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Efficient synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives in the presence of triethylamine

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Abstract A convenient and efficient protocol for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives has been accomplished by a three-component reaction of 1,3-diaryl-2-propen-1-ones, dimedone and ammonium acetate catalyzed by triethylamine under solvent-free conditions. The simple experimental procedure, use of an inexpensive catalyst, short reaction times, and excellent yields make this procedure facile, practical, and sustainable.

Keywords 2,4-Diaryl hexahydroquinoline-5-one · Dimedone · Chalcone · Ammonium acetate · Et_3N

Introduction

Chalcones (1,3-diaryl-2-propen-1-ones) have been found to be versatile and convenient intermediates in the synthesis of a wide variety of heterocyclic compounds [1, 2]. Chalcones constitute an important group of natural products with widespread distribution in spices, tea, beer, fruits and vegetables, and belong to the flavonoid family, which possess a number of interesting biological and pharmacological activities [3–6]. Some of quinolines derivatives exhibit anti-bacterial, anti-asthmatic, anti-malarial, anti-hypertensive, and anti-platelet properties and are used as tyrosine kinase inhibitors [7, 8]. However, polyhydroquinoline derivatives show a broad range of biological activities such as calcium antagonistic activity [9] and as anticancer agents [10].

In addition, 1,4-dihydropyridines (DHPs) play a predominant role in medicinal chemistry owing to their significant biological activity [11]. DHPs are commercially

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used as calcium channel blockers for treatment of cardiovascular diseases, including hypertension [12].

Due to a wide range of applicability in medicine, bioorganics, industry, and synthetic organic chemistry, various approaches toward the synthesis of this class of compounds have been explored [10, 13–16]. 2,4-Diarylpolyhydroquinoline-5-ones have been synthesized through the reaction of 5,5-dimethyl-1,3-cyclohexanedione(dimedone), 1,3-diphenyl-2-propen-1-ones (chalcones) and ammonium acetate. For this synthesis, a number of methods have been reported such as DMF [17], microwave irradiation [18] infrared irradiation [19], ionic liquid [20] and $HClO_4$–SiO_2 [21]. However, there have always been the need to develop more efficient and greener procedures for the synthesis of polyhydroquinolines, as well as, of course, other kinds of organic compounds.

As a continuation of our interest in the area of development of practical and environmentally friendly procedures for synthesis of biologically active molecules by multicomponent reactions [22–24], here an efficient approach for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives has been described by three-component reaction of 1,3-diaryl-2-propen-1-ones, dimedone and ammonium acetate using triethylamine as a catalyst.

Experimental

1,3-diaryl-2-propen-1-ones (chalcones) have been synthesized through the cross-aldol condensation of arylaldehydes and acetophenones according to a modified reported method [25].

General procedure for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives

A mixture of dimedone (1 mmol), 1,3-diphenyl-2-propen-1-one derivatives (1 mmol), ammonium acetate (4 mmol) and triethylamine (0.1 ml) was stirred at 80 °C for the appropriate time, as shown in Table 1. After reaction completion, as monitored by TLC, the reaction mixture was cooled to ambient temperature, quenched with 1 N HCl, and extracted with chloroform. The combined organic layer was dried over anhydrous $NaSO_4$, filtered, and evaporated to give the crude product. The solid was recrystalized from ethanol to afford the pure product.

Spectral data

*7,7-Dimethyl-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-5-one (**4a**)*: IR (KBr, cm^{-1}): 3,290, 3,022, 2,981, 1,668, 1,626, 1,594, 1,488, 1,444, 778, 765, 690; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.92 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.24–2.35 (m, 4H, 2 × CH_2), 5.25 (d, J = 6.6 Hz, 1H), 5.94 (d, J = 6.6 Hz, 1H), 6.57 (s, 1H, NH), 7.42 (d, J = 8.0 Hz, 2H, ArH), 7.32–7.46 (m, 3H, ArH), 7.56–7.78 (m, 5H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.0, 18.0, 38.4, 59.9, 101.9, 105.7, 123.8, 126.4, 127.4, 128.4, 128.7, 129.8, 134.5, 140.6, 143.9, 147.4, 170.9 ppm;

Table 1 The effect of solvent on the model reaction

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	180	82
2	MeOH	180	78
3	H_2O	150	60
4	CH_3CN	150	80
5	Solvent-free	45	97

