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Research Paper

[DBN][HSO_4]-Promoted facile and green synthesis of 2-Amino-4H-pyrans derivatives under microwave irradiation

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Abstract

The [DBN][HSO_4] -promoted Knoevenagel condensation followed by cyclization protocol has been developed for the first time by a successive reaction of aldehydes, dimedone and malononitrile to afford 2-Amino-4H-pyrans derivatives in high to excellent yields at room temperature. The synergic couple of microwave and ionic liquid provided the capability to allow a variability of functional groups, short reaction times, easy workup, high yields, recyclability of the catalyst, and solvent-free conditions, thus providing economic and environmental advantages.

Keywords: [DBN][HSO_4], Environmentally benign, 2-Amino-4H-pyrans, Knoevenagel condensation, Microwave irradiation

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INTRODUCTION

2-Amino-4H-pyrans derivatives have been investigated for a wide range of pharmacologic indications such as potent bioactive compounds found in dyes, cosmetics, pigments and also utilized in agrochemicals because of their biodegradable properties.[1-3] Many of the natural product isolated resemble the structure of the poly functionalized 4H pyrans,[4-5] represented several biological activities,[6] such as antibacterial,[7-11] anti-allergic,[2] antitumor,[12] calcium channel antagonists,[13] anti-HIV,[14] antitubercular,[15] antimalarial[16] and anticancer,[17] The structures of representative compounds are shown in **Fig. 1**.

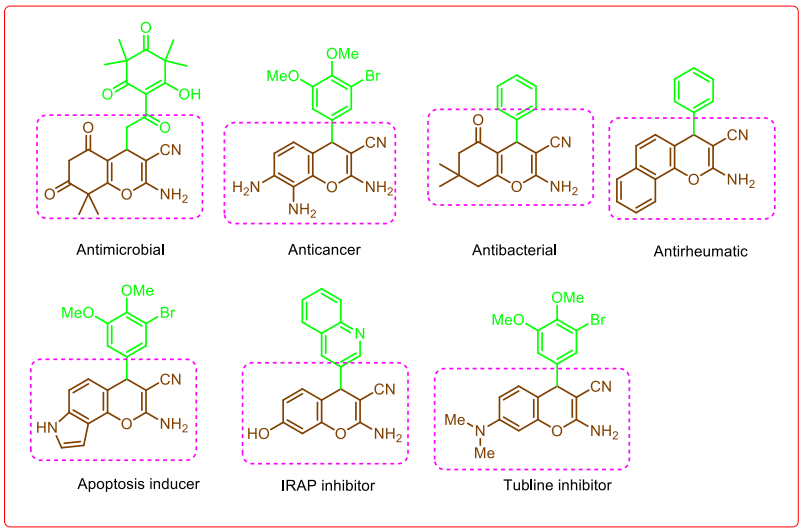


Figure 1: 2-Amino-4H-pyrans incorporated bioactive molecules.

Multicomponent reactions (MCRs) have received increasing attention due to their simplicity, efficiency, atom economy, short reaction times and the possibility for diversity-oriented synthesis.[18] Moreover, the incorporation of solvent-free methods in MCRs makes the process cleaner, safer and easier to perform.[19] Thus, the utilization of MCRs coupled with environmentally benign solvent-free condition is highly desirable. Owing to an extensive range of MCRs applications in different areas like the preparation of different structural scaffolds
and the detection of new drugs, these types of reactions have drawn considerable attention in organic synthesis and pharmaceutical chemistry.[20] Besides, Ionic liquids (ILs) have taken the attention of the chemical community all over the globe as a green alternative option to traditional ecofriendly media for catalysis, synthesis, separation, and other several chemical tasks.[21-26] ILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability.[27] ILs act as "neoteric solvents" for a wide range of industrial and chemical processes. In recent times, ILs have been originating to be valuable as environmental friendly media for countless organic revolutions.[28-29] Recently, DBN was widely used as catalysts in different research area. The combination of DBN with cation to give the formation of novel ionic liquids.[30] The large number of functionalized ILs has been considered for diverse purposes.[31]

The use of microwave irradiation in combination with ILs, which has very high heat capacity, high polarity and no vapor pressure, and their high potentiality to absorb microwaves and convert them into heat energy, may accelerate the reaction very quickly. The synergy of microwave and ionic liquid in catalyst-free methodologies for the synthesis of heterocyclic compounds has attracted much interest because of the shorter reaction time, milder conditions, reduced energy consumption and higher product selectivity and yields.[34]

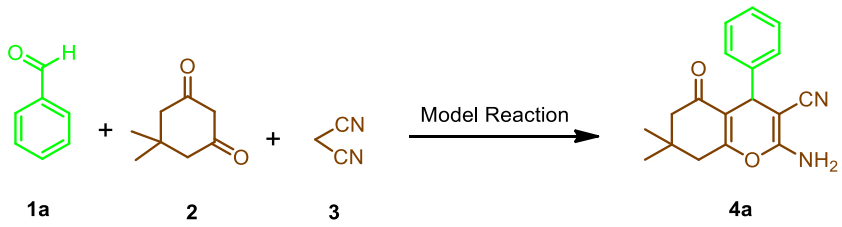
Thus, the extension of synthetic route for the construction of this molecule using an reusable, economical, nontoxic and mild catalyst is of massive importance from the academic and industrial points of view. Even though various modes have been reported in the literature, these reactions can be accomplished under a variability of tentative conditions, and several improvements have been reported in recent years, such as hexadecyltrimethylammonium bromide,[35] tetrabutylammonium bromide,[36] Mg/La mixed oxide,[37] (**S**)-proline,[38] Tetramethylguanidine-[bmim][BF4][39] and MgO.[40] Some of the new catalysts reported recently such as Ce^{V}/SiO_2,[41] $BNFe_3O_4$,[42] PPh3,[42] ZnFe2O4@ alginic acid,[43] Chitosan-CTAB,[44] MCM-41@Schiff base-Co(OAc)2,[45] Fe3O4@SiO2@TiO2,[46] Fe3O4@xanthan gum,[47] saccharose,[48] and muskmelon fruit shell (WEMFSA).[49] However, numerous of these testified methods become infected with several disadvantages such as strong acidic conditions, use of hazardous or costly reagents, long reaction times, low yields of products, and sophisticated treatment. Moreover, many of these schemes utilize organic solvents as the reaction medium. Hence, the further innovation toward contemporary reaction with easy isolation of product, reusability of catalyst, perhaps with minimal or no waste is highly attractive.

