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Synthesis of pyrazines and imidazoles using lemon juice (*Citrus limon*) as a recyclable catalyst

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One-pot four component synthesis of 2,5,6-triaryl pyrazines, 1,2,4,5-tetraaryl imidazoles and 2,2,4,5-tetraaryl imidazoles have been achieved from benzoin, aryl amine, ammonium acetate and aryl ketone /aryl aldehydes using lemon juice (*Citrus limon*) as an ecofriendly catalyst in good yield under mild conditions. The antibacterial action exhibited by the synthesized compounds against clinical isolates obtained from urinary tract catheters of infected patients is close to the standard drug tetracycline. Recovery of lemon juice after completion of reaction eliminates the need to handle side products, making this process more safe and user friendly.

Keywords: Green synthesis, pyrazines, imidazoles, natural acid catalyst, recyclable catalyst

Classical heating methods are being replaced by some sustainable and clean method in drug discovery due to efforts of adopting green chemistry protocol. Modern chemistry offers several approaches for diversity oriented synthesis for generation of diverse library of compound[1,2]. Some chemical transformation do not occur under conventional heating could be possible by microwave irradiation as well as grinding in mortar and pestle. Now a day's grinding method is highly recommended by chemists and biologists because of environment friendly and inexpensive protocol. Simple mechanochemical stirring is required to obtain the product without using any kind of energy[3]. Mineral acids such as HF, HCl and H_2SO_4 are of great demand in chemical reactions but have some limitations due to corrosive and harmful effect as catalysts. Natural acid is considered as alternate catalyst as concern for development of newer catalyst and environment benign reactions. Fruit lemon juice (*Citrus limon*) is easily available natural acid catalysts as contains important component citric acid (6-7%) along with carbohydrate, vitamin-C, protein, mineral, water and other organic acids also be used as acid catalyst in organic reactions.

Lemon juice containing citric acid initiates the reaction by activating the functional group *i.e.* carbonyl group of aldehydes and ketone in MCR to get the desire products[4]. The natural acids can catalyses cycloaddition as well as condensation reactions with greater improvement in yields beside this easy availability, handling, non-toxicity and recovery after reaction complete are the important characteristics of natural acid that make its green catalysts[5]. Some ionic liquid and surfactants in water are widely useful in synthetic chemistry but have some drawbacks such as high cost, require in large amount and low yields of product.

Pyrazines are significant class in heterocyclics with diverse biological application; particularly purines derivatives containing pyrazine nucleus possesses various pharmacological activities such as anti-inflammatory[6], antidepressant[7], antiproliferative activities[8], relaxing cardiovascular, antithrombotic, anti-aggregation, COX-2 inhibiting effects[9]. Some alkoxy pyrazines are relevant aromas components of vegetables and fruits, alkyl/aryl pyrazines recognized as flavour components in foods as well as pheromones in various insect species[10,11]. On the other hand novel drug molecules such as saripidem zolpidem and necopidem containing the imidazole moiety shows wide spectrum of biological properties[12-14]. The imidazoles also shows properties against the viral diseases[15], migraine[16], heart[17,18], and array of neurological syndromes[19], diabetic effects[20] and cancer cell growth effect[21]. Because of the variety applications associated with pyrazine and imidazole nucleus, herein, we report an efficient and green method for one-pot four component synthesis of

series of 2,5,6-triaryl pyrazines, 1,2,4,5-tetraaryl-imidazoles and 2,2,4,5-tetraaryl-imidazoles catalyzed by lemon juice (*Citrus limon*) under mild condition[22,23].

Results and Discussion

The condensation reaction involving benzoin **1**, aryl amine **2a-d**, acetophenone **3** and ammonium acetate using *Citrus limon* by stirring with magnetic stirrer at RT for 20-25 min. resulted the formation of 1-(4-aryl)-2,5,6-triphenyl-1,2-dihydro-pyrazines **4a-d** (Table I, Scheme I).

Similarly the condensation of benzoin **1**, aryl amine **2e-i**, benzophenone **5/** aryl aldehydes **7j-n** and ammonium acetate using *Citrus limon* by stirring with magnetic stirrer at RT for 20-25 min. resulted the formation of 2,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **6e-i** (Table II, Scheme II)/ 1,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **8j-n** (Table III, Table IV, Scheme III).

Table I — Optimization of reaction condition for synthesis of **4a-d** at RT

Catalyst	Time (min)	Yield (%)			
Lemon juice		**4a**	**4b**	**4c**	**4d**
0.5 mL	20-25	76	67	70	75
1.0 mL	15	70	66	67	72

It must be noted that carrying out 4 CRs involving benzoin, aryl amine, ammonium acetate and aryl aldehydes using lemon juice favours the formation of products in 80-90% yields. A series of 1-(4-aryl)-2,5,6-triphenyl-1,2-dihydro-pyrazines **4a-d**, 2,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **6e-i** and 1,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **8j-n** obtained by stirring the mixture with magnetic stirrer at RT is high yielding and operationally simple method.

