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Microwave Assisted One Pot Synthesis of Functionalized Pyrrole Derivatives Catalyzed by Uranyl Nitrate Hexa Hydrate

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Abstract: **An effective and simple method for the functionalized pyrrole synthesis has been developed using a $UO_2(NO_3)_2$· $6H_2O$ catalyst under conventional method. Pyrrole synthesis with uranyl nitrate hexa hydrate catalyst has various advantages, such as fast activity, good yields and reduces reaction times in ethanol media. The synthesized target compounds were characterized by FT-IR, elemental analysis, ^1H and ^{13}C NMR.**

Index Terms: **Microwave, Uranyl nitrate, Pyrrole.**

I. Introduction

The heterocyclic compounds contain nitrogen atom in their structures which provide a wide array of biological activities; the valence electron of nitrogen atom contribute to promoting the building of several supramolecular structures. Pyrrole moieties are among the most important compound in heterocyclic chemistry [1]. Pyrrole derivatives have been higher attention in recent times because they could be used in many therapeutic areas such as anti-HIV [2] and antimicrobial agents [3-7].

There have been significant advances in the methodology of multi-component reactions (MCRs) over the past decade and substantial efforts continue to develop new MCRs. The pyrrole ring has found a massive number of therapeutic applications and seems to be found in several natural products [8] Pyrroles tend to build the main framework of porphyrin rings in chlorophyll, heme and vitamin B12, with an increasing medically important drug molecules, like atorvastatin and tolmetin (Fig.1). Several synthetic methods for the construction of pyrroles have been developed till date [9, 10].

Among the most common pathways to construction of pyrroles is the Paal–Knorr reaction in which 1,4-dicarbonyl compounds in the presence of primary amines are converted to pyrroles. Some catalysts such as montmorillonite KSF [11], iodine [12], montmorillonite [13], $Zr(KPO_4)_2$ [14], $Sc(OTf)_3$ [15], alumina [16], microwave irradiation [17,18], ionic liquid [19], $InCl_3$ [20] and $Ga(OTf)_3$ [21] $ZrCl_4$/ultrasonic irradiation [22], have been used for this conversion.

Aryl glyoxal containing functional groups such as aldehyde and ketone undergo condensation reaction, play a vital role in organic synthesis, particularly in heterocyclic molecule synthesis. The cost effective and easy method for the synthesis of pyrrole derivatives under mild conditions from a one-pot reaction of aryl glyoxal derivatives and equimolar mixture of 1,3-dicarbonyl compounds in the presence $UO_2(NO_3)_2$· $6H_2O$ catalyst.

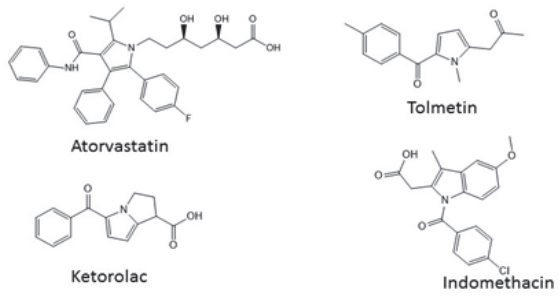


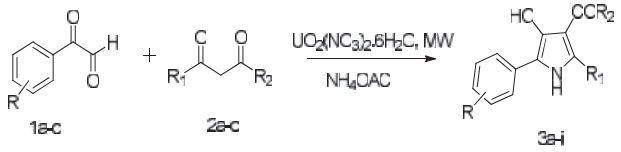
Figure.1 Pharmaceutically active molecules containing pyrrole ring

II. Results and Discussion

As a basic model system, the reaction between aryl glyoxal (1 mmol) with an equimolar amount of 1,3-dicarbonyl compound and catalytic amount of uranyl nitrate was investigated to assess the efficiency of the method and enhance the reaction conditions. Choosing a suitable reaction medium is well known to be of crucial importance for efficient synthesis. The mixture of the reactions was tested under various conditions. Solvent and temperature outcomes for this reaction have been measured, and the findings are summarized in Table 1. $UO_2(NO_3)_2$· $6H_2O$ is a more economical catalyst compared to the other Lewis acid catalysts mentioned in the literature for the synthesis of functionalized pyrrole compounds.

