting point: 186 – 187 °C.

FT-IR: υ (cm^{-1}) = 3457, 2202, 1664, 1596, 1517, 1444, 1339, 1227, 1125, 1068, 1024, 812, 752, 684, 650.

^{1}H NMR δ 7.83 – 7.75 (m, 2H), 7.54 – 7.45 (m, 2H), 7.36 – 7.27 (m, 3H), 7.27 – 7.13 (m, 4H), 4.73 (s, 1H), 1.79 (s, 3H).

^{13}C NMR δ 161.6 (d, *J* = 242.9), 159.8, 145.7, 144.3, 140.3 (2c), 138.0, 130.1 (d, *J* = 8.1), 129.7, 126.6, 120.4, 115.7 (d, *J* = 21.4), 98.9, 58.6, 36.5, 13.0.

^{19}F NMR δ -113.63.

HRMS calcd. for $C_{17}H_{15}FN_2O$ ($[M – C_3N_2]+H)^+$ 283.1247, found. 283.1247.

6-amino-4-(2,6-difluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3f):

(335 mg, 92%), R_f: 0.10, Melting point: 203 – 205 °C.

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FT-IR: υ (cm^{-1}) = 3477, 3330, 2193, 1655, 1589, 1518, 1459, 1393, 1270, 1122, 1030, 966, 835, 785, 753, 687, 633.

^{1}H NMR δ 7.81 – 7.74 (m, 2H), 7.55 – 7.45 (m, 2H), 7.45 – 7.30 (m, 4H), 7.12 (t, *J* = 8.9, 2H), 5.12 (s, 1H), 1.86 (s, 3H).

^{13}C NMR δ 161.1 (dd, *J* = 248.5, 7.1), 160.9, 145.1, 144.7, 137.9, 130.3 (t, *J* = 10.7), 129.8, 126.7, 120.3, 120.2, 118.4 (t, *J* = 14.7), 112.5 (d, *J* = 23.5), 96.9, 55.1, 26.4, 12.3.

^{19}F NMR δ -115.17.

HRMS calcd. for $C_{17}H_{12}F_2N_2O$ ($[M - C_3H_2N_2]+H)^+$ 299.0996, found. 299.0996.

6-amino-4-(3,5-difluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3g):

(342 mg, 94%), R_f: 0.12, Melting point: 185 – 186 °C.

FT-IR: υ (cm^{-1}) = 3662, 2988, 2884, 2194, 1664, 1451, 1393, 1252, 1061, 893.

^{1}H NMR δ 7.83 – 7.76 (m, 2H), 7.55 – 7.46 (m, 2H), 7.38 – 7.29 (m, 3H), 7.20 – 7.02 (m, 3H), 4.79 (s, 1H), 1.83 (s, 3H).

^{13}C NMR δ 162.9 (dd, *J* = 246.8, 13.0), 160.1, 149.0 (t, *J* = 7.9), 145.5, 144.5, 137.9, 129.7, 126.7, 120.6, 120.2, 111.5 (dd, *J* = 18.6, 6.5), 103.12 (t, *J* = 25.8), 97.9, 57.5, 36.8, 13.0.

^{19}F NMR δ -107.42.

HRMS calcd. for $C_{17}H_{12}F_2N_2O$ ($[M - C_3H_2N_2]+H)^+$ 299.0996, found. 299.0999.

6-amino-4-(3,4-difluorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3h):

(338 mg, 93%), R_f: 0.21, Melting point: 184 – 186 °C.

FT-IR: υ (cm^{-1}) = 2981, 2902, 2201, 1664, 1594, 1517, 1494, 1439, 1393, 1283, 1121, 1067, 1025, 751, 686.

^{1}H NMR δ 7.83 – 7.76 (m, 2H), 7.54 – 7.46 (m, 2H), 7.45 – 7.26 (m, 5H), 7.20 – 7.12 (m, 1H), 4.76 (s, 1H), 1.81 (s, 3H).

^{13}C NMR δ 160.0, 150.6 (dd, *J* = 98.3, 12.5 Hz), 148.2 (dd, *J* = 97.2, 12.5), 145.6, 144.4, 142.0 (t, *J* = 3.6), 137.9, 129.7, 126.7, 125.0 (d, *J* = 3.5), 120.6, 120.3, 117.9 (d, *J* = 17.1), 117.3 (d, *J* = 17.2), 98.3, 57.9, 36.4, 13.0.

^{19}F NMR δ -136.18 (dd, *J* = 22.4, 13.3), -138.69 (dd, *J* = 22.4, 13.3).

HRMS calcd. for $C_{17}H_{12}F_2N_2O$ ($[M - C_3H_2N_2]+H)^+$ 299.0996, found. 299.1000.

6-amino-3-methyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3i):

(372 mg, 94%), R_f: 0.21, Melting point: 183 – 186 °C.

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FT-IR: υ (cm^{-1}) = 3332, 2199, 1664, 1591, 1517, 1388, 1327, 1135, 1124, 1067, 1017, 812, 750, 685.

^{1}H NMR δ 7.83 – 7.77 (m, 2H), 7.74 (d, *J* = 8.1, 2H), 7.55 – 7.46 (m, 4H), 7.37 – 7.30 (m, 3H), 4.85 (s, 1H), 1.79 (s, 3H).

^{13}C NMR δ 160.1, 148.7, 145.6, 144.4, 137.9, 129.8, 129.1, 128.2 (d, *J* = 31.6), 126.7, 126.0 (d, *J* = 3.5), 123.4, 120.5, 120.3, 98.3, 57.8, 36.9, 13.0.

^{19}F NMR δ -58.76.

HRMS calcd. for $C_{18}H_{13}F_3N_2O$ ([M – $C_3H_2N_2$]+H)$^+$ 331.1058, found. 331.1064.

6-amino-4-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3j):

(422 mg, 91%), R_f: 0.13, Melting point: 201 – 203 °C.

FT-IR: υ (cm^{-1}) = 3640, 3303, 2385, 2187, 1639, 1590, 1519, 1368, 1278, 1171, 1115, 1024, 909, 752, 687.

^{1}H NMR δ 8.06 (s, 3H), 7.85 – 7.78 (m, 2H), 7.54 – 7.46 (m, 2H), 7.43 (s, 2H), 7.37 – 7.30 (m, 1H), 5.09 (s, 1H), 1.78 (s, 3H).

^{13}C NMR δ 160.4, 147.5, 145.4, 144.6, 137.9, 131.04 (q, *J* = 32.8), 129.6, 127.9 (d, *J* = 262.0), 127.8, 123.7 (d, *J* = 272.9), 121.4, 120.5, 120.1, 119.6, 97.5, 57.0, 36.7, 12.9.

^{19}F NMR δ -59.40.

HRMS calcd. for $C_{19}H_{12}F_6N_2O$ ([M – $C_3H_2N_2$]+H)$^+$ 399.0932, found. 399.0948.

6-amino-4-(4-cyanophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3k):

(321 mg, 91%), R_f: 0.07, Melting point: 214 – 217 °C.

FT-IR: υ (cm^{-1}) = 3733, 3398, 3312, 2238, 2188, 1648, 1590, 1513, 1448, 1384, 1263, 1123, 1069, 1028, 815, 757, 692.

^{1}H NMR δ 7.88 – 7.75 (m, 4H), 7.54 – 7.46 (m, 4H), 7.41 – 7.29 (m, 3H), 4.85 (s, 1H), 1.79 (s, 3H).

^{13}C NMR δ 160.1, 149.6, 145.6, 144.5, 137.9, 133.1, 129.8, 129.4, 126.7, 120.6, 120.2, 119.2, 110.4, 98.1, 57.5, 37.1, 13.0.

HRMS calcd. for $C_{18}H_{15}N_3O$ ([M – C_3N_2]+H)$^+$ 290.1293, found. 290.1296.

6-amino-3-methyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3l):

(350 mg, 94%), R_f: 0.18, Melting point: 198 – 200 °C.

FT-IR: υ (cm^{-1}) = 3690, 3645, 2356, 2322, 2192, 1648, 1590, 1513, 1390, 1350, 1259, 1068, 899, 754, 690.

