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[DMImd-DMP]: A highly efficient and reusable catalyst for the synthesis of 4*H*-benzo[*b*]pyran derivatives

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Abstract: A series of substituted 4*H*-pyrans derivatives were synthesized by a one-pot, multi-component reaction of aromatic aldehydes, malononitrile, and pyrazolone derivatives or active methylene carbonyl compounds such as dimedone, in the presence of 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP] as a catalyst in aqueous ethanol. Recyclability of the catalyst, high yields, simple product isolation and high atom economy are the noteworthy aspects of this protocol.

Keywords: multicomponent reaction, *one-pot* synthesis, pyrano[2,3-c]pyrazoles, tetrahydrobenzo[*b*]pyrans, ionic liquids, [DMImd-DMP].

Introduction

Multicomponent reactions (MCRs) are one of the most important reactions in organic and medicinal chemistry because they are widely used for synthesis of diverse and complex organic molecules [1-3]. They are known to be selective, have effective atom economic, and are generally time saving and easy to perform. As such, MCRs have attracted much attention from both academia and the pharmaceutical industry [4,5].

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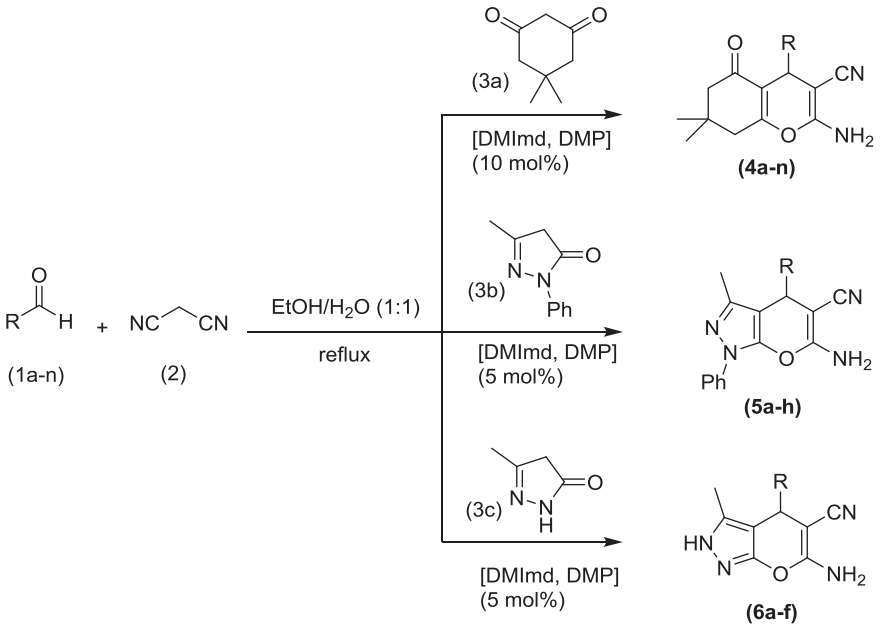
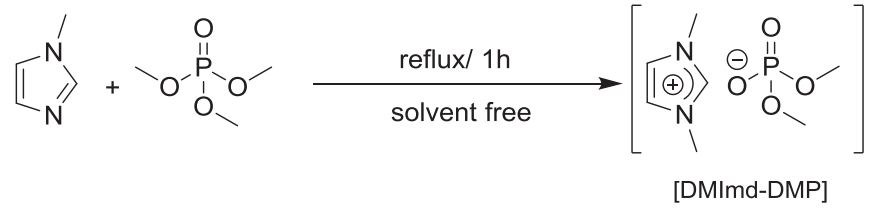
4*H*-pyran derivatives represent an important class of oxygen-containing heterocycles. They are often employed as cosmetics, pigments [6], and potential biodegradable agrochemicals [7] and exhibit a wide range of biological activities [8-17]. Moreover, they possess important medicinal properties such as antimicrobial, antibacterial, anticancer, anti-tubercular, anti-coagulant, anti-allergic, antibiotic, hypolipidemic, and immunomodulating activities [18-25]. In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases like Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome, as well as for the treatment of schizophrenia and myoclonus [26].

Realizing the importance of 4*H*-pyran derivatives, various synthetic approaches have been developed with the aim of obtaining more biologically potent heterocyclic systems using different catalysts such as magnesium oxide [27], silica-bonded 1,4-diazabicyclo[2.2.2]octane [28], silica nanoparticles [29], electro-generated base [30], baker's yeast [31], and amino-functionalized ionic liquid [32]. Other synthetic methods have included the use of microwaves [33], ultrasonic radiation [34], and utilizing additives like hexadecyltrimethylammonium bromide [35], triethylbenzylammonium chloride [36], other alkylammonium salts [37], 4-dodecylbenzenesulfonic acid [38], morpholine triflate [39], Trichloroacetic acid [40], imidazole [41], lemon juice [42], DABCO [43], (*S*)-proline [44], triphenylphosphine [45], PEG-400 [46], β-cyclodextrin [47], [MNP-PIm-SO_3H]Cl [48], uncapped SnO_2 quantum dots (QDs) [49], Fe_3-xTixO_4@SO_3H magnetic nanoparticles [50], nano-structured diphosphate ($Na_2CaP_2O_7$) [51], γ-alumina [52], silica coated magnetic $NiFe_2O_4$ nanoparticles supported $H_3PW12O40$ (NFSPWA) [53] and cerium ammonium nitrate (CAN) [54].

However, these methods were shown to have limitations and proved ineffective, such as low yields and difficult work-up procedures. Bandgar and coworkers [55]



Scheme 1 Synthesis of 4*H*-pyran derivatives in the presence of 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP].



Scheme 2 Synthesis of 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP].

reported the synthesis of tetrahydrobenzo[b]pyrans in good yield without the use of a catalyst, although prolonged reaction times were required.

In recent years, ionic liquids (ILs) have become a powerful alternative to conventional molecular organic solvents due to their favourable properties, such as undetectable vapor pressure, and the ability to dissolve many organic and inorganic substances [56]. Furthermore, the ILs are readily recycled and tunable to specifics chemical tasks [57]. Imidazolium-based ILs have proved their catalytic activity and have attracted considerable attention from the scientific community, due to the ease of preparation from readily available and inexpensive starting materials [57j-k].

