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Highly effectual synthesis of 4*H*-pyrano [2, 3-*c*] pyrazoles using N_1, N_1, N_2, N_2-tetramethyl-N_1, N_2-bis (sulfo) ethane-1, 2-diaminium trifluoroacetate as a dual-functional catalyst

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KEYWORDS

4*H*-pyrano[2,3-*c*]pyrazole
Protic acidic ionic liquid
N_1, N_1, N_2, N_2-tetramethyl-N_1, N_2-bis (sulfo) ethane-1, 2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$)
Arylaldehyde
3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*)-one

ABSTRACT

In this research study, highly effective preparation of 4*H*-pyrano[2, 3-*c*]pyrazoles was discussed. The one-pot multi-component reaction between the malononitrile, arylaldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*)-one using protic acidic ionic liquid N_1, N_1, N_2, N_2-tetramethyl-N_1, N_2-bis (sulfo) ethane-1, 2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) under the mild and solvent-free conditions have furnished the title compounds with high yields in short times. Additionally, an attractive mechanism considering dual-functionality of the catalyst was proposed ([TMBSED][TFA]$_2$ with acidic and basic sites).

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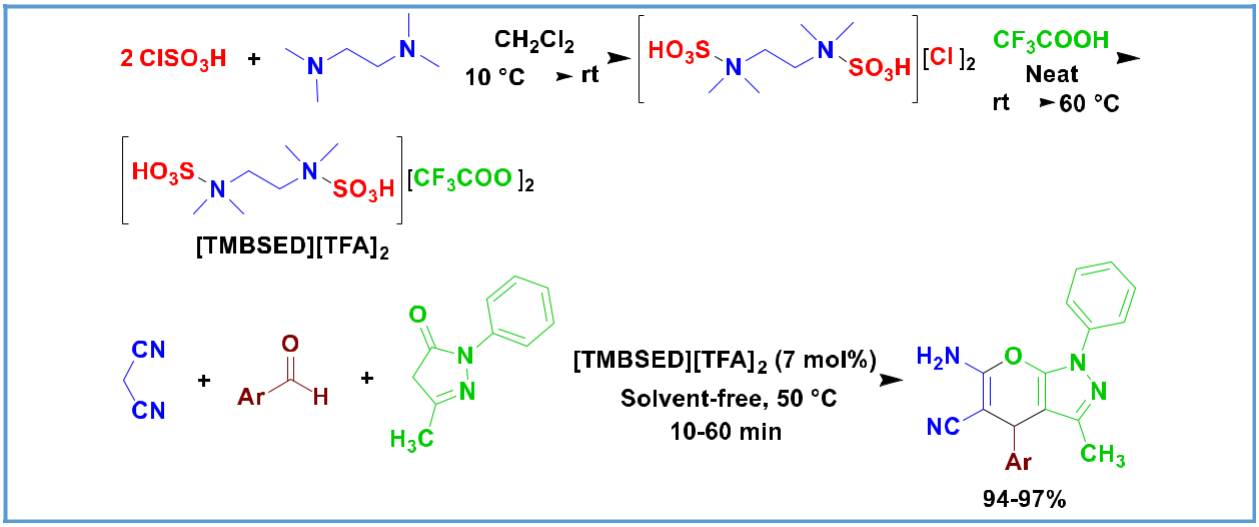
Graphical Abstract



Introduction

Room-temperature ionic liquids (RTILs) have extensive applications in various industries and chemistry due to their valuable properties including, the logical thermal and chemical stability, non-volatility, non-flammability, large liquid range, excellent ionic conductivity, tunable hydrophobicity, wide electrochemical windows, and green nature. Chemical and physical characteristics of the RTILs are adaptable by changing their cation and anion [1]. In consideration of the excellent physicochemical characteristics of ILs, they have been used in lithium batteries [2], electrode position [3], solar cells [4], and electric double layer capacitors [5], and as solvent, reagent and catalyst in organic synthesis [6–12]. It should be mentioned that protic acidic ILs, as an important class of ionic liquids, could be applied as catalysts for a wide range of organic transformations [8–14].

