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One-pot synthesis of 5-[1-substituted 4-acetyl-5-methyl-1*H*-pyrrol-2-yl]-8-hydroxyquinolines using DABCO as green catalyst

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Abstract: A green and simple method for the synthesis of the title compounds **4** by the reaction of 5-chloroacetyl-8-hydroxyquinoline (**1**), pentane-2,4-dione (**2**), and amines **3** in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane at 60°C is described. The procedure is amenable for the synthesis of other substituted pyrroles. Short reaction time, environmentally friendly procedure, and excellent yields are the main advantages. The structures of products **4a–n** were characterized by ¹H NMR, IR, and MS spectra.

Keywords: 1,4-diazabicyclo[2.2.2]octane (DABCO); multi-component reactions; substituted pyrrole.

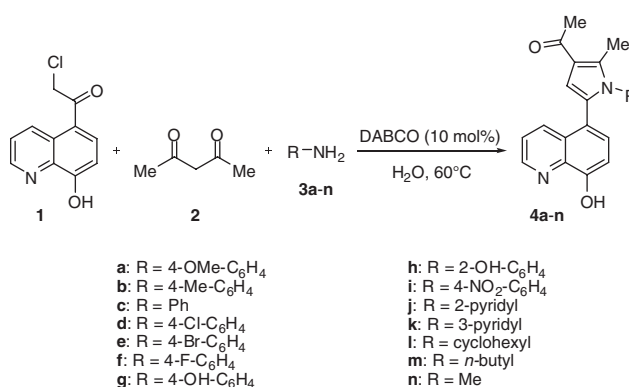
Introduction

Multicomponent reactions have emerged as a valuable tool in modern combinatorial synthesis. Moreover, one-pot multicomponent reactions, because of their productivity, facile execution, and simple reaction profile, are an important strategy in multicomponent reactions [1–4]. The pyrrole ring is widely distributed in many natural and biologically important molecules such as porphyrins, coenzymes, and alkaloids [5]. There has been an enhanced interest in the synthesis of pyrrole and its oligomers due to their potential application as conducting materials [6]. Owing to their diverse biological and pharmaceutical applications [7–9], there is a continuous interest in the synthesis of pyrroles by simple methods [10, 11]. Recently, a synthesis of pyrroles was accomplished by the multi-component reaction of phenacyl bromide, amine, and

acetylacetone in the presence of β -cyclodextrin in water [12]. However, the reported method is limited to the use of phenacyl bromide and aryl amines. The use of an aqueous medium has attracted considerable interest because of environmental and economic issues [13]. Very recently, 1,4-diazabicyclo[2.2.2]octane (DABCO) has emerged as a promoter for various organic reactions [14–18]. DABCO is an organic base that can act as nucleophile and is soluble in water. In continuation of our research program to develop environmentally friendly reactions [19–22], we report herein a simple, practical, and general three-component reaction for the construction of pyrrole derivatives by the reaction of 5-chloroacetyl-8-hydroxyquinoline, acetylacetone, and aryl-, heteroaryl-, and alkylamines in aqueous medium in the presence of DABCO.

