Solid state synthesis of 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives without using solvent and catalyst

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Abstract
A series of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives have been synthesized from 1,3-diaryl-2-propen-1-one and 5,5-dimethyl-1,3-cyclohexanedione in the presence of ammonium acetate by solid state reaction at 80 °C with high yields (82-92%) without using solvent and catalyst. This method provides several advantages such as operational simplicity, neutral condition, high yields and environment friendly.

Keywords: 5-Oxo-1,4,5,6,7,8-hexahydroquinoline derivatives, 1,3-diaryl-2-propen-1-one, 5,5-dimethyl-1,3-cyclohexanedione, solid state reaction

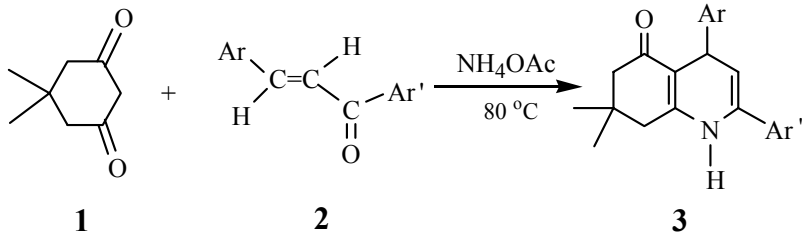
Introduction

It is common knowledge that quinolines and their derivatives are very useful compounds because a large number of natural products and drugs contain this heterocyclic unit.[1-4] They have attracted strong interest due to their useful biological and pharmacological properties, such as antitumor, antiviral, antitubercle, antidiabetic, and antibacterial activities.[5-9]

Substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives are the types of 1,4-dihydropyridine compounds. Usually these compounds are synthesized with aldehydes, dimethyl cyclohexanedione, ethyl acetoacetate and NH_4OAc or NH_4OH in organic solvents or under microwave irradiation.[10-14] Although each of the above methods has its own merit, some of them have not been entirely satisfactory owing to cumbersome experimental conditions such as requiring an organic solvent, higher temperature and pressure, and use of a microwave oven.

The solid state reaction method is used more and more frequently in organic synthesis. Compared with traditional methods, this method is more convenient and easily controlled. A great number of organic reactions can be carried out in higher yields, shorter times, or milder conditions by the method. It can even set off some reactions that cannot be carried out under traditional.[15-17]

In this paper we describe the synthesis of the substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives from 5,5-dimethyl-1,3-cyclo-hexanedione and 1,3-diaryl-2-propen-1-one in the presence of ammonium acetate by solid state reaction at 80 °C without using solvent and catalyst. When 1,3-diaryl-2-propen-1-one and 5,5-dimethyl-1,3- cyclohexanedione were treated with ammonium acetate at 80 °C for 2-5 h, the desired substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives were obtained in good to excellent yields (82-92%). This method has not been reported before, it is an efficient synthesis by solid state reaction, not only the operational simplicity and without any solvent and catalyst, but also accord with the demands of green organic synthesis. (Scheme 1).



1 **2** **3**

Scheme 1

In a typical general experimental procedure, a mixture of 5,5-dimethyl-1,3-cyclo-hexanedione **1**, 1,3-diaryl-2-propen-1-one **2** and ammonium acetate were performed at 80 °C by solid state reaction, higher yields of products **3** were obtained. The results are summarized in Table 1.

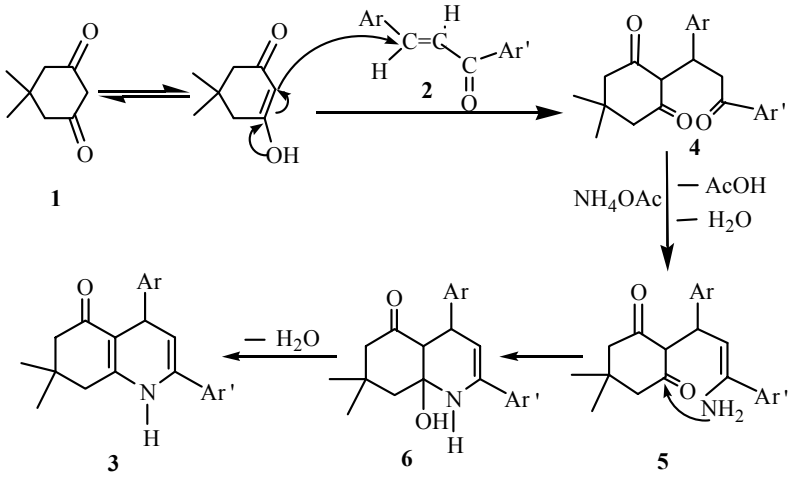
According to the results we have obtained (Table 1), the effect of electron deficiency and the nature of the substituents on the aromatic rings (Ar not Ar') showed some effect on this conversion. The reaction gave higher yields of substituted 5-oxo-1,4,5,6,7,8- hexahydroquinoline derivatives when the aromatic rings (Ar) bear an electron-withdrawing substituents (Table 1), probably because the Michael addition is easier.