As per our investigation, the existential of this work is to begin a rapid and efficient synthetic protocol for obtaining 2-Amino-4H-pyrans derivatives under ecofriendly conditions. As an extension of emerging economic and efficient strategy to develop pharmaceutically and biologically significant molecules, herein, we reported synthesis of library of 2-Amino-4H-pyrans derivatives promoted by synergistic effect of ionic liquid and microwave irradiation without any added catalyst in good to excellent yields.

RESULTS AND DISCUSSION

Chemistry

To achieve optimized conditions protocol based on the reaction of benzaldehyde (**1a**) (1 mmol), dimedone (**2**) (1 mmol) and malononitrile (**3**) (1 mmol) as model reaction (**Scheme 1**), we checked temperatures and solvents, catalyst loading and the results of this study are summarized in **Table 1**.



Scheme 1: Model reaction

Firstly, the model reaction was performed using 20 mol% of catalyst under reflux condition in different solvents (**Table 1**). The model reaction carried out in MeOH and EtOH (**Table 1**, entry 1, and 2) was completed in 10 min with the yield of 64 and 59%, respectively. Whereas, in *tert*-BuOH (**Table 1**, entry 3), a better yield (71%) was obtained in 45 min. In H_2O and THF, decreased yields (47 and 51%) of the product **3a** were obtained (**Table 1**, entries 4-5). Conducting the reaction in Toluene, CH_3CN and DMF (**Table 1**, entries 6-8), does not improve the yield of the product. However, when the model reaction was carried out under a solvent-free condition with 20 mol% [DBN][HSO_4], a significant increase in the yield was observed (**Table 1**). Therefore it proved that the solvent-free condition is best suited for the transformation. Therefore, it can be thought that [DBN][HSO_4] is green and a superior solvent and catalyst compared to the others shown in **Table 1**.

Table 1: Optimizations of the reaction conditions for the synthesis of 2-Amino-4H-pyrans derivatives **4a**[a]

Entry	Solvent	Temp (°C)	Yield[b] (%)
1	MeOH	Reflux	64
2	EtOH	Reflux	59
3	*Tert*-BuOH	Reflux	71
4	H_2O	Reflux	47
5	THF	Reflux	51
6	Toluene	Reflux	42
7	DMF	Reflux	47
8	CH_3CN	Reflux	51
9	**Solvent-free**	**80**	**95**

[a]Reaction conditions: aldehyde **1a** (1 mmol), dimedone **2** (1 mmol), malononitrile (**3**) (1 mmol) and [DBN][HSO_4] (20 mol%) stirred at under microwave irradiation (MW = 280 W). [b]Isolated yields. Bold values are for highlighting the good result.

In the next step we examine the efficiency of ionic liquid [DBN][HSO_4] for the synthesis of 2-Amino-4H-pyrans derivatives. When change in concentration of [DBN][HSO_4] on model reaction suggest that much more effect on yield of final product. The catalyst loading study suggest that 20 mol% of [DBN][HSO_4] catalyst are best for the synthesis of final product in 95% yields (**Table 2**).

Table 2: Effect of catalyst concentration[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	5	20	65
2	10	15	74
3	15	12	86
4	20	7	95
5	25	7	95

[a]Reaction conditions: **1a** (2 mmol), **2** (1 mmol), (**3**) (1 mmol) and [DBN][HSO_4] under microwave irradiation. [b]Isolated yield.

Furthermore, we also studied the power level of microwave effect on model reactions according to these study better results of the desired product when reaction carried at 280 W (**Table 3**, entry 3). Detailed reaction conditions are shown in **Table 3.**

Table 3: Optimization of reaction condition for the synthesis of **4a** under microwave set up[a]

Entry	Power levels in Watt	Time[b] (min)	Yield[c]
1	140	20	56
2	210	15	68
3	240	12	84
4	280	10	95
5	350	10	95

[a]Reaction conditions: **1a** (2 mmol), **2** (1 mmol) and **3** (1 mmol) in the presence of [DBN][HSO_4] 20 mol% under microwave irradiation. [b]Reaction progress monitored by TLC. [c]Isolated yield.

A extremely superlative method to economic and greener preparation is recovery and recyclability of a ionic liquid. Therefore we have to check the efficiency of catalyst after recover from the reaction media during the work-up procedure. When reaction is completed, then reaction mass was pour on ice cold water to obtained fine crystal of final 2-Amino-4H-pyrans derivatives. In the last step removal H_2O from filtrate using reduced pressure to gave viscous liquid, which is on cooling to give pure ionic liquid. Recovered catalysts were reused for next four repeated cycles without considerable loss in catalytic efficiency (**Table 4**).

Table 4: Reusability of [DBN][HSO_4] ionic liquid for model reaction

Entry	Run	Time[a] (min)	Yield[b]
1	fresh	10	95
2	2	10	95
3	3	10	89
4	4	10	88
5	5	10	82

[a]Reaction progress monitered by TLC. [b]Isolated yield.