Results and discussion

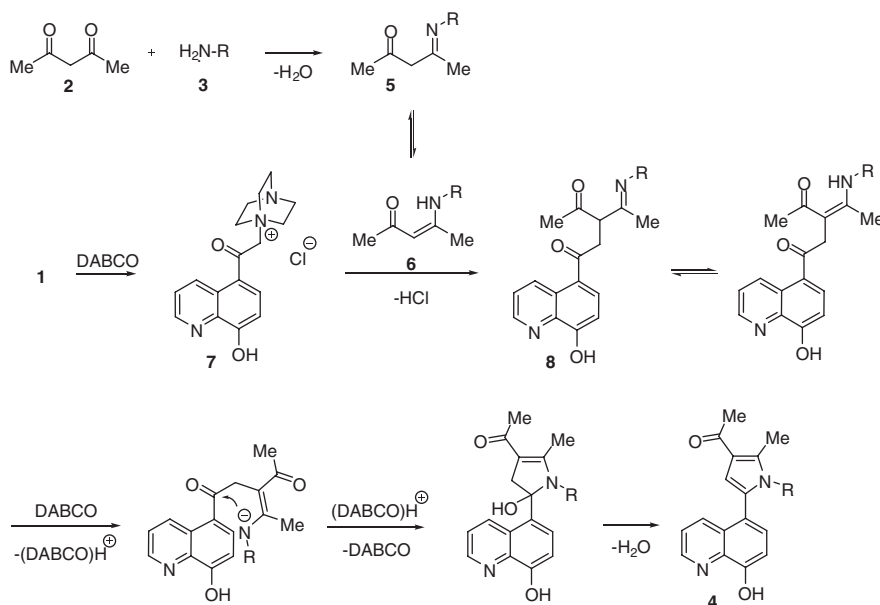
The one-pot three-component reaction between 5-chloroacetyl-8-hydroxyquinoline (**1**, 1 mmol), acetylacetone (**2**, 1 mmol), and 4-methoxyaniline (**3a**, 1 mmol) (Scheme 1) in the presence of different catalysts and in different solvents under reflux conditions was investigated as a model reaction. The results showed that the yield of the desired product **4a** was enhanced by using DABCO as a



Scheme 1 Synthesis of 5-(*N*-substituted pyrrol-2-yl)-8-hydroxyquinolines **4a–n**.

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Scheme 2 Mechanistic pathway to compounds **4a–n**.

catalyst. The product was formed in low yields of 21%, 30%, and 18% in the presence of Et_3N , L-proline, and pyridine, respectively. The use of Na_2CO_3 as a basic catalyst in water failed to give the target compound **4a**. Thus, DABCO was chosen as an optimal catalyst for further investigations. After extensive screening of the molar ratio (5, 10, 15, and 20 mol%) of DABCO to the substrates, it was found that the amount of 10 mol% promoted the maximum conversion to the product, in a yield of up to 93%. It was also evident that an increase in the molar ratio above 10 mol% did not increase the yield and did not shorten the reaction time. After conducting the reaction in a variety of solvents including 1,2-dichloroethane, tetrahydrofuran, acetonitrile, and methanol, it was concluded that water was the most suitable solvent for this transformation. Higher yields were obtained when the reaction was conducted at 60°C compared to reflux conditions.

Then, yields of the reactions conducted with various amines were compared. Under the optimized conditions as discussed above, the results showed that aromatic amines, heteroaromatic amines, and aliphatic amines successfully reacted with 5-chloroacetyl-8-hydroxyquinoline (**1**) and acetylacetone (**2**) to give the desired products **4a–n** in good to excellent yields (60–93%).

The structures of products **4a–n** were confirmed on the basis of their spectra and elemental analysis. In particular, the IR spectra of **4a–n** show characteristic absorption bands of a conjugated acetyl group at $1665\text{--}1679\text{ cm}^{-1}$. In the ^1H NMR spectra, the methyl protons of the

pyrrole-methyl moiety give a singlet at $2.06\text{--}2.30\text{ ppm}$ and the acetyl protons resonate at $2.45\text{--}2.75\text{ ppm}$, also as a singlet. A characteristic singlet at $6.40\text{--}6.672\text{ ppm}$ is ascribed to pyrrole H-3.

A suggested mechanism for the formation of pyrroles **4a–n** is shown in Scheme 2. It can be presumed that initially pentane-2,4-dione **2** undergoes a reaction with amine **3** to form the unsaturated amino ketone **5**, which is in equilibrium with its tautomer **6**. The quaternization reaction of substrate **1** with DABCO generates the quaternary salt **7**, which subsequently undergoes a reaction with **6** to form the intermediate product **8**, which is the suggested precursor to the final product **4**.

Conclusion

A novel, green, rapid, and efficient protocol for the synthesis of 5-(*N*-substituted pyrrol-2-yl)-8-hydroxyquinolines in water in the presence of DABCO was developed.

Experimental

Melting points were determined on a Kofler melting point apparatus and are not corrected. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using KBr pellets. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Jeol LA 400 instrument. Electron-impact mass spectra were taken on a JEOL JMS 600

spectrometer at an ionizing potential of 70 eV. Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyzer at Assiut University.