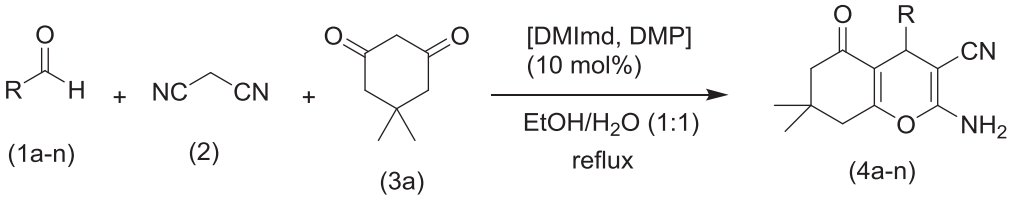
In this paper, we would like to report an efficient process for the synthesis of 4*H*-pyran derivatives by employing 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP] as an efficient and recyclable catalyst. We examined a wide variety of benzaldehydes with various substituents to establish the catalytic importance of this catalyst for this reaction (Scheme 1).

Results and discussion

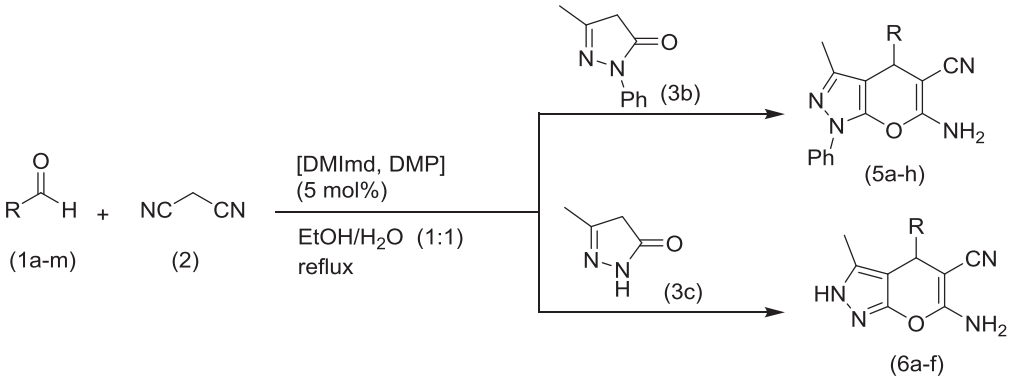
The first step in the execution of this process was the synthesis of [DMImd-DMP]. The catalyst was prepared from the quaternization of *N*-methylimidazole with trimethylphosphate as shown in Scheme 2. The catalyst structure was investigated by NMR spectroscopy. The pure *N,N*-methylimidazolium dimethylphosphate shows characteristic peaks at 3.85 ppm and 4.12 ppm corresponding to ($2 \times OCH_3$) and ($2 \times N\text{-}CH_3$) groups, respectively. These results prove that the methyl, provided from trimethylphosphate, was successfully added to *N*-methylimidazole to give 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP].

In order to find the best reaction conditions for the synthesis of 4*H*-pyran derivatives, our introductory explorations focused on the study of the efficacy of this catalyst.

To establish the feasibility of the strategy and optimize the reaction conditions, the condensation of benzaldehyde (**1a**) (1 mmol) with malononitrile (**2**) (1 mmol)



Scheme 3 One-pot three-component reaction of dimedone (**3a**), different aldehydes (**1a-n**), and malononitrile (**2**) catalyzed by [DMImd-DMP].



Scheme 4 One-pot three-component reaction different aldehydes (**1**), malononitrile (**2**) and 3-methyl-1-phenyl-2-pyrazolin-5-one (**3b**)/ 5-methyl-2,4-dihydro-3H-pyrazol-3-one (**3c**) catalyzed by [DMImd-DMP].

and 5,5-dimethylcyclohexane-1,3-dione (**3a**) (1 mmol) in the presence of 10 mol% of [DMImd-DMP] was selected as a reaction model to produce 4*H*-benzo[*b*]pyran (**4a**) (Scheme 3). Also, benzaldehyde (**1a**) (1 mmol) with malononitrile (**2**) (1 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (**3b**) (1 mmol) in the presence of 10 mol% of [DMImd-DMP] as a second reaction model for the synthesis of pyrano[2,3-c]pyrazole derivatives (**5**) and (**6**), respectively (Scheme 4).

The choice of a solvent is a crucial factor for MCRs. So, firstly we looked into the appropriate solvent for this reaction, especially in terms of starting materials solubility. We then tested the reaction in different solvents such as H_2O, EtOH, CH_3CN, THF, and DMF in the presence of 10 mol% of [DMImd-DMP] as a catalyst. Furthermore, the reaction was carried out under solvent-free conditions (Table 1, Entry 1). However, aqueous ethanol (1:1) turned to be the best solvent for this reaction. The obtained results are given in Table 1. We obtained the best results at reflux (Table 1, Entry 7); hence all the reactions were performed at reflux in solvent.

The temperature played an important role, there was a formation of trace amounts of product formed which longer reaction times. As the temperature increased, from room temperature to reflux in solvent, the yields were found to increase while the reaction time decreased (Table 1, entries 8 and 9). Higher yields and shorter reaction times to synthesis 4*H*-benzopyrans model reaction were obtained when the reaction was carried out in aqueous ethanol (1:1) at reflux (Table 1, entry 7).

Table 1 [DMImd-DMP]-catalyzed reaction of benzaldehyde, malononitrile, and 5,5-dimethylcyclohexane-1,3-dione in different solvents[a]

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	Solvent Free	10	1.5	78
2	CH_3CN	10	3.5	59
3	H_2O	10	2	68
4	EtOH	10	2.5	76
5	THF	10	3.5	89
6	DMF	10	24	Trace
7	**Aqueous EtOH (1:1)**	**10**	**1.5**	**91**
8	Aqueous EtOH (1:1)[c]	10	1.5	47
9	Aqueous EtOH (1:1)[d]	10	1.5	77

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol), [DMImd-DMP] (22 mg), and solvent (5 mL).
[b] Isolated yields.
[c] Room temperature.
[d] 50 °C.

Apart from the solvent, the efficiency of MCRs is mainly affected by the amount of catalyst. Next, to obtain the best conditions we carried out the above condensation, under the optimized conditions, with various

Table 2 Optimization of amount of catalyst for synthesis of 4*H*-benzopyrane.[a]

Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	5	1.5	75
2	**10**	**1.5**	**91**
3	15	1.5	84
4	20	1.5	74
5	30	1.5	59

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) and catalyst [DMImd-DMP] in 5 mL solvent H2O/EtOH (1:1) at reflux.
[b] Isolated yield.

amounts of catalyst increasing from 5 to 30 mol% (Table 2). After reviewing the results, it was found that an amount of 10 mol% was sufficient to provide a best yield. However, the use of 5 mol % of [DMImd-DMP] or increasing it to more than 10%, (Tables 2, entries 1-5) has no positive effect even on yield and reaction time. Thus, the optimal conditions for the preparation of 4*H*-benzo-[*b*] pyrans catalyzed by [DMImd-DMP] are: reflux in aqueous ethanol (1:1) and 10 mol% of catalyst. The same process was followed to optimize the best conditions for the pyranopyrazole **5** model reaction. As shown in Table 3, when the reaction was carried in the presence of 10 mol% of catalyst, in various solvents, desired product (5a) is obtained with yields ranging between 23 and 84 %, in which the shortest reaction time was 80 min (Table 3, entries 1-7). However, the reaction in aqueous ethanol (1:1) at reflux gave a better result with a yield of 88 % in presence of 5 mol% of our catalyst within 45 min (Table 3, entry 8).

