Grape Juice Catalyzed Synthesis of Substituted Pyrrole by Paal-Knorr Reaction

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Abstract: *In this research paper we have introduced the environmentally beningn protocol for synthesis of 1,2,5 trisubstituted pyrrole by Paal Knorr reaction. The reaction was performed between hexan-2,5-dione and aromatic amines in presence of grape juice as a catalyst in different solvents by simple stirring at room temperature. This novel and green method is found to be excellent in context to yield , reaction time and mild reaction conditions.*

Key Words: *Hexan-2,5-dione, Aniline, Grape Juice, Paal-Knorr Reaction*

1. INTRODUCTION:

Pyrrole the five member nitrogen heterocycle found in diversity of natural products[1] of which two molecules viz. haemoglobin and chlorophyll are life pigments. In spite of its natural abundance it is having versatile applications in industrial[2] and medicinal fields[3].The pharmaceutically important drugs also contains the pyrrole moiety which are used as antiinflammatant[4], antitumour[5] and antitubercular agents[6].The pyrrole is also having antimicrobial, antimalarial and cytotoxic properties[7].The tri and tetra substituted pyrroles are found to be more potent in medicinal chemistry due to their simple structure and simple methods of preparation. Due to versatile application of pyrrole for industrial and medicinal purpose several methods have been introduced for its synthesis of which Hentsch reaction 1890,Aza Witig reaction, Borton Lord and Kenner synthesis are conventional and well known. But in 1884 endeavours of Carl Paal and Ludwig Knorr became fruitful in pyrrole synthesis in which 1,4 diketones were condensed with aniline in presence of acid [8]. As far as synthetic routes are concerned numerous methods has been introduced for pyrrole synthesis. Surya De et.al reported the synthesis of 1,2,5 tri substituted pyrrole under solvent free condition by using aromatic amines and 1,4 dicabonyl compounds in presence of cobalt catalyst. [9] Similarly Maurizio Taddei[10] and co-workers reported the synthesis of pyrrole by microwave irradiation. Ahmed Kamal[11] and co-workers reported the Cerium Ammonium Nitrate catalysed synthesis of pyrrole by Paal Knorr reaction.Recently Bela Torock[12] and co-workers introduced the solvent and catalyst free synthesis of pyrrole by Paal Knorr method. In spite of importance of all these methods there are some limitations in the view of drastic reaction conditions ,microwave irradiations, longer reaction time ,use of strong acids as catalyst, poor yield and lengthy work up. In order to overcome from these limitations we have introduced the environmentally benign method for synthesis of pyrrole catalysed by grape juice by Paal Knorr reaction. The naturally occurring fruits are rich with diversity of compounds including salts, sugars, liquids, inorganic and organic compounds. The grapes (Vitis vinifera) is rich with chemical substances like sugars, organic acids, phenolic compounds and minerals[13].The tartaric acid and malic acid which are present in large extent in grapes shows the acidic character[14]. The properties of grapes like natural abundance acidic nature, cheapest and non toxic nature inspired us to develop such protocol for synthesis of pyrrole.

2. MATERIALS AND METHODS:

Melting points were determined in an open capillary by micro controller based melting point apparatus of Chemline company and are un corrected.^{1}H NMR spectra were recorded on Bruker 400 Mhz spectrometer TMS as standard. Mass Spectra were recorded using Thermo Fischer mass spectrometer. ^{13}C NMR spectra were recorded on Bruker 400 Mhz spectrometer. All the chemicals were synthetic grade of SD-Fine and Merck brand. The grapes juice extracted from *Vitis Viniferra Linne* species which is commonly known as *Anab e Shahi* purchased from market A representative experimental procedure for pyrrole synthesis To the solution of aniline 1a-j (0.01 mole)and hexan-2,5-dione (0.01) mole in R.B. falsk,2-3 drops of grape juice and solvent was added and reaction mixture was allowed to stir at room temperature for 1-3 hrs. After completion of the reaction as indicated by TLC the solvent was evaporated under reduced pressure. The residue was washed with water and air dried. The crude product was recrystallized from ethanol-water to get pure product.

3. DISCUSSION:

The Paal Knorr reaction was performed by taking aromatic aniline (1a-j) and hexane-2,5-dione (2a) in presence of grape juice as catalyst((scheme 1) and the product 1,2,5 tri substituted pyrrole (3a-j) abstained were tabulated. This greener approach for synthesis of pyrrole is found to be efficient because of non toxic nature of grape juice and natural abundance. In order to determine the efficiency of this green catalyst we performed the reaction in solvents like dichloromethane , acetonitrile, and ethanol and found that in polar solvent(ethanol) yield was excellent. Similarly the anilines which were in liquid state produced more yield than the anilines in solid state it is due to their miscibility in grape juice. The anilines having electron donating substituent produced more yield than electron withdrawing substituent as shown in table 1.