General procedure for the synthesis of 5-[1-substituted 4-acetyl-5-methyl-1*H*-pyrrol-2-yl]-8-hydroxyquinolines 4a–n

A mixture of 5-chloroacetyl chloride (**1**, 1 mmol), acetylacetone (**2**, 1 mmol), amine (**3a–n**, 1 mmol), and DABCO (10 mol%) in water (5 mL) was stirred at 60°C for the period of time indicated below. The progress of the reaction was monitored by TLC. The solid obtained was washed with distilled water (3×10 mL) for removal of the catalyst and extracted with dichloromethane. The extract was filtered and concentrated under reduced pressure. Pure product **4a–n** was obtained by crystallization from ethanol.

5-[4-Acetyl-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrol-2-yl]-8-hydroxyquinoline (4a) Reaction time 1.5 h; yield 93%; yellow crystals; mp 231–233°C; IR: ν 3040 (CH, aromatic), 2950, 2850 (CH, aliphatic), 1655 (C=O), 1630 cm^{-1} (C=C); ^1H NMR: δ 2.25 (s, 3H, CH_3), 2.45 (s, 3H, COCH_3), 3.55 (s, 3H, OCH_3), 6.60 (s, 1H, pyrrole H-3), 6.85–8.40 (m, 10H, aromatic H); ^{13}C NMR: δ 9.5, 23.2 (2 CH_3), 60.3 (OCH_3), 111.4 (C), 114.3 (CH), 115.7 (CH), 116.3 (2CH), 118.8 (C), 119.3 (C), 122.6 (CH), 123.3 (2CH), 124.1 (CH), 126.7 (C), 128.3 (C), 132.4 (C), 136.1 (CH), 139.4 (C), 150.7 (CH), 154.6 (C), 158.5 (C), 199.6 (C=O); MS: m/e 372.11 (M^+ , 62%). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_3$ (372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 74.51; H, 5.73; N, 7.89.

5-[4-Acetyl-1-(4-tolyl)-5-methyl-1*H*-pyrrol-2-yl]-8-hydroxyquinoline (4b) Reaction time 2 h; yield 90%; yellow crystals; mp 191–193°C; IR: ν 3055 (CH, aromatic), 2965, 2850 (CH, aliphatic), 1666 (C=O), 1637 cm^{-1} (C=C); ^1H NMR: δ 2.15 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.57 (s, 3H, COCH_3), 6.60 (s, 1H, pyrrole H-3), 6.80–8.45 (m, 10H, aromatic H). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ (356.42): C, 77.51; H, 5.66; N, 7.86. Found: C, 77.88; H, 5.94; N, 8.15.

5-(4-Acetyl-1-phenyl-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4c) Reaction time 2.5 h; yield 88%; light yellow crystals; mp 150–152°C; IR: ν 3015 (CH, aromatic), 2975, 2850 (CH, aliphatic), 1665 (C=O), 1630 cm^{-1} (C=C); ^1H NMR: δ 2.10 (s, 3H, CH_3), 2.55 (s, 3H, COCH_3), 6.70 (s, 1H, pyrrole H-3), 6.95–7.90 (m, 11H, aromatic H); MS: m/e 342.51 (M^+ , 17%). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ (342.39): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.52; H, 5.61; N, 8.45.

5-(4-Acetyl-1-(4-chlorophenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4d) Reaction time 2.5 h; yield 80%; yellow crystals; mp 213–215°C; IR: ν 3110 (CH, aromatic), 2980 (CH, aliphatic), 1675 (C=O), 1635 cm^{-1} (C=C); ^1H NMR: δ 2.25 (s, 3H, CH_3), 2.50 (s, 3H, COCH_3), 6.66 (s, 1H, pyrrole H-3), 6.98–8.12 (m, 10H, aromatic H). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{O}_2$ (376.48): C, 70.12; H, 4.55; Cl, 9.41; N, 7.43. Found: C, 70.43; H, 5.00; Cl, 9.68; N, 7.71.