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^{1}H NMR δ 8.20 – 8.13 (m, 2H), 7.84 – 7.76 (m, 3H), 7.72 – 7.64 (m, 1H), 7.55 – 7.47 (m, 2H), 7.42 – 7.30 (m, 3H), 4.98 (s, 1H), 1.81 (s, 3H).

^{13}C NMR δ 160.2, 148.4, 146.4, 145.6, 144.5, 137.9, 135.2, 130.7, 129.8, 126.7, 122.7 (2c), 120.5, 120.2, 98.1, 57.6, 36.7, 13.1.

HRMS calcd. for $C_{17}H_{13}N_3O_3$ ([M – $C_3H_2N_2$]+H)$^+$ 308.1035, found. 308.1040.

6-amino-3-methyl-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3m):

(347 mg, 93%), R_f: 0.14, Melting point: 205 – 207 °C.

FT-IR: υ (cm^{-1}) = 3431, 3334, 3199, 2211, 2186, 1664, 1593, 1510, 1446, 1389, 1351, 1264, 1124, 1063, 1029, 820, 752, 688.

^{1}H NMR δ 8.28 – 8.19 (m, 2H), 7.83 – 7.76 (m, 2H), 7.63 – 7.55 (m, 2H), 7.55 – 7.46 (m, 2H), 7.44 – 7.29 (m, 3H), 4.93 (s, 1H), 1.80 (s, 3H).

^{13}C NMR δ 160.2, 151.6, 147.1, 145.6, 144.5, 137.9, 129.8, 129.6, 126.8, 124.3, 120.5, 120.2, 98.0, 57.4, 36.9, 13.0.

HRMS calcd. for $C_{17}H_{13}N_3O_3$ ([M – $C_3H_2N_2$]+H)$^+$ 308.1035, found. 308.1037.

6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3n):

(295 mg, 90%), R_f: 0.32, Melting point: 195 – 197 °C.

FT-IR: υ (cm^{-1}) = 3320, 2197, 1654, 1588, 1512, 1449, 1385, 1125, 1024, 824, 753, 692.

^{1}H NMR δ 7.84 – 7.76 (m, 2H), 7.55 – 7.46 (m, 2H), 7.41 – 7.32 (m, 3H), 7.31 – 7.18 (m, 5H), 4.69 (s, 1H), 1.78 (s, 3H).

^{13}C NMR δ 159.9, 145.7, 144.3, 144.1, 138.0, 129.8, 129.0, 128.2, 127.5, 126.6, 120.4, 99.1, 58.6, 37.2, 13.0.

HRMS calcd. for $C_{17}H_{16}N_2O$ ([M – C_3N_2]+H)$^+$ 265.1341, found. 265.1340.

6-amino-3-methyl-1-phenyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3o):

(318 mg, 93%), R_f: 0.12, Melting point: 186 – 188 °C.

FT-IR: υ (cm^{-1}) = 3468, 3343, 2183, 1644, 1584, 1512, 1441, 1386, 1260, 1180, 1126, 1068, 1024, 794, 757.

^{1}H NMR δ 7.82 – 7.76 (m, 2H), 7.53 – 7.45 (m, 2H), 7.36 – 7.28 (m, 1H), 7.25 – 7.13 (m, 6H), 4.64 (s, 1H), 2.29 (s, 3H), 1.79 (s, 3H).

^{13}C NMR δ 159.8, 145.7, 144.3, 141.1, 138.0, 136.5, 129.8, 129.5 (2c), 128.1, 126.6, 120.4, 99.2, 58.9, 36.8, 21.1, 13.0.

HRMS calcd. for $C_{18}H_{16}N_2O$ ([M – $C_3H_2N_2$]+H)$^+$ 277.1341, found. 277.1346.

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6-amino-4-(4-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3p):

(333 mg, 93%), R_f: 0.12, Melting point: 197 – 198 °C.

FT-IR: υ (cm^{-1}) = 3388, 3322, 3208, 2190, 1656, 1592, 1509, 1490, 1455, 1390, 1250, 1172, 1128, 1026, 812, 757, 692.

^{1}H NMR δ 7.82 – 7.74 (m, 2H), 7.53 – 7.45 (m, 2H), 7.36 – 7.28 (m, 1H), 7.22 – 7.12 (m, 4H), 6.94 – 6.86 (m, 2H), 4.63 (s, 1H), 3.75 (s, 3H), 1.79 (s, 3H).

^{13}C NMR δ 159.7, 158.6, 145.8, 144.2, 138.0, 136.1, 129.8, 129.3, 126.6, 120.5, 120.4, 114.3, 99.3, 59.1, 55.5, 36.4, 13.0.

HRMS calcd. for $C_{18}H_{16}N_2O_2$ ([M – $C_3H_2N_2$]+H)$^+$ 293.1290, found. 293.1292.

6-amino-4-(3-ethoxy-4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3q):

(341 mg, 88%), R_f: 0.03, Melting point: 183 – 185 °C.

FT-IR: υ (cm^{-1}) = 3418, 3229, 3203, 3015, 2936, 2194, 1655, 1593, 1509, 1441, 1392, 1266, 1236, 1121, 1029, 808, 754.

^{1}H NMR δ 8.84 (s, 1H), 7.82 – 7.75 (m, 2H), 7.54 – 7.45 (m, 2H), 7.37 – 7.26 (m, 1H), 7.14 (s, 2H), 6.80 (d, *J* = 2.0, 1H), 6.75 (d, *J* = 8.1, 1H), 6.62 (dd, *J* = 8.1, 2.0, 1H), 4.56 (s, 1H), 3.98 (q, *J* = 7.0, 2H), 1.82 (s, 3H), 1.31 (t, *J* = 7.0, 3H).

^{13}C NMR δ 159.7, 146.9, 146.3, 145.9, 144.2, 138.1, 135.0, 129.7, 126.5, 120.7, 120.6, 120.3, 116.1, 113.9, 99.3, 64.4, 59.2, 36.8, 15.2, 13.1.

HRMS calcd. for $C_{19}H_{20}N_2O_3$ ([M – C_3N_2]+H)$^+$ 325.1552, found. 325.1546.

3. Results and discussion

3.1. Characterization of the catalyst

Successful synthesis of novel nanosized phosphonium based molten salt confirmed by varied analysis such as FT-IR, proton, carbon and phosphor NMR, XRD, SEM, HRTEM, TG and DTG as discussed in more detail in follow.

In FT-IR spectrum of nanosized phosphonium based molten salt catalyst the absorption bond at 3434 cm^{-1} is connected to stretching vibration of O–H in the SO_3H group. The two peaks at about 1530 cm^{-1} and 1384 cm^{-1} are linked to –NO_2 stretching on trinitromethanide counter ion. Also, the peak at 1213 cm^{-1} is related to S=O bond vibration mode (Figure 2).

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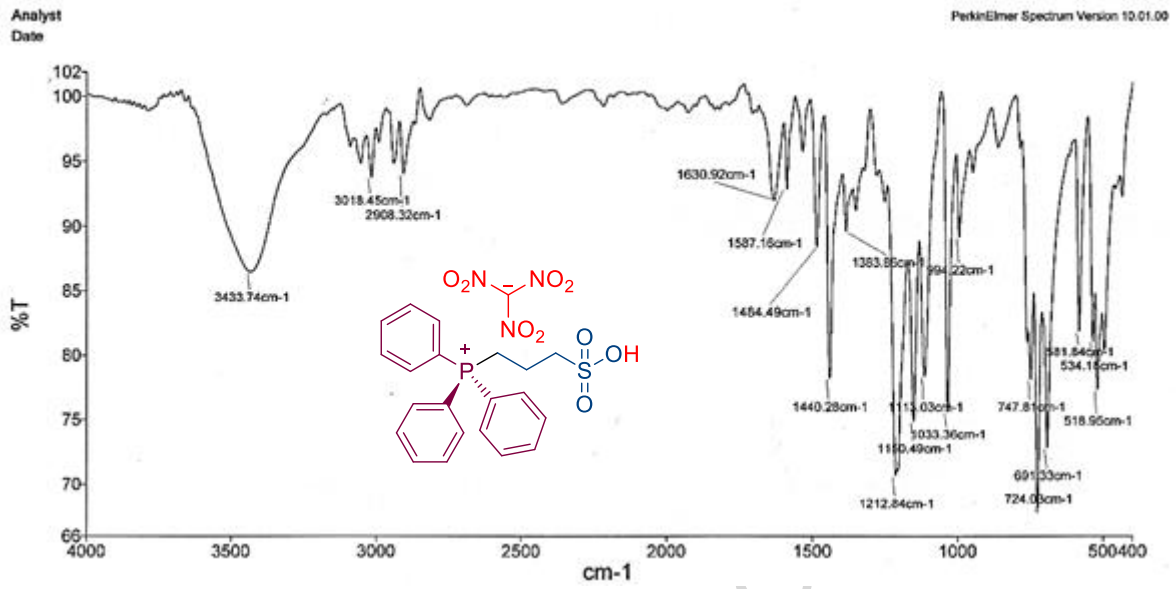

