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Fruit juice of *Citrus limon* as a biodegradable and reusable catalyst for facile, eco-friendly and green synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones and dihydropyrano[2,3-*c*]-pyrazole derivatives

Rajesh H. Vekariya[1] · Kinjal D. Patel[1] · Hitesh D. Patel[1]

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Abstract Fruit juice of *Citrus limon* (lemon juice) has been utilized as a natural and renewable catalyst for the green and environmentally friendly preparation of 3,4-disubstituted isoxazol-5(4*H*)-one derivatives and 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives in hydroalcoholic media at 90 °C. A one-pot three-component reaction of β-oxoesters with hydroxylamine hydrochloride and various aromatic aldehydes afforded 3,4-disubstituted isoxazole-5(4*H*)-one derivatives in excellent yields. The rate constant ($K = 6.12 \times 10^{-2}$ min^{-1} at 25 °C) for the formation of isoxazole derivative (**1g**) was also calculated. Similarly, a four-component reaction of ethyl acetoacetate, hydrazine hydrate, aryl aldehydes, and malononitrile gives pyrano[2,3-*c*]-pyrazole derivatives in very good yields. After completion of the reaction, the products were isolated by simple filtration. A simple work-up process, high product yields, short reaction times, and the use of an inexpensive and biodegradable catalyst are the advanced rewards of the present protocol.

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✉ Hitesh D. Patel
drhiteshpatel1@gmail.com

[1] Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India

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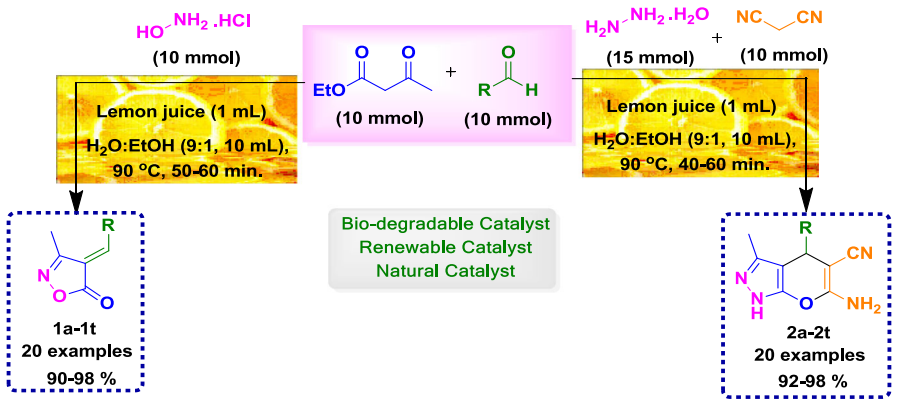
Graphical Abstract



Keywords Isoxazole-5(4*H*)-ones · Pyrano[2,3-*c*]-pyrazole · Lemon juice · One-pot · Multi-component reaction · Homogeneous catalysis · Green synthesis

Introduction

Recently, multi-component reactions (MCRs) have received much attention in the field of synthetic organic chemistry as well as medicinal chemistry, because the strategies of MCR offer significant advantages over conventional synthetic methodologies [1]. Therefore, planning reactions that achieve multi-bond formation in one operation is becoming one of the leading challenges in the field of green organic synthesis [2]. The approach of MCRs delivers numbers of advantages over conventional transformations, such as shorter reaction times, higher product yields, lower costs, an easy work-up process, and environmental being [3].

Isoxazole scaffolds are important class of heterocyclic compounds, and they are predominant in nature and display a wide range of biological and pharmaceutical activities such as β-adrenergic receptor antagonists [4], immunosuppressive [5], anti-inflammatory [6], antibacterial [7], HDAC inhibitors [8], antifungal **(I)** [9], antitumor [10], antioxidant [11], antiprotozoal [12], antiviral [13], anti-tubercular [14], anti-inflammatory [15], anti-HIV [16], analgesic [17], antibiotics [18, 19], and anti-androgens **(II)** [20, 21]. Furthermore, compound **(III)** (drazoxolon) [22] and compound **(IV)** [23], which possess an isoxazolone ring, have been investigated as a fungicide and an inhibitor of tumor necrosis factor-alpha (TNF-α), respectively. In addition, the isoxazole-5(4*H*)-one scaffold can also be found as the essential moiety of compound **(V)** (merocyanine dyes) (Fig. 1), which are used in optical recording and nonlinear optical research [24].

4*H*-Pyrans analogue heterocyclic scaffolds signify a privileged structural motif that is well-distributed in naturally occurring compounds [25]. This important class of heterocyclic compounds displays a broad spectrum of biological activities (Fig. 2) such as anticancer [26], anti-HIV [27], anti-inflammatory [28], antimalarial