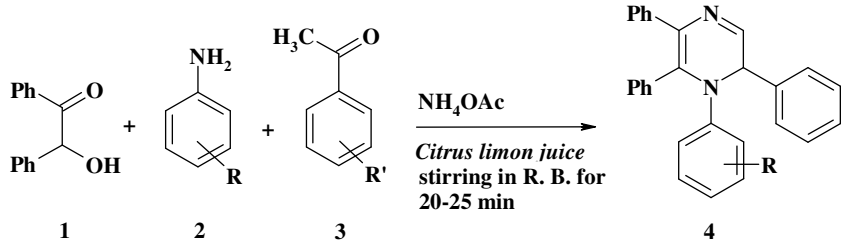
The spectral data was observed in good agreement with structure of the title products, IR spectrum of the representative compounds **4a, 6e, 8j** showed characteristic absorption band at 3061, 3056

Table II — Optimization of reaction condition for synthesis of **6e-i** at RT

Catalyst	Time (min)	Yield (%)				
Lemon juice		**6e**	**6f**	**6g**	**6h**	**6i**
0.5 mL	20-25	73	77	74	76	74
1.0 mL	10-15	68	70	71	72	68

Table III — Optimization of reaction condition for synthesis of **8j-n** at RT

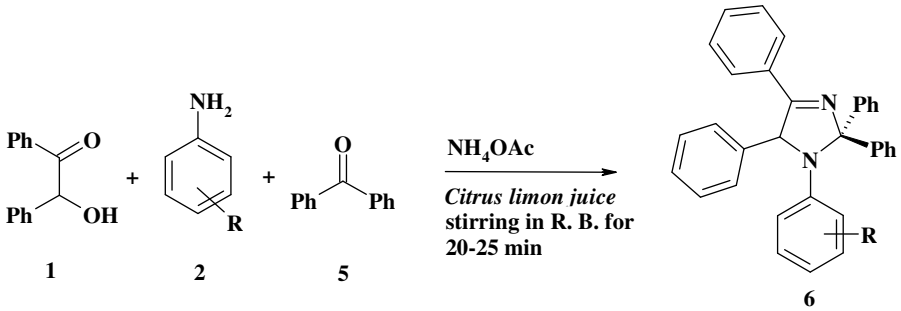
Catalyst	Time (min)	Yield (%)				
Lemon juice		**8j**	**8k**	**8l**	**8m**	**8n**
0.5 mL	10-15	87	85	88	93	90
1.0 mL	10-15	78	78	80	76	81



1 2 3 4

Where, R' = H and (2a-d), R = H, 4-Cl, 4-OMe, 4-NO_2 etc

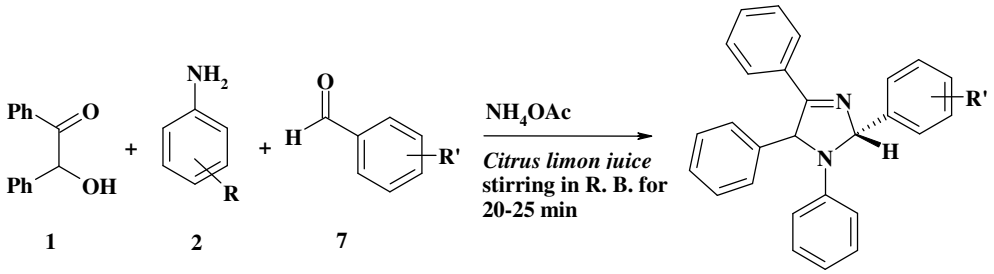
Scheme I



1 2 5 6

Where, (2e-i), R = -H, -4-OH, -4-COOH, -5-CH_3 (triazine diamine), -H (Napthyl amine) etc

Scheme II

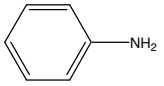
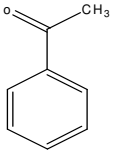
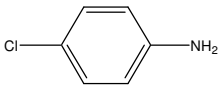
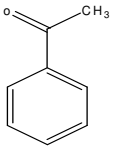
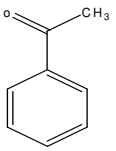
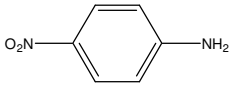
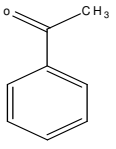
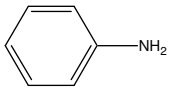
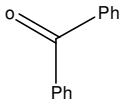
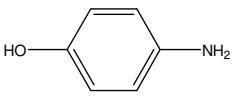
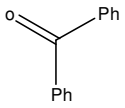
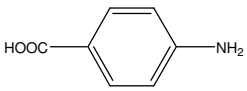
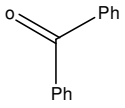
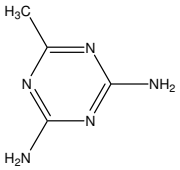
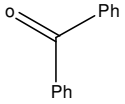