Comparison of [DBN][HSO_4] (IL) catalyst with previous reported protocol

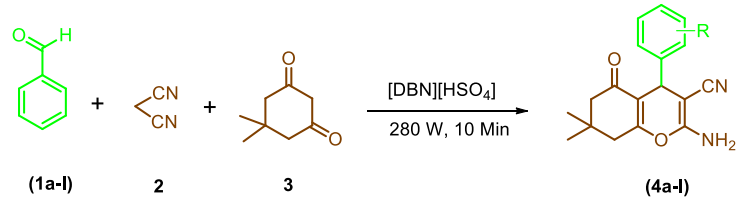
We have proved the comparison study of the [DBN][HSO_4] with other reported catalysts for the preparation of 2-Amino-4H-pyrans derivative. The comparison results proved that [DBN][HSO_4] is better catalyst in terms of excellent yield and reusability with less reaction time (**Table 5**, **entry 10**). In conclusion [DBN][HSO_4] is found to be a facile and environmentally benign protocol for the synthesis of 2-Amino-4H-pyrans derivatives.

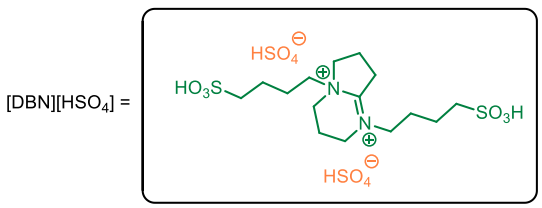
Table 5: Comparative Catalytic Performance of the [DBN][HSO_4] with Other Previously Reported Catalysts

Entry	Catalyst	Time (min)	Yield (%)	solvent/condition	Ref.
1	MNP-DMAP	1-3 h	96	Solvent free	50
2	Hydroxyapatite or modified sodium apatite	2-6 h	61-96	Solvent free, r.t	51
3	Fe_3O_4@g C_3N_4	190 min	80	EtOH, 60 °C	52
4	KF-Al_2O_3	3 hr	77	EtOH, rt	53
5	NH_4OAc	15 min	78	Neat, Grinding	54
6	MCM-41@Schiff-based- $Co(OAc)_2$	3 h	93	H_2O, 50 °C	45
7	Nano-ZnO	3 h	91	EtOH:H_2O, rt	55
8	TBAF	30 min	75	Reflux/H_2O	56
9	DABCO	2 h	94	Reflux/H_2O	57
10	PEG 1000-DAIL	60	93	Toluene	58
11	[DBN][HSO_4]	**10 min**	**95**	**[DBN][HSO_4] act as a solvent**	**Present work**

[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol) and **3** (1 mmol) in the presence of [DBN][HSO_4] 20 mol% under microwave irradiation.

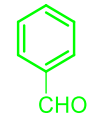
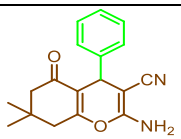
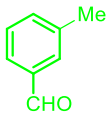
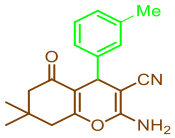
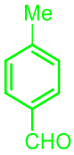
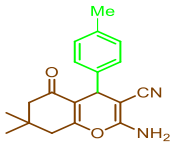
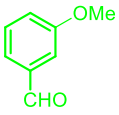
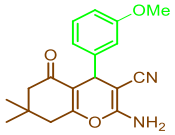
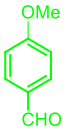
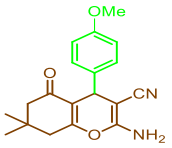
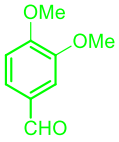
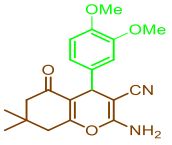
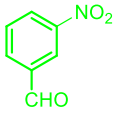
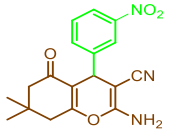
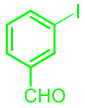
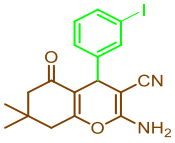
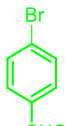
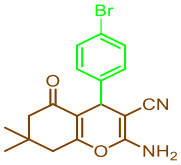
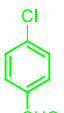
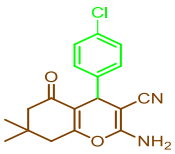
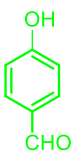
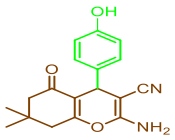
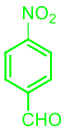
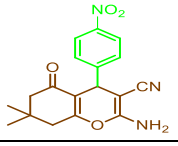
The structure of the titled product **4e** was confirmed by ^1H NMR and ^{13}C NMR. In ^1H NMR spectra of compound **4e** exhibit two singlet bands for two methyl groups at δ 0.95 and 1.06 ppm. The -CH_2-C=O protons observed at δ 2.42 ppm and CH_2 proton are observed at δ 2.21-210 ppm suggest that dimedone ring in the final compound. The aliphatic -CH proton was shown at δ 4.66 ppm suggests that formation of cyclic ring in our final compound. In the ^{13}C NMR spectrum of compound **4e**, distinct -C=O carbonyl group observed at δ 195.4 ppm. The OCH_3, CH, CH_2 and CH_3 peak observed at δ 54.0, 49.7, 40.8, 32.1, 30.9, 29.2 and 27.2 ppm confirmed that formation of compound **4e**.