The reaction conditions were efficiently established using condensation of aryl glyoxal and 1,3-dicarbonyl compound

with catalytic quantities of uranyl nitrate in classical and microwave irradiations using diverse solvent systems such as dichloromethane, chloroform, ethanol, acetonitrile, methanol and various percentage of catalytic mole ratio also examined, and the results were also summarized.



SCHEME 1 Facile one pot synthesis of functionalized pyrrole derivatives.

Table 1 showing that polar solvents such as methanol, ethanol, and acetonitrile yielded better than nonpolar solvents like chloroform, dichloromethane and the results suggesting that ethanol was the best solvent for this type of conversion. The results show that the reaction under microwave irradiation continues more effectively compared with traditional heating. Additionally, the catalyst loading effect was observed. The maximum percentage of the mole catalyst was 10 mole%. There was no change in the yield percentage when we increased the catalyst mole percentage.

TABLE I.
EFFECT OF SOLVENT

S. No	Solvents	Catalyst (mol %)	Time (min.)	Yield (%)
1	$CHCl_3$	10	20	16
2	DCM	10	20	23
3	Ethanol	10	15	85
4	Methanol	10	18	73
5	Acetonitrile	10	19	65

After examination of the optimized reaction conditions, this approach was used for the preparation of pyrrole using different aryl glyoxal and 1,3-dicarbonyl compounds under microwave and traditional heating conditions for the development of new pyrrole compounds in presence of uranyl nitrate catalyst. (Table 3). The highly water-soluble catalyst could be isolated by washing with more amount of ice-cold water by filtration. All the constructed derivatives distinguished by IR, elemental analysis, ^{1}H and ^{13}C NMR.

TABLE II.
EFFECT OF CATALYSTS LOADING

S. No	Catalyst	Catalyst (mol %)	Time (min.)	Yield (%)
1	$UO_2(NO_3)_2 \cdot 6H_2O$	5	15	75
2	$UO_2(NO_3)_2 \cdot 6H_2O$	10	15	85
3	$UO_2(NO_3)_2 \cdot 6H_2O$	15	15	85
4	$UO_2(NO_3)_2 \cdot 6H_2O$	20	15	85
5	Conc. H_2SO_4	1 mL	12 h	55

III. EXPERIMENTAL PROCEDURE

General protocol for the preparation of pyrrole derivatives (3a-i):

General Method

A mixture of aryl glyoxal (1 mmol), 1,3-dicaronyl compound (1 mmol), ammonium acetate (2 mmol), 10 mL of ethanol and uranyl nitrate (10 mol percent) was refluxed as shown in Table 3. After TLC indicated completion of the reaction, the reaction blend was transferred into ice-cold water. Stir the mixture for about 15-20 minutes and left 10 hours. The obtained solids were collected by the filtration through a funnel, washed with cold water and then purified from hot ethanol to provide **3a-i** pure derivatives.

TABLE III.
EXPERIMENTAL RESULTS AND PHYSICAL DATA OF PYRROLE DERIVATIVES

Compound	R	R_1	R_2	Reaction Time (min)	Yield (%)	m.p. (°C)
3a	H	Me	Me	15	91	dec. 234
3b	H	Me	OMe	16	90	dec. 231
3c	H	Me	OEt	17	86	dec. 233
3d	4-F	Me	Me	18	83	dec. 229
3e	4-F	Me	OMe	18	85	dec. 247
3f	4-F	Me	OEt	19	83	dec. 236
3g	4-NO_2	Me	Me	19	83	dec. 246
3h	4-NO_2	Me	OMe	18	86	dec. 224
3i	4-NO_2	Me	OEt	18	82	dec. 243

Microwave irradiation

In a small beaker, a mixture of aryl glyoxal (1 mmol), 1,3-dicaronyl compound (1 mmol), ammonium acetate (2 mmol), uranyl nitrate (10 mol percent) and ethanol 5 mL was taken and then microwave irradiation was applied to the reaction mixture at an interval of 2 min at 180 W for 11-18 minutes summarized in table 3. The reaction was monitored by TLC. After the reaction was finished, the reaction blend poured into cold water and the separated adduct was filtered, dried, and then purified from hot methanol to provide pure 3a-i compounds, and their physical data are provided in Table 3.