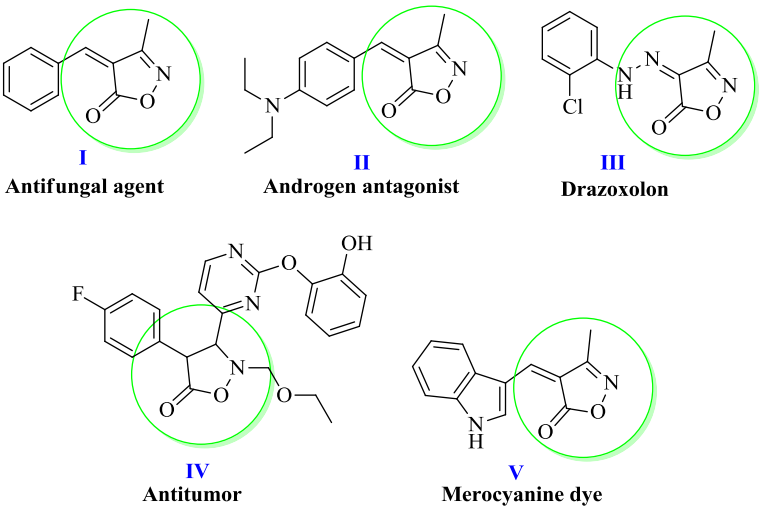


Fig. 1 Some biologically important isoxazolone compounds

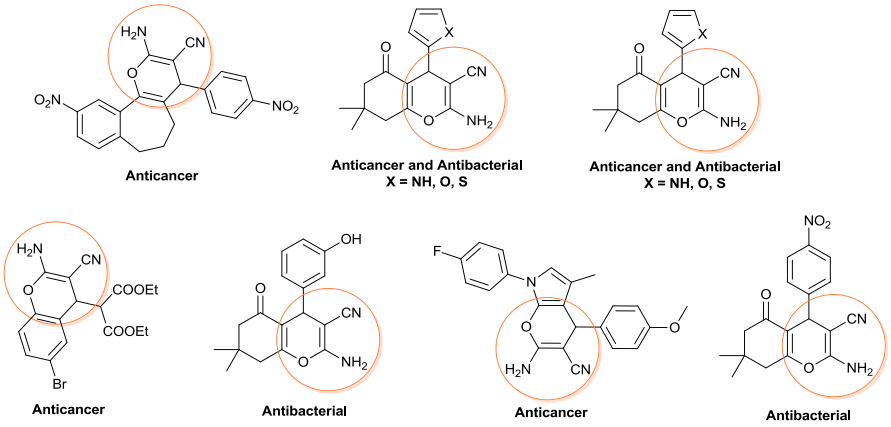


Fig. 2 Biologically active dihydropyrano derivatives

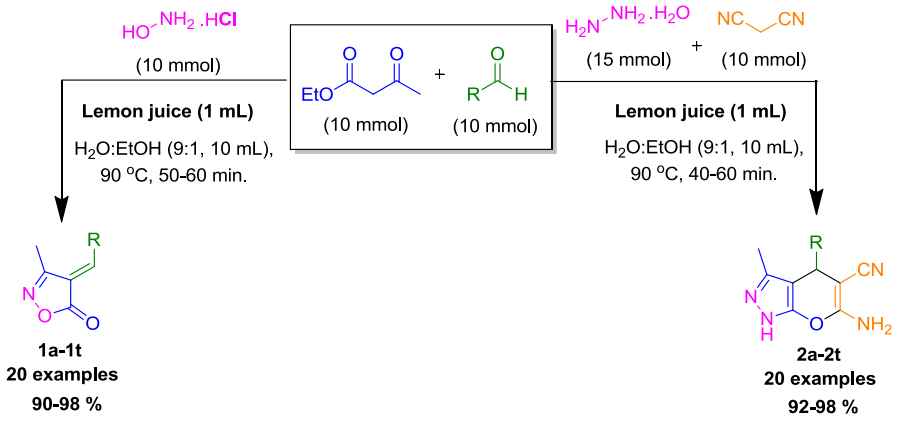
[29], antimicrobial [30], antiviral [31], molluscicidal [32], anticancer, fungicidal, analgesic, vasodilator, hypotensive, hypoglycemic [33], kinase inhibitor properties [34], and anti-proliferative [35]. Several pyrano[2,3-*c*]pyrazoles are reported to have beneficial biological activities such as anti-inflammatory and analgesic properties [36]. In addition, the biological activity of fused azoles has led to exhaustive research on their synthesis [37].

Due to the highly potent biological activities, isoxazoles and pyrano[2,3-*c*]-pyrazole scaffolds are attractive synthetic targets for investigation of efficient and green synthetic protocols for their synthesis. In the literature, α,β-unsaturated isoxazol-5(4*H*)-one derivatives have been prepared via a three-component

condensation of β-oxoesters, hydroxylamine hydrochloride and aromatic aldehydes by use of catalytic amounts of sodium benzoate [38], sodium sulfide [39], sodium silicate [40], catalyst-free/grinding or heating [41], nano $Fe2O_3$, clinoptilolite, and $H3PW12O_{40}$ [42], *N*-bromosuccinimide (NBS) [43], potassium hydrogen phthalate (KHP) [44], Ag/SiO_2 [45], 2-Hydroxy-5-sulfobenzoic acid (2-HSBA) [46], phthalimide-*N*-oxyl salts [47], tartaric acid [48], tetrabutylammonium perchlorate (TBAP) [49], potassium phthalimide (PPI) [50], sodium saccharin [51], pyridine [52–54], DABCO [55], CH3COONa [56], sodium ascorbate [57], sodium tetraborate [58], and boric acid [59]. Many of these methods have some limitations and drawbacks, such as the use of toxic reagents, strong acidic or basic conditions, expensive reagents and catalysts, a tedious work-up process, low product yields, and long reaction times. Similarly, several protocols have also been developed for the synthesis of pyrano[2,3-*c*]-pyrazoles through a one-pot synthetic approach that is of great attention. In this context, some catalysts have been used to promote these condensations, such as maltose [60], saccharose [61], urea [62], lipase [63], meglumine [64], diaminocyclohexane-thiourea [65], isonicotinic acid [66], acetic acid [67], DBU [68], DABCO [69], piperidine and pyridine [70], pyrrolidine [71], citric acid [72], disulfonic acid imidazolium chloroaluminate [73], sodium benzoate [74], nano-titania sulfuric acid [75], nano-ZnO [76], CuO-CeO2nanocomposite [77], nano-titania-supported preyssler-type heteropolyacid [78], nano TiO_2 [79], nano-$CuFe2O_4$ [80], nickel nanoparticles [81], nano-CuI [82], $Fe3O_4$ nanoparticles [83], SnO_2 quantum dots [84], amberlyst A21 [85], cetyltrimethylammonium chloride (CTACl) [86], NaOH [87], tetraethylammonium bromide (TEABr) [88], $CeCl_3$ [89], CSF [90], poly(4-vinylpyridine) [91], borax [92], silica-supported tetramethylguanidine [93], I_2 [94], cerium ammonium nitrate (CAN) [95], and tungstate sulfuric acid (TSA) [96].

In accordance with the demand for more sustainable chemistry, the search for more environmentally benign forms of catalysis has received irresistible attention, and one of the leading contestants for environmentally acceptable alternatives is the category of biodegradable and renewable materials [97–99]. Already, several biodegradable materials, such as chitosan [100, 101], gluconic acid [102, 103], cellulose sulfuric acid [104, 105], xanthan sulfuric acid [106, 107], starch sulfuric acid [108], sulfuric acid-modified PEG (PEG-OSO3H) [109, 110], melamine trisulfonic acid (MTSA) [111, 112], and eggshell [113] have been proposed as catalysts in many organic transformations. In addition, a number of organic reactions using natural catalysts such as clay [114–117], natural phosphate [118, 119], animal bone [120] and also various fruit juices [121] are reported in the literature. Due to their acidic nature, aqueous fruit juices like those from lemon [122–128], pineapple [129, 130], coconut [131], *Acacia concinna* [132], *Sapindus-trifolistus* [133] and *Tamarindusindica* [134, 135] have been found to be a suitable replacement for various homogeneous acid catalysts.