Scheme 2: Synthesis of 2-Amino-4H-pyrans derivatives (**4a-l**)

Table 6: [DBN][HSO_4] catalyzed synthesis of 2-Amino-4H-pyrans derivatives[a]

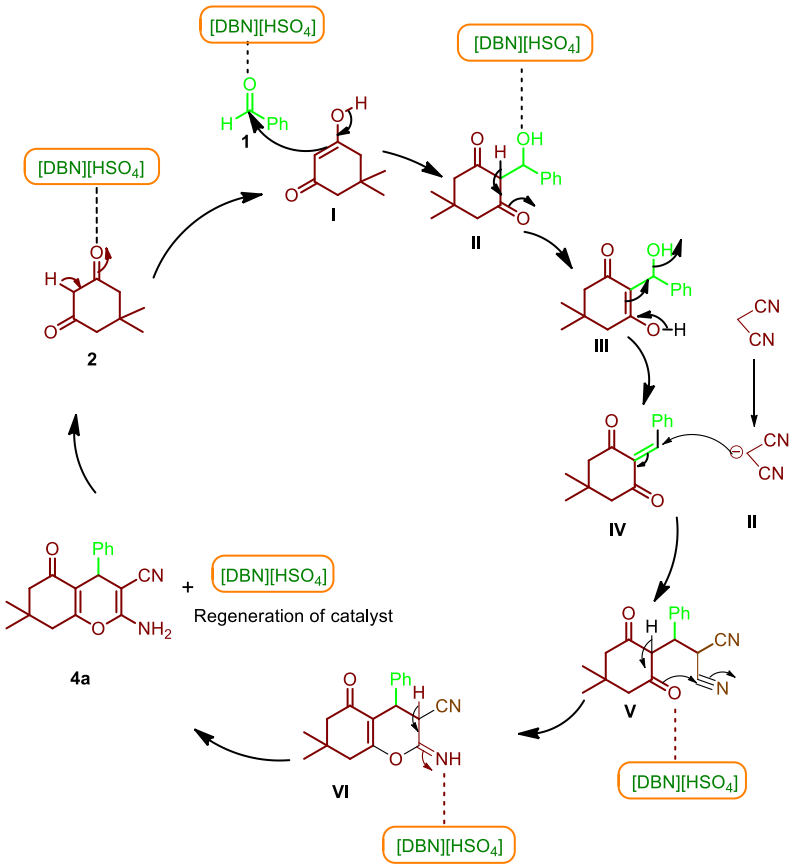
Entry	Aryl aldehyde	Xanthene	Time (min)	Yield (%)[b]	Mp (°C)[c]	
					Observed	Reported
1			10	95	231-232	231-233
2			10	89	205-206	204-206
3			10	92	214-216	213-216
4			10	88	196-198	197-200
5			10	93	195-196	196-198
6			10	90	208-210	-
7			10	84	213-214	212-214
8			10	85	270-272	-
9			10	87	202-204	201-203
10			10	91	209-211	208-210
11			10	85	204-206	203-205
12			10	85	177-178	178-180

[a]Reaction conditions: aldehydes (**1a-l**) (1 mmol), dimedone (**2**) (1 mmol), malononitrile (**3**) (1 mmol) in [DBN][HSO_4] 20 mol% stirred under microwave irradiations at 280 W; [b]isolated yields, [c]melting points are in good contact with those reported in the literature.[59-60]

In conclusion, the effectiveness and better reaction time for the model reaction was observed at 280 W by using 20 mol% of [DBN][HSO_4] as a catalyst under microwave conditions. With excellent reaction conditions in hand, the adaptableness of this approach was employing the synthesis 2-Amino-4H-pyrans analogues (**3a-l**). Various substituents on aryl aldehyde including methoxy, methyl, nitro, halogen (-Cl,-Br, -I), and hydroxyl groups were used. Synthesis of compounds (**3b-l**) using optimized reactions conditions and results are shown in **Scheme 2**. The result clearly suggest that the condensation reactions using [DBN][HSO_4] catalyst shows excellent and remarkable performance irrespective to the electron withdrawing/donating groups present on the aryl aldehydes and hence this method is facile, efficient and general for the synthesis of xanthene analogues. All the synthesized final compounds **3a-l** was well characterized by ^{1}H NMR and ^{13}C NMR spectroscopic techniques.

Plausible Reaction Mechanism

Reaction mechanism cycle for the preparation of 2-Amino-4H-pyrans analogues employing [DBN][HSO_4] is catalyst. In first step bezaldehyde activated by [DBN][HSO_4] results formation intermediate **I**. In next step [DBN][HSO_4] reacts dimedone to give enol product **II**. In the third step intermediate **I** reacts with **II** afforded addition product **III**. Further formation of alkylation product **V** from reaction of **II** and **III** to *via* removal of H_2O molecule. In the next step intramolecular cyclization of **V** to give **VI.** In the last step elimination of H_2O molecule using [DBN][HSO_4] to results formation of titled 2-Amino-4H-pyrans analogues **4a** and regeneration of catalyst. Details reaction mechanism is presented in **Scheme 3.**



Scheme 3: Reaction mechanism cycle for the preparation of compounds **4a**.

Experimental Section

Materials and Methods. All of the reagents used were of laboratory grade. Melting points of all of the synthesized analogues were resolute in an open capillary tube and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography on Merck's silica plates, and imagining was accomplished by iodine/ultraviolet light. ^{1}H NMR spectra were recorded with a Bruker AvIII HD-400 MHz spectrometer operating at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Waters UPLCTQD (ESI-MS and APCI-MS) instrument, and elemental analysis was recorded on the CHNS auto-analyzer (Thermo Fischer EA1112 SERIES). Chemical shifts (δ) are reported in parts per million using TMS as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), triplet (t); quartet (q); and multiplets (m).

Preparation of [DBN][HSO_4]

General Procedure for the Synthesis of [DBN][HSO_4] are given in supporting information.

General Procedure for Synthesis of 2-Amino-4H-pyrans Derivatives

A mixture of aldehyde **1a** (1 mmol), **2** dimedone (1 mmol) and **3** malononitrile (1 mmol) in [DBN][HSO_4] 20 mol% was stirred under microwave irradiations at 280 W; the evolution of reaction was supervised by thin-layer chromatography [ethyl acetate/*n*-hexane (3:7)] as a solvent

after a stirring reaction mixture was cooled for 15 min and a poured on crushed ice. Thus, acquired solid was filtered, dried, and purified by crystallization using ethanol as a solvent. The synthesis compound is confirmed by MP, ^{1}H NMR and ^{13}C NMR spectra.

