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A CONVENIENT SYNTHESIS OF 2,4-DIARYLPOLYHYDROQUINOLINE DERIVATIONS IN THE PRESENCE OF AMMONIUM ACETATE

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ABSTRACT

A series of substituted 5-oxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives have been synthesized from 5,5-dimethyl-1,3-cyclohexane-dione (dimedone) and 1,3-diaryl-2-propen-1-one in DMF at 80°C in the presence of ammonium acetate with high yields (64–98%), the structure of the product was confirmed by X-ray analysis.

Key Words: 2,4-Diarylpolyhydroquinoline; 1,3-Diaryl-2-propen-1-one; Ammonium acetate

1,4-Dihydropyridines (1,4-DHPS) are well-known compounds as a consequence of their pharmacological profile as calcium channel modulators.[1] The chemical modifications carried on the DHP ring such as the presence of different substituents[2] or heteroatoms[3] have allowed expansion of the structure activity relationship and afforded some insight into the

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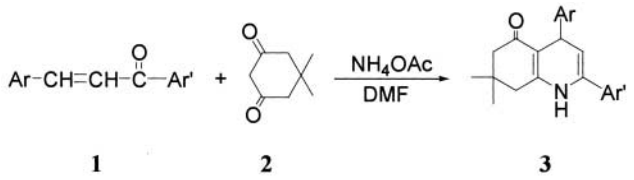
molecular interactions at the receptor level. The usual method for 1,4-DHPS synthesis is from meldrum's acid and dimedone in the presence of different aldehydes catalyzed by ammonium acetate[4] or NH_3H_2O.[5] In our previous paper,[6] we have reported one step synthesis of 4-arylpolyhydroquinoline derivatives from aromatic aldehyde, dimedone, ammonium acetate and ethyl acetoacete using microwave irradiation. In this paper we describe the synthesis of the 5-oxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives from dimedone **2** and 1,3-diaryl-2-propen-1-one **1** in the presence of ammonium acetate.

When 1,3-diaryl-2-propen-1-one **1** and dimedone **2** were treated with ammonium acetate in DMF at 80°C for 1–2 h (Sch. 1), the desired 5-oxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives **3** were obtained in good yields (64–98%) (Table 1).

The ^{1}H NMR spectra of compound **3d** show the NH proton ~8.64 ppm, the proton on C(9) exhibit double peaks at 4.54–4.63 ppm and form part of an AX system which is confirmed by another double peaks at 5.25–5.34 ppm corresponding to the proton on C(8) ($J = 5.4$ Hz). In order to confirm the structure of the product, the X-ray crystallographic study was carried out.[7] Figure 1 shows the molecular structure of the compound 3d.



Scheme 1.

Table 1. The Yields of the Products

Entry	Ar	Ar′	Yield (%)
3a	C_6H_5	C_6H_5	85.1
3b	C_6H_5	4-ClC_6H_4	64.7
3c	4-ClC_6H_4	C_6H_5	78.5
3d	C_6H_5	4-BrC_6H_4	94.3
3e	C_6H_5	2,4-Cl_2-5-FC_6H_2	98.0
3f	4-ClC_6H_4	2,4-Cl_2-5-FC_6H_2	97.7
3g	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	72.6
3h	3,4-$OCH_2OC_6H_3$	C_6H_5	92.0
3i	C_6H_5	4-$CH_3C_6H_4$	68.5
3j	3,4-$OCH_2OC_6H_3$	4-ClC_6H_4	90.5

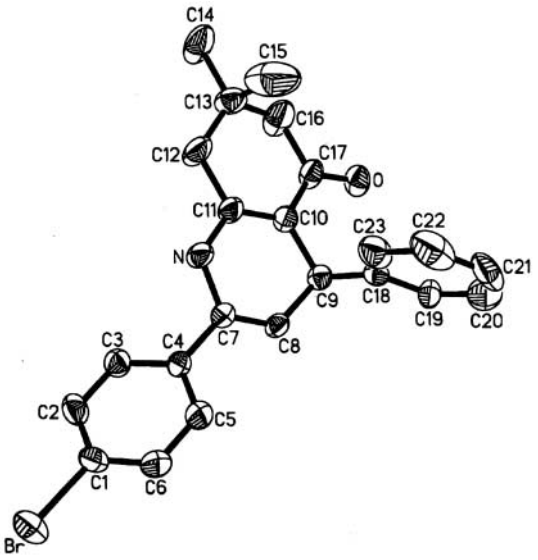


Figure 1. The structure of compound **3d**. AQ1

In conclusion, with high yields and mild conditions, we think that the present work described here in provide a useful method for the preparation of substituted 5-oxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer in KBr. ^{1}H NMR spectra were obtained for solution in DMSO-d_6 with Me_4Si as internal standard using an Inova-400 or R-1500A spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyzer. X-ray diffraction were measured on a Siemens P4 diffractometer.