There has been great attention in preparation, reactions and biological activities of 4*H*-pyrane-containing heterocyclic compounds. This heterocycle is an essential structural component of several pharmaceutical agents, drug candidates, photoactive materials and natural products [15, 16]. Among the different classes of heterocycles possessing 4*H*-pyrane moiety, the compounds containing 4*H*-pyrano[2, 3-*c*]pyrazole core has shown various pharmaceutical and biological activities; for example, analgesic [17], antibacterial [18], antitumor [19], anti-inflammatory [20], antimicrobial [21], molluscicidal [22] and Chk1 kinase inhibitory [23] properties. The one-pot multi-component condensation of malononitrile with aromatic aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one is the best protocol for construction of 4*H*-pyrano[2, 3-*c*]pyrazole derivatives [24– 32]. Some catalysts have been utilized for this synthesis, such as silica sodium carbonate [24], tungstate sulfuric acid [25], SnS nanoparticles [26], $NiFe_2O_4@SiO_2$-$H_3PW_{12}O_{40}$ [27], triethylbenzylammonium chloride [28], sodium fluoride (ultrasound) [29], *p*-dodecylbenzenesulfonic acid [30], and nano-structured $Na_2CaP_2O_7$ [31]. The synthesis has been also achieved in electro-catalysis conditions [32]. Nevertheless, several reported synthetic methods for 4*H*-pyrano[2, 3-*c*]pyrazoles suffer from the following

disadvantages: long reaction time, moderate yield, the use of expensive catalysts, the use of volatile organic solvents as reaction media and high reaction temperature. Thus, introducing a novel catalyst for this transformation which is not accompanied by the mentioned drawbacks is of importance.

In view of green chemistry, performing chemical reactions in solvent-free conditions are of significance, since many chemical, pharmaceutical and industrial compounds could be effectively prepared in an environment friendly manner in that. In comparison to the classical synthetic protocols, solvent-free synthesis has several advantages which consist of: (i) no need to utilize harmful solvents as reaction media, (ii) prevention or minimization of waste/by-products, (iii) safer reaction profile, (iv) shorter reaction time, (v) higher yield, (vi) higher selectivity in numerous reactions, (vii) maximum transformation of starting materials to aim product, (viii) easier work-up, and (ix) fewer energy requirement to carry out reaction [33–35].

Preparation of chemical, industrial and pharmaceutical compounds by multi-component reactions (MCRs) is very significant in consideration of combinatorial chemistry. In this technique, three or more starting materials react together in one step (one-pot) to form a product wherein all or most of the reactants atoms contribute. MCRs are have some advantages including, simplicity, synthesizing main product in high yield without by-product, saving energy and time, easier work-up and purification of product, minimizing the use of volatile organic solvents, and good agreement with the green chemistry protocols [36–39].

Bearing the above facts in mind, we report here highly efficient production of 4*H*-pyrano[2, 3-*c*]pyrazoles *via* the one-pot multi-component reaction of malononitrile with arylaldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*) -one using a dual-functional ionic liquid-catalyst namely N_1, N_1, N_2, N_2-tetramethyl-N_1, N_2-bis (sulfo) ethane-1, 2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) under mild and solvent-free conditions.

Experimental

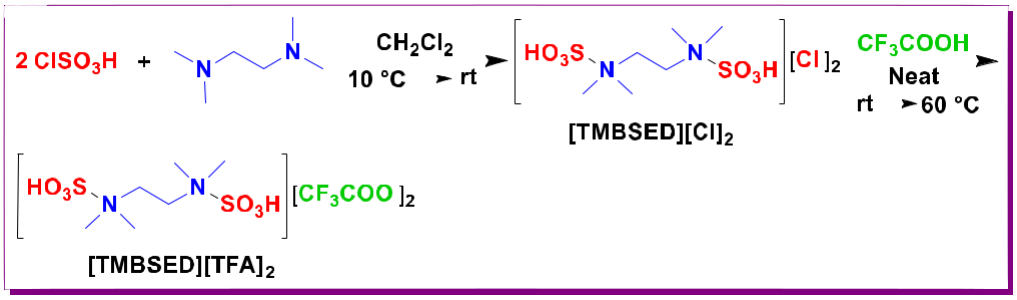
Materails and methods

All the chemicals were purchased from Merck, Fluka or Acros Chemical Companies. All known compounds were identified by comparison of their melting points and spectroscopic data with those reported in the literature. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Monitoring progress of the reactions was achieved by thin layer chromatography (TLC). Spectra were recorded on the following apparatus: ^{1}H NMR (250 or 500 MHz) and ^{13}C NMR (62.5 or 125.7 MHz) on Bruker Avance DPX, FT-NMR spectrometers; and mass spectra on spectrometer 5975C VL MSD model Tripe-Axis Detector.