Reaction conditions: dimedone (1 mmol), 1,3-diphenyl-2-propen-1-one (1 mmol) and ammonium acetate (4 mmol) in the presence of Et_3N (0.1 ml) at 80 °C

7,7-Dimethyl-2-phenyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4b)***: IR (KBr, cm^{-1}): 3,244, 3,032, 2,986, 1,666, 1,606, 1,584, 1,500, 1,456, 834, 776; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.30–2.42 (m, 4H, 2 × CH_2), 5.62 (d, J = 6.8 Hz, 1H), 6.32 (d, J = 6.8 Hz, 1H), 7.25 (s, 1H, NH), 7.33 (d, J = 8.0 Hz, 2H, ArH), 7.53 (d, J = 8.0 Hz, 2H, ArH), 7.55–7.77 (m, 5H, ArH) ppm;

7,7-Dimethyl-4-(2,4-dichlorophenyl)-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4c)***: IR(KBr, cm^{-1}): 3,224, 3,062, 2,960, 1,662, 1,580, 1,488, 820, 770, 694; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.04–2.10 (m, 4H, 2 × CH2), 2.42 (s, J = 16 Hz, 2H, CH2), 5.12 (d, J = 5.2 Hz, CH), 5.36 (d, J = 5.2 Hz, CH), 6.58 (s, 1H, NH), 7.16–7.38 (m, 3H, ArH), 7.38 (m, 5H, ArH) ppm;

7,7-Dimethyl-2-phenyl-4-(4-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4d)***: IR (KBr, cm^{-1}): 3,344, 3,040, 2,952, 2,862, 1,654, 1,588, 1,478, 832, 752, 696; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.33–2.42 (m, 4H, 2 × CH_2), 6.04 (d, J = 6.4 Hz, 1H), 6.54 (d, J = 6.4 Hz, 1H), 6.88 (s, 1H, NH), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.60 (d, J = 8.0 Hz, 2H, ArH), 7.50–7.62 (m, 5H, ArH) ppm;

7,7-Dimethyl-2-phenyl-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4e)***: IR (KBr, cm^{-1}): 3,222, 3,034, 2,952, 2,860, 2,828, 1,660, 1,584, 1,444, 840, 759, 696; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.94 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.19–2.31 (m, 4H, 2 × CH_2), 3.78 (s, 3H, OCH_3), 5.80 (d, J = 7.0 Hz, 1H), 6.64 (d, J = 7.0 Hz, 1H), 7.15 (s, 1H, NH), 7.36 (d, J = 8.4 Hz, 2H, ArH), 7.64 (d, J = 8.4 Hz, 2H, ArH), 7.46–7.72 (m, 5H, ArH) ppm;

7,7-Dimethyl-2-phenyl-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4f)***: IR (KBr, cm^{-1}): 3,228, 3,044, 2,948, 2,872, 1,662, 1,582, 1,490, 812, 762, 694; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.92 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.31–2.45 (m, 4H, 2 × CH_2), 2.24 (s, 3H, CH_3), 5.61 (d, J = 7.0 Hz, 1H), 5.84 (d, J = 7.0 Hz, 1H), 6.22 (s, 1H, NH), 7.40 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 7.41–7.63 (m, 5H, ArH) ppm;

7,7-Dimethyl-2-(4-chlorophenyl)-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one ***(4g)***: IR (KBr, cm^{-1}): 3,228, 3,074, 2,966, 1,668, 1,588, 1,534, 1,492, 1,344, 826; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.94 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.23–2.33 (m, 4H, 2 × CH_2), 5.74 (d, J = 6.6 Hz, 1H), 6.62 (d, J = 6.6 Hz, 1H),

7.12 (s, 1H, NH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 7.44–7.60 (m, 4H, ArH) ppm;

*7,7-Dimethyl-2-(4-nitrophenyl)-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (**4h**)*: IR (KBr, cm^{-1}): 3,226, 3,076, 2,964, 1,664, 1,584, 1,534, 1,496, 1,348, 828; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.82 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.18–2.29 (m, 4H, 2 × CH_2), 5.64 (d, J = 6.5 Hz, 1H), 5.81 (d, J = 6.5 Hz, 1H), 6.20 (s, 1H, NH), 7.48 (d, J = 8.0 Hz, 2H, ArH), 7.60 (d, J = 8.0 Hz, 2H, ArH), 7.38–7.46 (m, 4H, ArH) ppm;