General Procedure

A dry 50 mL flask was charged with 1,3-diaryl-2-propen-1-one **1** (2 mmol), 5,5-dimethyl-1,3-cyclohexanedione **2** (2.5 mmol), ammonium acetate (5 mmol) and DMF (10 mL). The mixture was stirred at 80°C for 1–2 h, then cooled to room temperature. The mixture was poured into

200 mL water, the yellow solid was filtered off and washed with water. The crude product was purified by recrystallization from 95% EtOH to give **3**.

3a: M.p. 206–208°C; IR (KBr, ν, cm^{-1}): 3260, 3030, 2990, 1660, 1630, 1590, 1490, 1450, 770, 760, 695; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.96 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.98–2.02 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.16–2.20 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.48 (2H, s, CH_2), 4.56–4.57 (1H, d, $J = 5.6$ Hz, C^9-H), 5.21–5.22 (1H, dd, $J = 2.0$ Hz, $J' = 3.6$ Hz, C^8-H), 7.09–7.50 (10H, m, ArH), 8.63 (1H, s, NH); Elemental analysis: Found (%): C, 83.93; H, 6.86; N, 4.03. Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25.

3b: M.p. 250–252°C; IR (KBr, ν, cm^{-1}): 3240, 3020, 2980, 1665, 1610, 1580, 1500, 1450, 835, 760, 690; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.98 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.10 (2H, s, CH_2), 2.14 (2H, s, CH_2), 4.54–4.63 (1H, d, $J = 5.4$ Hz, C^9-H), 5.24–5.33 (1H, d, $J = 5.4$ Hz, C^8-H), 7.24 (5H, s, ArH), 7.50 (4H, s, ArH), 8.69 (1H, b, NH); Elemental analysis: Found (%): C, 76.04; H, 5.94; N, 3.68. Calcd. for $C_{23}H_{22}ClNO$: C, 75.91; H, 6.10; N, 3.85.

3c: M.p. 224–226°C; IR (KBr, ν, cm^{-1}): 3250, 3030, 2980, 1665, 1610, 1580, 1500, 1450, 830, 770, 700; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.94 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.98–2.02 (1H, d, $J = 16.4$ Hz, C^{12}-H), 2.16–2.20 (1H, d, $J = 16.4$ Hz, C^{12}-H), 2.46 (1H, s, C^{16}-H), 2.48 (1H, s, C^{16}-H), 4.57–4.58 (1H, d, $J = 5.2$ Hz, C^9-H), 5.18–5.20 (1H, dd, $J = 1.2$ Hz, $J' = 4.0$ Hz, C^8-H), 7.23–7.50 (9H, m, ArH), 8.68 (1H, s, NH); Elemental analysis: Found (%): C, 75.98; H, 5.90; N, 3.69. Calcd. for $C_{23}H_{22}ClNO$: C, 75.91; H, 6.10; N, 3.85.

3d: M.p. 264–266°C; IR (KBr, ν, cm^{-1}): 3250, 3010, 2980, 1670, 1610, 1590, 1510, 1490, 830, 770, 695; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.99 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.10 (2H, s, CH_2), 2.13 (2H, s, CH_2), 4.54–4.63 (1H, d, $J = 5.4$ Hz, C^9-H), 5.25–5.34 (1H, d, $J = 5.4$ Hz, C^8-H), 7.24 (5H, s, ArH), 7.54 (4H, s, ArH), 8.64 (1H, b, NH); Elemental analysis: Found (%): C, 67.82; H, 5.29; N, 3.21. Calcd. for $C_{23}H_{22}BrNO$: C, 67.65; H, 5.43; N, 3.43.

3e: M.p. 166–168°C; IR (KBr, ν, cm^{-1}): 3280, 3010, 2990, 1670, 1600, 1510, 1470, 830, 680; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.91 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.96–2.00 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.15–2.19 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.26–2.30 (1H, d, $J = 16.4$ Hz, C^{16}-H), 2.37–2.42 (1H, d, $J = 16.4$ Hz, C^{16}-H), 4.56–4.57 (1H, d, $J = 5.6$ Hz, C^9-H), 4.92–4.94 (1H, dd, $J = 1.6$ Hz, $J' = 3.6$ Hz, C^8-H), 7.08–7.91 (7H, m, ArH), 10.61 (1H, s, NH); Elemental analysis: Found (%): C, 66.52; H, 4.64; N, 3.13. Calcd. for $C_{23}H_{20}Cl_2FNO$: C, 66.35; H, 4.84; N, 3.36.