Preparation of [TMBSED][TFA]$_2$

A solution of N_1, N_1, N_2, N_2-tetramethylethane-1, 2-diamine (5 mmol, 0.581 g) in dry CH_2Cl_2 (30 mL) was added dropwise to a stirring solution of chlorosulfonic acid (10 mmol, 1.165 g) in dry CH_2Cl_2 (30 mL) over a period of 10 min, at 10 °C. After that, the reaction mixture was allowed to heat to room temperature (accompanied with stirring), and stirred for another 4 hours. The solvent was evaporated under reduced pressure, and the liquid residue was triturated with dry petroleum ether (3×2 mL), and dried under powerful vacuum at 90 °C to give [TMBSED][Cl]$_2$. Then, trifluoroacetic acid (10 mmol, 1.140 g) was added dropwise to [TMBSED][Cl]$_2$ (5 mmol, 1.746 g) over a period

of 3 min at room temperature under pressure of nitrogen gas (to remove HCl produced during the reaction). The resulting mixture was stirred for 10 h at room temperature, and 2 h at 60 °C under a continuous flow of nitrogen gas to afford [TMBSED][TFA]$_2$ as a viscous pale yellow liquid (Scheme 1) [11].



Scheme 1. The preparation of [TMBSED][TFA]$_2$

General procedure for the synthesis of 4H-pyrano[2, 3-c]pyrazoles

To a mixture of malononitrile (1 mmol, 0.066 g), aldehyde (1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1 mmol, 0.174 g) was added [TMBSED][TFA]$_2$ (0.07 mmol, 0.035 g), and the resultant mixture was stirred vigorously with a small rod at 50 °C. After completion of the reaction, as observed by TLC, and cooling the mixture to room temperature, the solid residue was recrystallized from ethanol (95%) to give the pure product.

Selected physical and spectroscopic data of 4H-pyrano[2, 3-c]pyrazoles

*6-Amino-3-methyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2, 3-c]pyrazol-5-carbonitrile (**4c**)*

Yellow solid, mp 190−192 °C, ^{1}H NMR (250 MHz, DMSO): *δ* 1.77 (s, 3H), 4.94 (s, 1H), 7.27-7.50 (m, 5H), 7.61-7.78 (m, 4H), 8.13 (s, 2H). ^{13}C NMR (62.5 MHz, DMSO): *δ* 12.5, 36.1, 56.9, 97.6, 110.5, 119.7, 120.0, 122.2, 126.2, 129.3, 130.8, 134.7, 137.4, 143.9, 145.1, 145.9, 147.9, 159.7.

*6-Amino-3-methyl-4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyrano[2, 3-c]pyrazol-5-carbonitrile (**4f**)*

Yellow solid, mp 175−177 °C, ^{1}H NMR (500 MHz, DMSO): *δ* 2.22 (s, 3H), 4.79 (d, *J* = 11.0 Hz, 1H), 7.23 (m, 2H), 7.45 (m, 4H), 7.65-7.72 (m, 3H), 11.68 (s, 2H). ^{13}C NMR (125 MHz, DMSO): *δ* 12.6, 34.2, 57.1, 101.4, 119.1, 120.5, 124.9, 128.0, 129.2, 129.7, 131.9, 134.0, 137.2, 138.9, 144.3, 146.1, 159.4.