1 2 7 8

Where, R= H and (7j-n), R' = -H, -4-Cl, -4-OMe, -4-OH, 4-NO_2 etc

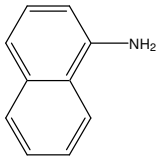
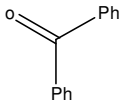
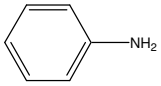
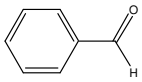
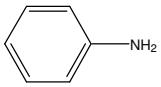
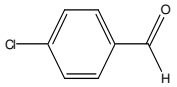
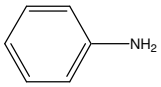
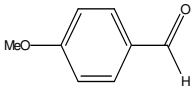
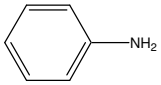
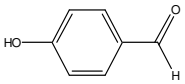
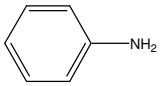
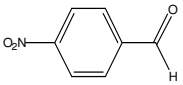
Scheme III

Table IV — Synthesis of compounds **4a-d**, **6e-i** and **8j-n**

Entry	**2**	**3**	Products	Yield (%)	m.p.(°C)	Time (min)
1			**4a**	76	102	10
2			**4b**	67	150	10
3			**4c**	70	80	10
4			**4d**	75	135	10
5			**6e**	73	100	10
6			**6f**	77	158	12-15
7			**6g**	74	122	15
8			**6h**	76	138	15

Contd.

Table IV — Synthesis of compounds **4a-d**, **6e-i** and **8j-n** (*Cont*d.)

Entry	**2**	**3**	Products	Yield (%)	m.p.(°C)	Time (min)
9			**6i**	74	95	15
10			**8j**	87	72	5
11			**8k**	85	155	10
12			**8l**	88	160	12-15
13			**8m**	93	150	10
14			**8n**	90	80	15

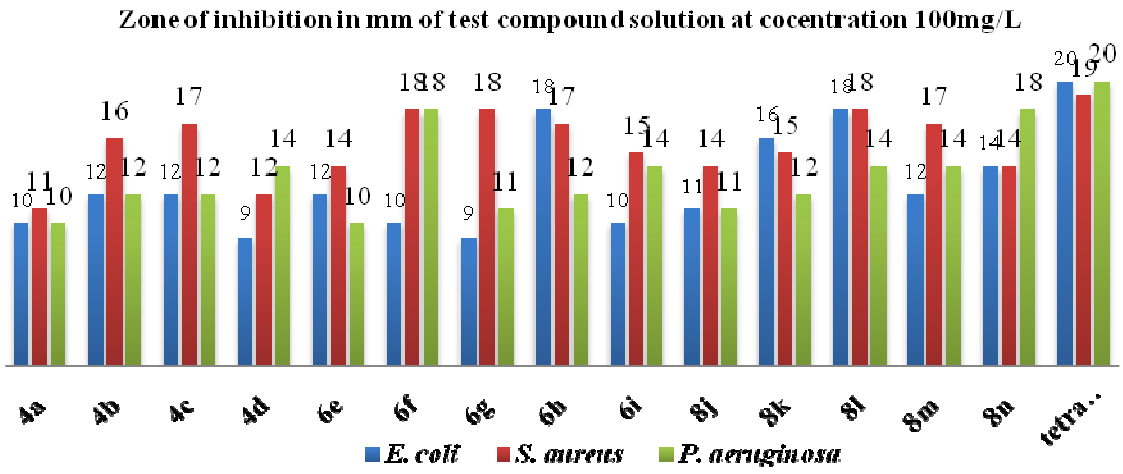


Figure 1

and 3056 cm^{-1} indicated -CH stretching vibrational frequency[24], ^1H NMR spectrum indicated signal at δ 3.36, 3.38 and 3.37ppm for the presence of pyrazine and imidazole ring proton respectively[25]. In mass spectrum, molecular ion peak for above compounds was observed at 388, 449 and 374 *m/z* respectively.