To probe the efficiency and the scope of our method, a broad range of structurally diverse aldehydes (**1**) were condensed with 5,5-dimethylcyclohexane-1,3-dione (**3a**)/3-methyl-1-phenyl-2-pyrazolin-5-one(**3b**)/5-methyl-2,4-dihydro-3H-pyrazol-3-one (**3c**) and malononitrile (**2**) to furnish the corresponding 4*H*-pyran derivatives in high yields and in relatively short reaction times (Scheme 1). The corresponding results are given in Table 4. For all the entries, aqueous ethanol (1:1) was used as solvent and the reaction was conducted at reflux. In all cases, the conversion was completed within 20-120 min with good to excellent yields of desired products, without forming any by-products. We found that the reaction proceeded efficiently employing either electron-releasing or electron-withdrawing substituents on the aldehyde's aryl ring. Moreover, heteroaromatic aldehydes such as thiophene-2-carbaldehyde and indole-3-carbaldehyde, were applied successfully in the reaction to provide the corresponding

Table 3 Optimization of reaction conditions for the synthesis of pyranopyrazole.[a]

Entry	Solvent	Catalyst (mol%)	Time (h or min)	Yield (%)[b]
1	Solvent Free	10	3 h	68
2	CH_3CN	10	24 h	71
3	H_2O	10	24 h	Trace
4	EtOH	10	3 h	36
5	THF	10	3 h	69
6	DMF	10	5 h	23
7	Aqueous EtOH (1:1)	10	80 min	84
8	**Aqueous EtOH (1:1)**	**5**	**45 min**	**88**
9	Aqueous EtOH (1:1)	15	90 min	77
10	Aqueous EtOH (1:1)	20	2 h	73
11	Aqueous EtOH (1:1)	30	2 h	65
12	Aqueous EtOH (1:1)	-	3 h	16
13	Aqueous EtOH (1:1)[c]	5	45 min	58
14	Aqueous EtOH (1:1)[d]	5	45 min	71

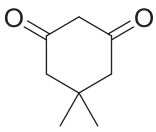
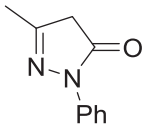
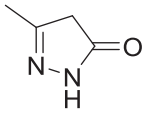
[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), pyrazolone derivative (1 mmol), catalyst [DMImd-DMP] in 5 mL solvent at reflux.
[b] Isolated yield.
[c] room temperature.
[d] 50 °C.

4*H*-pyran derivatives without by-products (Table 4, entries 12, 20 and 21).

In view of green chemistry, reuse of the catalyst is highly preferable. The reusability of the catalyst was studied on the synthesis of compounds **4a** and **4h**. After separating the products, the IL catalyst was easily recovered and recycled by removing the filtrate. Products **4a** and **4h** were obtained with excellent yields in consecutive 1 to 7 runs, respectively, which indicated that the catalyst could be reused for at least 6 runs without losing its activity (Figure 1).

The role of [DMImd-DMP] in the synthesis of 4*H*-pyrans (**4-6**) can be explained by the strict sequence of the reactions shown in Scheme 5. Based on this mechanism, [DMImd-DMP] is an effective catalyst for the formation of olefin (**7**), which is readily prepared *in-situ* from the Knoevenagel condensation of aldehyde (**1**) with highly active CH-acidic malononitrile (**2**). Carbonyl compound (**3**), in the presence of [DMImd-DMP], subsequently converts to its corresponding enolate form (**8**), and adds to the unsaturated nitrile (**7**) by Michael reaction to produce intermediate (**9**), and enolate oxygen nucleophilically attacks nitrile group (Thorpe-Ziegler type reaction).

Table 4 Synthesis of 4*H*-pyran derivatives in the presence of [DMImd-DMP] under Optimized conditions.[a]

Entry	R	Substrate	Product	Time (min)	Yield [b] (%)	Melting point (°C)	
						Found	Reported
1	C_6H_5	 (3a)	4a	90	92	235-237	(234-236) [58]
2	4-Me-C_6H_4		4b	45	85	230-232	(219-221) [58]
3	4-Et-C_6H_4		4c	90	86	231-233	(230-232) [59]
4	4-OH-C_6H_4		4d	60	86	198–200	204-205 [60]
5	4-Me_2N-C_6H_4		4e	50	89	218-221	223-225 [60]
6	4-Cl-C_6H_4		4f	75	87	218-220	210-212 [60]
7	4-NO_2-C_6H_4		4g	30	91	184-186	178-180 [60]
8	3-NO_2-C_6H_4		4h	30	93	209-212	208-209 [60]
9	2-NO_2-C_6H_4		4i	45	89	228-230	228–229 [60]
10	4-Ac-C_6H_4		4j	30	91	232-234	-
11	4-CHO-C_6H_4 [c]		4k	90	93	>260	264-267 [61]
12	2-Thienyl		4l	120	80	228-230	226-228 [58]
13	3-OH-4-OMe-C_6H_3		4m	30	83	235-237	238-240 [60]
14	C_6H_5	 (3b)	5a	50	86	164-166	168-170 [62]
15	4-Et-C_6H_4		5b	60	81	184-186	182-184 [45]
16	4-OH-C_6H_4		5c	80	78	216-218	205-207 [62]
17	4-NO_2-C_6H_4		5d	120	92	216-218	196-198 [62]
18	3-NO_2-C_6H_4		5e	90	91	206-208	190-192 [62]
19	4-Ac-C_6H_4		5f	90	84	242-244	-
20	2-thienyl		5g	120	70	>260	168-169 [63]
21	3-indolyl		5h	45	78	254-256	-
22	4-Me-C_6H_4	 (3c)	6a	90	80	209-211	198-200 [65]
23	4-Me_2N-C_6H_4		6b	60	83	201-203	218-220 [66]
24	4-Cl-C_6H_4		6c	60	75	223-224	243 [66]
25	4-NO_2-C_6H_4		6d	60	93	249	249-250 [66]
26	4-CHO-C_6H_4		6e	20	87	214-216	-
27	4-CHO-C_6H_4 [c]		6f	60	83	235-237	238-240 [64]

[a] Reaction conditions: Aldehyde (1 mmol), malononitrile (1 mmol), C–H activated ketones (1 mmol), catalyst [DMImd-DMP] in 5 mL solvent at reflux.