Figure 2: FT-IR spectrum of nanosized molten salt catalyst

As it can be seen in Figure 3, proton NMR spectrum confirmed the existence of all anticipated protons within the structure of TPSPPTNM as catalyst. In aliphatic region the methylenic protons resonate as three separate peaks which confirmed the existence of propyl chain. Also, all fifteen protons of phenyl rings can be easily distinguished in aromatic region. Acidic proton of the described phosphonium based molten salt verified by observing of the corresponding broad singlet at 8.71 ppm. In another study, the successful formation of the catalyst was approved by ^{13}C and ^{31}P NMR spectra as depicted in Figure 4a-b. In ^{13}C NMR spectrum, three separate peaks at aliphatic region appear at 23.1, 29.5 and 52.7 are related to propyl moiety. Aromatic carbons resonate at 123.0, 124.5, 130.1 and 134.4 ppm as four separate peaks. Furthermore, the resonance peak at 152.7 ppm is related to the trinitromethanide carbon atom (Figure 4a). Also, the phosphor atom within the structure confirmed by a peak at 23.5 ppm in ^{31}P NMR spectrum (Figure 4b).

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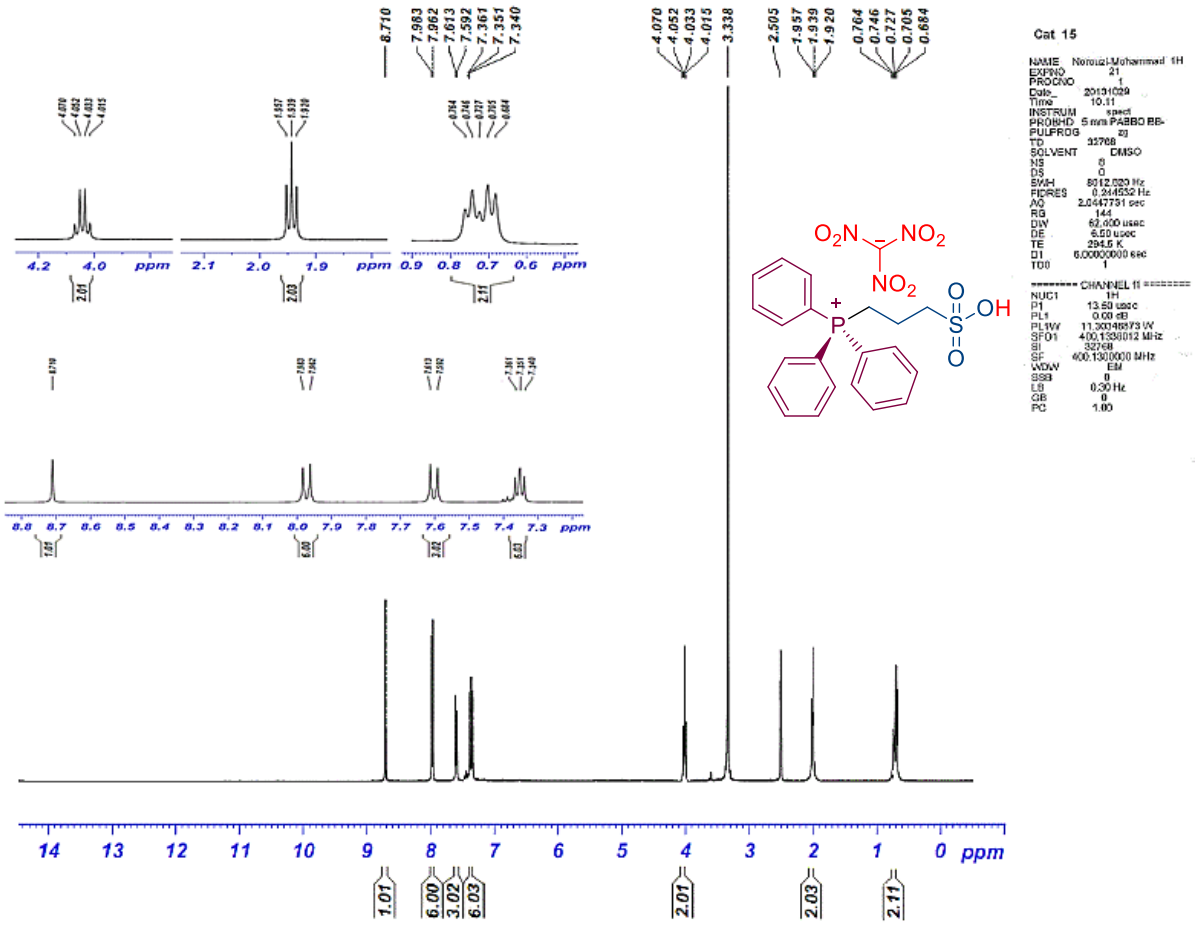

Figure 3: ^{1}H NMR spectrum of TPSPPTNM

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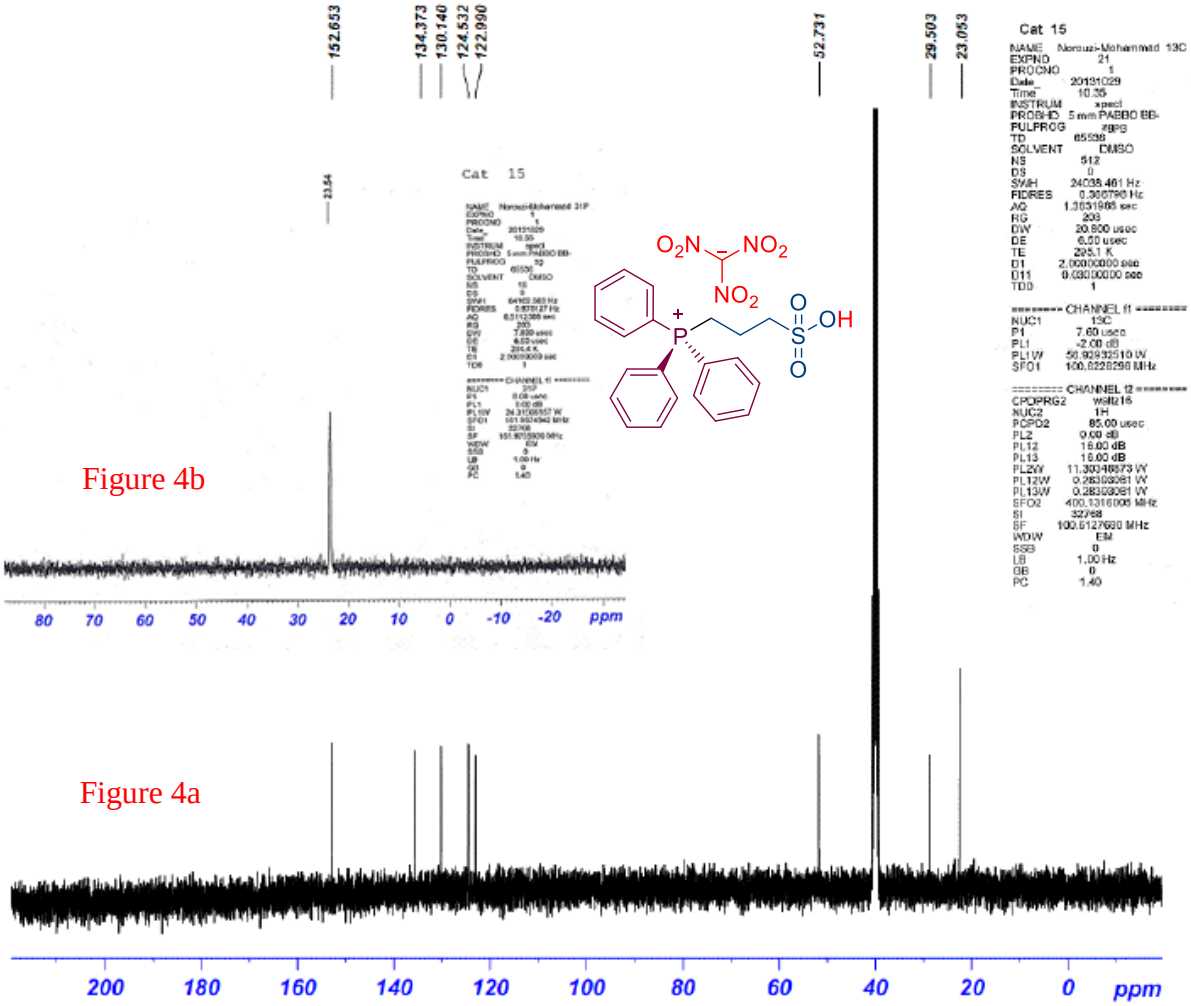