Citrus limonium, *Citrus aurantium*, and *Citrus indica* are some of the important species of the citrus family, commonly known as the lemon. The lemon is indigenous to the northwestern regions of India and is also cultivated in Asia and Europe. It is now widely grown in all tropical and subtropical countries. In India, it is also cultivated in home gardens. The main ingredients of the extract of *Citrus*



Scheme 1 Synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones and 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles catalyzed by lemon juice as a *green catalyst*. (Color figure online)

limonium species of lemon are moisture (85 %), carbohydrates (11.2 %), citric acid (5–7 %), protein (1 %), ascorbic acid or vitamin-C (0.5 %),fat (0.9 %), minerals (0.3 %), fibers (1.6 %), and some other organic acids [122]. The juice is soluble in water. Due to the presence of citric and ascorbic acids, lemon juice is acidic (pH = 2–3) in nature, and thus it works as an acid catalyst in organic reactions. Considering the above facts, we performed research on the development of green and sustainable protocols for the preparation of important organic compounds [136–138], and herein we report lemon juice as a new biodegradable and renewable natural catalyst for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones from the one-pot cyclocondensation of aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride in aqueous ethanol at 90 °C (Scheme 1). Similarly, we have demonstrated the synthesis of a series of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles via the one-pot, four-component reaction of ethyl acetoacetate (10 mmol), hydrazine hydrate (15 mmol, 80 %), aromatic aldehydes (10 mmol), and malononitrile (10 mmol) in water–ethanol media at 90 °C using lemon juice as a catalyst (Scheme 1).

Results and discussion

In the beginning, the optimal conditions for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (**1a–1t**) were investigated. Conducting a reaction between ethyl acetoacetate, hydroxylamine hydrochloride, and 4-hydroxybenzaldehyde in the presence of 1 mL of lemon juice as a catalyst for 60 min at refluxing temperature in different solvents such as methanol, ethanol, toluene, acetonitrile, dichloromethane, ethyl acetate, chloroform, water, and a mixture of water:ethanol (9:1) as well as water:acetone (9:1) resulted in the corresponding product **1b** in 65, 70, 27, 45, 36, 34, 31, 86, 94, and 67 % of yields, respectively (Table 1, entries 4–13). Among all of these solvents, water:ethanol (9:1) was found to be the best

Table 1 Optimization of the reaction conditions for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones

Entry	Solvent (10 ML)	Catalyst loading (mL)	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	–	r.t.	60	Trace
2	–	–	90 °C	60	24
3	–	1.00	90 °C	60	62
4	MeOH	1.00	Reflux	60	65
5	EtOH	1.00	Reflux	60	70
6	Toluene	1.00	Reflux	60	27
7	MeCN	1.00	Reflux	60	45
8	$CH2Cl_2$	1.00	Reflux	60	36
9	EtOAc	1.00	Reflux	60	34
10	$CHCl_3$	1.00	Reflux	60	31
11	H2O	1.00	90 °C	60	86
12	**H2O:EtOH (9:1)**	**1.00**	**90 °C**	**55**	**94**
13	H2O:Acetone (9:1)	1.00	Reflux	60	67
14	H2O:EtOH (5:5)	1.00	90 °C	60	84
15	H2O:EtOH (9:1)	1.00	40 °C	60	45
16	H2O:EtOH (9:1)	1.00	50 °C	60	58
17	H2O:EtOH (9:1)	1.00	60 °C	60	68
18	H2O:EtOH (9:1)	1.00	70 °C	60	77
19	H2O:EtOH (9:1)	1.00	80 °C	60	89
20	H2O:EtOH (9:1)	0.25	90 °C	60	52
21	H2O:EtOH (9:1)	0.50	90 °C	60	70
22	H2O:EtOH (9:1)	0.75	90 °C	60	82
23	H2O:EtOH (9:1)	1.25	90 °C	60	94

Bold letters in the table demonstrated the optimize reaction conditions

[a] Isolated product yield

reaction media in terms of the yield of the product and time of completion in comparison with other solvents. The amount of lemon juice required for this transformation was also evaluated. On conducting the same reaction in the absence of solvent at room temperature (r.t.), only trace amounts of yield of (**1b**) was achieved even after a prolonged reaction (Table 1, entry 1). Increasing the reaction temperature from r.t. to 90 °C had considerable influence on the yield of the product (Table 1, entry 2). In addition, we also carried out the model reaction using 1 mL lemon juice as a catalyst under solvent-free conditions (Table 1, entry 3). However, only moderate yield (62 %) of the product (**1b**) was observed, which allowed us to conclude that solvent is also necessary to accomplish the reaction in the forward direction. Variations of the amount of lemon juice such as 0.25, 0.50, 0.75, and 1.25 mL led to product (**1b**) in 52, 70, 82, and 94 % of yields, respectively (Table 1, entries 20–23). These results indicated that 1 mL of lemon juice gives high yield of the product over the duration of the reaction. Having optimized the solvent for this reaction, we proceeded to investigate the use of different temperatures: 40, 50, 60,

70, and 80 °C (Table 1, entries 15–19). Increasing the temperature of the reaction from 40 to 80 °C led to a reduction in the reaction time with an increase in product yield. Hence, using 1 mL of lemon juice in water:ethanol (9:1) at 90 °C is the optimal condition for this reaction.

After optimizing the conditions, the broad view of this process was studied by the reaction of various substituted aryl aldehydes and heterocyclic aldehydes with hydroxylamine hydrochloride and ethyl acetoacetate in the presence of 1 mL lemon juice in water:ethanol (9:1) at 90 °C. The results of this study are presented in Table 2. The reaction was clean, and no chromatographic separation was required because no impurities were observed. After completion of the reaction, the solid product was collected by simple filtration and, if required, was then recrystallized in ethanol to afford pure products. The structure of the title compounds were confirmed by IR, ESI–MS, 1H-NMR, and 13C-NMR as well as by comparison of their melting points with those of the reported compounds. For example, the 1H-NMR spectrum of **1b** exhibited a sharp singlet signal at $\delta = 2.25$ ppm due to the methyl group in the isoxazol unit. Two doublets were observed at $\delta = 6.95$ ($J = 8.76$ Hz) and $\delta = 8.45$ ($J = 8.8$ Hz), which assigned four protons of aromatic

Table 2 The synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (**1a–1t**) catalyzed by lemon juice