[b] Isolated yield.

[c] Aldehyde (1 mmol), malononitrile (2 mmol), 5-methyl-2,4-dihydro-3H-pyrazol-3-one/dimedone (2 mmol) and catalyst [DMImd-DMP] in 5 mL solvent at reflux.

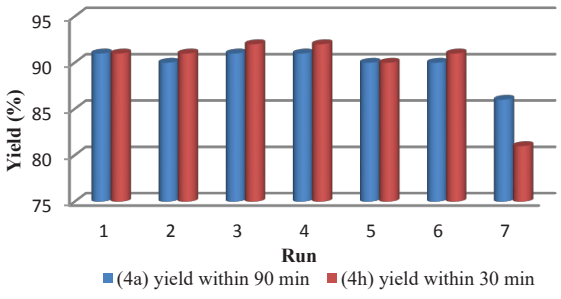
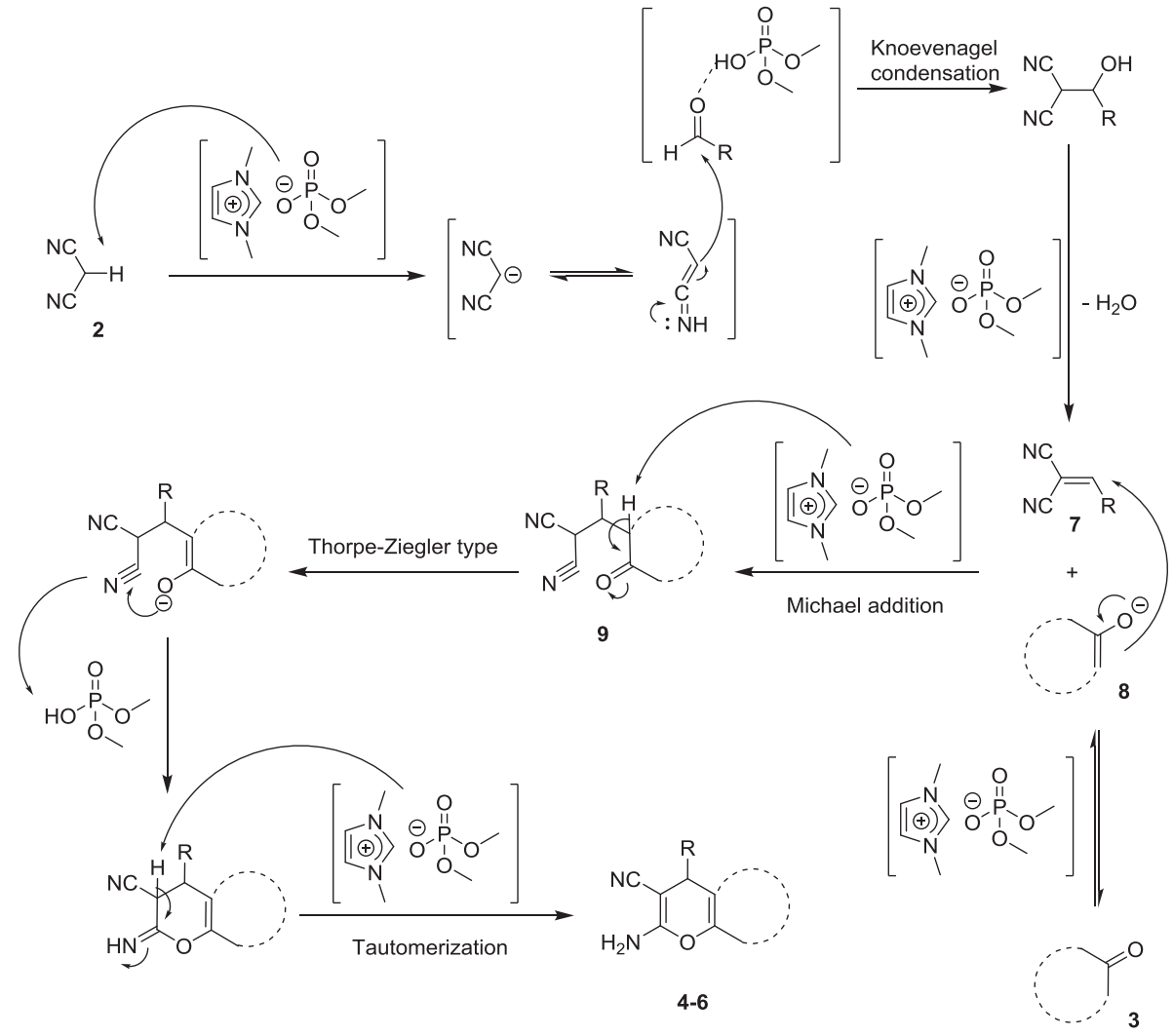


Figure 1 Reusability of the catalyst [DMImd-DMP] in the synthesis of compounds 4a and 4h.

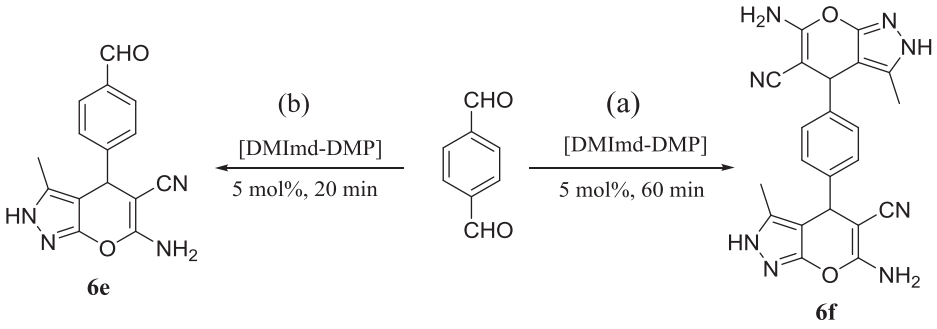
Finally, after the tautomeric proton shift, 2-amino-4*H*-pyran is formed.

The reaction of terephthalaldehyde with equimolar amounts of malononitrile, hydrazine and ethyl acetoacetate under optimized conditions selectively produced mono-pyran (**6e**) in 87 % yield within 20 min, (Scheme 6). However, the reaction of terephthalaldehyde with two equivalents of malononitrile, hydrazine and ethyl acetoacetate led to 83 % of *bis*-pyran (**6f**) after 60 min (Scheme 6).