Figure 4a-b: ^{13}C and ^{31}P NMR spectrum of TPSPPTNM

Also, The XRD pattern of the TPSPPTNM as molten salt catalyst was inspected (Figure 5). From the obtained XRD profile, it can be concluded that the prepared catalyst has a crystalline nature with diffraction lines at 2θ = 12.90°, 15.70° and 24.60°. Using Scherrer equation "$D = K\lambda/(\beta \cos\theta)$", where λ is the X-ray wavelength of Cu kα (1.54Å), K is the Scherrer constant with a value of 0.9, β is the peak width at half maximum (FWHM) of the peak in radians, and θ is the Bragg diffraction angle, XRD pattern data were extracted and inserted in Table 1. Based on calculated XRD data as depicted in Table 1, it is verified that the catalyst has a nanosized structure.

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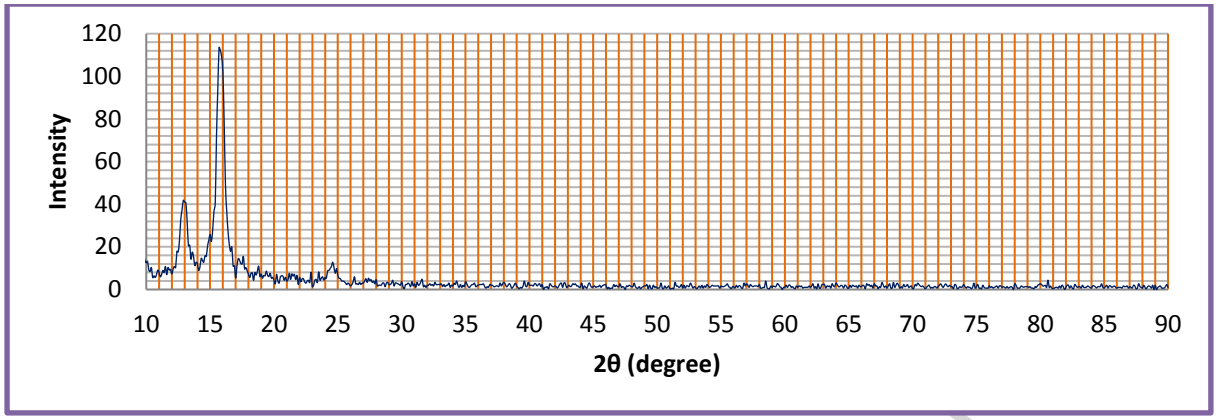

Figure 5: XRD pattern of novel phosphonium based molten salt catalyst.

Table 1: XRD data of the novel phosphonium based molten salt.

Entry	2θ	Peak width [FWHM] (degree)	Size [nm]	Interplanar distance [nm]
1	12.90	0.76	10.52	0.685443
2	15.70	0.71	11.30	0.563772
3	24.60	0.56	14.52	0.361451

The recorded field emission scanning electron microscopy (FESEM), and images of novel nanosized molten salt catalyst illustrated in Figure 6. According to the provided FESEM images the novel catalyst consists of nanosized particles in the domain of 8.93-18.10 nm.