4. ANALYSIS :

2,5-Dimethyl-1-phenyl-1H-pyrrole (3a)
^{1}H NMR ($CDCl_3$, 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}C NMR ($CDCl_3$ 75 MHz) 139.09, 129.13 128.33, 127.70, 13.11

2,5-Dimethyl-1-p-tolyl-1H-pyrrole (3b)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 6H), 2.41 (s, 3H) 5.88 (s, 2H), 7.07 (d, J=8 Hz,2H), 7.23 (d, J=7.6 Hz,2H); LC–MS: *m/z*: 186(M+1)$^+$; ^{13}C NMR ($CDCl_3$ 75 MHz) 137.50, 136.41, 129.74, 128.04, 105.50, 21.22, 13.09

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole (3c)
^{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), LC-MS: m/z: 202 (M+1) $^+$; ^{13}C NMR ($CDCl_3$ 75 MHz) 158.89, 131.79, 129.26, 129.07, 114.23, 105.29, 55.49, 13.01

1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (3d)
^{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

4-(2,5-Dimethyl-pyrrol-1-)-phenol (3e)
^{1}HNMR ($CDCl_3$, 400 MHz): δ 2.09 (s, 6H), 5.72 (s, 2H), 6.85 (d, 2H, *J* = 7.6 Hz), 6.97 (d, 2H, *J* =7.6 Hz), 9.6 (s,1H exchangeable with D_2O) LC-MS: m/z: 188 (M+1)$^+$. ^{13}C NMR ($CDCl_3$ 75 MHz) 157.12, 135.78, 129.26, 132.11, 123.41, 118.33, 55.109.18, 13.45

1-Benzyl-2,5-dimethyl-1H-pyrrole (3f)
^{1}HNMR ($CDCl_3$, 400MHz): ∂ 2.12(s, 6H), 4.99(s, 2H), 5.85(s, 2H), 6.86(d, 2H, J = 7.2Hz), 7.20-7.29(m, 3H). LC–MS: *m/z*: 186 (M+ 1) $^+$; ^{13}C NMR ($CDCl_3$ 75 MHz) 137.50, 136.41, 129.74, 128.04, 105.50, 21.22, 13.09

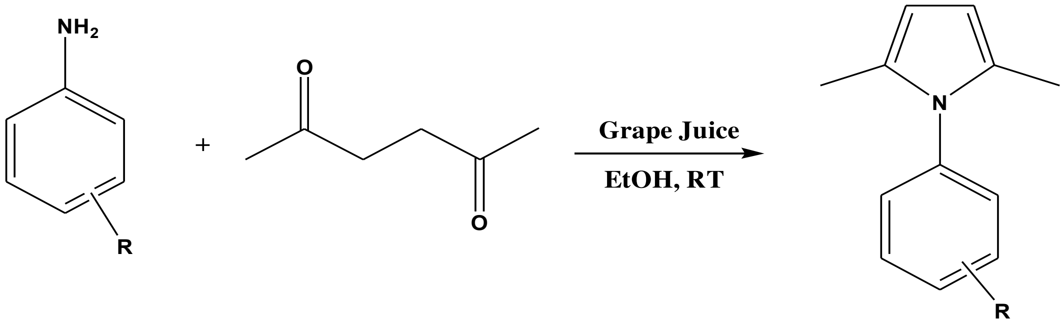
2,5-Dimethyl-1-(naphthalen-1-yl)-1H-pyrrole (3g)
^{1}HNMR ($CDCl_3$, 400MHz): ∂ 1.89(s, 6H), 6.0(s, 2H), 7.1(t, 1H, *J* = 8.08 Hz), 7.40 (t, 1H, *J* = 8.08 Hz), 7.44 (d, 1H, *J* = 8.28 Hz), 7.50 (d, 1H *J* = 8.35 Hz), 7.52 (d, 1H *J* = 8.35 Hz), 7.57 (d, 1H) , LC–MS: *m/z*: 222 (M+ 1) $^+$. ^{13}C NMR ($CDCl_3$ 75 MHz) 140.17, 135.78, 132.27, 129.92, 129.47.127.15, 126.52,125.118.31, 12.94