The formation of mono-dihydropyrano[*b*]pyrazole intermediate (**6e**), was isolated during the reaction of

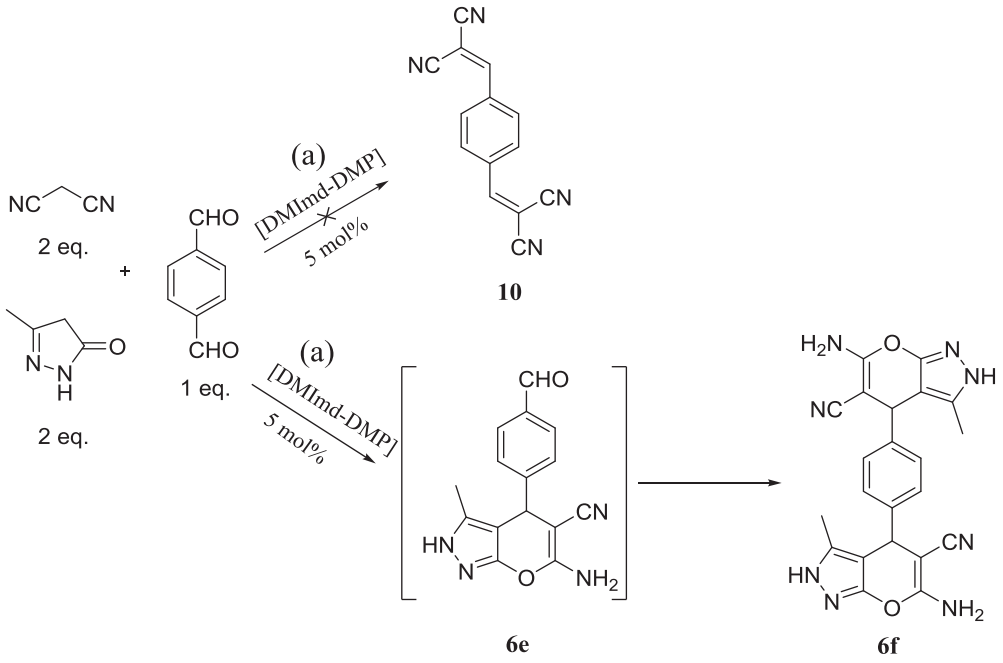


Scheme 5 Probable mechanism for the formation of 4*H*-pyrans derivatives using [DMImd-DMP] as a catalyst.



Scheme 6 Selective synthesis of mono- and *bis*-pyran: (**a**): terephthalaldehyde (1 mmol), malononitrile (2 mmol), hydrazine (2 mmol) and ethyl acetoacetate (2 mmol), (**b**): terephthalaldehyde (1 mmol), malononitrile (1 mmol), hydrazine (1 mmol) and ethyl acetoacetate (1 mmol).

terephthalaldehyde with malononitrile (2 equiv.) and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (2 equiv.), this can be explained by the chemoselectivity of the catalyst which involves the formation of monoaldehyde intermediate (**6e**) by promoting the formation of the key intermediate **9** *via* Michael addition (Scheme 5). However, a second Knoevenagel condensation lead to *bis*-dihydropyrano[b]pyrazole intermediate (**6f**) as reported with other catalysts[64][67] (Scheme 7). With the above results, we can suggest that the [DMImd-DMP]



Scheme 7 Selective synthesis of *bis*-dihydropyrano[b]pyrazole, **(a)**: terephthalaldehyde (1 mmol), malononitrile (2 mmol), hydrazine (2 mmol) and ethyl acetoacetate (2 mmol).

facilitates the Michael reaction instead of Knoevenagel condensation.

Conclusion

In conclusion, we report the catalytic application of ionic liquid 1,3-dimethyl imidazolium dimethyl phosphate [DMImd-DMP] for the efficient one-pot, multicomponent synthesis of tetrahydrobenzo[*b*]pyrans and dihydropyrano[2,3-c]pyrazole derivatives in aqueous ethanol media. A library of 4*H*-pyrans was obtained in good to excellent yields using inexpensive and commercially available compounds. Also, the advantages of this method are the operational simplicity, mild reaction conditions, use of inexpensive starting materials, reusability of the catalyst, facile work-up and purification, and finally a non-toxic solvent was used. Thus, this reaction is an environmentally-friendly process.

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Experimental

General

Melting points (uncorrected) were measured using a Kofler bench and are uncorrected. IR spectra were recorded from KBr disk on a Shimadzu FT-IR-8201 PC spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained with a Brüker 250 MHz spectrometer, Brüker 300 MHz spectrometer and Brüker 400 MHz spectrometer in DMSO-d_6 (or $CDCl_3$). The progress of the reactions was monitored by thin layer chromatography (TLC) analyses using (Merck 60 F_{254} silica gel).

Procedure for the synthesis of 1,3-dimethyl imidazolium dimethylphosphate [DMImd-DMP]:

Trimethylphosphate (16.7 mL, 20 mmol) was added dropwise to a 100 mL flask containing *N*-methyl imidazole (1.64 g, 20 mmol) at room temperature. No temperature increase was observed on initial addition. However, when the temperature was slowly increased to 140 °C. Addition was continued at 140 °C until all the material had been added to the flask, and the reaction mixture was subsequently stirred for another hour. The product was moved to a rotary evaporator to yield viscous yellow oil.[68] ^{1}H NMR (250 MHz, $CDCl_3$): 3.85 (d, 6H, J = 11.0 Hz, 2×CH_3-O-P); 4.12

(s, 6H, 2×N-CH_3); 7.20 (s, 2H, 2× CH); 10.71(s, 1H, N=CH-N). ^{13}C NMR (63 MHz, $CDCl_3$): 36.0; 52.2; 123.1; 139.7. ^{31}P NMR (162 MHz, $CDCl_3$): 2.26 (P=O).

General Procedure for the synthesis of fused-pyranes:

A mixture of aldehyde **1** (1.0 mmol), malononitrile **2** (1.0 mmol), C-H activated carbonyl compound **3** (1 mmol), and [DMIm-DMP] 10 mol % (or 5 mol %) was stirred and heated in 4 mL of aqueous ethanol (1:1 v/v) for the appropriate time indicated in tables 4 (reaction was monitored by TLC). After the completion of the reaction, the resulted mixture was cooled to room temperature; 10 mL of cold water were added, stirred for 5 min then filtered and washed with cold water to remove the catalyst ([DMIm-DMP] is soluble in water and the product precipitated with high purity). The target benzopyrans and pyranopyrazoles were obtained in isolated yields of 80-93% and 70-96% respectively. Finally, crude products were recrystallized from EtOH to give the pure products for experimental analysis.