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)

The compound **4a** was synthesized from condensation reaction **1a, 2** and **3** as white solid; Mp: 231-232 ^{o}C; Yield: 93%; ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.40 (s, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.18-7.04 (m, 3H), 4.59 (s, 1H), 2.61-2.07 (m, 4H), 1.11 (dd, *J* = 60.4, 28.0 Hz, 6H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.5, 163.0, 142.2, 136.1, 128.5, 126.5, 118.7, 49.4, 41.2, 31.5, 30.3, 28.5 and 28.3.

2-amino-7,7-dimethyl-5-oxo-4-(m-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b)

The compound **4b** was synthesized from condensation reaction **1b, 2** and **3** as white solid; Mp: 205-206 ^{o}C; Yield: 89%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.40 (s, 2H), 7.10-6.92 (m, 3H), 6.83 (d, *J* = 6.8 Hz, 1H), 4.62 (s, 1H), 2.39 (s, 2H), 2.21 (s, 3H), 2.16-2.13 (m, 2H), 1.01 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 196.4, 167.1, 140.3, 132.2, 128.9, 127.6, 125.2, 122.6, 121.2, 49.1, 39.7, 32.9, 31.1, 28.1, 25.5 and 22.3.

2-amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c)

The compound **4c** was synthesized from condensation reaction **1c, 2** and **3** as yellow solid; Mp: 214-216^{o}C; Yield: 91%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.34 (s, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.5 Hz, 2H), 4.58 (s, 1H), 2.45 (s, 2H), 2.19 (s, 3H), 2.14-2.04 (m, 2H), 1.02 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.3, 161.1, 140.2, 134.6, 127.7, 127.2, 114.6, 49.7, 39.8, 31.1, 30.4, 28.2, 26.3 and 20.0.

2-amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d)

The compound **4d** was synthesized from condensation reaction **1d, 2** and **3** as pale yellow solid; Mp: 196-198 ^{o}C; Yield: 87%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.38 (s, 2H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 6.8 Hz, 2H), 6.52 (d, *J* = 7.0 Hz, 1H), 4.52 (s, 1H), 3.64 (s, 3H), 2.40 (s, 2H), 2.05 (q, *J* = 16.5 Hz, 2H), 1.00 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.2, 161.3, 158.2, 144.6, 127.7, 119.7, 114.4, 113.2, 110.7, 54.0, 49.7, 39.7, 31.0, 30.7, 28.1, 26.2.

2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

The compound **4e** was synthesized from condensation reaction **1e, 2** and **3** as pale yellow solid; Mp: 195-196 ^{o}C; Yield: 92%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.36 (s, 2H), 7.18-7.16 (m, 2H), 7.72-7.70 (m, 2H), 4.66 (s, 1H), 3.68 (s, 3H), 2.42 (s, 2H), 2.21-2.10 (m, 2H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.4, 161.0, 156.9, 135.4, 128.2, 114.7, 112.4, 54.0, 49.7, 40.8, 32.1, 30.9, 29.2 and 27.2.

2-amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f)

The compound **4f** was synthesized from condensation reaction **1f, 2** and **3** as yellow solid; Mp: 208-210 ^{o}C; Yield: 93%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.30 (s, 2H), 6.90 (s, 1H), 6.75 (td, *J* = 8.2, 4.3 Hz, 2H), 4.65 (s, 1H), 3.81 (d, *J* = 1.8 Hz, 3H), 3.74 (d, *J* = 1.7 Hz, 3H), 2.40 (s, 2H), 2.23–2.04 (m, 2H), 1.04 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 189.8, 167.5, 153.6, 151.8, 140.6, 131.6, 126.2, 125.6, 119.8, 54.4, 53.6, 49.1, 41.1, 31.8, 29.9, 28.2 and 26.1.

2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g)

The compound **4g** was synthesized from condensation reaction **1g, 2** and **3** as red solid; Mp: 213-214^{o}C; Yield: 87%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.02–7.85 (m, 2H), 7.74 (d, *J* = 6.7 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.28 (s, 2H), 4.78 (s, 1H), 2.45 (s, 2H), 2.14 (q, *J* = 16.1 Hz, 2H), 1.04 (s, 3H), 0.94 (s, 3H), ^{13}C NMR (101 MHz, cdcl$_3$) δ 196.4, 166.9, 146.5, 140.4, 130.5, 127.5, 126.2, 124.8, 119.6, 50.9, 40.6, 31.9, 30.2, 28.5 and 26.1.

92-amino-4-(3-iodophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h)

The compound **4h** was synthesized from condensation reaction **1h, 2** and **3** as red solid; Mp: 270-272 ^{o}C; Yield: 90%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.51 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.8 Hz, 1H), 4.54 (s, 1H), 2.39 (s, 2H), 2.26–2.07 (m, 2H), 1.05 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 190.0, 164.8, 139.4, 131.5, 128.0, 126.6, 126.3, 122.8, 111.4, 49.4, 40.5, 32.0, 29.9, 28.2 and 26.4.

2-amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4i)

The compound **4i** was synthesized from condensation reaction **1i, 2** and **3** as red solid; Mp: 202-204 ^{o}C; Yield: 91%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.42 (s, 2H), 7.30 (d, *J* = 6.9 Hz, 2H), 7.15 (d, *J* = 6.8 Hz, 2H), 4.61 (s, 1H), 2.41 (s, 2H), 2.18 (q, *J* = 16.4 Hz, 4H), 1.08 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.2, 161.4, 142.1, 130.0, 129.1, 119.1, 114.1, 49.6, 39.8, 31.1, 30.5, 28.2 and 26.2.

2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j)

The compound **4j** was synthesized from condensation reaction **1j, 2** and **3** as pale yellow solid; Mp: 209-211 ^{o}C; Yield: 92%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.42 (s, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.18–7.11 (m, 2H), 4.68 (s, 1H), 2.42 (s, 2H), 2.15 (q, *J* = 16.3 Hz, 4H), 1.07 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 195.2, 161.4, 141.7, 130.9, 128.7, 127.1, 114.1, 49.6, 39.7, 31.1, 30.4, 28.2 and 26.2.