5-(4-Acetyl-1-(4-bromophenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4e) Reaction time 2.5 h; yield 72%; yellow crystals; mp 303–305°C; IR: ν 3095 (CH, aromatic), 2990 (CH, aliphatic), 1670 (C=O), 1627 cm^{-1} (C=C); ^1H NMR: δ 2.30 (s, 3H, CH_3), 2.55 (s, 3H, COCH_3), 6.77 (s, 1H, pyrrole H-3), 6.95–8.15 (m, 10H, aromatic

H); MS: m/e 421.13 (M^+ , 55%). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{O}_2$ (421.29): C, 62.72; H, 4.07; Br, 18.97; N, 6.65. Found: C, 63.09; H, 4.41; Br, 19.16; N, 6.89.

5-(4-Acetyl-1-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4f) Reaction time 3.5 h; yield 69%; yellow crystals; mp 258–260°C; IR: ν 3085 (CH, aromatic), 2985 (CH, aliphatic), 1666 (C=O), 1625 cm^{-1} (C=C); ^1H NMR: δ 2.11 (s, 3H, CH_3), 2.65 (s, 3H, COCH_3), 6.65 (s, 1H, pyrrole H-3), 6.80–7.80 (m, 10H, aromatic H). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{FN}_2\text{O}_2$ (360.38): C, 73.32; H, 4.75; N, 7.77. Found: C, 73.58; H, 5.11; N, 8.13.

5-(4-Acetyl-1-(4-hydroxyphenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4g) Reaction time 3.5 h; yield 70%; yellow crystals; mp 323–325°C; IR: ν 3455 (OH), 3100 (CH, aromatic), 2980 (CH, aliphatic), 1670 (C=O), 1633 cm^{-1} (C=C); ^1H NMR: δ 2.10 (s, 3H, CH_3), 2.70 (s, 3H, COCH_3), 6.57 (s, 1H, pyrrole H-3), 7.12–8.15 (m, 10H, aromatic H), 9.85 (s, 1H, OH); ^{13}C NMR: δ 11.1, 21.8 (2 CH_3), 109.3 (CH), 112.4 (C), 113.2 (CH), 115.4 (2CH), 118.6 (2CH), 120.1 (C), 122.3 (2CH), 122.9 (CH), 126.5 (CH), 126.8 (C), 128.6 (C), 131.9 (C), 134.3 (CH), 138.1 (C), 153.2 (C), 156.4 (C), 205.3 (C=O); MS: m/e 358.51 (M^+ , 17%). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$ (358.39): C, 73.73; H, 5.06; N, 7.82. Found: C, 74.05; H, 5.41; N, 8.07.

5-(4-Acetyl-1-(2-hydroxyphenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4h) Reaction time 4 h; yield 75%; pale yellow crystals; mp 270–272°C; IR: ν 3440 (OH), 3090 (CH, aromatic), 2990 (CH, aliphatic), 1656 (C=O), 1616 cm^{-1} (C=C); ^1H NMR: δ 2.06 (s, 3H, CH_3), 2.56 (s, 3H, COCH_3), 5.90 (s, 1H, OH), 6.48 (s, 1H, pyrrole H-3), 6.99–8.02 (m, 10H, aromatic H). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$ (358.39): C, 73.73; H, 5.06; N, 7.82. Found: C, 73.99; H, 5.39; N, 8.19.

5-(4-Acetyl-1-(4-nitrophenyl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4i) Reaction time 4 h; yield 60%; yellow crystals; mp 284–286°C; IR: ν 3095 (CH, aromatic), 2899 (CH, aliphatic), 1660 (C=O), 1626 cm^{-1} (C=C); ^1H NMR: δ 2.12 (s, 3H, CH_3), 2.55 (s, 3H, COCH_3), 6.45 (s, 1H, pyrrole H-3), 6.95–8.12 (m, 10H, aromatic H); MS: m/e 378.03 (M^+ , 12%). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_4$ (378.39): C, 68.21; H, 4.42; N, 10.85. Found: C, 68.43; H, 4.75; N, 11.11.