Spectral data of fused-pyranes derivatives

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a): IR (KBr): 3394, 2966, 2198, 1670, 1369 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 0.94 (s, 3H); 1.02 (s, 3H); 2.09 (d, 1H , *J*= 16.1 Hz); 2.24 (d, 1H, *J*= 16.1 Hz); 2.55 (s, 2H); 4.15 (s, 1H); 6.97 (s, 2H); 7.07-7.17 (m, 3H); 7.27 (t, 1H, *J*= 7.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) : 26.8; 28.4; 31.8; 35.5; 49.9; 58.4; 112.7; 119.7; 127.1; 128.3; 144.7; 158.4; 162.5; 195.6.

2-amino-7,7-dimethyl-5-oxo-4-(p-tolylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b): IR (KBr): 3375; 3178; 2187; 1678; 1639; 1365; 1141; 1029 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 0,96 (s, 3H); 1.05 (s, 3H); 1.96 (d, 1H, *J*= 14.8 Hz); 2.04-2.12 (m, 4H); 2,51 (s, 2H); 4.14 (s, 1H); 6.95 (s, 2H, -NH_2); 7.04-7.10 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 20.7; 26.9; 28.5; 31.8; 35.2; 50.1; 58.5; 112.9; 119.8; 127.1; 128.9; 135.7; 141.9; 158.5; 162.3; 195.7.

2-amino-7,7-dimethyl-5-oxo-4-(4-ethylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c): IR (KBr): 3313; 2962; 2187; 1604; 1369; 1149 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.96 (s, 3H); 1.03 (s, 3H); 1.15 (t, 3H, *J*= 7.6 Hz); 2.10 (d, 1H, *J*= 16.1 Hz); 2.25 (d, 1H, *J*= 16.1 Hz); 2.52 (s, 2H); 2.55 (q, 2H, *J*= 7.6 Hz, masked by methylene signal); 4.13 (s, 1H); 6.93 (s, 2H); 7.04 (d, 2H, *J*= 8.2 Hz); 7.12 (d, 2H, *J*= 8.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 15.9; 27.3; 28.2; 28.8; 32.3; 35.6; 50.5; 59.0; 113.3; 120.3; 127.5; 128.2; 142.4; 142.5; 158.9; 162.9; 196.2.

2-amino-7,7-dimethyl-5-oxo-4-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d): IR (KBr): 3332, 2962, 2194, 1647, 1369 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 0.92 (s, 3H); 1.01 (s, 3H); 2.06 (d, 1H, *J*= 16.1 Hz); 2.22 (d, 1H, *J*= 16.1 Hz); 2.46 (s, 2H); 4.05 (s, 1H); 6.65 (d, 2H, *J*= 6.2 Hz); 6.88-6.95 (m, 4H); 9.25 (s, 1H, -OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): 26.7; 28.3; 31.8; 35.4; 49.8; 57.1; 111.7; 119.3; 121.6; 121.7; 129.9; 134.1; 147.0; 147.7; 158.6; 163.1; 195.7.

2-amino-7,7-dimethyl-5-oxo-4-(4-dimethylaminophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e): IR (KBr): 3382; 2893; 2187; 1650; 1612; 1519; 1365; 1033 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.95 (s, 3H); 1.04 (s, 3H); 2.08 (d, 1H, *J*= 16.1 Hz); 2.24 (d, 1H, *J*= 16.1 Hz); 2.53 (s, 2H); 2.85 (s, 6H); 4.05 (s, 1H); 6.64 (d, 2H, *J*= 8.7 Hz); 6.86 (s, 2H); 6.95 (d, 2H, *J*= 8.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 27.2; 28.9; 32.2; 35.1; 50.6; 59.5; 112.8; 113.8; 120.4; 128.2; 133.0; 149.7; 158.8; 162.3; 196.1.

2-amino-7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f): IR (KBr): 3402; 3298; 2184; 1612; 1407; 1056 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.94 (s, 3H); 1.03 (s, 3H); 2.10 (d, 1H, *J*= 16.1 Hz); 2.25 (d, 1H, *J*= 16.1 Hz); 2.51 (s, 2H); 4.19 (s, 1H); 7.03 (s, 2H); 7.17 (d, 2H, *J*= 8.4 Hz); 7.34 (d, 2H, *J*= 8.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 27.3; 28.8; 32.2; 35.5; 40.4; 50.5; 58.4; 112.7; 119.9; 128.8; 129.6; 131.6; 144.2; 158.9; 163.2; 196.2.

2-amino-7,7-dimethyl-5-oxo-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g): IR (KBr): 3402; 3174; 2163; 1523; 1674; 1631; 1461-1407 (NO_2); 1354 (C-N); 1022 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$,): 0.93 (s, 3H); 1.01 (s, 3H); 2.08 (d, 1H, *J*= 16.0 Hz); 2.17 (d, 1H, *J*= 16.0 Hz); 2.48 (s, 2H); 4.34 (s, 1H); 7.16 (s, 2H); 7.42 (d, *J*= 8.8 Hz, 2H); 8.14 (d, *J*= 8.8 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 18.5; 26.9; 28.2; 31.8; 35.6; 49.8; 56.0; 56.9; 111.7; 119.3; 123.6; 128.6; 139.1; 146.2; 152.2; 158.5; 163.1; 195.7.

2-amino-7,7-dimethyl-5-oxo-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h): IR (KBr): 3433; 2958; 2191; 1596; 1249 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 0.93 (s, 3H); 1.01 (s, 3H); 2.10 (d, 1H, *J*= 16.1 Hz); 2.24 (d, 1H, *J*= 16.3 Hz); 2.53 (s, 2H); 4.39 (s, 1H); 7.16 (s, 2H); 7.53-7.64 (m, 2H); 8.01-8.08 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 26.7; 28.3; 31.8; 35.3: 49.8; 57.1; 111.7; 119.3; 121.6; 121.7; 130.0; 134.1; 147.0; 147.7; 158.6; 163.1; 195.7.

2-amino-7,7-dimethyl-5-oxo-4-(2-nitrophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4i): IR (KBr): 3467; 2954; 2194; 1674; 1523; 1361; 1149 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): 0.81 (s, 3H); 0.94 (s, 3H); 1.94 (d, 1H, *J*= 16.1 Hz); 2.13 (d, 1H, *J*= 16.1 Hz); 2.44 (s, 2H); 4.87 (s, 1H); 7.11 (s, 2H); 7.29 (dd, 1H, *J*= 7.8-1.0 Hz); 7.37 (t, 1H, *J*= 7.2 Hz); 7.56-7.63 (m, 1H); 7.75 (dd, 1H, *J*= 8.1-0.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): 26.7; 28.2; 29.9; 31.8; 49.5; 56.3; 112.4; 119.3; 123.7; 127.8; 130.2; 133.3; 138.9; 148.9; 159.1; 162.7; 195.8.