***2-amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile* (4k)**

The compound **4k** was synthesized from condensation reaction **1k, 2** and **3** as red solid; Mp: 204-206 ^{o}C; Yield: 85%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.31 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.54 (d, *J* = 7.8 Hz, 2H), 4.66 (s, 1H), 2.46 (s, 4H), 2.21 (q, *J* = 16.4 Hz, 4H), 1.08 (s, 6H), 0.99 (s, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 196.3, 161.4, 153.7, 134.4, 128.2, 114.8, 114.2, 49.7, 39.8, 31.2, 29.9, 28.1 and 26.3.

2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l)

The compound **4l** was synthesized from condensation reaction **1l, 2** and **3** as white solid; Mp: 177-178 ^{o}C; Yield: 84%; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.67 (s, 2H), 5.46 (s, 1H), 3.31 (s, 2H), 2.50 (s, 4H), 2.23 (s, 4H), 1.22 (s, 1H), 1.03 (d, *J* = 18.0 Hz, 12H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 192.3, 164.5, 110.7, 49.4, 39.7, 33.5, 32.0, 30.2, 28.2, 26.4, 24.9, 23.5, 22.2, 22.1 and 22.0.

CONCLUSION

In conclusion, an environmentally and highly efficient green methodology has been established for the synthesis of functionalized 2-Amino-4H-pyrans derivatives using an inexpensive and recoverable [DBN][HSO$_4$] catalytic solvent-free under microwave irradiations. This, to the best of our

knowledge, has no examples. This reaction scheme exposes a number of advantages, such as uniqueness, high atom efficiency, mild reaction conditions, clean reaction profiles, easy workup procedure and Eco friendliness. Furthermore, the prevention of hazardous organic solvents during the entire procedure (synthesis, ionic liquid preparation, and workup
procedure) makes it a convenient and attractive method for the synthesis of these important compounds.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