*6-Amino-3-methyl-1-phenyl-4-(p-tolyl)-1,4-dihydropyrano[2, 3-c]pyrazol-5-carbonitrile (**4j**)*

Yellow solid, mp 160−162 °C, ^{1}H NMR (250 MHz, DMSO): *δ* 2.16 (s, 3H), 2.39 (s, 3H), 4.66 (d, *J* = 10.8 Hz, 1H), 7.05-7.22 (m, 3H), 7.43 (t, *J* = 8.2 Hz, 4H), 7.68 (d, *J* = 7.8 Hz, 2H), 11.53 (s, 2H). ^{13}C NMR (62.5 MHz, DMSO): *δ* 20.5, 26.2, 41.1, 57.5, 102.2, 114.1, 118.7, 120.4, 124.9, 127.5, 128.9, 129.2, 130.6, 136.2, 137.1, 147.8, 161.2.

Results and Discussion

After identification of the ionic liquid structure, its catalytic performance was examined for the synthesis of 4*H*-pyrano[2, 3-*c*]pyrazoles. The condensation of malononitrile (1 mmol) with 4-chlorobenzaldehyde (1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*)-one (1 mmol) was selected as a model reaction for optimizing the reaction conditions (Scheme 2). The model reaction was tested in the presence

of various amounts of [TMBSED][TFA]$_2$ (0-10 mol%) at a range of 35-60 °C in solvent-free conditions. Higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 7 mol% of the catalyst at 50 °C (time: 10 min; yield: 96%).

Scheme 2. The synthesis of 4*H*-pyrano[2, 3-*c*]pyrazoles using [TMBSED][TFA]$_2$

Then, generality and effectiveness of the catalyst was evaluated by the reaction of malononitrile with various aromatic aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*) -one under the optimized reaction conditions. The results are summarized in Table 1. As the data in this Table illustrate, the catalyst was general and highly efficient for the reaction; all aromatic aldehydes (containing electron-deficient and electron-rich ones) afforded the corresponding 4*H*-pyrano[2, 3-c]pyrazole in high yields within short reaction times. These results showed the generality and high effectiveness of the catalyst for the synthesis.

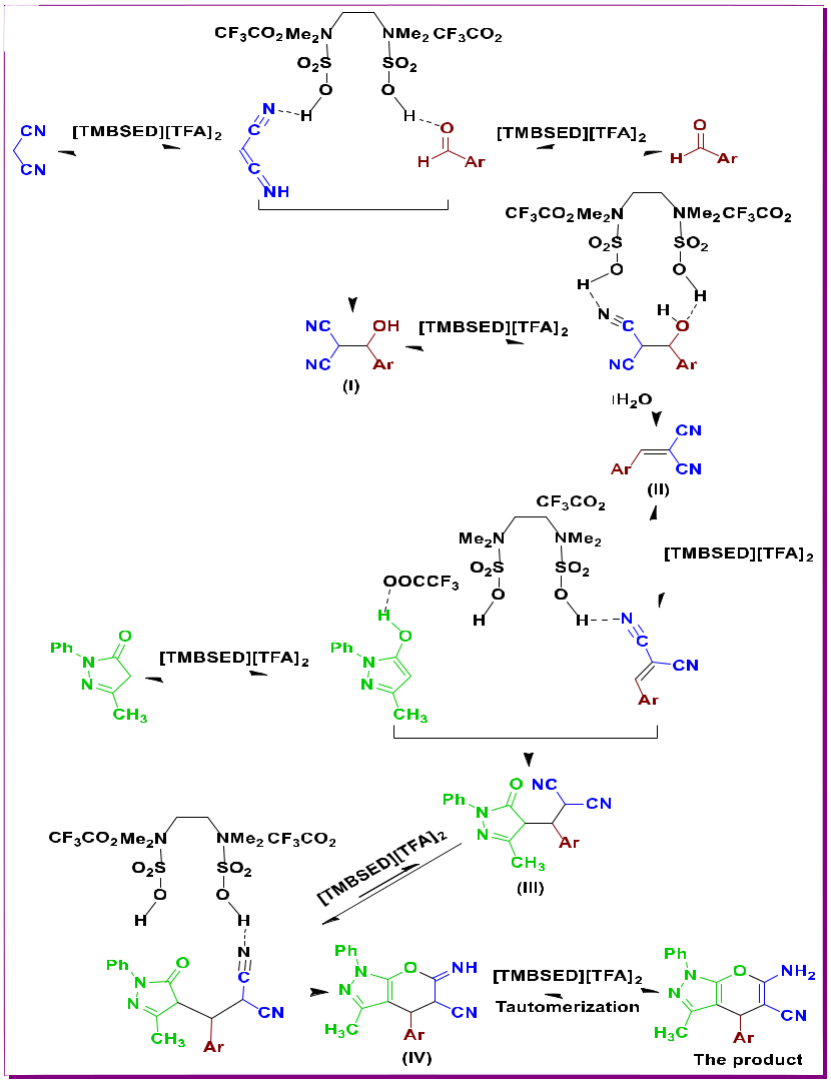
Table 1. The [TMBSED][TFA]$_2$-catalyzed reaction of malononitrile with arylaldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one leading to 4*H*-pyrano[2, 3-*c*]pyrazoles