2-amino-7,7-dimethyl-5-oxo-4-(4-acetylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j): IR (KBr): 3382 (N-H); 3201 (-NH_2); 2191 (C≡N); 1651(C=O); 1600 (C=N); 1365 (C=C); 1415 (C-N); 1037 cm^{-1} (C-O-C) cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): 0.96 (s, 3H); 1.05 (s, 3H); 2.10 (d, 1H, *J*= 16.2 Hz); 2.26 (d, 1H, *J*= 16.4 Hz); 2.55 (s, 3H); 4.27 (s, 1H); 7.11 (s, 2H); 7.29 (d, 2H, *J*= 8.4 Hz); 7.89 (d, 2H, *J*= 8.6 Hz) . ^{13}C NMR (100 MHz, DMSO-d_6): 27.2; 27.3; 28.8; 32.3; 36.1; 50.4; 58.0; 112.6; 120.0; 128.0; 129.0; 135.9; 150.4; 159.0; 163.3; 196.1; 197.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1547, found 337.1549.

4,4'-(1,4-phenylene)bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (4k): IR (KBr): 3452 (NH2); 2962 (C-H); 2195 (C≡N); 1666 (C=O); 1604 (C=N); 1365 $(C=C)_{Ar}$ cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 0,95 (s, 3H); 0,99 (s, 3H); 1.04 (s, 6H); 2.28-2.10 (m, 4H); 2.56-2.47 (m, 4H); 4.15 (s, 2H); 6.96 (s, 4H, 2×NH_2); 7.06 (s, 4H, H_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): 27.2; 28.2; 31.8; 34.9; 49.9; 58.3; 112.7; 112.8; 119.7; 126.9; 142.8; 158.5; 162.7; 195.8.

2-amino-7,7-dimethyl-5-oxo-4-(2-thienyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l): IR (KBr): 3379; 3201; 2194; 1666; 1600; 1365; 1141; 1033 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 1.00 (s, 3H); 1.07 (s, 3H), 2.15 (d, 1H, *J*= 16.2 Hz); 2.26 (d, 1H, *J*= 16.2 Hz); 2.39 (d, 1H, *J*= 17 Hz); 2.49 (d, 1H, *J*= 17 Hz); 4.56 (s, 1H); 6.85 (d, 2H *J*= 2.8 Hz); 6.90 (s, 2H, -NH_2); 7.16 (t, 1H, *J*= 2.9 Hz). ^{13}C NMR (63 MHz, DMSO-d_6): 26.4; 28.4; 30.0; 31.4; 49.7; 57.9; 112.7; 119.2; 123.5; 126.2; 148.7; 158.5; 161.8; 195.0.

2-amino-7,7-dimethyl-5-oxo-4-(3-hydroxy-4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4m): IR (KBr): 3310, 3254, 2890, 2192, 1670, 1596 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.96 (s, 3H); 1.03 (s, 3H); 2.09 (d, 1H, *J*= 16.1 Hz); 2.25 (d, 1H, *J*= 16.1 Hz); 2.50 (s, 2H); 3.71 (s, 3H); 4.01 (s, 1H); 6.51 (dd, 1H, *J*= 8.1 Hz, *J*= 2.2 Hz); 6.56 (d, 1H, *J*= 2.2 Hz); 6.80 (d, 1H, *J*= 8.1 Hz); 6.90 (s, 2H); 8.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 27.2; 28.9; 32.2; 35.3; 50.5; 56.1; 59.2; 112.5; 113.6; 115.0; 118.3; 120.3; 137.9; 146.7; 146.8; 158.9; 162.5; 196.2.

6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a): IR (KBr): 3337 (N-H); 2194 (C≡N); 1589 (C=N); 1261(C-N); 1658 (C=C); 1446 (C=C) Ar; 1126 cm^{-1} (C-O-C) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 1.79 (s, 3H); 4.60 (s, 1H); 6.75-7.47 (m, 10H) 7.74-7.79 (m, 2H). ^{13}C NMR (63 MHz, DMSO-d_6): 12.6; 37.0; 58.4; 98.3; 119.9; 120.4; 125.8; 126.9; 127.6; 128.3; 128.5; 129.0; 137.5; 143.8; 143.3; 145.3; 159.3.

6-amino-3-methyl-1-phenyl-4-(4-ethylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b): IR (KBr): 3440; 3337; 2881; 2353; 2199; 1593; 1411; 1167 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 1.18 (t, 3H, *J*= 7.6 Hz); 1.29 (s, 3H); 2.60 (q, 2H, *J*= 7.6 Hz); 4.64 (s, 1H); 7.11-7.24 (m, 6H); 7.32 (t, 1H, *J*= 7.4 Hz); 7.49 (t, 2H, *J*= 7.5 Hz); 7.78 (d, 2H, *J*= 7.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 12.7; 15.5; 27.8; 36.4; 58.4; 98.8; 120.2; 126.2; 127.7; 127.9; 129.4; 137.6; 141.0; 142.4; 145.4; 159.4.

6-amino-3-methyl-1-phenyl-4-(4-hydroxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5c): IR (KBr): 3413; 3205; 2179; 1654; 1589; 1396; 1026 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 1.79 (s, 3H); 4.56 (s, 1H); 6.72 (d, 2H, *J*= 8.5 Hz); 7.04 (d, 2H, *J*= 8.5 Hz); 7.10 (s, 2H); 7.31 (t, 1H, *J*= 7.4 Hz); 7.49 (t, 2H, *J*= 7.9 Hz); 7.78 (d, 2H, *J*= 7.7 Hz); 9.33 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 13.0; 36.5; 59.3; 99.5; 115.7; 120.4; 126.6; 129,2; 129.8; 134.4; 138.1; 144.3; 145.8; 156.7; 159.7.

6-amino-3-methyl-1-phenyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d): IR (KBr): 3433 (N-H); 2225 (C≡N); 1600 (C=N); 1319(C-N); 1739 (C=C); 1500 (C=C)Ar; 1396-1450 (NO_2); 1161 cm^{-1} (C-O-C) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 1.81 (s, 3H); 4.93 (s, 1H); 7.31-7.39 (m, 3H); 7.51 (t, 2H, *J*= 7.6 Hz); 7.59 (d, 2H, *J*= 8.8 Hz), 7.80 (d, 2H, *J*= 7.6 Hz); 8.24 (d, 2H, *J*= 8.8 Hz). ^{13}C NMR (63 MHz, DMSO-d_6): 12.5; 36.4; 56.9; 97.6; 119.7; 120.1; 123.9; 126.3; 129.2; 129,3; 137.4; 144.0; 145.1; 146.1; 151.2; 159.7.