Entry	Product code	Ar	Time (min)	Yield (%)[a]	(Mp °C) found	(Mp °C) literature
1	**1a**	$C6H_5$	50	96	142–143	141–142 [46]
2	**1b**	4-$OHC6H_4$	55	94	211–212	211–213 [46]
3	**1c**	2-$OHC6H_4$	60	93	198–200	198–199 [46]
4	**1d**	4-$OMeC6H_4$	56	98	173–175	174–175 [46]
5	**1e**	4-$CH3C6H_4$	60	97	135–137	135–136 [46]
6	**1f**	3-$OHC6H_4$	57	94	200–201	200–201 [46]
7	**1g**	4-$N(CH_3)2C6H_4$	60	95	225–226	225–227 [46]
8	**1h**	3-OCH_3-4-$OHC6H_3$	52	96	215–217	216–217 [46]
9	**1i**	2-Pyridyl	120	NR[b]	–	–
10	**1j**	2-Thienyl	60	90	144–145	144–146 [46]
11	**1k**	3-Thienyl	60	92	143–145	145–146 [46]
12	**1l**	2-Furyl	58	90	238–240	239–241 [50]
13	**1m**	4-OH-3-NO_2-$C6H_3$	54	96	265–267	266–267 [50]
14	**1n**	4-Cl-$C6H_4$	120	NR[b]	–	–
15	**1o**	4-NO_2-$C6H_4$	120	NR[b]	–	–
16	**1p**	2,3-diOMe-$C6H_3$	50	94	210–212	210–211 [45]
17	**1q**	2,5-diOMe-$C6H_3$	52	96	178–180	178–179 [45]
18	**1r**	3,4-diOH-$C6H_3$	56	98	212–214	212–213 [45]
19	**1s**	3,5-diOMe-4-$OHC6H_2$	55	97	194–197[c]	–
20	**1t**	3-OH-4-$OCH3C6H_3$	52	95	185–187[c]	–

[a] Isolated product yields

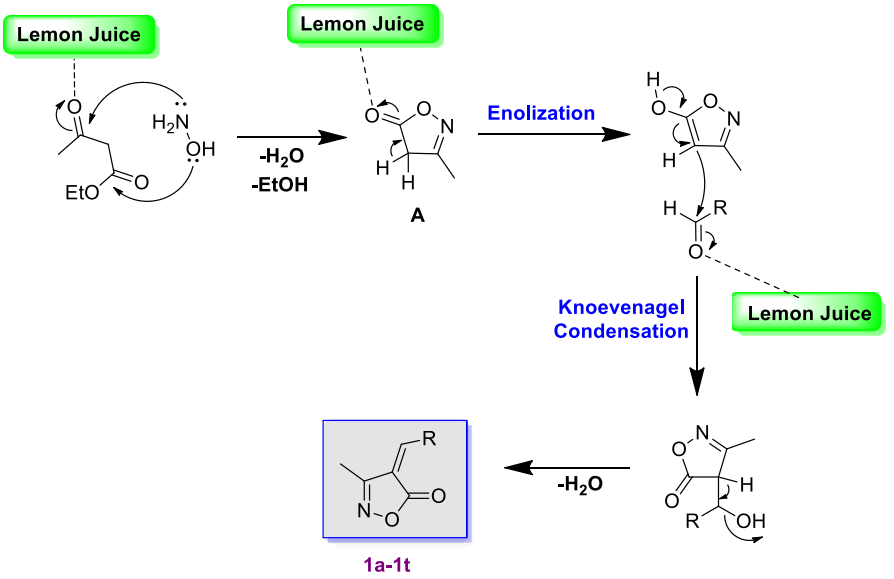
[b] No product was formed

[c] Novel compounds

rings. Also, the 1H-NMR showed one singlet signal at $\delta = 7.78$ ppm for the =CH proton between the isoxazol and aromatic rings. In addition, a proton of 4-OH exhibited a singlet at $\delta = 11.06$ ppm. The 13C-NMR spectrum of **1b** displayed the isoxazol ring carbons C=O and C=N at $\delta = 168.80$ and 163.82 ppm, respectively, which confirms the isoxazol unit. The signal at $\delta = 11.25$ ppm corresponds to the CH_3 group. The other carbon signals were observed at the expected chemical shifts. Furthermore, the ESI–MS spectrum of compound **1b** shows a peak at 204.2 (M + H)+, which confirms the structure of compound **1b**.

We found that aromatic substrates having electron-donating functional groups afforded good to high yields of products. In addition, the reaction with electron-reaching heterocyclic aldehydes also preceded smoothly with high yields in shorter reaction times. It is important to note that the aldehydes with electron-withdrawing (–NO_2) as well as ring-deactivating (–Cl) groups and deficient heterocyclic aldehyde-like pyridine-2-carbaldehyde are not favored under these conditions (Table 2, entries 9, 14, and 15). Interestingly, when the 4-hydroxy-3-nitrobezaldehyde containing both electron-withdrawing (–NO_2) and electron-donating (–OH) groups was used, the corresponding product (1 m) was obtained in a shorter reaction time and with higher yield (Table 2, entry 13). Similarly, 2-hydroxy-5-bromobezaldehyde gave a corresponding product in excellent yield within a shorter period of time (Table 2, entry 19). Accordingly, we concluded that the electronic nature of the functional groups and their position on aryl aldehydes have various effects on this reaction.

Although the exact mechanism of this transformation is not completely clear, a possible reaction mechanism is proposed based on these results and the provided mechanism in the literature (Scheme 2). According to the proposed reaction



Scheme 2 The proposed mechanism for the lemon juice-mediated synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (**1a–1t**)

mechanism, at first, the nucleophilic attack of the amino group and hydroxyl group of hydroxylamine hydrochloride on the two carbonyl carbon of the ethyl acetoacetate in the presence of lemon juice resulted in a cyclized adduct (**A**). The aldehyde was attacked on the cyclized adduct (**A**) and a subsequent Knoevenagel adduct is formed via removal of the water molecule.

In all reactions, the catalytic system is recoverable. After completion of the reaction, the product was filtered off. The filtrated solution could be applied up to three times in the same model reaction under the optimized conditions (1st use: 94 % isolated yield, 2nd use: 90 % isolated yield, and 3rd use: 87 % isolated yield). Decreases in the yield are probably related to a minor reduction in the efficiency of the catalyst or decrease in the amount of catalyst recycled, which is accredited to the handling.

The kinetics of this cyclocondensation reaction were studied in a standard quartz cuvette with a 1-cm path length and 4.5-mL volume. Initially, 2 mL of ethanol and 8 mL water were mixed with 10 mmol of ethyl acetoacetate and 10 mmol of hydroxylamine hydrochloride. Then, the reaction mixture was stirred for 10 min at room temperature. After that 10 mmol of *Para*-dimethylaminobenzaldehyde was added into the reaction mixture. After mixing these solutions, 1 mL lemon juice was added in the reaction flask. Now, the reaction mixture was heated at 90 °C. After 10 min we took 0.5 mL of the reaction mixture and performed an extraction with 2.5 mL ethyl acetate, which is 4.0×10^{-4} M solution of *Para*-dimethylaminobenzaldehyde. This solution was diluted with ethyl acetate to make it 16 nM. UV–visible spectra were recorded at every 10 min interval in the range of 250–550 nm for at least 60 min at 25 °C of the above diluted solution (Fig. 3).

