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SYNTHESIS OF NEW N-ALKYL(ARYL)-2,4-DIARYL-1H-PYRROL-3-OLS *VIA* ALDOL PAAL–KNORR REACTIONS

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New N-alkyl(aryl)-2,4-diaryl-1H-pyrrol-3-ol derivatives have been synthesized in moderate to good yields in a novel and efficient process by aldol reaction of 1-(4-methoxyphenyl)propan-2-ones with phenylglyoxal in the presence of DABCO in water, followed by Paal–Knorr reaction with amines in the presence of a catalytic amount of p-TSA in toluene at reflux.

Keywords: 1,4-diazabicyclo[2.2.2]octane, phenylglyoxal, pyrrole derivatives, aldol reaction, Paal–Knorr reaction.

Pyrroles are important heterocycles widely used in material science (for recent work, see [1]) and found in naturally occurring and biologically important molecules [2-8]. Pyrroles can be found in a large range of natural products [9] and bioactive molecules [10-14], including the blockbuster drug Atorvastatin calcium [10], as well as important anti-inflammatory agents [11], antitumor agents [12], and immunosuppressants [13]. Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles [1-8, 15-17].

One of the most common approaches to pyrrole synthesis is the Paal–Knorr reaction in which 1,4-dicarbonyl compounds are converted to pyrroles *via* acid-mediated dehydrative cyclization in the presence of a primary amine [18-30]. In this reaction, the 1,4-dicarbonyl compound provides the four carbons of the pyrrole with their substituents, whereas the amine provides the nitrogen with its substituent. The main limitations to intensive use of this reaction are the harsh reaction conditions required for cyclization (use of boiling acetic acid for extended times) and the low availability of nonsymmetrically substituted 1,4-dicarbonyl compounds. The classical approach to this class of products is the condensation of enolates with phenacyl bromides [31], thus limiting the method to pyrroles with aryl substituents. Alternative approaches need several reaction steps with chromatographic separations to obtain the intermediates for cyclization. Therefore, mild reaction conditions that can overcome some of the shortcomings of the previous methods are necessary.

In this paper, we describe a simple method for synthesis of new N-alkyl(aryl)-2,4-diaryl-1H-pyrrol-3-ol derivatives *via* aldol reaction of 1-(4-methoxyphenyl)propan-2-one with phenylglyoxal in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) in water at room temperature, followed by

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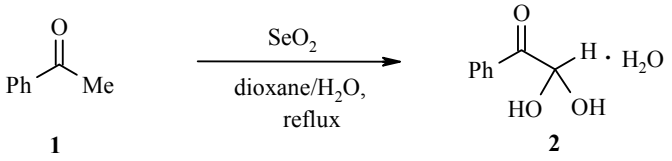
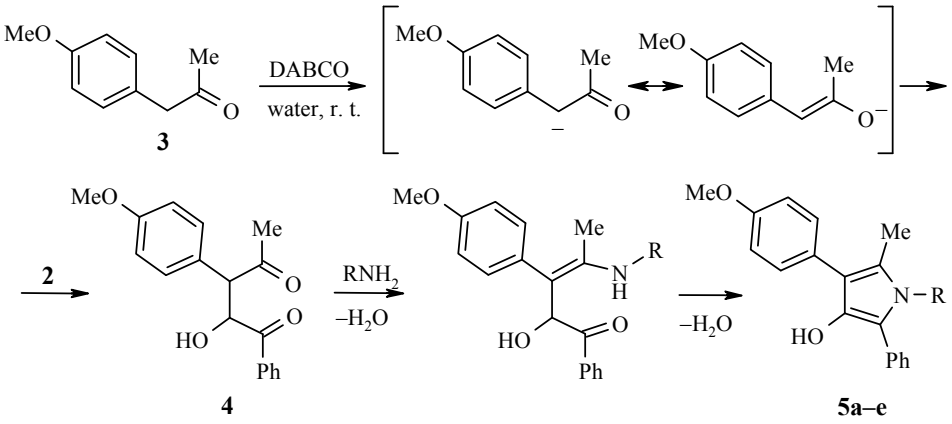
Paal–Knorr cyclization with primary amines in the presence of *p*-TSA in toluene at reflux condition. To the best of our knowledge, there are few reports in the literature [32] for the formation of pyrrol-3-ol derivatives *via* condensation of ketones with arylglyoxals.

Phenylglyoxal monohydrate (**2**) was prepared from commercially available acetophenone (**1**) using selenium dioxide [33].



1 **2**

2-Hydroxy-3-(4-methoxyphenyl)-1-phenylpentane-1,4-dione (**4**) was synthesized in 89% yield *via* aldol reaction of 1-(4-methoxyphenyl)propan-2-one (**3**) with phenylglyoxal monohydrate (**2**) in the presence of a catalytic amount of DABCO in water at room temperature. The structure of compound **4** was established by elemental analysis and IR, ^{1}H, and ^{13}C NMR spectra.



