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Lemon Juice Catalyzed Synthesis of N-substituted Pyrrole by Paal-Knorr Reaction

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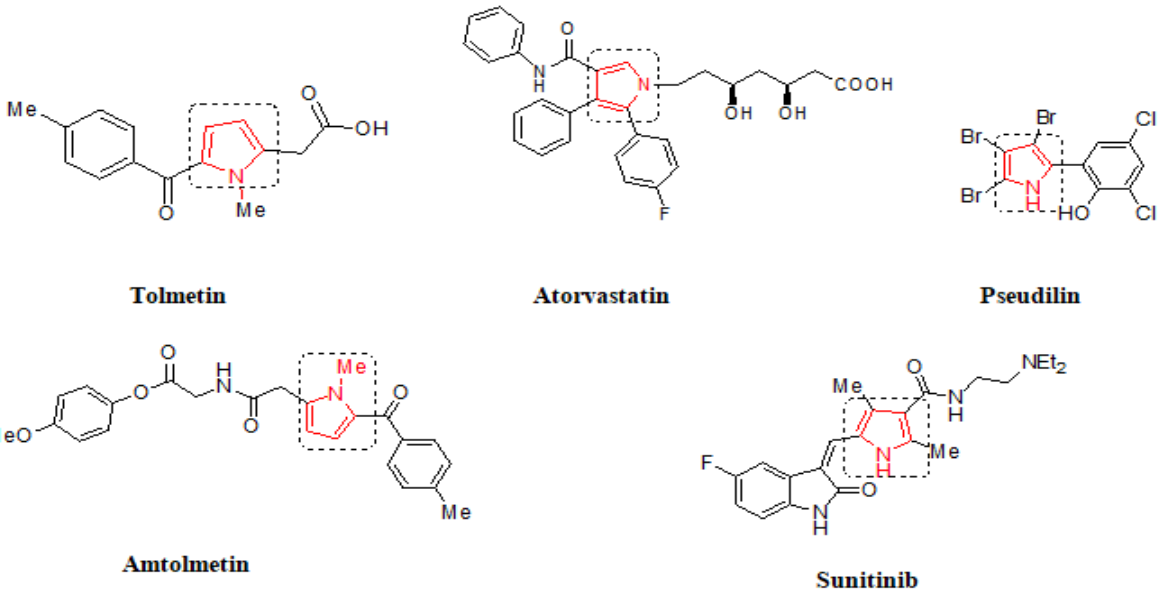
ABSTRACT

A novel, environmentally benign and efficient protocol has been introduced for the synthesis of N-substituted pyrrole through Paal-Knorr reaction catalysed by naturally available, inexpensive, nonhazardous lemon juice. During synthesis aromatic amines were condensed with 1,4 dione to obtain the pyrrole in presence of lemon juice. The use of lemon juice as catalyst for pyrrole synthesis results in good to excellent yield , shorter reaction time and easy work up procedure. Moreover the easy availability, non hazardous and eco-friendly nature are salient features of this green catalyst.

Keywords: Hexane-2,5-dione, Aniline, Lemon Juice, Pyrrole

I. INTRODUCTION

The five membered nitrogen heterocycle pyrrole was first found in coal tar in 1834 [1]. The pyrrole is available naturally in haemoglobin, chlorophyll, alkaloid and marine sponges [2- 4].The pyrrole moiety is also an important bioactive compound having antifungal[5], antitubercular[6], antitumour[7], antitubercular[8], anti-inflammatory[9], antimalarial and anticancer [10-14] activities. The most important cholesterol lowering drug Atorvastatin and anti-inflammatory drug also contain tri and tetra substituted pyrrole moiety[15]. The pyrrole is not only having medicinal applications but also more important in industrial and agricultural fields. Following are some examples of pyrrole containing drugs available in market.