Compound (3a): mp: Decomp at 234 °C; FT-IR (KBr): ν 3370, 3123, 3023, 1676, 1532, 1454, 1387, 1216, 1083 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, ppm), δ_H = 10.65 (s, 1H, NH), 9.23 (s, 1H, OH), 7.09 (d, J = 7.3 Hz, 2H, Ar-H), 6.45 (t, J = 7.0 Hz, 2H, Ar-H), 6.51 (t, J = 7.23 Hz, 1H, Ar-H), 2.12 (s, 3H, CH_3), 1.79 (s, 3H, CH_3). ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 196.9, 142.3, 134.4, 130.5, 127.5, 123.3,

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121.3, 109.4, 109.1, 22.9, 14.4; Elemental analysis, calculated for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Experimental: C, 72.51; H, 6.10; N, 6.53%.

Compound (3b): mp: Decomp at 231 °C; FT-IR (KBr): ν 3430, 3079, 2976, 2872, 1698, 1643, 1523, 1423, 1313,1191, 1012 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 10.43 (s, 1H, NH), 8.98 (s, 1H, OH), 7.34 (m, 2H, Ar-H), 7.28 (m,3H, Ar-H), 2.12 (s, 3H, CH_3), 1.79 (s, 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 169.4, 142.1, 132.4, 131.4, 126.5, 125.9, 121.8, 113.7, 109.9, 61.2, 16.2; Elemental analysis, calculated for $C_{13}H_{13}NO_3$: C, 67.52; H,5.67; N, 6.06. Experimental: C, 67.87; H, 5.65; N, 6.22%.

Compound (3c): mp: Decomp at 233 °C; FT-IR (KBr): ν 3338, 3067, 2978, 1688, 1667, 1523, 1421, 1312, 1178, 1087, 1023 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δH = 10.23 (s, 1H, NH), 8.98 (s, 1H, OH), 7.56 (d, *J* = 6.9 Hz, 2H, Ar-H),7.12 (t, *J* = 7.23 Hz, 2H, Ar-H), 7.06 (t, *J* = 7.12 Hz, 1H, Ar-H), 3.87 (q, *J* = 6.98 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.42 (t, *J* = 6.95 Hz, 3H, CH_3). ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 169.4, 146.7, 132.9, 131.2, 127.6, 123.9, 121.7, 110.1, 109.7, 60.1, 18.1, 15.2; Elemental analysis, calculated for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Experimental: C, 68.56; H, 6.09; N, 5.76%.

Compound (3d): mp: Decomp at 229 °C; FT-IR (KBr): ν 3448, 3205, 3030, 1684, 1632, 1509, 1409, 1303, 1225, 1168, 1094, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 10.81 (s, 1H, NH), 8.69 (s, 1H, OH), 7.67 (dd, *J* = 8.94 Hz, & *J* = 5.25 Hz, 2H, Ar-H), 7.05 (m, 2H, Ar-H) 2.23 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); 13C NMR (100.128 MHz, DMSO, ppm), δ_C = 194.3, 165.4, 131.4, 129.3, 127.8, 116.4, 115.9, 112.8, 111.9, 25.8, 16.9; Elemental analysis, calculated for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Experimental: C, 66.88; H, 5.14; N, 6.06%.