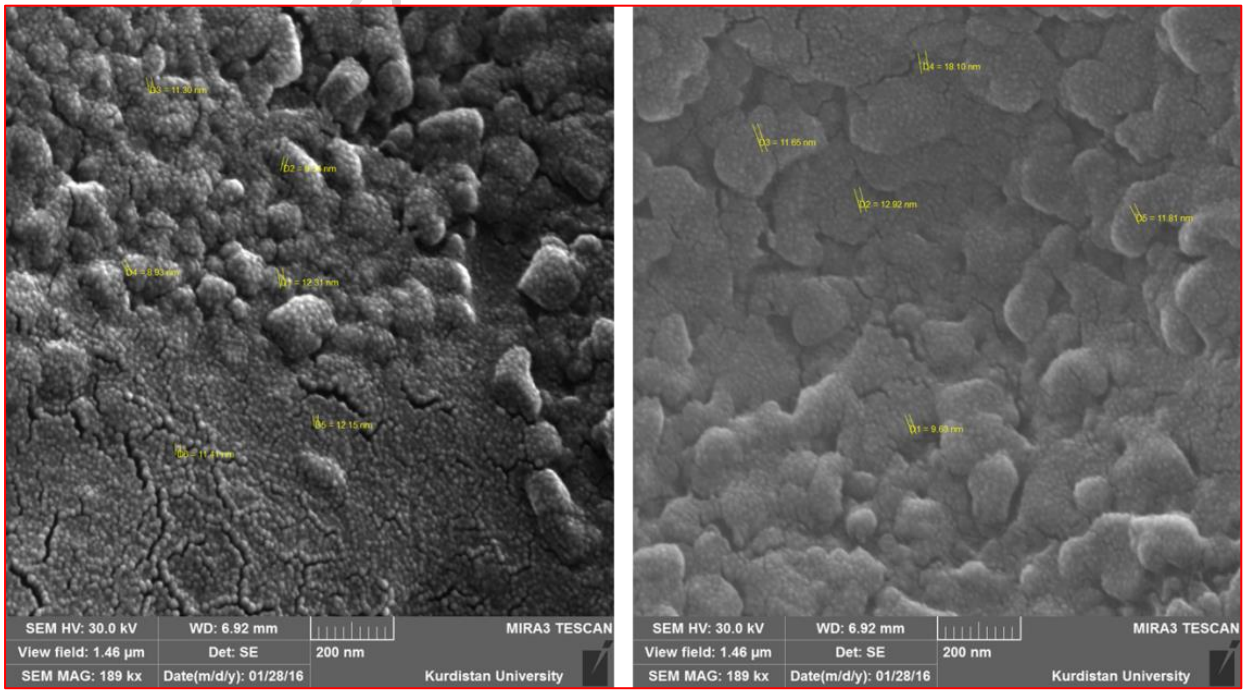

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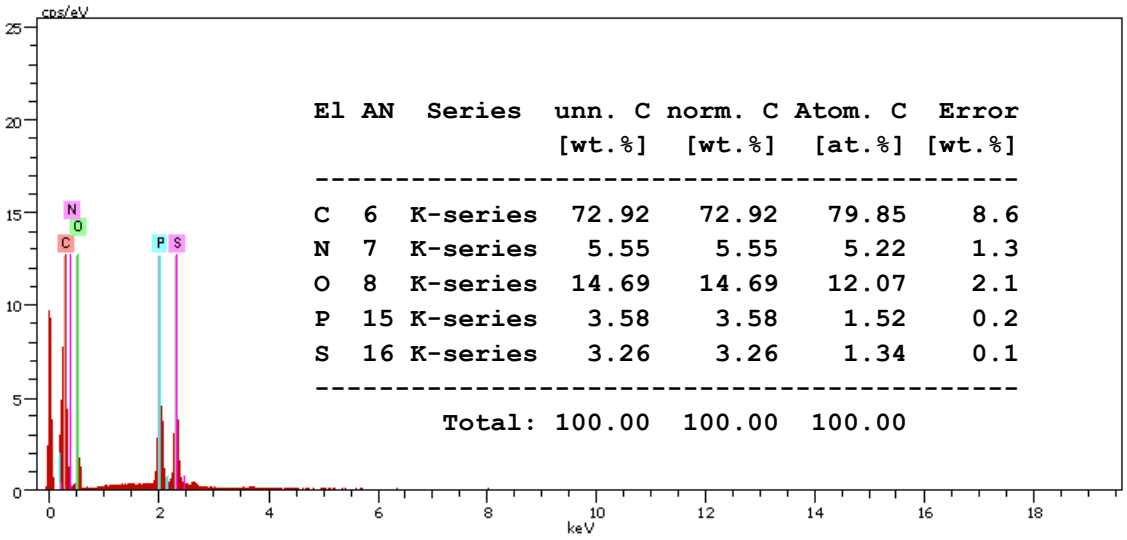
Figure 6: Field emission scanning electron microscopy (FESEM) images of novel nanosized molten salt catalyst

Furthermore, the EDX data of catalyst confirms the presence of the anticipated elements in the structure of the catalyst: carbon, nitrogen, oxygen, phosphorus and sulfur (Figure 7). On the other hand, the atomic (at%) or weight percentage (wt%) of sulfur and phosphor were same in the catalyst which has confirmed the presence of triphenyl phosphine and SO_3H in a same molar ratio.



El	AN	Series	unn. C [wt.%]	norm. C [wt.%]	Atom. C [at.%]	Error [wt.%]
C	6	K-series	72.92	72.92	79.85	8.6
N	7	K-series	5.55	5.55	5.22	1.3
O	8	K-series	14.69	14.69	12.07	2.1
P	15	K-series	3.58	3.58	1.52	0.2
S	16	K-series	3.26	3.26	1.34	0.1
		Total:	100.00	100.00	100.00	

Figure 7. EDX spectrum of cat **2**.

In order to approve the elemental composition of the catalyst, SEM images and WDX elemental maps were done and shown in Figure 8. Presence of C, N, O, S and P elements in the catalyst are shown *via* WDX analysis.

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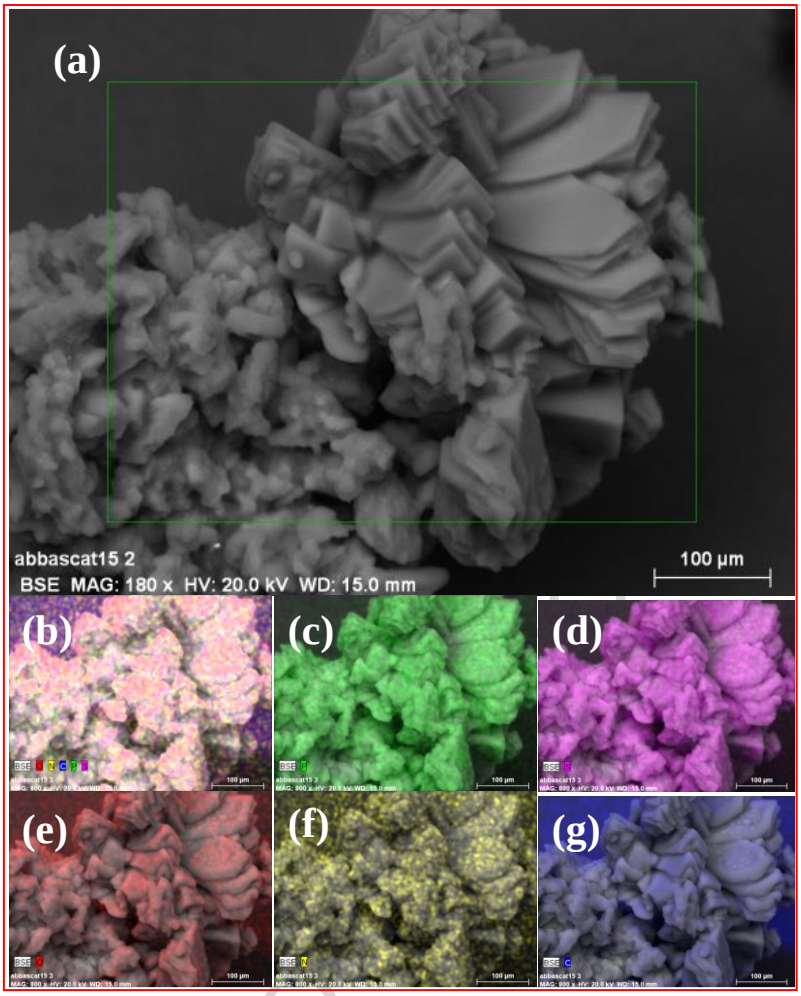

Figure 8: SEM image (a) and WDX elemental mapping images of cat 2 (b) sulfur (c), phosphorus (d), oxygen (e) nitrogen (f), and carbon (g).

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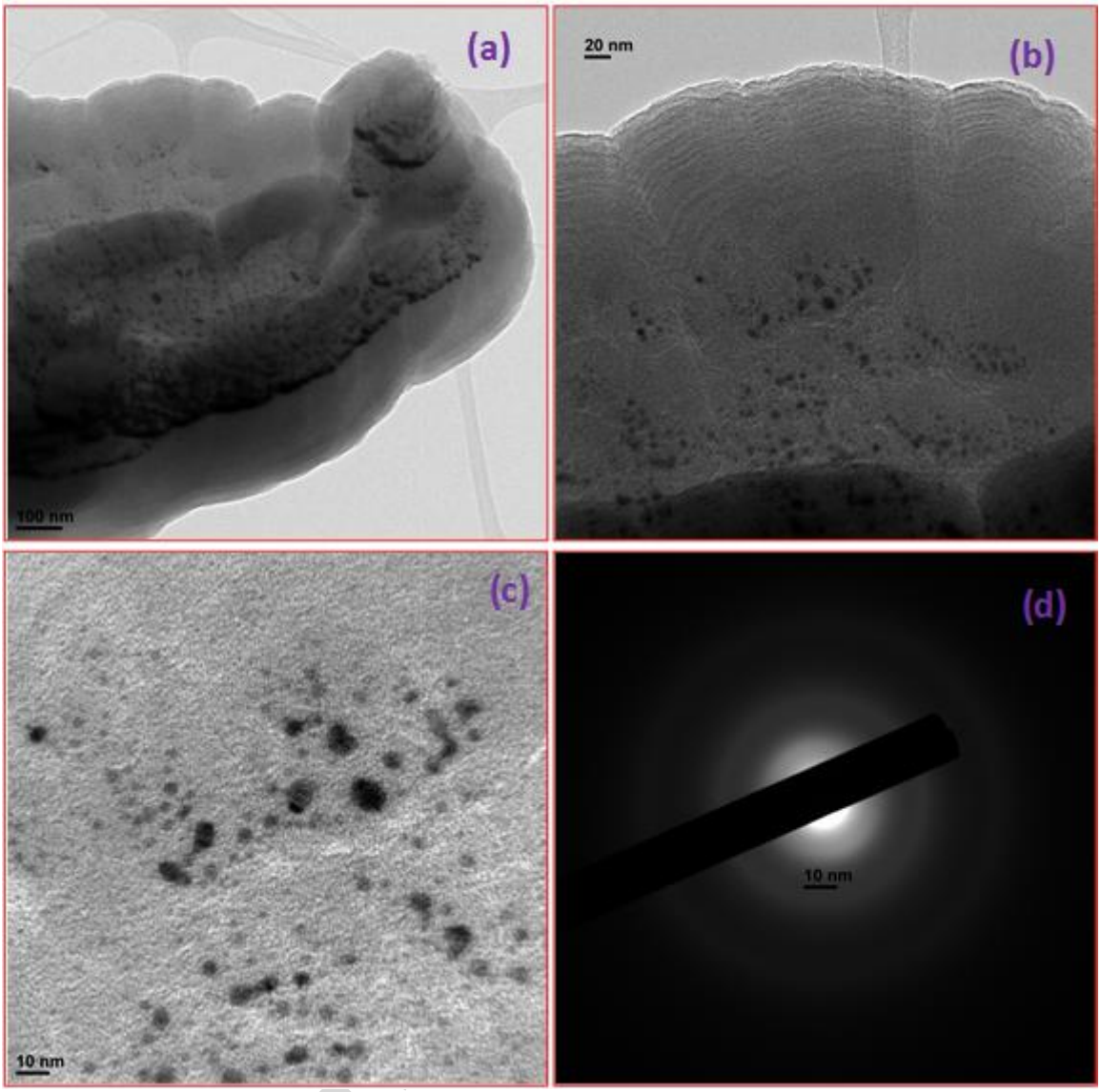

Figure 9: a-c) High resolution transmission electron microscopy (HRTEM) images of novel nanosized molten salt catalyst, d) electron diffraction (SAED) patterns.