3 **4** **5a–e**

5, **6 a** R = Pr, **b** R = Bn, **c** R = Ph, **d** R = 4-MeOC$_6$H$_4$, **e** R = 4-ClC$_6$H$_4$

The reactions were performed by adding primary amines to the solution of the 1,4-dicarbonyl compound **4** in toluene in the presence of a catalytic amount of *p*-TSA at reflux. Arylamines as well as alkyl-amines worked well in the Paal–Knorr reaction with 1,4-dicarbonyl compound **4**. The structure of pyrroles **5a-e** was established by elemental analysis and IR, ^{1}H, and ^{13}C NMR spectra.

The proposed mechanism involves the attack of the *in situ* generated enolate on the phenylglyoxal. The obtained 1,4-dicarbonyl compound **4** in the presence of primary amine is converted to enamine, which attacks the second carbonyl group, and the loss of H_2O molecule affords the pyrrol-3-ol derivatives **5a-e**.

New fully substituted pyrrol-3-ol derivatives were synthesized in moderate to good yields *via* aldol reactions of 1-(4-methoxyphenyl)propan-2-ones with phenylglyoxal in the presence of DABCO in water, followed by Paal–Knorr reaction with amines in the presence of a catalytic amount of *p*-TSA in toluene at reflux. Synthesis of the pyrrole ring with hydroxyl substituent is one of the most noticeable characteristics of this work.

EXPERIMENTAL

All chemicals were purchased and used without any further purification. Melting points were determined on an Electrothermal MEL-TEMP apparatus (model 1202D) and are uncorrected. FT-IR spectra

were obtained with a Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker spectrometer operating at 500 and 125 MHz, respectively, in $CDCl_3$ (compound **4**) and DMSO-d_6 (compounds **5a-e**), relative to TMS as the internal standard. Elemental analyses were done by a Vario EL III Elementar instrument.

2-Hydroxy-3-(4-methoxyphenyl)-1-phenylpentane-1,4-dione (4). To the stirred solution of phenylglyoxal monohydrate **2** (0.76 g, 0.5 mmol) in water, 1-(4-methoxyphenyl)propan-2-one **3** (0.82 g, 0.5 mmol) and DABCO (0.15 g) were added at room temperature. After 0.5 h, the reaction mixture solidified. The obtained solid was filtered off and crystallized from ethanol, and compound **4** was obtained as a colorless crystalline solid, yield 89%; mp 95-95.3°C. FT-IR spectrum, ν, cm^{-1}: 3316 (O–H), 2891-3068 (C–H), 1712 (C=O), 1674 (C=O), 1645 (C=C), 1051 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (2H, dd, *J* = 7.9, *J*=8.4, H Ar); 7.66 (1H, m, H Ar); 7.53 (2H, t, *J* = 7.9, H Ar); 7.01 (2H, d, *J* = 9.5, H Ar); 6.86 (2H, d, *J* = 9.6, H Ar); 5.85 (1H, d, *J* = 4.0, CH); 4.03 (1H, d, *J* = 4.1, CH); 3.82 (3H, s, OCH_3); 3.26 (1H, br. s, OH, exchange with D_2O); 2.14 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 206.8 (C=O), 200.4 (C=O), 159.9, 134.8, 134.2, 131.5, 129.3, 129.0, 125.4, 114.6, 73.3, 62.1, 55.6, 29.5. Found, %: C 72.51; H 6.10. $C_{18}H_{18}O_4$. Calculated, %: C 72.47; H 6.08.

Pyrrole Derivatives 5a-e (General Method). To the solution of ompound **4** (0.12 g, 0.4 mmol) in toluene, primary amine (1.5 mmol) and *p*-TSA (0.15 g) were added. The reaction mixture was heated at reflux conditions overnight. After completion of the reaction (monitored by TLC), upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel using hexane–ethyl acetate mixture as eluent.

4-(4-Methoxyphenyl)-5-methyl-2-phenyl-1-propyl-1H-pyrrol-3-ol (5a). Yield 82%. White solid, mp 233°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3209 (O–H), 2883-3060 (C–H), 1659 (C=C), 1038 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32-7.38 (4H, m, H Ar); 7.23 (1H, t, *J* = 7.1, H Ar); 6.87 (2H, d, *J* = 8.4, H Ar); 6.61 (2H, d, *J* = 8.3, H Ar); 6.46 (1H, s, OH); 3.93 (2H, t, *J* = 7.3, CH_2); 3.81 (3H, s, OCH_3); 2.51 (3H, s, CH_3); 1.30–1.27 (2H, m, CH_2); 0.51 (3H, t, *J* = 7.4, CH_3). ^{13}C NMR spectrum, δ, ppm: 161.3, 136.6, 134.5, 130.0, 129.9, 127.5, 127.4, 127.1, 124.8, 116.4, 98.8, 55.8, 51.2, 23.9, 18.1, 12.0. Found, %: C 78.34; H 7.14; N 4.51. $C_{21}H_{23}NO_2$. Calculated, %: C 78.47; H 7.21; N 4.36.