The rate constant was determined by measuring the change in absorbance of a peak at 300 nm, the initially observed peak for the *Para*-dimethylaminobenzaldehyde, as a function of time. The peak shows a gradual decrease in intensity with time and a new peak appeared at 455 nm, indicating the formation of 3-Methyl-4-(4-dimethylaminophenyl)methylene-isoxazole-5(4*H*)-one.

The reaction shows pseudo first-order kinetics with respect to *Para*-dimethylaminobenzaldehyde, and the rate constants were calculated to be 6.12×10^{-2} min^{-1} at 25 °C (Figs. 4, 5).

After the successful synthesis of a series of 3,4-disubstituted isoxazol-5(4*H*)-ones, we turned our attention toward the synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-

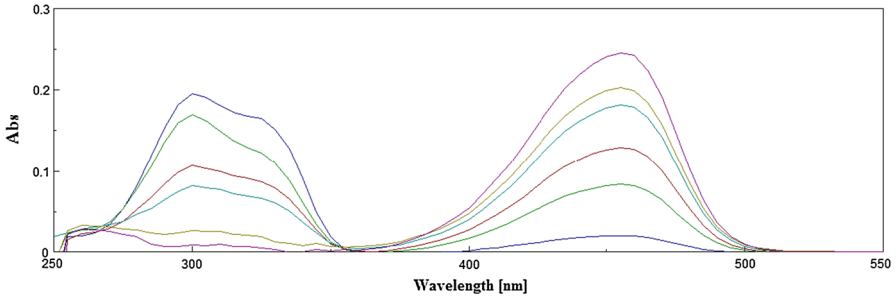


Fig. 3 UV–visible spectra for the formation of product **1g** measured at 10-min intervals at 25 °C

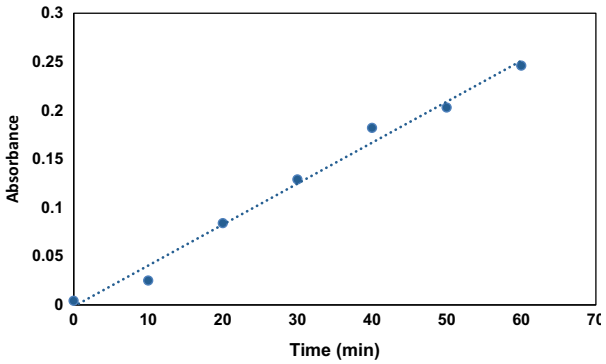


Fig. 4 Plot of absorbance versus time for the formation of product **1g**

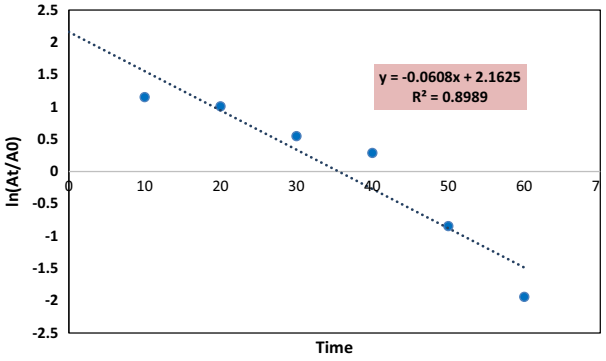


Fig. 5 Plot of ln(At/A0) versus time for the formation of product **1g**

pyrazole-5-carbonitriles in the presence of lemon juice as a catalyst in a non-toxic solvent, e.g., the mixture of water and ethanol. In the beginning, the reaction of equimolar quantities of ethyl acetoacetate (10 mmol), hydrazine hydrate (15 mmol, 80 %), benzaldehyde (10 mmol), and malononitrile (10 mmol) was selected as a model reaction to identify suitable reaction conditions using lemon juice (1 mL) as a catalyst.

Different reaction conditions were examined including solvents, amounts of catalyst, and temperatures, to identify the optimal reaction conditions. The results are summarized in Table 3. From the results table, we concluded that the product yield obtained was very poor in the absence of a solvent at room temperature as well as at 90 °C under catalyst-free conditions (Table 3, entries 1, 2). We also carried out the model reaction using 1 mL lemon juice as a catalyst under solvent-free conditions, however, only a moderate yield (68 %) of the product (**2a**) was observed in this case (Table 3, entry 3). The model reaction was then performed in water, methanol, ethanol, toluene, acetonitrile, dichloromethane, ethyl acetate, and chloroform using lemon juice (1 mL) as a catalyst (Table 3, entries 4–11). The reactions furnished poor yields when aprotic solvents like toluene, acetonitrile, dichloromethane, ethyl acetate, and chloroform were used (Table 3, entries 6–10). Therefore, these solvents were determined to be unsuitable for this model reaction.

Table 3 Optimization of the reaction conditions for the synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (**2a–2t**)

Entry	Solvent	Catalyst loading (mL)	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	–	r.t.	60	Trace
2	–	–	90 °C	60	17
3	–	1.00	90 °C	60	68
4	MeOH	1.00	Reflux	60	72
5	EtOH	1.00	Reflux	60	76
6	Toluene	1.00	Reflux	60	32
7	MeCN	1.00	Reflux	60	55
8	$CH2Cl_2$	1.00	Reflux	60	43
9	EtOAc	1.00	Reflux	60	38
10	$CHCl_3$	1.00	Reflux	60	36
11	H2O	1.00	90 °C	60	84
12	**H2O:EtOH (9:1)**	**1.00**	**90 °C**	**45**	**96**
13	H2O:EtOH (5:5)	1.00	90 °C	60	88
14	H2O:EtOH (9:1)	1.00	r.t.	60	54
15	H2O:EtOH (9:1)	1.00	40 °C	60	60
16	H2O:EtOH (9:1)	1.00	50 °C	60	66
17	H2O:EtOH (9:1)	1.00	60 °C	60	75
18	H2O:EtOH (9:1)	1.00	70 °C	60	83
19	H2O:EtOH (9:1)	1.00	80 °C	60	90
20	H2O:EtOH (9:1)	0.25	90 °C	60	62
21	H2O:EtOH (9:1)	0.50	90 °C	60	76
22	H2O:EtOH (9:1)	0.75	90 °C	50	89
23	H2O:EtOH (9:1)	1.50	90 °C	45	95

Bold letters in the table demonstrated the optimize reaction conditions

[a] Isolated product yields

The product (**2a**) was obtained in a moderate yield and with a long reaction time in protic solvents like methanol, ethanol, and water (Table 3, entries 4, 5, 11), and the reaction in the mixture of water:ethanol (9:1) was performed in the shortest reaction time with the best yield. Therefore, it can be concluded that water:ethanol (9:1) is a superior solvent as compared to the others (Table 3, entry 12). We also demonstrated the water:ethanol (5:5) solvent system for this transformation. However, it did not yield any better results compared to the water:ethanol (9:1) solvent system (Table 3, entry 13).