6-amino-3-methyl-1-phenyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e): IR (KBr): 3298 (N-H); 2191 (C≡N); 1589 (C=N); 1257(C-N); 1651 (C=C); 1446 (C=C)Ar; 1118 cm^{-1} (C-O-C); 1346-1446 (NO_2) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): 1.88 (s, 3H); 4.96 (s, 1H); 7.28-7.56 (m, 5H); 7.63-7.81 (m, 4H); 8.08-8.15 (m, 2H). ^{13}C NMR (63 MHz, DMSO-d_6): 12.8; 36.4; 57.3; 97.9; 120.1; 120.4; 122.4; 122.6; 126.6; 129,3; 129.6; 130.6; 134.9; 137.6; 144.2; 145.5; 146.1; 148.2; 160.0.

*6-amino-3-methyl-1-phenyl-4-(4-acetylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5f):*IR(KBr): 3413; 3205; 2179; 1654; 1589; 1396; 1026 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 1.79 (s, 3H); 2.58 (s, 3H); 4.81 (s, 1H); 7.26-7.37 (m, 3H); 7.42 (d, 2H, *J*= 8.3 Hz); 7.50 (t, 2H, *J*= 7.5 Hz); 7.79 (d, 2H, *J*= 8.5 Hz); 7.96 (d, 2H, *J*= 8.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 13.0; 36.4; 59.2; 99.4; 115.6; 120.4; 120.6; 121.0; 126.5; 129,2; 129.7; 134.4; 137.9; 144.2; 145.9; 156.7; 159.7. HRMS (ESI) m/z calcd for $C_{22}H_{19}N_4O_2$ $[M+H]^+$ 371.1503, found 371.1503.

6-amino-3-methyl-1-phenyl-4-(2-thienyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g): IR (KBr): 3403; 3168; 2878; 2305; 1609; 1319(C-N); 1161 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 2.32 (s, 3H); 5.13 (s, 1H); 6.76 (s_L, 1H); 6.91 (t, 1H, *J*= 3.4 Hz); 7.24 (d, 1H, *J*= 7.4 Hz); 7.29 (d, 1H, *J*= 5.2 Hz), 7.45 (t, 2H, *J*= 7.9 Hz), 7.71 (d, 2H, *J*= 7.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 12.0 29.9; 62.5; 100.4; 119.6; 121.1; 124.5; 124.6; 126.1; 127,2; 129.4; 142.6; 143.8; 146.3; 148.0; 159.7.

6-amino-4-(1H-indol-3-yl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h): IR (KBr): 3448 (NH); 2156 (C≡N); 1651(C=N); 1600(C=C); 1492 (C-N); 3247(-NH_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 2.20 (s, 3H); 7.08-7.12 (m, 1H); 7.22-7.28 (m, 2H); 7.36 (t, 2H, *J*= 8.3 Hz); 7.49 (d, 1H, *J*= 3.3 Hz); 7.90 (d, 2H, *J*= 9.4 Hz); 7.99 (d, 2H, *J*= 8.7 Hz); 9.75 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 11.9; 37.8; 49.9; 111.1; 111.6; 116.7; 117.2; 117.4; 118.4; 120.9; 122.1; 122.7; 126.9; 127.4; 135.2; 135.3; 137.2; 137.8; 149.2; 154.91; 161.8.

6-amino-3-methyl-4-(p-tolylphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6a): IR (KBr): 3479; 3201; 2153; 1651; 1600; 1303; 1033 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 1.78 (s, 3H,); 2.27 (s, 3H); 4.54 (s, 1H); 6.84 (s, 2H); 7.04 (d, 2H, *J*=7.9 Hz); 7.11 (d, 2H, *J*=7.7 Hz); 12.08 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 9.8; 20.7; 35.8; 57.3; 97.7; 120.8; 127.4; 129.0; 135.5; 135.7; 141.5; 154.8; 160.8.

6-amino-3-methyl-4-(4-dimethylaminophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6b): IR (KBr): 3382; 2908; 2187; 1600; 1357; 1168 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 1.79 (s, 3H); 2.87 (s, 6H); 4.32 (s, 1H); 6.18 (s, 2H); 6.59 (d, 2H, *J*= 8.6 Hz); 6.96 (d, 2H, *J*= 8,6 Hz); 11.70 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 9.7; 35.4; 58.7; 97.8; 112.0; 120.8; 127.8; 131.5; 135.4; 149.0; 154.8; 160.3.

6-amino-3-methyl-4-(4-chlorophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6c): IR (KBr): 3402; 3298; 2183; 1407; 1612; 1408; 1056; 810 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 1.77 (s, 3H); 4.52 (s, 1H); 6.57 (s, 2H); 7.12 (d, 2H, *J*=8,4 Hz); 7.22 (d, 2H, *J*=8,4 Hz); 11.93 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 9.8; 35.9; 57.5; 96.9; 120.6; 128.2; 128.7; 129.0; 129.6; 131.7; 135.8; 142.7; 154.7; 160.5; 160.8.

6-amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6d): IR (KBr): 3475; 3224; 2194; 1600; 1350; 1168 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 1.80 (s, 3H); 4.74 (s, 1H); 6.80 (s, 2H); 7.42 (d, 2H, *J*= 8.0 Hz); 8.14 (d, 2H, *J*=6.7 Hz); 12.10 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 9.7; 36.2; 56.0; 96.3 120.4; 123.6; 128.6; 135.7; 146.3; 151.8; 161.1.

6-amino-3-methyl-4-(4-formyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6e): IR (KBr): 3479; 3201; 2153; 1651; 1600; 1303; 1033 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): 1.76 (s, 3H); 4.58 (s, 1H); 6.39 (s, 2H); 7.24 (d, 2H, *J*= 8.2 Hz); 7.84 (d, 2H, *J*= 8.2 Hz); 11.95 (s, 1H). ^{13}C NMR (63 MHz, DMSO-d_6): 9.9; 36.5; 57.3; 96.6; 120.6; 127.7; 128.4; 135.5; 136.0; 149.2; 154.8; 161.0; 197.3.

4,4'-(1,4-phenylene)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (6f): IR (KBr): 3228; 3124; 2191; 1639; 1600; 1404; 1053 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 1.74 (s, 6H); 4.57 (s, 2H); 6.85 (s, 4H); 7.11 (s_L, 4H); 12.08 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 9.6; 35.8; 57.0; 120.6; 120.7; 127.5; 135.5; 142.6; 154.6; 160.7.

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