1. Morinaka Y, Takahashi K, Jpn. Patent 1977; JP52017498
2. Witte EC, Neubert P, Roesch A, Ger. Offen. 1986; DE3427985.
3. Hafez EA, Elnagdi MH, Elagamey AG, El-Taweel, FMA, Nitriles in heterocyclic synthesis: novel synthesis of benzo[c]coumarin and of benzo[c]pyrano[3,2-cc]quinoline derivatives, Heterocycles 1987; (26) 903-907
4. Kuthan J, Pyrans, Thiopyrans, and Selenopyrans, Adv. Heterocycl. Chem. 1983; (34): 145-303
5. Hatakeyama S, Ochi N, Numata H, Takano S, A new route to substituted 3-methoxycarbonyldihydropyrans; enantioselective synthesis of (–)-methyl elenolate, J. Chem. Soc. Chem. Commun. 1988; (17): 1202-1204
6. Zamocka J, Misikova E, Durinda J, Pharmazie 1991; (46): 610-611
7. Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES, Huang Z, Structure-based discovery of an organic compound that bind Bc1-2 protein and induces apoptosis of tumor cells. Proc. Natl. Acad. Sci. U. S. A. 2007; (97): 7124-7129
8. El-Saghier AMMM, Naili B, Rammash BK, Saleh NA, Kreddan KM, Synthesis and antibacterial activity of some new fused chromenes, Arkivoc 2007; (16): 83-91
9. Kumar RR, Perumal S, Senthilkumar P, Yogeeswari P, Sriram D, An atom efficient, solvent-free, green synthesis and antimycobacterial evaluation of 2-amino-6-methyl-4-aryl-8-[(*E*)-arylmethylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles, Bioorg. Med. Chem. Lett. 2007; 23(17): 6459-6462
10. Fairlamb IJSL, Marrison R, Dickinson JM, Lu FJ, Schmidt JP, 2-pyrones possessing antimicrobial and cytotoxic activities, Bioorg. Med. Chem. 2004; 12(15): 4285-4299
11. Aytemir MD; Erol DD, Hider RC, Synthesis and Evaluation of Antimicrobial Activity of New 3-Hydroxy-6-methyl-4-oxo-4*H* -pyran-2-carboxamide Derivatives, Turk. J. Chem. 2003; (27): 757-764
12. Kidwai M, Saxena S, Khan MKR, Thukral SS, Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents, Bioorg. Med. Chem. Lett. 2005; 15(19): 4295-4298
13. Suarez M, Salfran E, Verdecia Y, Ochoa E, Alba L, Martin N, Martinez R, Quinteiro M, Seoane C, Novoa H, Blaton N, Peeters OM, De RC, X-Ray and theoretical structural study of novel 5,6,7,8-tetrahydrobenzo-4H-pyrans, Tetrahedron 2002; (58): 953-960
14. Kumari G, Nutan, Modi M, Gupta SK, Singh R.K, Rhodium(II) acetate-catalyzed stereoselective synthesis, SAR and anti-HIV activity of novel oxindoles bearing cyclopropane ring, Eur. J. Med. Chem., 2011; (46): 1181-1188
15. Vintonyak VV, Warburg K, Kruse H, Grimme S, Hubel K, Rauh, D, Waldmann H, Identification of Thiazolidinones Spiro-Fused to Indolin-2-ones as Potent and Selective Inhibitors of the Mycobacterium tuberculosis Protein Tyrosine Phosphatase B, Angew. Chem., Int. Ed., 2010; 49(34): 5902-5905
16. Yeung BKS, Zou B, Rottmann MS, Lakshminarayana B, Ang SH, Leong SY, Tan J, Wong J, Keller-Maerki S, Fischli C, Goh A, Schmitt EK, Krastel P, Francotte E, Kuhen K, Plouffe D, Henson K, Wagner T, Winzeler EA, Petersen F, Brun R, Dartois V, Diagana TT, Keller TH, Spirotetrahydro β-Carbolines (Spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria, J. Med. Chem., 2010; 53(14): 5155-5164
17. Ding K, Lu Y, Nikolovska-Coleska Z, Qiu S, Ding Y, Gao W, Stuckey J, Krajewski K, Roller PP, Tomita Y, Parrish DA, Deschamps JR, Wang S, Structure-based design of potent non-peptide MDM2 inhibitors. J. Am. Chem. Soc., 2005; 127(29): 10130-10131
18. Cioc RC, Ruijter E, Orru RVA, Multicomponent reactions: advanced tools for sustainable organic synthesis, Green Chem., 2014; 16(6): 2958-2975
19. Isambert N, Duque MMS, Plaquevent JC, Genisson Y, Rodriguez J, Constantieux T, Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis. Chem. Soc. Rev., 2011; 40(3): 1347-1357
20. Norouzi F, Javanshir S, Magnetic γFe_2O_3@Sh@Cu_2O: an efficient solid-phase catalyst for reducing agent and base-free click synthesis of 1,4-disubstituted-1,2,3-triazoles, BMC Chem. 2020; (14): 1
21. Welton T, Ionic Liquids in Green Chemistry, Green Chem. 2011; (13): 225
22. Wang C, Guo L, Li H, Wang Y, Weng J, Wu L, Preparation of simple ammonium ionic liquids and their application in the cracking of dialkoxypropanes, Green Chem. 2006; 8(7): 603-607
23. Wang C, Zhao W, Li H, Guo L, Solvent-free synthesis of unsaturated ketones by the Saucy–Marbet reaction using simple ammonium ionic liquid as a catalyst, Green Chem. 2009; 11(8): 843-847
24. Weng J, Wang C, Li H, Wang Y, Novel quaternary ammonium ionic liquids and their use as dual solvent-catalysts in the hydrolytic reaction, Green Chem. 2006; 8(1): 96-99
25. Dupont J, de Souza RF, Suarez PAZ, Ionic Liquid (Molten Salt) Phase Organometallic Catalysis, Chem. Rev. 2002; 102(10): 3667-3692
26. Sheldon R, Catalytic reactions in ionic liquids, Chem. Commun. 2001: (23): 2399-2407
27. Dolzhenko AV, Dolzhenko AV, Green Solvents for Eco-Friendly Synthesis of Bioactive Heterocyclic Compounds. Green Synthetic Approaches for Biologically Relevant Heterocycles, Elsevier: Perth, WA, Australia, 2015; 101-139
28. Jiang T, Gao H, Han B, Zhao G, Chang Y, Wu W, Gao L, Yang G, Ionic liquid catalyzed Henry reactions, Tetrahedron Lett. 2004; 45(12): 2699-2701
29. Wilkes JS, A short history of ionic liquids-from molten salts to neoteric solvents, Green Chem. 2002; 4(2): 73-80
30. Zhu X, Song M, Xu Y, DBU-Based Protic Ionic Liquids for CO_2 Capture, ACS Sustain. Chem. Eng. 2017; 5(9): 8192-8198
31. Carta A, Loriga M, Zanetti S, Sechi LA, Quinoxalin-2-ones. Part 5. Synthesis and antimicrobial evaluation of 3-alkyl-, 3 halomethyl-and 3-carboxyethylquinoxaline-2-ones variously substituted on the benzo-moiety. IL Farmaco 2003; (58): 1251-1255
32. Wei L, Cheng W, Xia Y, Synthesis of Cyclic Carbonate Catalyzed by DBU Derived Basic Ionic Liquids, Chin. J. Chem. 2018; 36(4): 293-298
33. Cole AC, Jensen JL, Ntai I, Tran KLT, Weave KJ, Novel Brønsted acidic ionic liquids and their use as dual solvent-catalysts, J. Am. Chem. Soc. 2002; 124(21): 5962-5963
34. Shi H, Zhu W, Li H, Liu H, Zhang M, Yan Y, Wang Z, Microwave-accelerated esterification of salicylic acid using Brönsted acidic ionic liquids as catalysts. Catal. Commun. 2010; 11(7): 588-591
35. Jin TS, Wang AQ, Wang X, Zhang JS, Li TS, A Clean One-pot Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives Catalyzed by Hexadecyltrimethyl Ammonium Bromide in Aqueous Media, Synlett 2004; (5): 871-873
36. Jin TS, Xiao JC, Wang SJ, Li TS, Song XR, An Efficient and Convenient Approach to the Synthesis of Benzopyrans by a Three-Component Coupling of One-Pot Reaction, Synlett 2003; (13): 2001-2004