Scheme 1

Due to versatile applications of heterocyclic pyrrole in diverse fields, several methods have been introduced for its synthesis. The most familiar and fruitful method was produced by German chemist Carl Paal and Ludwig Knorr for the synthesis of pyrrole in 1884[16].This synthesis involves acid catalyzed condensation of amines with 1,4 dione to yield pyrrole. Similarly the Hantzsch reaction and Knorr reaction are common methods for pyrrole synthesis. Recently Bela torok[19] and co-workers proposed the solvent and catalyst free synthesis of pyrrole but it require longer reaction time with less yield. Similarly Maurizio Taddei[20] and co-workers reported the synthesis of pyrrole by microwave irradiation.Yang and co-workers have introduced ionic liquid catalysed synthesis of pyrrole with good yield [21].In spite of their importance, some limitations have been observed in these methods such as use of hazardous chemicals as catalyst, longer reaction time, less yield, microwave irradiation and tedious work up procedure. Therefore in order to overcome from these limitations we have proposed lemon juice catalysed green synthesis of pyrrole through well known Paal-Knorr reaction. The natural availability, non hazardous, inexpensive and solubility in water and other solvents are the salient features of lemon juice which enhanced us to use it as catalyst.

II. MATERIAL AND METHODS

General Procedure

All chemicals were purchased from Sigma-Aldrich brand .The lemons of Citrus Indica species were obtained from market. The synthesised compounds were characterised by ^{1}HNMR, ^{13}CNMR, and Mass spectra. The melting points were determined by Chemline melting point apparatus and were uncorrected.

Preparation of lemon juice : Fresh lemons of Citrus Indica species were purchased from market and converted into small pieces. From these pieces juice was extracted and filtered to remove solid material. The p^{H} of juice was found to be 2.5.
This juice was used as catalyst.

Preparation of Compounds 3a-3j

In 50 ml of round bottom flask anilines 1a-j (0.01 mole) and hexane-2,5-dione (0.01mole) were dissolved in solvent. To this mixture 0.1 to 0.5 ml of lemon juice was added and stirred for 01 hr to 06 hrs. After completion of reaction as indicated by TLC ,the solvent was evaporated under reduced pressure and residue was washed with water and air dried. In order to get the purity the product was recrystallised from ethanol-water mixture.

Spectral Data of Compounds 3a-j

2,5-Dimethyl-1-phenyl-1H-pyrrole (3a)

^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.03 (s, 6H), 5.90 (s, 2H), 7.20 (m, 2H), 7.21-7.47 (m, 3H), LC–MS: m/z: 194 $(M+ Na)^+$, ^{13}CNMR ($CDCl_3$,75 MHz) 139.09, 129.13 128.33, 127.70, 13.11

2,5-Dimethyl-1H-pyrrolyl-1-benzoic acid

^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.03 (s, 6H), 5.83 (s, 2H), 7.33 (d J= 8.31 Hz, 2H), 8.27 (d, J=8.31 Hz ,2H), LC–MS: m/z: 216 $(M+ 1)^+$, ^{13}CNMR ($CDCl_3$,75 MHz) 170.13, 145.55, 131.77, 129.70, 127.31,126.21,107.38,14.31

2,5-Dimethyl-1-p-tolyl-1H-pyrrole (3c)

^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 6H), 2.41 (s, 3H) 5.88 (s, 2H), 7.07 (d, 2H, J=8 Hz), 7.23 (d, 2H, J=7.6 Hz); LC–MS: m/z: 186$(M+1)^+$, ^{13}CNMR ($CDCl_3$ 75 MHz) 137.50, 136.41, 129.74, 128.04, 105.50, 21.22, 13.09

2,5-Dimethyl-1-(4-nitro-phenyl)-1H-pyrrole (3d)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 6H), 5.96 (s, 2H), 7.40(d,2H,J=8.8 Hz), 8.36 (d, 2H, J=9.2 Hz), LC–MS: m/z: 217$(M+1)^+$. ^{13}CNMR ($CDCl_3$ 75 MHz) 150.13, 142.78, 132.15, 131.18, 129.51,121.17, 116.42,113.11, 11.98

2,5-Dimethyl-1-(3-nitro-phenyl)-1H-pyrrole (3e)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (s, 6H), 5.94 (s, 2H), 8.1(s, 1H), 8.26-8.29 (m, 3H); LC–MS: m/z: 217$(M+1)^+$. ^{13}CNMR ($CDCl_3$ 75 MHz) 148.34, 146.41, 133.47, 125.17, 123.53,113.17, 12.24

2,5-Dimethyl-1-(naphthalen-1-yl)-1H-pyrrole (3f)