*7,7-Dimethyl-2-(4-chlorophenyl)-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (**4i**)*: IR (KBr, cm^{-1}): 3,318, 3,040, 2,956, 2,878, 1,666, 1,584, 1,496, 816, 774; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.27–2.39 (m, 4H, 2 × CH_2), 2.22 (s, 3H, CH_3), 6.37 (d, J = 7.0 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 7.21 (s, 1H, NH), 7.42 (d, J = 8.0 Hz, 2H, ArH), 7.78 (d, J = 8.0 Hz, 2H, ArH), 7.57–7.71 (m, 4H, ArH) ppm;

*7,7-Dimethyl-2-(4-nitrophenyl)-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-5-one (**4j**)*: IR (KBr, cm^{-1}): 3,278, 3,076, 2,972, 2,888, 1,655, 1,590, 1,556, 1,494, 1,398, 1,344, 843, 759, 695; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.22–2.36 (m, 4H, 2 × CH_2), 5.73 (d, J = 6.8 Hz, 1H), 6.69 (d, J = 6.8 Hz, 1H), 6.79 (s, 1H, NH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.78 (d, J = 8.4 Hz, 2H, ArH), 7.28–7.36 (m, 5H, ArH) ppm;

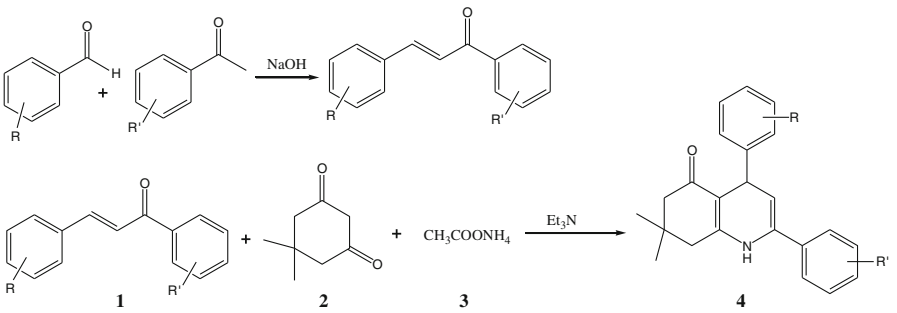
*7,7-Dimethyl-2-(4-chlorophenyl)-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-5-one (**4k**)*: IR (KBr, cm^{-1}): 3,244, 3,028, 2,984, 1,628, 1,588, 1,500, 834, 766, 696; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.98 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.31–2.44 (m, 4H, 2 × CH_2), 5.70 (d, J = 6.6 Hz, 1H), 6.64 (d, J = 6.6 Hz, 1H), 6.89 (s, 1H, NH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.52–7.66 (m, 5H, ArH) ppm;

*7,7-Dimethyl-2-(4-bromophenyl)-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-5-one (**4l**)*: IR (KBr, cm^{-1}): 3,242, 3,038, 2,974, 1,666, 1,602, 1,506, 1,496, 832, 778, 692; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.92 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.24–2.32 (m, 4H, 2 × CH_2), 6.76 (d, J = 6.4 Hz, 1H), 7.10 (d, J = 6.4 Hz, 1H), 7.29 (s, 1H, NH), 7.44 (d, J = 8.4 Hz, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.48–7.62 (m, 5H, ArH) ppm;

*7,7-Dimethyl-2-(4-methylphenyl)-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-5-one (**4m**)*: IR (KBr, cm^{-1}): 3,248, 3,030, 2,996, 2,980, 1,640, 1,624, 1,592, 1,490, 8,31, 770, 696; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.92 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.27–2.31 (m, 4H, 2 × CH_2), 2.26 (s, 3H, CH_3), 5.42 (d, J = 6.4 Hz, 1H), 6.23 (d, J = 6.4 Hz, 1H), 6.65 (s, 1H, NH), 7.32 (d, J = 8.4 Hz, 2H, ArH), 7.58 (d, J = 8.4 Hz, 2H, ArH), 7.44–7.56 (m, 5H, ArH) ppm;

Results and discussion

First, 1,3-diaryl-2-propen-1-ones (chalcones) have been synthesized through the cross-aldol condensation of arylaldehydes and acetophenones according to a modified reported method (Scheme 1) [25].