We propose the possible following mechanism to account for the reaction. Firstly, the active methylene of 5,5-dimethyl-1,3-cyclo-hexanedione **1** reacted with 1,3-diaryl-2- propen-1-one **2** via Michael addition reaction to give addition product **4**. Then the intermediate **4** was condensed with ammonium acetate, lose the acetic acid and water to afford the intermediate **5**. After that cyclised by the nucleophilic attack of NH_2 group on the carbonyl (C=O) moiety and gave the intermediate **6**. Finally the intermediate **6** loses a water to give the expected product **3**. (Scheme 2).

Table 1. Solid state synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives

Entry	Ar	Ar′	Product	Time(h)	Yield(%)[a]	Mp (°C)	
						Found	Reported[11,14]
1	C_6H_5	C_6H_5	**3a**	5.0	84	203-205	206-208
2	4-ClC_6H_4	C_6H_5	**3b**	4.5	91	222-224	224-226
3	2,4-$Cl_2C_6H_3$	C_6H_5	**3c**	4.0	92	206-208	204-206
4	4-$NO_2C_6H_4$	C_6H_5	**3d**	4.0	90	211-213	212-214
5	4-$CH_3OC_6H_4$	C_6H_5	**3e**	5.0	86	190-192	192-194
6	4-$CH_3C_6H_4$	C_6H_5	**3f**	5.0	83	184-186	186-188
7	3,4-$(OCH_2O)C_6H_3$	C_6H_5	**3g**	5.0	86	234-236	236-238
8	3-$NO_2C_6H_4$	4-ClC_6H_4	**3h**	4.0	92	236-238	237-239
9	4-ClC_6H_4	4-$NO_2C_6H_4$	**3i**	4.0	92	243-245	242-244
10	4-$CH_3C_6H_4$	4-ClC_6H_4	**3j**	5.0	85	233-235	234-236
11	3,4-$(OCH_2O)C_6H_3$	4-ClC_6H_4	**3k**	4.0	88	248-250	250-252
12	C_6H_5	4-$NO_2C_6H_4$	**3l**	4.5	86	222-224	224-226
13	C_6H_5	4-ClC_6H_4	**3m**	5.0	85	248-250	250-252
14	C_6H_5	4-BrC_6H_4	**3n**	5.0	84	232-234	234-236
15	C_6H_5	4-$CH_3C_6H_4$	**3o**	5.0	82	208-210	210-212

[a] Isolated yield



Scheme 2

In conclusion, we have described a general and highly efficient procedure for the preparation of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives by the solid state reaction. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and isolated procedure which makes it a useful and attractive process for the synthesis of these compounds.

Experimental Section

General Procedures. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal reference and DMSO-d_6 as solvent. Elemental analyses were determined using Perkin-Elmer 2400 II elemental analyzer.

General procedure for the preparation of 3. A mixture of 5,5-dimethyl-1,3-cyclohexanedione (**1**, 3 mmol), 1,3-diaryl-2-propen-1-one (**2**, 2 mmol), ammonium acetate (4 mmol) was stirred at 80 °C for a period as indicated in Table1. The completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, add ethanol (10 mL) to dilute mixture. The mixture was poured into 80 mL ice-water, the precipitate was filtered off and washed with water, the crude products were got. The crude products were purified by recrystallization from ethanol (95%) to give **3**. Data of compounds are shown below:

7,7-Dimethyl-5-oxo-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline (3a). IR (KBr): ν_{max} = 3262, 3032, 2988, 1658, 1630, 1590, 1492, 1450, 772, 761, 696 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 0.96 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.98-2.04 (d, 1H, J=16.0 Hz, CH_2), 2.16-2.22 (d, 1H, J=16.0 Hz, CH_2), 2.46 (s, 2H, CH_2), 4.68 (d, 1H, J=5.6 Hz, CH), 5.22 (d, 1H, J=5.6 Hz, =CH),

6.62 (s, 1H, NH), 7.08-7.52 (m, 10H, ArH) ppm. Anal. Calcd. for $C_{23}H_{23}NO$: C 83.86, H 7.04, N 4.25; Found C 83.93, H 7.11, N 4.32 %.