3f: M.p. 238–239°C; IR (KBr, ν, cm^{-1}): 3250, 3020, 2980, 1670, 1600, 1510, 1470, 830, 680; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.91 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.96–2.00 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.15–2.19 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.26–2.30 (1H, d, $J = 16.4$ Hz, C^{16}-H), 2.37–2.42

(1H, d, $J = 16.4$ Hz, C^{16}-H), 4.56–4.57 (1H, d, $J = 5.6$ Hz, C^{9}-H), 4.92–4.94 (1H, dd, $J = 1.6$ Hz, $J' = 3.6$ Hz, C^{8}-H), 7.31–7.92 (6H, m, ArH), 8.85 (1H, s, NH); Elemental analysis: Found (%): C, 61.44; H, 4.01; N, 3.00. Calcd. for $C_{23}H_{19}Cl_3FNO$: C, 61.28; H, 4.25; N, 3.11.

3g: M.p. 196–198°C; IR (KBr, ν, cm^{-1}): 3260, 3020, 2990, 2980, 1660, 1620, 1590, 1510, 1495, 1460, 760, 700; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.98 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.98–2.02 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.17–2.21 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.46 (1H, s, C^{16}-H), 2.48 (1H, s, C^{16}-H), 3.68 (6H, s, $2 \times OCH_3$), 4.49–4.50 (1H, d, $J = 5.2$ Hz, C^{9}-H), 5.20–5.22 (1H, dd, $J = 1.6$ Hz, $J' = 4.0$ Hz, C^{8}-H), 6.70–7.49 (8H, m, ArH), 8.59 (1H, s, NH); Elemental analysis: Found (%): C, 77.28; H, 6.72; N, 3.37. Calcd. for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60.

3h: M.p. 236–238°C; IR (KBr, ν, cm^{-1}): 3240, 3020, 2980, 1660, 1600, 1570, 1500, 1480, 830, 770, 700; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.96 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.99–2.03 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.15–2.19 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.47 (2H, s, CH_2), 4.48–4.50 (1H, d, $J = 5.2$ Hz, C^{9}-H), 5.18–5.20 (1H, dd, $J = 2.0$ Hz, $J' = 3.6$ Hz, C^{8}-H), 5.92 (2H, s, OCH_2O), 6.67–7.50 (8H, m, ArH), 8.61 (1H, s, NH); Elemental analysis: Found (%): C, 77.36; H, 6.07; N, 3.54. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75.

3i: M.p. 210–212°C; IR (KBr, ν, cm^{-1}): 3250, 3010, 2995, 2980, 1650, 1620, 1590, 1490, 830, 770, 695; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.96 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.97–2.01 (1H, d, $J = 16.4$ Hz, C^{12}-H), 2.15–2.19 (1H, d, $J = 16.4$ Hz, C^{12}-H), 2.30 (3H, s, CH_3), 2.48 (2H, s, CH_2), 4.54–4.55 (1H, d, $J = 5.6$ Hz, C^{9}-H), 5.17–5.18 (1H, dd, $J = 1.6$ Hz, $J' = 4.0$ Hz, C^{8}-H), 7.08–7.65 (9H, m, ArH), 8.56 (1H, s, NH); Elemental analysis: Found (%): C, 84.05; H, 7.18; N, 3.89. Calcd. for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08.

3j: M.p. 176–177°C; IR (KBr, ν, cm^{-1}): 3250, 3020, 2990, 2980, 1675, 1620, 1590, 1500, 1480, 810; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.93 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.97–2.01 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.14–2.18 (1H, d, $J = 16.0$ Hz, C^{12}-H), 2.26–2.30 (1H, d, $J = 16.4$ Hz, C^{16}-H), 2.36–2.40 (1H, d, $J = 16.4$ Hz, C^{16}-H), 4.48–4.49 (1H, d, $J = 4.8$ Hz, C^{9}-H), 4.92–4.93 (1H, dd, $J = 1.2$ Hz, $J' = 4.0$ Hz, C^{8}-H), 6.77–7.91 (7H, m, ArH), 8.77 (1H, s, NH); Elemental analysis: Found (%): C, 70.86; H, 5.23; N, 3.15. Calcd. for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43.

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