^{1}HNMR ($CDCl_3$, 400MHz): δ 1.89(s, 6H), 6.1(s, 2H), 7.1(t, 1H, J = 8.08 Hz), 7.40 (t, 1H, J = 8.08 Hz), 7.44 (d, 1H, J = 8.28 Hz), 7.50 (d, 1H J = 8.35 Hz), 7.52 (d, 1H J = 8.35 Hz), 7.57 (d, 1H) , LC–MS: m/z: 222 (M+ 1) $^+$,^{13}CNMR ($CDCl_3$,75 MHz)140.17, 135.78, 132.27, 129.92, 129.47, 127.15, 126.52,125.10,118.31, 12.94

1-Benzyl-2,5-dimethyl-1H-pyrrole (3g)

^{1}HNMR ($CDCl_3$, 400MHz): δ 2.12(s, 6H), 4.99(s, 2H), 5.85(s, 2H), 6.86(d, 2H, J = 7.2 Hz), 7.20-7.29(m, 3H). LC–MS: m/z: 186 (M+ 1) $^+$, ^{13}CNMR ($CDCl_3$ 75 MHz) 137.50, 136.41, 129.74, 128.04, 105.50, 21.22, 13.09

1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (3h)

^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 6H), 5.90 (s, 2H), 7.13 (d, 2H, J = 8 Hz), 7.41 (d, 2H, J =8.8 Hz), LC-MS: m/z: 206 $(M+1)^+$. ^{13}C NMR ($CDCl_3$ 75 MHz) 139.12, 132.17, 130.76, 131.14, 122.49, 112.73, 13.12

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole (3i)

^{1}HNMR (($CDCl_3$, 400 MHz): δ 2.01 (s, 6H), 3.85 (s, 3H), 5.85 (s, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.24 (d, 2H, J =7.7 Hz), LC-MS: m/z: 202 $(M+1)^+$; ^{13}CNMR ($CDCl_3$ 75 MHz) 158.89, 131.79, 129.26, 129.07, 114.23, 105.29, 55.49, 13.01

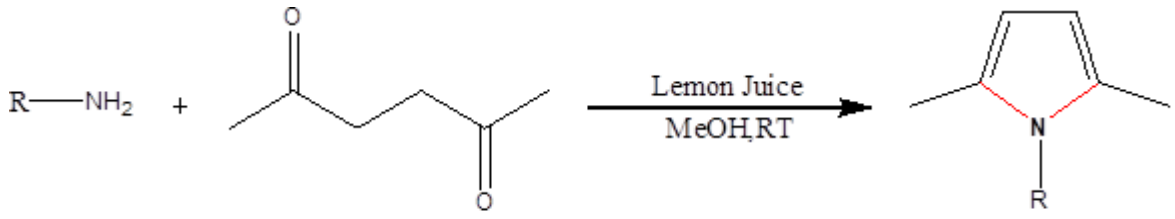
2,5-Dimethyl-1-m-tolyl-1H-pyrrole (3j)

^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 6H), 2.39 (s, 3H) 5.88 (s, 2H), 6.99 (s, 1H), 7.01-7.34 (m, 3H), LC–MS: m/z: 186$(M+1)^+$, ^{13}CNMR ($CDCl_3$ 75 MHz) 142.13, 139.65,133.45, 131.35, 127.34, 123.15, 119.34, 112.10, 21.45,11.93

III. RESULTS AND DISCUSSION

In order to develop the environmentally benign, mild reaction conditions and easy work up protocol we have performed the Paal-Knorr synthesis of pyrrole catalysed by lemon juice (scheme 1) and results obtained are discussed. Lemon is naturally available and inexpensive fruit of which Citrus Indica ,Citrus Limonium and Citrus Aurantium are very common species of Citrus family. The sour taste of lemon is due to citric acid which contributes 5-7 % of overall mass of lemon. The other components includes proteins and minerals[22]. The lemon juice catalysed synthesis of Schiff's base was proposed by Azadeh Alikhani[23] and co-workers. The p^H of lemon juice is found to be 2-3,which is suitable to act as acidic. In order to find out the efficiency of this green catalyst we have performed the Paal Knorr reaction with different concentration of lemon juice. The optimisation of reaction was performed with different quantity of lemon juice from 0.1ml to 0.5ml in different solvents like dichloromethane, acetonitrile, ethanol, methanol, water and in catalyst and solvent free conditions (table.1.)After optimisation it was observed that the 0.5 ml lemon juice in methanol was the best combination with respective to reaction time(1 hr) and yield (91%) as shown in table 1 (entry 6).