7,7-Dimethyl-4-(4-chlorophenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3b). IR (KBr): ν_{max} = 3248, 3030, 2982, 1664, 1610, 1580, 1502, 1450, 830, 770 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 0.96 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.98-2.04 (d, 1H, *J*=16.4 Hz, CH_2), 2.16-2.20 (d, 1H, *J*=16.4 Hz, CH_2), 2.48 (s, 2H, CH_2), 4.58-4.72 (d, 1H, *J*=5.2 Hz, CH), 5.22-5.32 (d, 1H, *J*=5.2 Hz, =CH), 6.64 (s, 1H, NH), 7.24-7.50 (m, 9H, ArH) ppm. Anal. Calcd. for $C_{23}H_{22}ClNO$: C 75.92, H 6.09, N 3.85; Found C 75.96, H 5.98, N 3.87 %.

7,7-Dimethyl-4-(2,4-dichlorophenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3c). IR (KBr): ν_{max} = 3224, 3062, 2960, 1662, 1580, 1488, 820, 770, 694 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.04-1.14 (s, 6H, 2×CH_3), 2.04 (d, 1H, *J*=12 Hz, CH_2), 2.10 (d, 1H, *J*=12 Hz, CH_2), 2.42 (s, 2H, *J*=16 Hz, CH_2), 5.12 (d, 1H, *J*=5.2 Hz, CH), 5.36 (d, 1H, *J*=5.2 Hz, =CH), 6.58 (s, 1H, NH), 7.16-7.38 (m, 3H, ArH), 7.38 (m, 5H, ArH) ppm. Anal. Calcd. for $C_{23}H_{21}Cl_2NO$: C 69.35, H 5.31, N 3.52; Found C 69.41, H 5.35, N 3.58 %.

7,7-Dimethyl-4-(4-nitrophenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3d). IR (KBr): ν_{max} = 3350, 3048, 2956, 2868, 1658, 1594, 1486, 836, 758, 698 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.02-2.18 (d, 2H, *J*=16.4 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.82 (d, 1H, *J*=4.8 Hz, CH), 5.36 (d, 1H, *J*=4.8 Hz, =CH), 6.42 (s, 1H, NH), 7.32-7.46 (m, 5H, ArH), 7.54 (d, 2H, *J*=8.4 Hz, ArH), 8.14 (d, 2H, *J*=8.4 Hz, ArH) ppm. Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C 73.78, H 5.92, N 7.48; Found C 73.73, H 5.95, N 7.58 %.

7,7-Dimethyl-4-(4-methoxyphenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3e). IR (KBr): ν_{max} = 3220, 3038, 2956, 2868, 2832, 1664, 1582, 1442, 848, 762, 698 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.98-2.42 (d, 4H, 2×CH_2), 3.78 (s, 3H, OCH_3), 4.72 (d, 1H, *J*=5.2 Hz, CH), 5.30 (d, 1H, *J*=5.2 Hz, =CH), 6.46 (s, 1H, NH), 7.06 (d, 2H, *J*=8.4 Hz, ArH), 7.28-7.32 (d, 2H, ArH), 7.36-7.46 (m, 5H, ArH) ppm. Anal. Calcd. for $C_{24}H_{25}NO_2$: C 80.19, H 7.01, N 3.90; Found C 80.23, H 6.96, N 3.98 %.