The amount of the catalyst plays a crucial role in the success of the reactions in terms of the rate and the yields, and these experiments are summarized in Table 3. Having optimized the solvent for this reaction, we proceeded to investigate the use of different temperatures including room temperature, 40, 50, 60, 70, and 80 °C (Table 3, entries 14–19). Increasing the temperature of the reaction from room temperature to 90 °C led to a reduction in the reaction time with increments of product yield. The greatest yield in the shortest reaction time was obtained in

water:ethanol (9:1) at 90 °C (Table 3, entry 12). In the next step, the reaction was carried out with various amounts of catalyst in water:ethanol (9:1) at 90 °C. (Table 3, entries 20–23). Increasing the catalyst to 0.25, 0.50, 0.75, and 1.50 mL resulted in increasing the reaction yields to 62, 76, 89, and 96 %, respectively. In addition, a higher amount of catalyst, i.e., 1.5 mL of lemon juice, does not improve product yield or the reaction time (Table 3, entry 23). Hence, the best result was obtained by performing the reaction in the presence of 1 mL of lemon juice at 90 °C in water:ethanol (9:1) system.

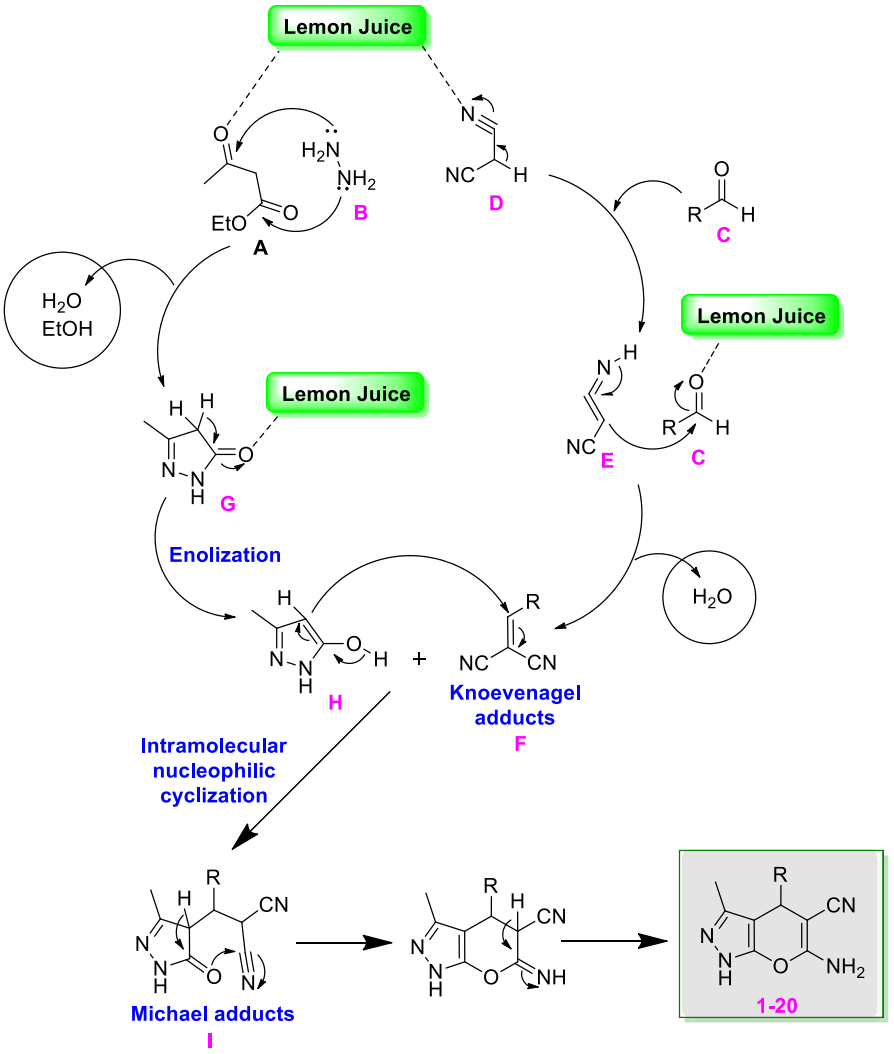
With the above optimized reaction conditions, a series of the 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (**2a–2t**) were synthesized using various aldehydes (Table 4, entries 1–20). A wide range of aromatic aldehydes bearing either electron-releasing or electron-withdrawing substituents reacted successfully to give the corresponding products in high to excellent yields over short reaction times. In all cases, the reaction was found to be selective and afforded the desired products in high purity without any evidence of the formation of any side products. In addition, heterocyclic aldehydes such as 2-furfuraldehyde also reacted efficiently with this protocol and afforded excellent product yields (Table 4, entry 20).

We also proposed a possible mechanism for the building of final products (**2a–2t**) (Scheme 3). The nitrile anion **(E)** is formed by the removal of acidic hydrogen from

Table 4 The synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (**2a–2t**) catalyzed by lemon juice

Entry	Product code	Ar	Time (min)	Yield (%)[a]	(Mp °C) found	(Mp °C) literature [136]
1	**2a**	$C6H_5$	45	96	245–246	244–246
2	**2b**	2-OH-$C6H_4$	40	95	209–211	208–210
3	**2c**	4-OH-$C6H_4$	42	97	226–227	224–226
4	**2d**	3-NO_2-$C6H_4$	55	93	193–195	193–195
5	**2e**	4-NO_2-$C6H_4$	60	94	251–252	251–253
6	**2f**	3-OH-$C6H_4$	45	95	224–226	225–228
7	**2g**	2-Cl-$C6H_4$	40	98	147–148	145–147
8	**2h**	4-OMe-$C6H_4$	45	95	211–212	210–212
9	**2i**	4-CN-$C6H_4$	60	96	196–197	196–198
10	**2j**	4-Cl-$C6H_4$	45	94	233–235	234–236
11	**2k**	4-Me-$C6H_4$	48	92	207–209	206–208
12	**2l**	4-Br-$C6H_4$	55	97	179–180	178–180
13	**2m**	4-F-$C6H_4$	60	94	242–244	240–242
14	**2n**	4-$N(Me)_2$-$C6H_4$	52	94	168–170	167–169
15	**2o**	3,5-diOMe-4-OH-$C6H_2$	45	93	199–201	199–201
16	**2p**	3,4-diOMe-$C6H_3$	48	96	190–191	192–194
17	**2q**	3,4,5-triOMe-$C6H_2$	45	97	209–210	209–211
18	**2r**	2-OH-5-NO_2-$C6H_3$	55	92	254–255	254–255
19	**2s**	2-OH-5-Br-$C6H_3$	52	94	227–228	227–228
20	**2t**	2-furayl	48	92	218–219	217–219

[a] Isolated product yields



Scheme 3 The proposed mechanism for the lemon juice-mediated synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles

malononitrile **(D)** catalyzed by lemon juice. Finally, the arylidene nitrile intermediates (Knoevenagel adducts, **F**) are formed through the Knoevenagel condensation reaction of the intermediate nitrile anion **(E)** with aldehydes (C). On other hand, the reaction of ethyl acetoacetate and hydrazine hydrate afforded compound (G), which was enolized in the presence of lemon juice to form compound (H). Subsequently, the enolizable compound **(H)** condensed with the Knoevenagel adducts **(F)** via the Michael addition, which results in the in-situ formation of intermediate **(I)** (Michael adducts). Finally, it subsequently undergoes intramolecular nucleophilic cyclization (Thorpe–Ziegler type reaction) and tautomerization to afford the desired compounds (**2a–2t**).