2,5-Dimethyl-1-m-tolyl-1H-pyrrole (3h)
^{1}H NMR ($CDCl_3$, 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}C NMR ($CDCl_3$ 75 MHz) 142.13, 139.65,133.45, 131.35, 127.34, 123.15, 119.34, 112.10, 21.45,11.93

2,5-Dimethyl-1-(4-nitro-phenyl)-1H-pyrrole (3i)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 6H), 5.96 (s, 2H), 7.40(d, J=8.8 Hz 2H), 8.36 (d, 2H J=9.2 Hz); LC–MS: *m/z*: 217(M+1)$^+$. ^{13}C NMR ($CDCl_3$ 75 MHz) 150.13, 142.78, 132.15, 131.18, 1279.51,121.17, 116.42,113.11, 11.98

2,5-Dimethyl-1-(3-nitro-phenyl)-1H-pyrrole (3j)
^{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}C NMR ($CDCl_3$ 75 MHz) 148.34, 146.41, 133.47, 125.17, 123.53.113.17, 12.24

Scheme 1

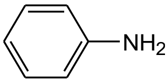
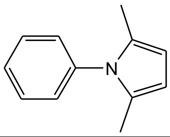
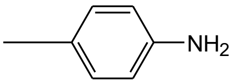
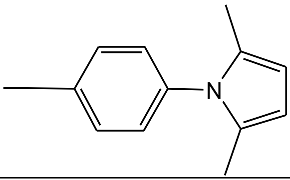
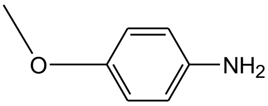
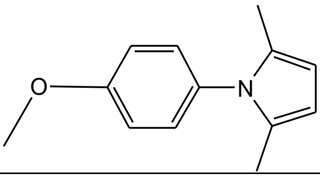
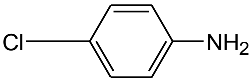
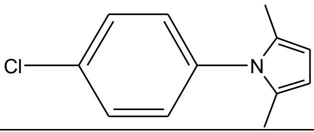
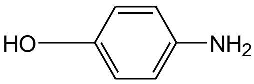
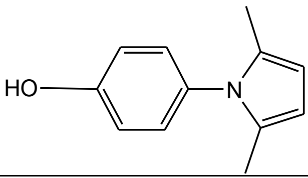
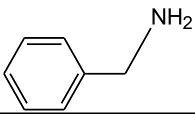
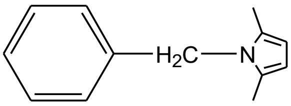
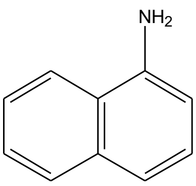
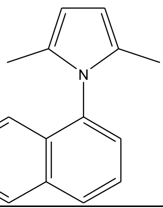


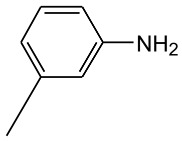
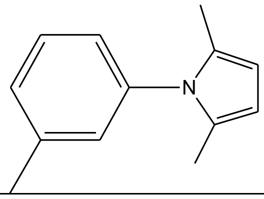
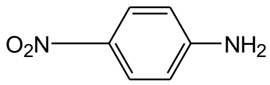
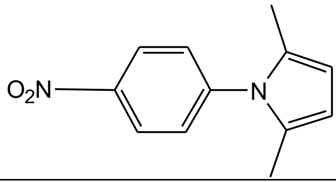
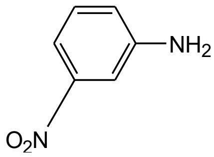
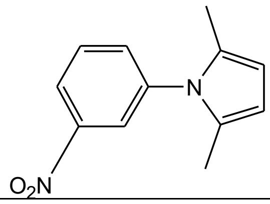
1a-j **2a** **3a-j**

Synthesis of substituted Pyrrole by Paal Knorr reaction using Grape juice as catalyst

5. RESULT:

Table 1

Entry	Anilines (1a-j)	Substituted Pyrrole (3a-j)	M.P. in °C	Yield (%)[a]
a			49-51	91
b			45-47	93
c			55-59	94
d			47-52	88
e			39-43	87
f			55-58	91
g			63-67	84

h			79-83	78
i			51-55	67
j			63-69	73

[a] Isolated Yield

6. CONCLUSION:

We have demonstrated the greener protocol for synthesis of pyrrole by Paal Knorr reaction catalysed by grape juice. The naturally available and non toxic nature of grape juice which act as green catalyst is an alternative to harsh chemicals. The developed method produced significant advantages such as mild reaction conditions, easy work up procedure and excellent yield.

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