7,7-Dimethyl-4-(4-methylphenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3f). IR (KBr): ν_{max} = 3232, 3046, 2950, 2874, 1660, 1582, 1490, 810, 760, 696. ^1H NMR (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.10 (d, 1H, *J*=16 Hz, CH_2), 2.12 (d, 1H, *J*=16 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.72 (d, 1H, *J*=5.2 Hz, CH), 5.30 (d, 1H, *J*=5.2 Hz, =CH), 6.36(s, 1H, NH), 7.10-7.28 (m, 4H, ArH), 7.36-7.42 (m, 5H, ArH) ppm. Anal. Calcd. for $C_{24}H_{25}NO$: C 83.93, H 7.34, N 4.08; Found C 84.03, H 7.38, N 4.15 %.

7,7-Dimethyl-4-(3,4-dioxymethylenephenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (3g). IR (KBr): ν_{max} = 3242, 3034, 2980, 1664, 1600, 1572, 1510, 1480, 840, 770, 710 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.98-2.04 (d, 1H, *J*=16.0 Hz, CH_2), 2.08-2.12 (d, 1H, *J*=16.0 Hz, CH_2), 2.48 (s, 2H, CH_2), 4.56-4.76 (d, 1H, *J*=5.2 Hz, CH), 5.36 (d, 1H, *J*=5.2 Hz, =CH), 5.92 (s, 2H, OCH_2O), 6.62 (s, 1H, NH), 6.98-7.50 (m, 8H, ArH) ppm. Anal. Calcd. For $C_{24}H_{23}NO_3$: C 77.19, H 6.21, N 3.75; Found C 77.26, H 6.27, N 3.79 %.

7,7-Dimethyl-2-(4-chlorophenyl)-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (3h). IR (KBr): ν_{max} = 3235, 3076, 2968, 1664, 1587, 1531, 1491, 1349, 827. 1H NMR (DMSO-

d_6): δ_H = 0.98 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.04 (d, 1H, *J*=16 Hz, CH_2), 2.10 (d, 1H, *J*=16 Hz, CH_2), 2.47 (s, 2H, CH_2), 4.74 (d, 1H, *J*=4.8 Hz, CH), 5.36 (d, 1H, *J*=4.8 Hz, =CH), 6.84 (s, 1H, NH), 7.42 (d, 2H, *J*=8.0 Hz, ArH), 7.50 (d, 2H, *J*=8.0 Hz, ArH), 7.55 (d, 1H, *J*=8.0 Hz, ArH), 7.68 (d, 1H, *J*=8.0 Hz, ArH), 7.96 (d, 1H, *J*=8.0 Hz, ArH), 8.02 (s, 1H, ArH) ppm. Anal. Calcd. for $C_{23}H_{21}ClN_2O_3$: C 67.56, H 5.18, N 6.85; Found: C 67.66, H 5.21, N 6.88 %.

7,7-Dimethyl-4-(4-chlorophenyl)-2-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (3i). IR (KBr): ν_{max} = 3330, 3080, 2954, 1660, 1586, 1490, 1390, 850, 754 cm^{-1}. ^1H NM R (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.06 (d, 1H, *J*=16 Hz, CH_2), 2.12 (d, 1H, *J*=16 Hz, CH_2), 2.46 (s, 2H, CH_2), 4.74 (d, 1H, *J*=4.8 Hz, CH), 5.42 (d, 1H, *J*=4.8 Hz, =CH), 6.98 (s, 1H, NH), 7.20 (d, 2H, *J*=8.0 Hz, ArH), 7.28 (d, 2H, *J*=8.0 Hz, ArH), 7.74 (d, 2H, *J*=8.0 Hz, ArH), 8.21 (d, 2H, *J*=8.0 Hz, ArH) ppm. Anal. Calcd. for $C_{23}H_{21}ClN_2O_3$: C 67.56, H 5.18, N 6.85; Found: C 67.65, H 5.20; N, 6.92 %.

7,7-Dimethyl-2-(4-chlorophenyl)-4-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (3j). IR (KBr): ν_{max} = 3320, 3042, 2952, 2870, 1658, 1580, 1490, 812, 770 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.20 (d, 1H, *J*=12 Hz, CH_2), 2.26 (d, 1H, *J*=12 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.72 (d, 1H, *J*=4.8 Hz, CH), 5.36 (d, 1H, *J*=4.8 Hz, =CH), 6.86 (s, 1H, NH), 7.08-7.26 (m, 4H, ArH), 7.28-7.36 (m, 4H, ArH) ppm. Anal. Calcd. for $C_{24}H_{24}ClNO$: C 76.28, H 6.40, N 3.71; Found: C 76.26, H, 6.34; N, 3.80 %.