Product	Aldehyde	Time (min)	Yield (%)[a]	M.p. (°C) [Lit.]
4a	Benzaldehyde	10	95	169-171 (171-173) [25]
4b	4-Nitrobenzaldehyde	20	97	192-194 (192-194) [28]
4c	3-Nitrobenzaldehyde	25	96	190-192 (190-192) [25]
4d	4-Bromobenzaldehyde	15	96	183-185 (184-186) [26]
4e	3-Bromobenzaldehyde	15	97	158-160 (159-160) [25]
4f	4-Chlorobenzaldehyde	10	96	175-177 (175-176) [30]
4g	2, 4-Dichlorobenzaldehyde	30	95	177-179 (180-182) [26]
4h	4-Methoxybenzaldehyde	35	94	172-174 (171-172) [30]
4i	4-Benzyloxybenzaldehyde	60	94	159-161 (158-159) [25]
4j	4-Methylbenzaldehyde	45	95	160-162 (159-161) [26]

[a] Isolated yield

It is noteworthy that [TMBSED][TFA]$_2$ is a dual-functional catalyst, because it has two acidic sites (SO_3H) and two basic sites (trifluoroacetate). Based on this topic, an attractive mechanism is proposed for the synthesis of 4*H*-pyrano[2, 3-*c*]pyrazoles (Scheme 3); this mechanism is supported by the literature [26]. Initially, malononitrile is converted to its tautomer form, activated by the catalyst, and added to the activated aldehyde by [TMBSED][TFA]$_2$ to afford intermediate **I** (trifluoroacetate also assist to absorb a proton from NH of malononitrile tautomer). Afterward, the acidic ionic liquid helps for removing a molecule of H_2O from **I** to give intermediate **II** (trifluoroacetate also assist to attract a proton for removing H_2O). **II** is activated by the catalyst to accept a nucleophile, and then the tautomer

form of 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*)-one adds to it leading to intermediate **III** (the ionic-liquid anion helps for removing a proton from the OH). $[TMBSED][TFA]_2$ activates the cyano group of **III**, and then **IV** forms by cyclization reaction. IV is converted to 4*H*-pyrano[2,3-c]pyrazole by tautomerization. The anion also facilitates achieving the two last steps by assistance to absorption of a proton. The high efficacy of the catalyst can attribute to: (i) activating both nucleophiles and electrophiles, and (ii) aggregating nucleophile and electrophile by its two SO_3H groups in two steps of the mechanism, (iii) helping to remove H_2O, (iv) assisting for tatumerization, and (v) in general, facilitating all steps of the reaction.



Scheme 3. The plausible mechanism for the production of 4*H*-pyrano[2,3-*c*]pyrazoles using $[TMBSED][TFA]_2$

Conclusions

In this work, we introduced a protic acidic ionic liquid (N_1, N_1, N_2, N_2-tetramethyl-N_1,N_2-bis (sulfo) ethane-1, 2-diaminium trifluoroacetate) as a catalyst for the one-pot multi-component reaction between malononitrile, arylaldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5 (4*H*)-one

to afford 4*H*-pyrano[2,3-*c*]pyrazoles. The hopeful points for the presented protocol are high efficiency, generality, high yields of the products, short reaction times, cleaner reaction profile, simplicity, low cost, easy preparation of the catalyst from easy available reactants, dual-functionality of the catalyst, application of low amount of the catalyst, mild conditions, performing the reactions in the absence of solvent, and good compliance with green chemistry protocols.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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