By keeping the this combination of catalyst and solvent we have synthesised the N- substituted pyrrole with different anilines with electron donating and withdrawing substituent on ring. After synthesis, it was observed that the anilines with electron donating groups delivered the product in short time as compare to those anilines with electron withdrawing substituent. Similarly the yield was also affected by electron donating and withdrawing groups on ring which is discussed table 2.



1a-j **2** **3a-j**

R = Alkyl & Aryl

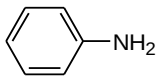
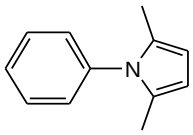
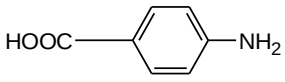
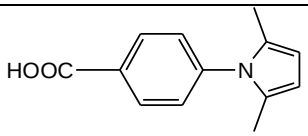
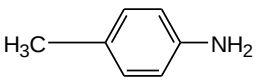
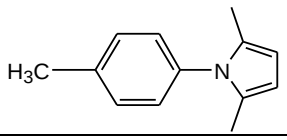
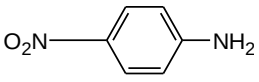
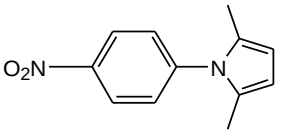
Scheme 2. Lemon juice catalysed synthesis of N-substituted pyrrole by Paal-Knorr Reaction.

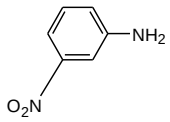
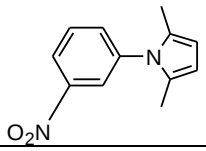
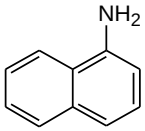
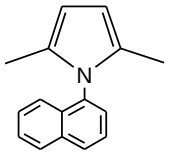
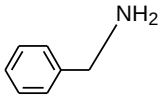
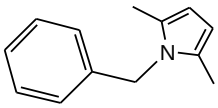
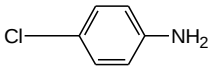
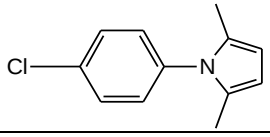
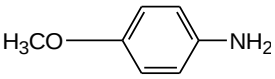
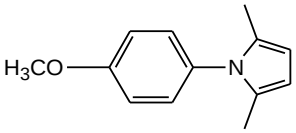
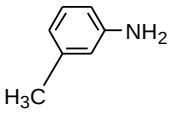
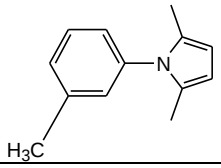
Table 1. Optimisation of Reaction of Aniline with Hexane-2,5-dione in lemon juice and different solvents

Entry	Lemon Juice in ml	Solvent	Time in hrs	Yield(%) [a]
1.	0.1	Toluene	07	45
2.	0.2	Toluene	6.3	62
3.	0.3	DCM	5.5	71
4.	0.4	DCM	4.3	77
5.	0.5	EtOH	03	83
6.	**0.5**	**MeOH**	**01**	**91**
7.	0.5	Acetonitrile	02	81
8.	0.5	Aqueous Medium	-	-
9.	Without Catalyst	Without Solvent	24	53

[a] Isolated Yield

Table 2

Entry	Anilines **1a-j**	N-Substituted Pyrrole **3a-j**	Reaction Time (hr)	Yield
1			2	83
2			3	69
3			1.2	84
4			3.1	53

5			3	62
6			1.5	89
7			1.2	93
8			1.3	91
9			1	94
10			1.3	89

IV. CONCLUSION

In conclusion we have introduced a simple, environmentally benign, cost effective, and green protocol for the synthesis of substituted pyrrole via Paal-Knorr reaction catalysed by lemon juice. The lemon juice being naturally available ,nonhazardous ,inexpensive, non toxic and easily soluble in almost all organic solvents is an alternative to synthetic catalyst .Therefore this green synthesis of pyrrole is more advantageous than other organic synthesis of pyrrole.

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