5-(4-Acetyl-1-(pyridin-2-yl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4j) Reaction time 2.5 h; yield 70%; buff crystals; mp 166–168°C; IR: ν 3097 (CH, aromatic), 2898 (CH, aliphatic), 1667 (C=O), 1633 cm^{-1} (C=C); ^1H NMR: δ 2.09 (s, 3H, CH_3), 2.48 (s, 3H, COCH_3), 6.50 (s, 1H, pyrrole H-3), 6.95–8.39 (m, 10H, aromatic H); ^{13}C NMR: δ 8.6, 22.4 (2 CH_3), 108.3 (C), 108.7 (CH), 116.1 (CH), 118.8 (CH), 119.4 (C), 122.6 (CH), 123.3 (CH), 124.1 (CH), 127.6 (C), 128.8 (C), 130.7 (C), 134.3 (CH), 136.2 (CH), 139.6 (C), 150.1 (CH), 153.7 (CH), 155.2 (C), 160.3 (C), 202.4 (C=O). Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_2$ (343.38): C, 73.45; H, 4.49; N, 12.24. Found: C, 73.71; H, 4.79; N, 12.53.

5-(4-Acetyl-1-(pyridin-3-yl)-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4k) Reaction time 5.5 h; yield 75%; buff crystals; mp 229–231°C; IR: ν 3108 (CH, aromatic), 2895 (CH, aliphatic), 1672 (C=O), 1629 cm^{-1} (C=C); ^1H NMR: δ 2.25 (s, 3H, CH_3), 2.65 (s, 3H, COCH_3), 6.58 (s, 1H, pyrrole H-3), 6.90–8.51 (m, 10H, aromatic H); ^{13}C NMR: δ 9.3, 22.6 (2 CH_3), 108.7 (C), 110.3 (CH), 115.2 (CH), 118.2 (CH), 120.5 (C), 123.1 (CH), 123.6 (CH), 124.4 (CH), 125.5 (C), 129.8 (C), 131.9 (C), 133.6 (CH), 135.8 (CH), 138.4 (C), 148.2 (CH), 151.2 (CH), 152.6 (CH), 155.1 (C), 196.2 (C=O); MS: m/e 343.27 (M^+ , 9 %). Anal. Calcd

for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.49; N, 12.24. Found: C, 73.66; H, 4.82; N, 12.50.

5-(4-Acetyl-1-cyclohexyl-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4l) Reaction time 2 h; yield 69%; pale yellow crystals; mp 192–194°C; IR: ν 3009 (CH, aromatic), 2965 (CH, aliphatic), 1664 (C=O), 1623 cm^{-1} (C=C); 1H NMR: δ 0.99 (m, 2H, CH_2), 1.39 (m, 4H, $2CH_2$), 1.58 (m, 4H, $2CH_2$), 2.25 (s, 3H, CH_3), 2.65 (s, 3H, $COCH_3$), 3.66 (m 1H, N-CH), 6.60 (s, 1H, pyrrole H-3), 6.85–7.99 (m, 6H, aromatic H). Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.44): C, 75.83; H, 6.94; N, 8.04. Found: C, 76.08; H, 7.29; N, 8.39.

5-(4-Acetyl-1-butyl-5-methyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4m) Reaction time 4.5 h; yield 65%; yellow crystals; mp 167–169°C; IR: ν 3088 (CH, aromatic), 2977 (CH, aliphatic), 1679 (C=O), 1639 cm^{-1} (C=C); 1H NMR: δ 1.15 (t, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.25 (t, 2H, CH_2), 6.72 (s, 1H, pyrrole H-4), 6.90–8.09 (m, 6H, aromatic H); MS: m/e 322.31 (M^+ , 33%). Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.84; H, 7.15; N, 8.97.

5-(4-Acetyl-1,5-dimethyl-1*H*-pyrrol-2-yl)-8-hydroxyquinoline (4n) Reaction time 2 h; yield 79%; yellow crystals; mp 110–112°C; IR: ν 3070 (CH, aromatic), 2975 (CH, aliphatic), 1675 (C=O), 1633 cm^{-1} (C=C); 1H NMR: δ 2.20 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 3.50 (s, 3H, N- CH_3), 6.40 (s, 1H, pyrrole H-3), 6.95–8.30 (m, 6H, aromatic H); MS: m/e 280.42 (M^+ , 16%). Anal. Calcd for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99. Found: C, 73.10; H, 6.07; N, 10.23.

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