Compound (3e): mp: Decomp at 247 °C; FT-IR (KBr): ν 3325, 3067, 2976, 1703, 1659, 1514, 1505, 1489, 1314, 1218, 1158, 1098, 1080 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 10.43 (s, 1H, NH), 8.65 (s, 1H, OH), 7.64 (m, 2H, Ar-H), 7.09 (t, *J* = 7.9 Hz, 2H, Ar-H), 3.28 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C =168.5, 161.9, 134.9, 131.2, 126.8, 120.0, 115.9, 112.8, 111.9, 52.4, 18.1; Elemental analysis, calculated for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Experimental: C, 62.76; H, 4.89; N, 5.39%.

Compound (3f): mp; Decomp at 236 °C; FT-IR (KBr): ν 3345, 3086, 3010, 1738, 1548, 1545, 1528, 1329, 1252, 1173, 1102, 1084, 1028 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 10.32 (s, 1H, NH), 8.37 (s, 1H, OH), 7.67 (dd, *J* = 5.4 Hz, *J* = 7.6 Hz 2H, Ar-H), 7.08 (m, 2H, Ar-H), 3.92 (q, *J* = 6.78 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.06 (t, *J* = 6.9 Hz 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 167.9, 161.9, 131.4, 131.0, 129.2, 117.4, 115.9, 112.8, 111.7, 52.3, 18.3, 13.9. Elemental analysis, calculated for $C_{14}H_{14}FNO_3$: C, 63.87; H, 5.36; N, 5.32. Experimental: C, 63.83; H, 5.45; N, 5.32%.

Compound (3g): mp; Decomp at 246 °C; FT-IR (KBr): ν 3482, 3345, 1647, 1583, 1511, 1318, 1213, 1176, 1098, 1043, 1011 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 11.12 (s, 1H, NH) 10.43 (s, 1H, OH), 8.17 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.67 (d, *J* = 8.2 Hz, 2H, Ar-H), 2.42 (s, 3H, CH_3), 2.12 (s, 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 197.3, 148.6, 142.6, 138.9, 134.2, 123.6, 121.5, 109.8, 196.7, 28.7, 14.9; Elemental analysis, calculated $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76%. Experimental: C, 60.23; H, 4.35; N, 10.54%.

Compound (3h): mp; Decomp at 224 °C; FT-IR (KBr): ν 3523, 3432, 1676, 1621, 1512, 1312, 1232, 1163, 1198, 1056, 1031 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 11.43 (s, 1H, NH), 8.98 (s, 1H, OH), 8.18 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.76 (s, 3H, CH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 168.7, 148.9, 142.3, 139.6, 135.7, 123.7, 121.9, 109.6, 100.7, 50.7, 13.9; Elemental analysis, calculated for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14%. Experimental: C, 56.34; H, 4.45; N, 10.48%.

Compound (3i): mp; Decomp at 243 °C; FT-IR (KBr): ν 3498, 3434, 1683, 1589, 1532, 1323, 1212, 1178, 1102, 1054, 1023 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm), δ_H = 11.65 (s, 1H, NH), 9.05 (s, 1H, OH), 8.19 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.79 (d, *J* = 8.7 Hz, 2H, Ar-H), 4.29 (q, *J* = 6.9 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 1.23 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100.128 MHz, DMSO, ppm), δ_C = 168.5, 148.6, 144.3, 139.7, 135.7, 123.8, 121.9, 111.5, 100.3, 61.2, 14.9, 14.0; Elemental analysis, calculated for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65%. Experimental: C, 57.99; H, 4.79; N, 9.89%.

IV. Conclusions

A simple and effective method for the synthesis of acetyl-4-hydroxy-2-methyl-5-phenyl-1H-pyrrole derivatives was proposed using $UO_2(NO_3)_2.6H_2O$ as a catalyst for the condensation of various substituted aryl glyoxal, 1,3-dicarbonyl compounds and ammonium acetate under traditional heating and microwave irradiation conditions. The profits of this technique are operational simplicity, short reaction time, easy work-up, easily available catalyst and, high conversion of yields.

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