The antibacterial activity against *E. coli*, *S. aureus* and *P. aeruginosa* was fixed at concentration 100 mg/L. The compounds **6h,** 8lagainst *E. coli*, **6f, 6g, 8l** against *S. aureus* and **6f, 8n** against *P. aeruginosa* exhibited promising activity with inhibition zone of 18mm. The compounds **4a-d**, **6e-i** and **8j-n** inhibited the growth of bacteria demonstrating a good enough activity against selected bacteria (Figure 1).

Experimental Section

The series of 2,5,6-triaryl pyrazines, 1,2,4,5-tetraaryl imidazoles and 2,2,4,5-tetraaryl imidazoles have been

obtained using lemon juice catalysts under mild condition to afford products **4a-d**, **6e-i** and **8j-n**. The excess of lemon juice was removed by washing with distilled water. Melting points were determined on a digital melting point apparatus (Veego-DMP) and are uncorrected. Formation of the compounds checked till single spot visualised in TLC plate of silica gel using benzene: acetone (9:1) as solvent and spectral analysis of representative **4a**, **6e**, **8j** compounds were carried out. The IR spectra were recorded on Shimadzu FT-IR spectrophotometer using KBr pellets, ^{1}H NMR spectra were recorded on a BRUKER AVANCE II spectrophotometer with TMS as internal standard using DMSO-d_6 as solvent and mass spectral measurements were carried out by ESI-MS method on a Q-TOF MICROMASS spectrometer.

Bacterial action of synthesized compounds was tested against Urinary Tract Infection (UTI) pathogens isolated and identified using UTI chromogenic media (Hi media make). The infectious bacteria were characterized as *E. coli*, *S. aureus* and *P. aeruginosa* and for determination of antibacterial activity fresh bacterial cultures with standardized dilutions were spreaded on Muller Hinton Agar (MHA) plates. Plates were allowed to stand for 10-15 min for proper attachment of bacteria on media. Wells of 7 mm diameter and 4 mm depth were bored in each plate followed by addition of dissolved compounds in the wells. Plates were incubated for 24 h at 37°C, thereafter zone of inhibition were measured. Tetracycline was taken as positive control and sterile distilled water as negative control.

Spectral data of representative compounds, 4a, 6e, 8j

4a: Yield: 76%. R_f 0.65 (benzene-acetone, 9:1); IR (KBr): 3061 (-CH), 1663 (C=C), 1495 cm^{-1} (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.36 (s, 1H, pyrazine), 8.14 (s, 1H, pyrazine), 7.28-7.96 (m, Aromatic ring-H); ESI-MS: *m/z* 388 (M^+), 385, 309, 232.

6e: Yield: 73%. R_f 0.63 (benzene-acetone, 9:1); IR (KBr): 3056 (-CH), 1654 (C=C), 1446 cm^{-1} (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.38 (s, 1H, imidazole); 6.02-7.99 (m, Aromatic ring-H); ESI-MS: *m/z* 449 (M+), 373, 297.

8j: Yield: 87%. R_f 0.63 (benzene-acetone, 9:1); IR (KBr): 3056 (-CH), 1653 (C=C), 1448 cm^{-1} (C=N); ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.37 (s, 1H,), 5.74 imidazole (s, 1H, imidazole), 7.22-7.75 (m, Aromatic ring-H); ESI-MS: *m/z* 374 (M+), 373, 296, 220.

Antimicrobial activity 4a-d, 6e-i and 8j-n

Unlike other antibacterial studies of heterocyclic compounds; the pathogenic bacteria from urinary catheters of infected patients were used for the activity and the efficacy of synthesized compounds against them was determined using agar well diffusion method[26,27].

The results of antibacterial activity obtained clearly reveal that most of the compounds inhibit the growth of bacteria demonstrating a significant activity particularly the compounds **6h, 8l** against *E. coli*, **6f, 6g, 8l** against *S. aureus* and **6f, 8n** against *P. aeruginosa* that were near to the reference standard (Figure 1). Most of the compounds exhibited zones of inhibition more than 12 mm at concentration 100 mg/L reveal the potency of the compounds.

Conclusions

One-pot 4CRs of series of 1-(4-aryl)-2,5,6-triphenyl-1,2-dihydro-pyrazines **4a-d**, 2,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **6e-i** and 1,2,4,5-tetra-phenyl-1-aryl-2,5-dihydro-1*H*-imidazoles **8j-n** have been achieved under mild conditions in good-excellent yields using lemon juice as an ecofriendly catalyst. The remarkable feature of this route is inexpensive and recyclable catalyst and reactions performed at RT for avoiding complications such as unacceptable yields and side products. The compounds of particular interest are **6h**, **8l**, **6f**, **6g** and **8n** and their strong action against these bacteria is suggestive of their possible use in coating of catheters and also future drug against UTI pathogens.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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