To investigate the morphology, topography and resolve the interior of the structures of the described catalyst, high-resolution transmission electron microscopy (HRTEM) was carried out as shown in figure 9. As it is clear in the figures 9 a-c, clearly aproved the spherical uniform of the catalyst particles and confirmed that the catalyst has nanosized particles. This observation is in good agreement with obtained data from XRD and SEM images. Morover, Figure 9d was shown a polycrystaline system for desired catalyst.

In a separate study, the thermal stability of the synthesized molten salt catalyst in elevated temperatures was explored as portrayed in Figure 10. Conducted thermogravimetry (TG) and derivative thermogravimetry (DTG) analysis plot indicated a main weight loss at around 375

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^{o}C which present high thermal stability for the TPSPPTNM at elevated operational temperatures.

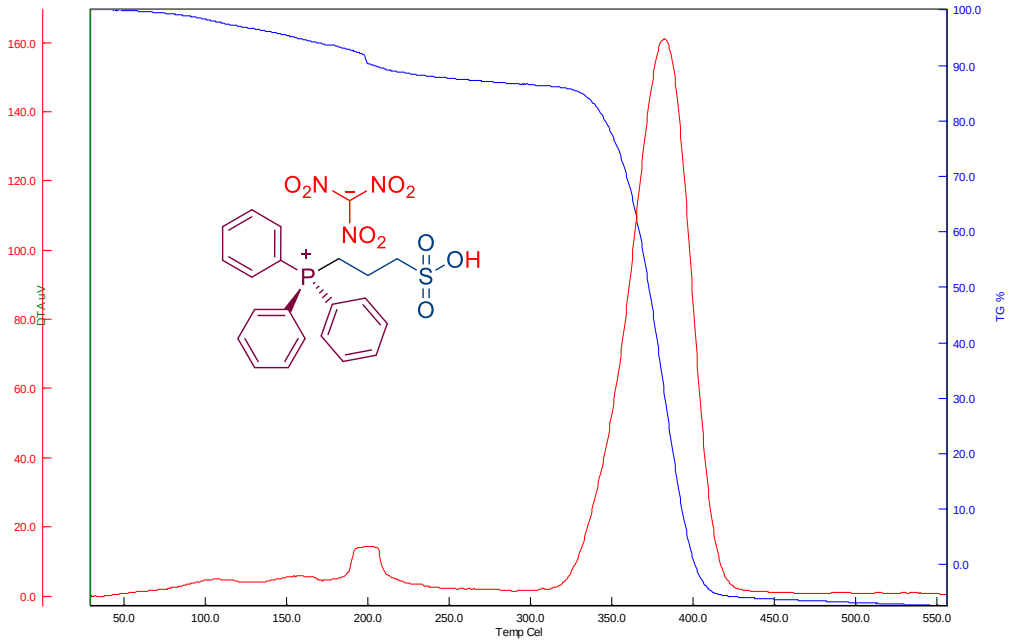

Figure 10: TG and DTG plot of novel nanosized phosphonium based molten salt catalyst

3.2. Catalytic performance of the novel nanosized molten salt

From the interpretation of applied techniques, it can be concluded that the catalyst has a dual activation rule due to the presence of both acidic and basic cites within its structure. It has also a nanoscale structure with high thermal stability. After insurance the successful synthesis of the novel nanosized molten salt with varied important techniques as discussed in section 3.1, we decided to test its catalytic activity in a multicomponent reaction. Based on the structure of the prepared catalyst which bears both acidic and basic sites, it is predicted that it can act as a powerful multi rule catalyst for multicomponent reactions. Therefore, we examined its catalytic activity upon a four component condensation reaction between arylaldehydes, malononitrile, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one and ammonium acetate as nitrogen source for the synthesis of pyridine derivatives (4a-u) (Scheme 3). These structures are very important to us for developing the anomeric based oxidation. This significance comes from there that the pyridines 4a-n could be a puzzle piece of our new introduced concept entitled "anomeric based oxidation (ABO)" mechanism [43]. But, scrutinizing of obtained spectral data disclose that the reaction proceed towards the formation of dihydropyrano[2,3-c]pyrazoles (structure 3a-u). As in the case of pyridine systems, dihydropyrano[2,3-c]pyrazole derivatives are very influential scaffolds. Therefore,

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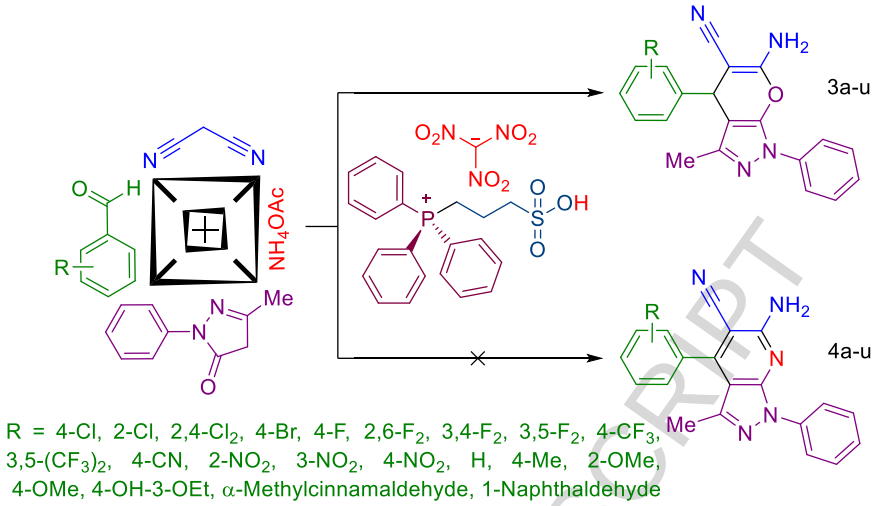
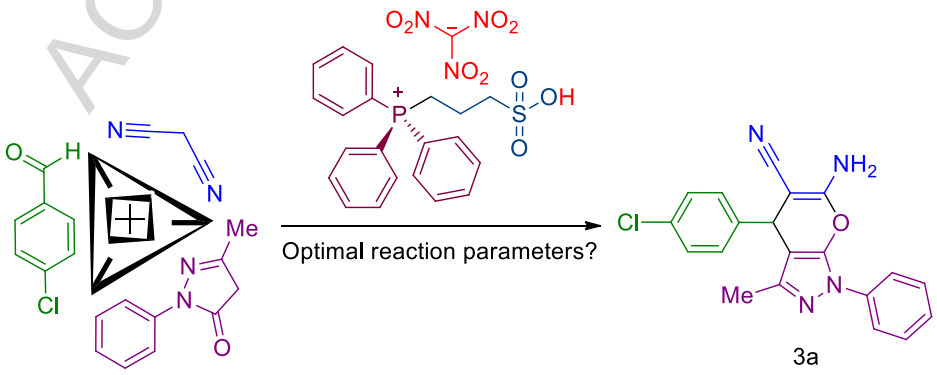
we persuade to complete the exploration and report an efficient protocol for their synthesis *via* a three component approach.