Table 5 Comparison of various catalysts in this reaction

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a]	References
1	Sodium benzoate (15 mol%)	Water, r.t.	60	85	[74]
2	Saccharose (20 mol %)	Solvent-free, 100 °C	10	75	[61]
3	Cetyltrimethylammonium chloride (CTACl) (30 mol %)	Water, 90 °C	240	89	[86]
4	Nano-ZnO (5 mol %)	Water, 70 °C	60	94	[76]
5	Nano-CuI (1.2 mol %)	Water, reflux	40	90	[82]
6	TBABr (10 mol %)	Water, reflux	15	90	[88]
7	γ-Alumina (30 mol %)	Water, reflux	50	80	[139]
8	β-Cyclodextrin (10 mol %)	Water–ethanol (9:1), 80 °C	15	92	[140]
9	Urea (10 mol %)	Water–ethanol (1:1), r.t.	480	86	[141]
10	DABCO (5 mol %)	Water, reflux	15	92	[142]
11	DCDBTSD (10 mol%)	Water, 80 °C	60	85	[143]
12	[bmim]OH (20 mol%)	Solvent-free, 50–60 °C	45	90	[144]
13	**Lemon juice (1** mL)	**Water–ethanol (9:1), 90 °C**	**45**	**96**	**This work**

Bold letters in the table demonstrated the optimize reaction conditions

Table 5 indicates the comparison of the activity of the different catalysts by considering the yield for the reaction. We observed that the lemon juice catalyst gives the best catalytic activity in terms of product yield and reaction time compared to the other catalysts in the literature such as γ-Alumina, nano-ZnO, TBABr, Sodium benzoate, β-Cyclodextrin, Cetyltrimethylammonium chloride (CTACl), Urea, DABCO, nano-CuI, Saccharose, DCDBTSD, and [bmim]OH. Lemon juice is easily available as a natural and inexpensive catalyst, which makes this protocol green and clean. In addition, lemon juice is a renewable catalyst, thus it follows one of the green chemistry principles regarding the maximum use of renewable sources. Therefore, the present protocol is considered as a sustainable and environmentally friendly protocol.

In general, at the end of the reaction, the system became a suspension and finally the product was precipitated. The products were obtained through simple filtration and washed with water and recrystallized in ethanol (if required) to afford pure products. The filtered solution could be reused three times without major loss of efficiency (1st use: 96 % isolated yield, 2nd use: 92 % isolated yield, and 3rd use: 87 % isolated yield). The structure of the products (**2a–2t**) were characterized by IR, ESI–MS, 1H-NMR, and 13C-NMR spectral data and by comparison of their melting points with those of authentic samples.

Experimental

Apparatus and analysis

All chemicals, unless otherwise specified, were purchased from commercial sources and were of used analytical grade. The products were characterized by a comparison

of their physical data and melting points with those of known samples or by their spectral data. Melting points were measured on an Optimelt MPA 100 melting point apparatus and are uncorrected. Fourier transform infrared spectroscopy (FT-IR) spectra were recorded on a Perkin Elmer FT-IR 377 spectrometer using KBr. Proton NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO as solvent and TMS as the internal reference. Mass spectra were recorded at Advion expression CMS, USA. Acetone was used as the mobile phase, and electron spray ionization (ESI) was used as the ion source. The progress of the reaction was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure for extraction of lemon juice (preparation of catalyst)

Fresh lemon was cut using a knife and pieces were pressed in a fruit juicer to obtain the juice extract. Then the juice was filtered through cotton/muslin cloth and finally through filter paper to remove solid material and to get the clear juice that was used as a catalyst. The pH of the lemon juice was between 3.0 and 3.4.

General method for the preparation of 3,4-disubstituted isoxazol-5(4*H*)-ones (1a–1t)

A mixture of hydroxylamine hydrochloride (10 mmol), ethyl acetoacetate (10 mmol), and lemon juice (1 mL) in 10 mL water:ethanol (9:1) was stirred at room temperature for 15 min, then aromatic aldehyde (10 mmol) was added to the mixture. The reaction mixture was stirred at RT until the reaction was completed. The reaction was monitored by TLC analysis. After completion of the reaction, the precipitate was separated by simple filtration, and washed with cold distilled water and dried in the air. Crude products were recrystallized from ethanol (95 %) to afford the title pure compounds. After filtration, the filtered solution could reused for the three subsequent reactions. The identity of the known products was confirmed by comparison of their spectroscopic data and physical properties with those available in recent articles. The novel products were identified by spectral data (i.e., IR, 1H-NMR, and 13C-NMR and Mass). The spectral data of the novel compounds as well as some representative compounds are described below.

4-(3-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**1b**) *Yellow solid* IR ν_{max} (KBr) cm^{-1}: 3232, 2363, 1734, 1559, 1358, 1297, 1179, 669. 1H-NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.25 (s, 3H, CH_3), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.78 (s, 1H, = CH), 8.45 (d, $J = 8.80$ Hz, 2H, ArH), 11.06 (s, 1H, OH). 13C-NMR (100 MHz, DMSO-d_6): δ_C (ppm) 11.25, 113.81, 116.12, 124.54, 135.42, 137.51, 151.15, 151.48, 162.23, 163.82, 168.80. MS (ESI) *m/z* for (203.19): 203.1 (M)+, 204.2 (M + 1)+.

4-(3-(dimethylamino)benzylidene)-3-methylisoxazol-5(4*H*)-one (**1g**) *Red solid* IR ν_{max} (KBr) cm^{-1}: 1734, 1589, 1530, 1429, 1180, 1096, 870. 1H-NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.22 (s, 3H, CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 6.86 (d,

$J = 9.16$ Hz, 2H, ArH), 7.63 (s, 1H, = CH), 8.47 (d, $J = 8.20$ Hz, 2H, ArH). 13C-NMR (100 MHz, DMSO-d_6): δ_C (ppm) 11.31, 108.95, 111.61, 120.96, 137.54, 150.47, 154.31, 162.11, 169.81. MS (ESI) *m/z* for (230.26): 230.2 (M)+, 253.2 (M + Na)+.