1-Benzyl-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrol-3-ol (5b). Yield 76%. White solid, mp 262°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3211 (O–H), 2891–3064 (C–H), 1660 (C=C), 1042 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51 (2H, d, *J* = 6.1, H Ar); 7.41-7.33 (3H, m, H Ar); 7.27 (2H, d, *J* = 8.6, H Ar); 7.22 (2H, t, *J* = 7.0, H Ar); 7.18 (1H, t, *J* = 7.1, H Ar); 6.83 (2H, d, *J* = 7.4, H Ar); 6.65 (2H, d, *J* = 8.4, H Ar); 6.42 (1H, s, OH); 5.47 (2H, s, CH_2); 3.76 (3H, s, OCH_3); 2.49 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 161.3, 136.7, 135.4, 134.7, 132.4, 132.2, 130.2, 129.6, 128.7, 127.7, 126.7, 124.9, 115.3, 99.0, 56.0, 48.7, 18.3. Found, %: C 81.20; H 6.38; N 3.91. $C_{25}H_{23}NO_2$. Calculated, %: C 81.27; H 6.27; N 3.79.

4-(4-Methoxyphenyl)-5-methyl-1,2-diphenyl-1H-pyrrol-3-ol (5c). Yield 71%. White solid, mp 203°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3218 (O–H), 2880-3051 (C–H), 1648 (C=C), 1032 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.41-7.30 (5H, m, H Ar); 7.04 (2H, t, *J* = 7.3, H Ar); 6.84 (2H, d, *J* = 7.1, H Ar); 6.65 (2H, d, *J* = 8.0, H Ar); 6.63 (1H, t, *J* = 7.3, H Ar); 6.50 (2H, d, *J* = 7.7, H Ar); 6.31 (1H, s, OH); 3.73 (3H, s, OCH_3); 2.51 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 161.3, 136.6, 134.6, 134.5, 130.0, 129.9, 127.6, 127.5, 127.1, 124.8, 122.0, 120.0, 116.4, 100.6, 54.9, 19.7. Found, %: C 81.11; H 6.04; N 3.88. $C_{24}H_{21}NO_2$. Calculated, %: C 81.10; H 5.96; N 3.94.

1,4-Bis(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrol-3-ol (5d). Yield 63%. White solid, mp 283°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3206 (O–H), 2887-3054 (C–H), 1653 (C=C), 1019 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.36 (2H, d, *J* = 7.1, H Ar); 7.32 (2H, t, *J* = 7.4, H Ar); 7.23 (1H, t, *J* = 7.2, H Ar); 6.76 (2H, d, *J* = 8.9, H Ar); 6.63 (2H, d, *J* = 7.4, H Ar); 6.58 (2H, d, *J* = 7.8, H Ar); 6.46 (2H, d, *J* = 8.9, H Ar); 6.23 (1H, s, OH); 3.82 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 2.48 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 160.6,

157.4, 143.3, 133.1, 132.6, 129.9, 129.7, 129.2, 128.7, 127.5, 127.1, 123.4, 114.9, 114.8, 100.8, 55.8, 55.7, 20.7. Found, %: C 78.02; H 5.98; N 3.56. $C_{25}H_{23}NO_3$. Calculated, %: C 77.90; H 6.01; N 3.63.

1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrol-3-ol (5e). Yield 61%. White solid, mp 278°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3211 (O–H), 2879-3049 (C–H), 1660 (C=C), 1023 (C–O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.39-7.26 (5H, m, H Ar); 7.04 (2H, d, *J* = 8.3, H Ar); 6.83 (2H, d, *J* = 8.4, H Ar); 6.62 (2H, d, *J* = 8.6, H Ar); 6.50 (1H, d, *J* = 8.2, H Ar); 6.29 (1H, s, OH); 3.80 (3H, s, OCH_3); 2.45 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 160.5, 150.0, 133.1, 132.5, 131.1, 129.7, 129.4, 129.2, 128.7, 127.5, 127.1, 123.4, 120.7, 114.8, 100.8, 55.6, 20.9. Found, %: C 74.06; H 5.14; N 3.49. $C_{24}H_{20}ClNO_2$. Calculated, %: C 73.94; H 5.17; N 3.59.

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