Scheme 3: Catalytic behavior of the novel phosphonium based molten salt in a multicomponent reaction.

In the first phase of our investigation, to get an insight into the optimal operational reaction conditions, we consider the 4-chlorobenzaldehyde, malononitrile and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one as model substrates and performed the reaction using different conditions to yield the corresponding desired molecule 1a as depicted in scheme 4. In order to establish the most congruous reaction conditions, different crucial experimental variables including solvents, temperatures and load of nano molten salt catalyst were screened. Table 2 exhibits the obtained experimental data. From the achieved data it can be concluded that, the optimal reaction conditions is where the reaction performed under solvent free conditions, at 60 ^{o}C and in the presence of 1 mol% of TPSPPTNM as catalyst. Increasing the amount of catalyst, elevating the reaction temperature or carrying out the model reaction in different solvents shows no further improvement in the obtained data.



Scheme 4: Synthesis of molecule 3a as model reaction.

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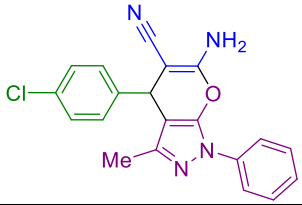
Table 2: Optimizing of the reaction conditions for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives[a]

Entry	Solvent	Temperature (˚C)	Load of catalyst (mol%)	Time (min.)	Yield (%)[b]
1	-	r.t.	1	50	70
2	**-**	**60**	**1**	**12**	**94**
3	-	80	1	13	93
4	-	60	-	60	55
5	-	60	0.5	18	87
6[d]	-	60	1.5	11	94
9	H_2O	60	1	10	60
10	C_2H_5OH	60	1	16	88
11	CH_3CN	60	1	70	40
12	EtOAc	60	1	60	35
14	*n*-Hexane	60	1	40	56

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol, 0.141 g), malonontrile (1 mmol, 0.066 g) 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol, 0.174 g), [b]Isolated yields,

In next step, because of the satisfactory results from the synthetic point of view from previous stage, we decided to study the scope, limitations and productivity of the presented three component process for the synthesis of target molecules by screening of different aromatic aldehyde substrates as presented in Table 3. The resulting data illustrated that under the optimal reaction conditions, the applied substrates underwent the presented three component process gently and generate the corresponding desired molecules in short reaction periods with high to excellent yields.

Table 3: Catalytic synthesis of dihydropyrano[2,3-c]pyrazole derivatives in the presence of nano molten salt 2[a]

Entry	Time (min)	Structure	Product	Yield (%)[b]	M.p. (°C): found (Lit.)
1	12		3a	94	193-195 (179-182)[15a]

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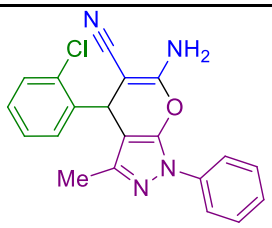
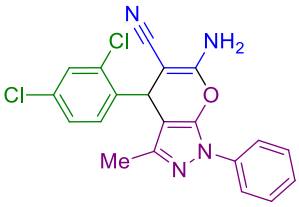
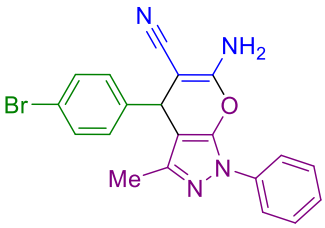
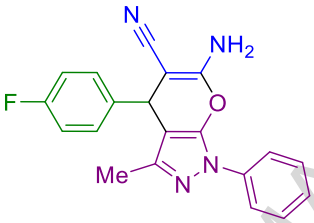
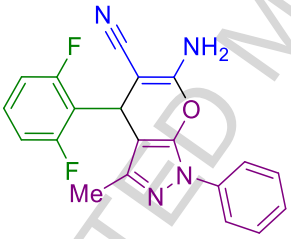
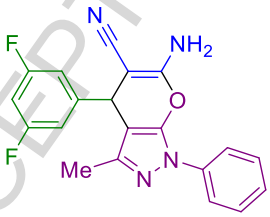
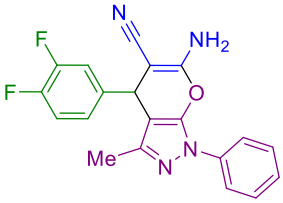
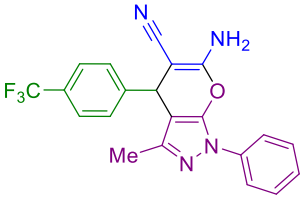
2	17		3b	91	176-178 (164-167)[15a]
3	16		3c	92	196-197 (189-194)[15a]
4	14		3d	92	201-203 (187-188)[13]
5	13		3e	94	186-187 (163-165)[15a]
6	14		3f	92	203-205 (New)
7	15		3g	94	185-186 (New)
8	14		3h	93	184-186 (New)
9	13		3i	94	183-186 (163-165)[15d]

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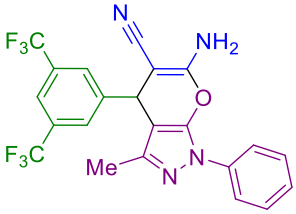
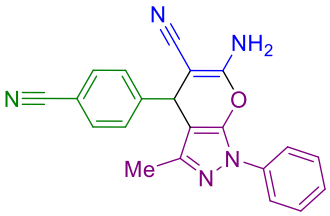
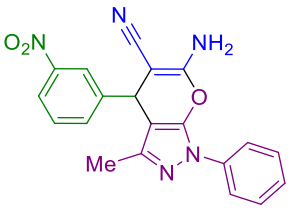
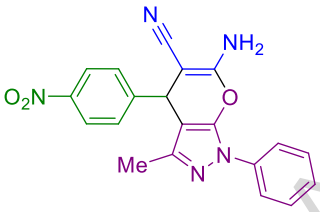
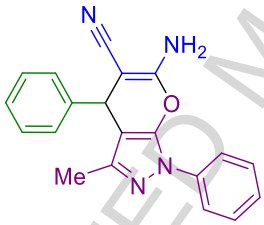
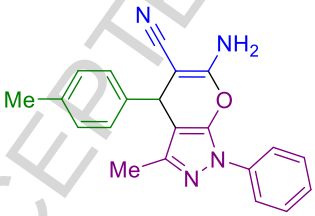
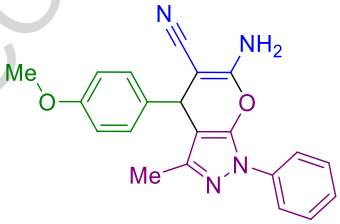
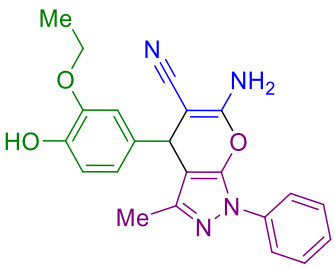
10	16		3j	91	201-203 (New)
11	17		3k	91	214-217 (212-214)[15a]
12	13		3l	94	198-200 (207)[15a]
13	14		3m	93	205-207(197-198)[15b]
14	15		3n	90	195-197 (178)[15a]
15	15		3o	93	186-188 (177-178)[15a]
16	15		3p	93	197-198 (204-206)[15a]
17	20		3q	88	183-185 (178)[15a]

[a]Reaction conditions: aromatic aldehyde (1 mmol), malononotrile (1 mmol, 0.066 g) 5-methyl-2-phenyl-2,4-