4-(3-hydroxy-2,4-dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**1s**) *Yellowish orange solid* IR ν_{max} (KBr) cm^{-1}: 3532, 2358, 1711, 1587, 1377, 1201, 1165, 670. 1H-NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.19 (s, 3H, CH_3), 3.83 (s, 6H, 2 OCH_3), 7.66 (s, 1H, =CH), 7.99 (s, 2H, ArH), 10.20 (s, 1H, OH). 13C-NMR (100 MHz, DMSO-d_6): δ_C (ppm) 11.15, 55.83, 112.46, 113.75, 123.94, 143.13, 147.40, 151.88, 162.08, 168.93. MS (ESI) *m/z* for (263.25): 263.1 (M)+, 264.2 (M + 1)+.

4-(3-hydroxy-4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**1t**) *Orange solid* IR ν_{max} (KBr) cm^{-1}: 3502, 2367, 1699, 1529, 1264, 1126, 674. 1H-NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.25 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.13 (d, $J = 8.60$ Hz, 1H, ArH), 7.73 (s, 1H, = CH), 7.90 (d, $J = 10.56$ Hz, 1H, ArH), 8.19 (s, 1H, ArH), 9.61 (s, 1H, OH). 13C-NMR (100 MHz, DMSO-d_6): δ_C (ppm) 11.25, 15.77, 55.84, 111.68, 114.70, 119.52, 126.72, 129.61, 146.51, 151.75, 153.68, 158.11, 162.23, 168.54, 170.92. MS (ESI) *m/z* for (233.22): 233.3 (M)+, 256.1 (M + Na)+.

General method for the preparation of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (2a–2t)

In a typical experiment, ethyl acetoacetate (10 mmol), hydrazine hydrate (15 mmol, 80 %), aromatic aldehydes (10 mmol), malononitrile (10 mmol), and lemon juice (1 mL) in water: ethanol (9:1, 10 mL) were placed in a 25-ml round-bottom flask. During the reflux (90 °C), the progress of the reaction mixture was monitored by TLC analysis. After completion of the reaction, the solid precipitate was filtered off and washed with water and purified by recrystallization from hot ethanol, if necessary. The reaction products were identified by comparing their physical and spectral data (i.e., IR, 1H NMR and 13C NMR and Mass) with those reported in the literature. The spectral data of the representative compounds are described below.

6-amino-4-(4-nitrophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2e**) *Yellow solid* IR ν_{max} (KBr) cm^{-1}: 3414, 3389, 3323, 3073, 3025, 2936, 2209, 1485, 1354, 1563, 818. 1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.82 (s, 3H, CH_3), 4.84 (s, 1H, 4*H*), 7.08 (s, 2H, NH_2), 7.46-7.48 (d, 2H, $J = 8.48$ Hz, Ar–H), 8.20-8.22 (d, 2H, $J = 8.48$ Hz, Ar–H), 12.22 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 9.71, 35.84, 55.84, 96.52, 120.47, 123.87, 128.81, 135.84, 146.34, 152.08, 154.63, 161.11. MS (ESI) *m/z* for (297.1): 397.2 (M)+, 398.3 (M + 1)+.

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2j**) Off-white solid, IR ν_{max} (KBr) cm^{-1}: 3400, 3391, 3317, 3066, 3017, 2931, 2211, 1488, 1058, 815. 1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.79 (s,

3H, CH_3), 4.64 (s, 1H, 4*H*), 6.96 (s, 2H, NH_2), 7.19–7.21 (d, 2H, $J = 8.40$ Hz, Ar–H), 7.37-7.39 (d, 2H, $J = 8.40$ Hz, Ar–H), 12.17 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 9.71, 35.51, 56.68, 97.15, 120.65, 128.43, 129.07, 129.34, 129.70, 130.00, 131.20, 135.67, 143.44, 154.65, 160.87. MS (ESI) *m/z* for (286.06): 286.1 (M)+, 288.1 (M + 2)+.

6-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2o**) *Off-white solid* IR ν_{max} (KBr) cm^{-1}: 3452, 3393, 3384, 3310, 3059, 3010, 2925, 2590, 2205, 1481, 742, 772, 805. 1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.86 (s, 3H, CH_3), 3.71 (s, 6H, 2 × OCH_3), 4.53 (s, 1H, 4*H*), 6.43 (s, 2H, NH_2), 6.85 (s, 2H, Ar–H), 8.28 (s, 1H, –OH), 12.08 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 9.88, 36.24, 55.93, 57.32, 97.63, 104.82, 120.89, 134.25, 134.45, 135.66, 147.80, 154.66, 160.73. MS (ESI) *m/z* for (328.1): 329.1 (M + 1)+, 351.1 (M + Na)+.

6-amino-4-(3,4,5-trimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2q**) *Off-white solid* IR ν_{max} (KBr) cm^{-1}: 3432, 3391, 3382, 3316, 3069, 3017, 2922, 2593, 2207, 1487, 742, 772, 805. 1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.89 (s, 3H, CH_3), 3.55 (s, 9H, 3 × OCH_3), 4.61 (s, 1H, 4*H*), 6.49 (s, 2H, NH_2), 6.92 (s, 2H, Ar–H), 12.13 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 9.91, 36.46, 55.74, 56.84, 59.91, 97.28, 104.49, 105.50, 120.87, 135.73, 136.07, 140.07, 152.76, 153.13, 154.67, 160.95. MS (ESI) *m/z* for (342.13): 343.1 (M + 1)+, 366.2 (M + Na)+.

Conclusion

In summary, we have established effective and practical one-pot protocols for the synthesis of a library of 3,4-disubstituted isoxazol-5(4*H*)-ones (**1a–1t**) as well as 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (**2a–2t**) in the presence of biodegradable, renewable, easily assessable, inexpensive, and highly efficient lemon juice as the catalyst in a hydroalcoholic system. Moreover, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution. These protocols, which enabled 3,4-disubstituted isoxazol-5(4*H*)-ones and 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles to be prepared in excellent yields and with the shortest reaction times, represent some rather attractive synthetic methods for use in the near future. The rate constant ($K = 6.12 \times 10^{-2}$ min^{-1} at 25 °C) for the formation of Isoxazole derivative (**1g**) was also calculated, which indicated that the reaction shows pseudo-first-order kinetics. The use of lemon juice in these MCRs has benefits such as clean reaction profiles, lack of side reactions, green properties, minimization of waste, a simple experimental procedure, recyclability of the catalyst, simplicity of operation, and easy work-up.

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