Scheme 1 Synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives

Table 2 Optimization of temperature

Entry	Temperature	Time (min)	Yield (%)
1	r.t.	180	50
2	50	100	76
3	60	100	82
3	70	60	88
4	80	45	96
5	90	45	89
6	100	45	87

Reaction conditions: dimedone (1 mmol), 1,3-diphenyl-2-propen-1-one (1 mmol) and ammonium acetate (4 mmol) in the presence of Et_3N (0.1 ml)

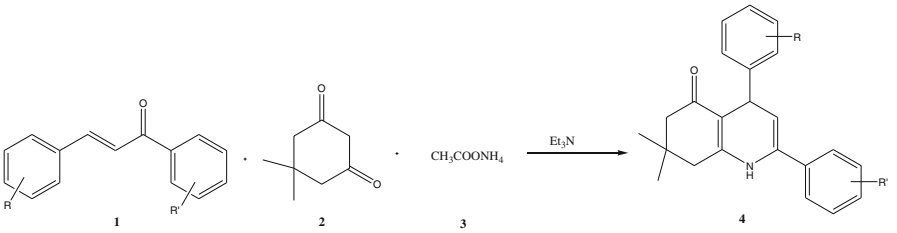
In the initial experiment, various conditions have been investigated in the model three-component reaction of 1,3-diphenyl-2-propen-1-one **1**, dimedone **2** and ammonium acetate **3** in the presence of Et_3N.

The reactions were scrutinized using different conditions. In this context, various solvents, such as EtOH, CH_3CN, H_2O, MeOH and solvent-free conditions, were investigated. Under solvent-free conditions, the best level for the synthesis of diaryl hexahydroquinoline was determined (Table 1). The effect of temperature was also evaluated for the model reaction. However, at room temperature, it was found that reaction time increases with a decrease in yield of the product. The best results have been obtained at 80 °C. So, 80 °C was chosen as the reaction temperature for all subsequent reactions (Table 2).

Therefore, the results show that the reaction proceeds cleanly at 80 °C in 45 min affording the product **4a** in 97 % yield using 0.1 ml of triethylamine under solvent-free conditions.

As represented in Table 3, all chalcones reacted well to give the expected products at high yields, either bearing electron-withdrawing groups or electron-donating groups. The structures of **4a–m** were determined on the basis of their NMR and IR spectral data [17–21].

Table 3 Reaction of dimedone, 1,3-diaryl-2-propen-1-one derivatives and ammonium acetate



Entry	R	R′	Product	Time (min)	Yield (%)	m.p. (°C) [17–21]
1	H	H	**4a**	45	97	204–206
2	4-Cl	H	**4b**	25	93	222–224
3	2,4-$Cl_2C_6H_3$	H	**4c**	20	91	205–207
4	4-NO_2	H	**4d**	35	93	210–213
5	4-OCH_3	H	**4e**	40	86	192–194
6	4-CH_3	H	**4f**	55	84	185–187
7	3-NO_2	4-Cl	**4g**	30	93	235–237
8	4-Cl	4-NO_2	**4h**	35	93	241–143
9	4-CH_3	4-Cl	**4i**	50	85	234–236
10	H	4-NO_2	**4j**	25	87	220–223
11	H	4-Cl	**4k**	30	91	249–251
12	H	4-Br	**4l**	45	89	231–233
13	H	4-CH_3	**4m**	55	88	211–213

Under the optimal reaction conditions, a range of 1,3-diaryl-2-propen-1-ones were treated with dimedone and ammonium acetate in order to examine the scope of the three-component reaction. It was found that most of the reactions proceeded smoothly to afford the corresponding 2,4-diaryl hexahydroquinoline-5-one **4a-m** in good to excellent yields (84–97 %), and several representative examples are summarized in Table 3.

Conclusion

In conclusion, a convenient and novel alternative method has been described for the synthesis of 2,4-diaryl hexahydroquinoline-5-one derivatives by a three-component reaction of 1,3-diaryl-2-propen-1-ones, dimedone and ammonium acetate catalyzed by triethylamine at 80 °C under solvent-free conditions. This method has the advantages of short reaction times with excellent yields, mild reaction conditions, simple workup, and using an inexpensive catalyst.

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