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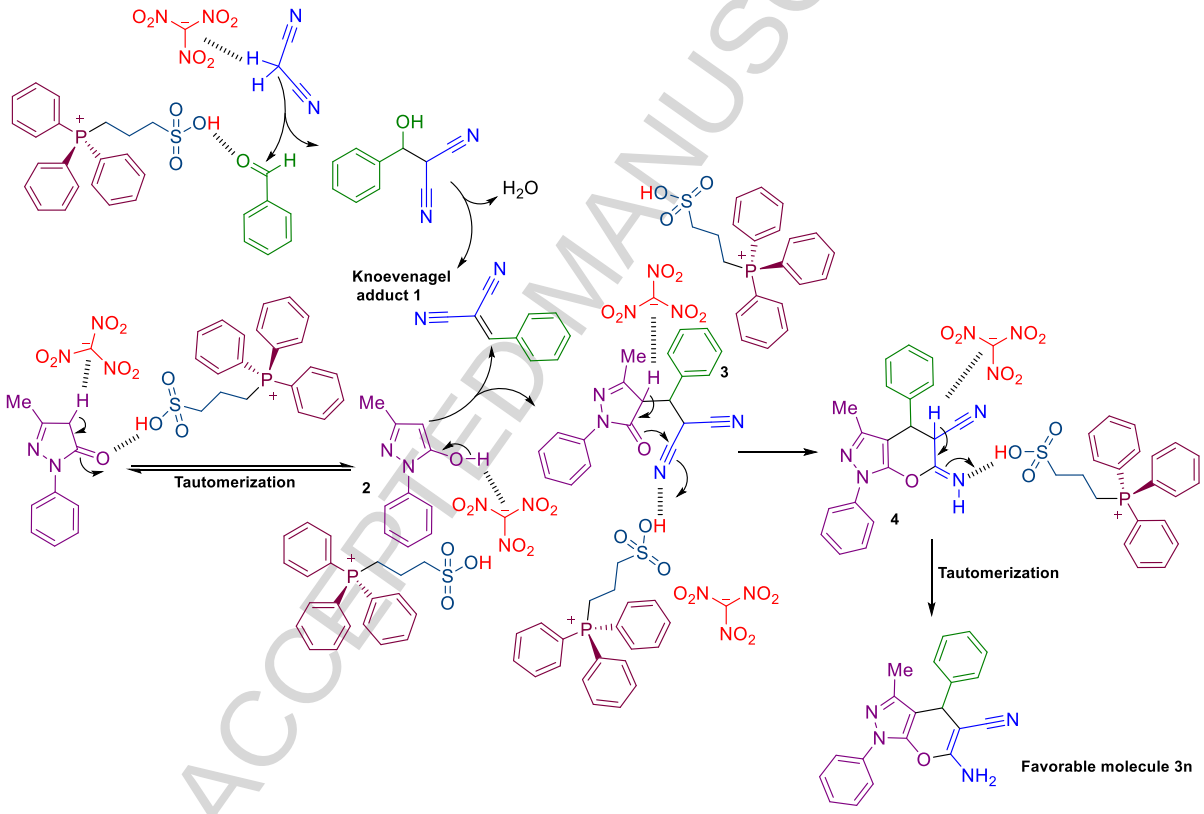
dihydro-3*H*-pyrazol-3-one (1 mmol, 0.174 g), [b]Isolated yields

As a model, a reasonable mechanism for the synthesis of target molecule 3n was depicted in Scheme 5. The mechanistic route triggers by a nucleophilic attack from malononitrile to the activated benzaldehyde to produce the corresponding Knoevenagel adduct 1 through dehydration. At the same time, tautomerization in the presence of the catalyst generates the enol form 2. Subsequently, the nucleophilic attack of enol form 2 to Knoevenagel adduct 1, yields intermediate 3. In the next stage, an intramolecular nucleophilic attack from oxygen of carbonyl functional group to nitrile functional group in the presence of nano molten salt catalyst generates intermediate 4. Finally, intermediate 4 is converted to the desired molecule 3n via a tautomerization process in the presence of catalyst.



Scheme 5: Plausible catalytic mechanism for the synthesis of favorable molecule 3n.

In the another investigation, in order to show the effectiveness and catalytic efficiency of the presented method towards the synthesis of dihydropyrano[2,3-*c*]pyrazole**s** as target molecules, we compared our achieved operational data with some of other those previously reported protocols. The data embedded in Table 4. The collected data revealed that our new

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protocol has a high competitive power with other reported methods in the literatures and represent encouraging results towards the synthesis of target molecules.

Table 4: Comparison of the catalytic activity of described novel molten salt catalyst with other those reported catalytic systems for synthesis of dihydropyrano[2,3-*c*]pyrazoles

Entry	Reaction conditions	Time	Yield (%)	Reference
1	Ultasonication, H_2O, Ni NPs (10 mol%)	5-14 min.	85-90	12
2	DIPH (20 mol %), H_2O, Reflux	10-20 min.	80-93	13
3	$Fe_{3-x}Ti_xO_4$@SO_3H MNPs (0.05 g), Solvent free, 105 ^oC	60-90 min.	87-96	14
4	Uncapped SnO_2 QDs, H_2O, r.t.	1.5-3 h	88-98	16
5	ZrO_2 (10 mol%), EtOH-H_2O (6:1), r.t.	2-10 min.	90-98	17
6	CTACl (20 mol%), H_2O, 90 ^oC	4 h	72-90	18
7	[DMDBSI]-2HSO_4 (10 mol%), H_2O, 60 ^oC	10-15 min.	74-90	20
8	MorT (10 mol%), EtOH-H_2O (9:1), Reflux,	10-12 h	57-89	21
9	TPSPPTNM (1 mol%), Solvent free, 60 ^oC	12-20 min.	88-94	This work

4. Conclusion

In the present study, we unveiled the synthesis of a novel nanosized molten salt and its application for the preparation of dihydropyrano[2,3-c]pyrazole derivatives via a three component reaction. The catalyst synthesized through a two steps process. Sophisticated physicochemical tools like FT-IR, ^1H, ^{13}C and ^{31}P NMR, XRD, FESEM, HRTEM, EDX, SEM, elemental mapping, TG and DTG have been applied for the structural approving of the above said nanostructured catalyst. Mild reaction conditions, high catalytic activity, easy work-up, short reaction time and excellent yields are the major advantages of the represented investigation.

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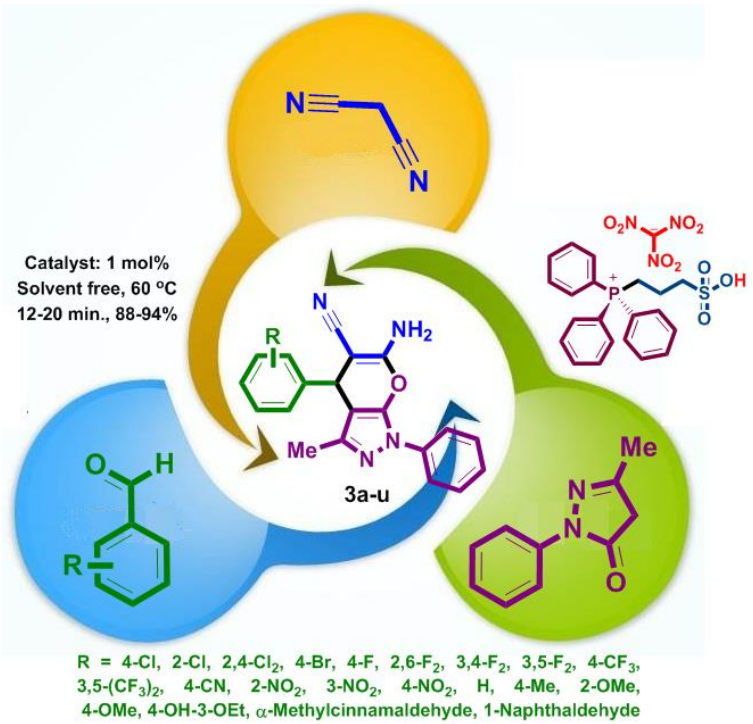
Graphical abstract



Triphenyl(3-sulfopropyl)phosphonium trinitromethanide, efficiently promoted the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives under mild reaction conditions with high to excellent yields.

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Highlights

1: Triphenyl(3-sulfopropyl)phosphonium trinitromethanide as a novel nanosized molten salt was designed and synthesized.

2: The structure of catalyst was characterized using FT-IR, ^{1}H, ^{13}C and ^{31}P NMR, XRD, FESEM, HRTEM, TG and DTG analysis.

3: The catalyst successfully applied for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives.

4: Products were obtained under mild reaction conditions with easy work-up, short reaction time and excellent yields.

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