7,7-Dimethyl-2-(4-chlorophenyl)-4-(3,4-dioxymethylenephenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (3k). IR (KBr): ν_{max} = 3250, 3024, 2989, 1624, 1590, 1502, 810, 694 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.10 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.22 (d, 1H, *J*=16 Hz, CH_2), 2.28 (d, 1H, *J*=16 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.72 (d, 1H, *J*=4.8 Hz, CH), 5.32 (d, 1H, *J*=4.8 Hz, =CH), 5.90 (s, 2H, OCH_2O), 6.64 (s, 1H, NH), 7.06-7.26 (m, 3H, ArH), 7.28-7.46 (m, 4H, ArH) ppm. Anal. Calcd. for $C_{24}H_{22}ClNO_3$: C 70.67, H 5.44, N 3.43; Found: C 70.73, H, 5.53; N, 3.50 %.

7,7-Dimethyl-2-(4-nitrophenyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (3l). IR (KBr): ν_{max} = 3274, 3074, 2968, 2886, 1646, 1596, 1557, 1490, 1393, 1340, 848, 756, 698 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.06 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.18 (d, 2H, *J*=16 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.76 (d, 1H, *J*=5.2 Hz, CH), 5.42 (d, 1H, *J*=5.2 Hz, =CH), 6.62 (s, 1H, NH), 7.16-7.36 (m, 5H, ArH), 7.56 (d, 2H, *J*=8.0 Hz, ArH), 8.20 (d, 2H, *J*=8.0 Hz, ArH) ppm. Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C 73.79, H 5.92, N 7.48; Found: C 73.73, H, 5.83; N, 7.50 %.

7,7-Dimethyl-2-(4-chlorophenyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (3m). IR (KBr): ν_{max} = 3240, 3024, 2980, 1612, 1580, 1506, 832, 760, 694 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.10 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.20 (d, 1H, *J*=16.4 Hz, CH_2), 2.24 (d, 1H, *J*=16.4 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.72 (d, 1H, *J*=5.2 Hz, CH), 5.36 (d, 1H, *J*=5.2 Hz, =CH), 6.74 (s, 1H, NH), 7.22-7.54 (m, 9H, ArH) ppm. Anal. Calcd. for $C_{23}H_{22}ClNO$: C 75.92, H 6.09, N 3.85; Found: C 76.00, H 6.14; N, 3.88 %.

7,7-Dimethyl-2-(4-bromophenyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (3n). IR (KBr): ν_{max} = 3240, 3040, 2970, 1670, 1600, 1510, 1490, 830, 770, 696 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 1.04 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.00-2.06 (d, 2H, *J*=16.4 Hz, CH_2), 2.42 (s, 2H,

CH_2), 4.72 (d, 1H, *J*=5.6 Hz, CH), 5.32 (d, 1H, *J*=5.6 Hz, =CH), 6.54 (s, 1H, NH), 7.06-7.24 (m, 5H, ArH), 7.42 (d, 2H, *J* =8.4 Hz, ArH), 7.54 (d, 2H, *J*=8.4 Hz, ArH) ppm. Anal. Calcd. for $C_{23}H_{22}BrNO$: C 67.65, H 5.43, N 3.43; Found C, 67.72, H 5.49; N 3.47 %.

7,7-Dimethyl-2-(4-methylphenyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (3o). IR (KBr): ν_{max} = 3248, 3030, 2996, 2980, 1640, 1624, 1592, 1490, 831, 770, 696 cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 0.96 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.98-2.02 (d, 1H, *J*=16.4 Hz, CH_2), 2.14-2.20 (d, 1H, *J*=16.4 Hz, CH_2), 2.42 (s, 2H, CH_2), 4.76 (d, 1H, *J*=5.6 Hz, CH), 5.30 (d, 1H, *J*=5.6 Hz, =CH), 6.64 (s, 1H, NH), 7.08–7.66 (m, 9H, ArH) ppm. Anal. Calcd. for $C_{24}H_{25}NO$: C 83.93, H 7.34, N 4.08; Found C 84.00, H, 7.38, N 4.12 %.

Acknowledgments

This project was supported by the National Natural Science Foundation of China, Educational Ministry of China, Science and Technology Commission of Hebei Province.

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