37. Babu NS, Pasha N; Venkateswara KT, Prasad PS, Lingaiah N, A heterogeneous strong basic Mg/La mixed oxide catalyst for efficient synthesis of poly functionalized pyrans. Tetrahedron Lett. 2008; 49(17): 2730-2733
38. Balalaie S, Bararjanian M, Amani AM, Movassagh B, (S)-Proline as a neutral and efficient catalyst for the one-pot synthesis of tetrahydrobenzo [b] pyran derivatives in aqueous media, Synlett 2006; (2): 263-266
39. Peng Y, Song G, Huang F, Tetramethylguanidine-[bmim][BF4]. An Efficient and Recyclable Catalytic System for One-Pot Synthesis of 4H-Pyrans, Monatsh. Chem. 2005; (136): 727-731
40. Kumar D, Reddy VB, Mishra BG, Rana RK, Nadagouda MN, Varma RS, Nanosized magnesium oxide as catalyst for the rapid and green synthesis of substituted 2-amino-2-chromenes, Tetrahedron 2007; 63(15): 3093-3097
41. Maddila SN, Maddila S, van Zyl WE, Jonnalagadda SB, Ceria–Vanadia/Silica-Catalyzed Cascade for C-C and C-O Bond Activation: Green One-Pot Synthesis of 2-Amino-3-cyano-4*H*-pyrans, Chemistry Open 2016; 5(1): 38-42
42. Molla A, Hussain S, Base free synthesis of iron oxide supported on boron nitride for the construction of highly functionalized pyrans and spirooxindoles, RSC Adv. 2016; 6(7): 5491-5502
43. Ramadoss H, Kiyani H, Mansoor SS, Triphenylphosphine Catalysed Facile Multicomponent Synthesis of 2-Amino-3-Cyano-6-Methyl-4-Aryl- 4*H*-Pyrans, Iran. J. Chem. Chem. Eng. 2017; 36(1): 19-26
44. Maleki A, Varzi Z, Hassanzadeh-Afruzi F, Preparation and characterization of an eco-friendly ZnFe2O4@ alginic acid nanocomposite catalyst and its application in the synthesis of 2-amino-3-cyano-4H-pyran derivatives, Polyhedron 2019; (171): 193-202
45. Pan S, Li P, Xu G, Guo J, Ke L, Xie C, Zhang Z, Hui Y, MCM-41@Schiff base-Co(OAc)$_2$ as an efficient catalyst for the synthesis of pyran derivatives, Res. Chem. Intermed. 2020; (46): 1353-1371
46. Khazaei A, Gholami F, Khakyzadeh V, Moosavi-Zare AR, Afsar J, Magnetic core-shell titanium dioxide nanoparticles as an efficient catalyst for domino Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and dimedone, RSC Adv. 2015; 5(19): 14305
47. Esmaeili MS, Khodabakhshi MR, Maleki A, Varzi Z, Green, Natural and Low Cost Xanthum Gum Supported Fe_3O_4 as a Robust Biopolymer Nanocatalyst for the One-Pot Synthesis of 2-Amino-3-Cyano-4*H*-Pyran Derivatives, Polycycl. Aromat. Compd. 2020; https://doi.org/10.1080/10406638.2019.1708418.
48. Maghsoodlou, MT, Hazeri N, Lashkari M, Shahrokhabadi FN, Naghshbandi B, Kazemidoost MS, Rashidi M, Mir F, Kangani M, Salahi S, Saccharose as a new, natural, and highly efficient catalyst for the one-pot synthesis of 4,5-dihydropyrano[3,2-*c*]chromenes, 2-amino-3-cyano-4*H*-chromenes, 1,8 dioxodeca hydroacridine, and 2-substituted benzimidazole derivatives, Res. Chem. Intermed. 2015; (41): 6985-6997
49. Hiremath PB, Kantharaju K, An Efficient and Facile Synthesis of 2-Amino-4*H*-pyrans &Tetrahydrobenzo[*b*]pyrans Catalysed by WEMFSA at Room Temperature, Chemistry Select. 2020; 5(6): 1896-1906
50. Fihri A, Len C, Varma RS, Solhy A, Hydroxyapatite: A review of syntheses, structure and applications in heterogeneous catalysis, Coord. Chem. Rev. 2017; 347 (48): 61
51. Dangolani SK, Panahi F, Nourisefat M, Khalafi-Nezhad A, 4-Dialkylaminopyridine modified magnetic nanoparticles: as an efficient nano-organocatalyst for one-pot synthesis of 2-amino-4H-chromene-3-carbonitrile derivatives in water, RSC Adv. 2016; (6): 92316-92324
52. Najmedin A, Ahooie TS, Hashemi MM, Yavari I, Magnetic Graphitic Carbon Nitride-Catalyzed Highly Efficient Construction of Functionalized 4H-Pyrans, Synlett 2018; 29(05): 645-649
53. Kharbangar I, Rohman R, Mecadon H, Myrboh B, KFAl2O3 as an Efficient and Recyclable Basic Catalyst for the Synthesis of 4H-Pyran-3-Carboxylates and 5-Acetyl-4H Pyrans. Int. J. Org. Chem. 2012; (2): 282-286
54. Smits R, Belyakov S, Plotniece A, Dubur G, Synthesis of 4*H*-Pyran Derivatives Under Solvent-Free and Grinding Conditions, Synth. Commun. 2013; 43(4): 465-475
55. Bhattacharyya P, Pradhan K, Paul S, Das AR, One-pot synthesis of dihydropyrano[2,3-*c*]chromenes via a three component coupling of aromatic aldehydes, malononitrile, and 3-hydroxycoumarin catalyzed by nano-structured ZnO in water: a green protocol, Tetrahedron Lett. 2012; 52(36): 4687-4641
56. Gao S.; Tsai CH, Tseng C, Yao C, Fluoride ion catalyzed multicomponent reactions for efficient synthesis of 4H-chromene and N-arylquinoline derivatives in aqueous media, Tetrahedron 2008; 64(38): 9143-9149
57. Tahmassebi D, Bryson JA, Binz SI, 1,4-Diazabicyclo[2.2.2]octane as an Efficient Catalyst for a Clean, One-Pot Synthesis of Tetrahydrobenzo[b]pyran Derivatives via Multicomponent Reaction in Aqueous Media, Synth. Commun. 2011; 41(18): 2701-2711
58. Zhi H, Lu C, Zhang Q, Luo J, A new PEG-1000-based dicationic ionic liquid exhibiting temperature-dependent phase behavior with toluene and its application in one-pot synthesis of benzopyrans, Chem. Commun. 2009; (20): 2878-2880
59. Shirini F, Goli-Jolodar O, Akbari M, Seddighi M, Preparation, characterization, and use of poly(vinylpyrrolidonium) hydrogen phosphate ([PVP-H]H2PO4) as a new heterogeneous catalyst for efficient synthesis of 2-amino-tetrahydro-4H-pyrans, Res Chem Inter. 2016; (42): 4733-4749
60. Amirnejat S, · Nosrati A, · Peymanfar R, · Javanshir S, Synthesis and antibacterial study of 2-amino-4H-pyrans and pyrans annulated heterocycles catalyzed by sulfated polysaccharide-coated BaFe12O19 nanoparticles, Res. Chem. Inter. 2020; (46): 3683-3701