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ONE-POT SYNTHESIS OF HEXAHYDROQUINOLINES VIA HANTZSCH FOUR-COMPONENT REACTION CATALYZED BY A CHEAP AMINO ALCOHOL

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An economic, efficient access to hexahydroquinolines was found. In the presence of* threo-*(1S,2S)-2-amino-1-(4′-nitrophenyl)-1,3-propanediol, a waste product formed in the production of chloromycetin, a one-pot, four-component Hantzsch reaction of dimedone, aldehydes, ethyl acetoacetate, and ammonium acetate at room temperature furnished hexahydroquinoline derivatives in excellent yield. A possible catalytic mechanism was also suggested.

Keywords: Amino alcohol; Hantzsch reaction; hexahydroquinolines; one-pot synthesis

INTRODUCTION

Hexahydroquinoline derivatives possess a variety of biological activities, such as vasodilatory, bronchodilatory, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic activity,[1] and some of them have been used as calcium channel modulators and curatives for cardiovascular diseases.[2] For example, dihydropyridyl compounds nifedipine, nicardipine, amlodipine, and other related derivatives are effective in the treatment of hypertension.[3] In past years, their uses as neuroprotectants, platelet anti-aggregatory agents, and cerebral anti-ischemic agents in the treatment of Alzheimer's disease and as chemosensitizers in tumor therapy have been also reported.[4] They clearly show the remarkable potential of novel dihydropyridine derivatives as sources of valuable drug candidates.

Hexahydroquinolines generally are synthesized by condensation of aldehydes, ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohol.[5] This method, however, requires long reaction times, harsh reaction conditions, and large quantities of volatile organic solvents and commonly gives poor yields. In the past several years, some Lewis acids,[6,9] bases,[10,11] and salts[12,14] have been examined as catalysts for the preparation of hexahydroquinolines, and microwave irradiation,[15] ionic liquids,[16] and solvent-free reactions[17] have been utilized in their preparation. Although some of these are successful to a certain degree, they are not perfect for reasons such as utilization of expensive reagents or poor yield.

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Therefore, development of convenient, economic, high-yielding preparative procedure for hexahydroquinolines is of much practical importance.

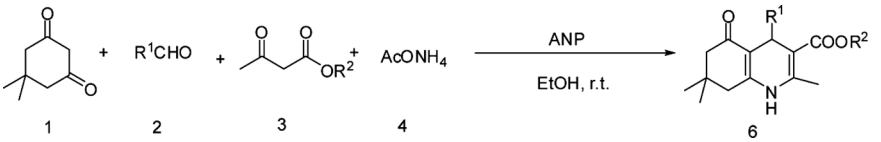
RESULTS AND DISCUSSION

*Threo-(*1*S*,2*S*)-2-amino-1-(4′-nitrophenyl)-1,3-propanediol [ANP], a waste product in the production of chloromycetin, is one of the cheapest amino alcohols available. Previously, Jiang et al. utilized ANP and its derivatives to catalyze alkynylation of aldehydes or α-keto esters[18] to excellent effect. Our group is also interested in ANP chemistry and has revealed some novel chemistry of it and its derivatives, including selective oxazolidination of ANP,[19] selective oxidation formylation of the N,N-dimethyl derivative of ANP,[20] resolution of racemic 1,1′-bi-2-naphthol[21] using ANP derivatives, and asymmetric Henry reaction catalyzed by ANP derivatives.[22] As a part of our interest, the catalytic activity of ANP toward a four-component synthesis of hexahydroquinolines was examined (Scheme 1).

In an initial experiment, dimedone was allowed to react directly with benzaldehyde, acetoacetate, ester and ammonium acetate in ethanol for 4 h, and the product **6a** was obtained in only 10% yield. By extending the reaction time to 24 h, the yield was upgraded to 35%. However, when the reaction was performed for 4 h in the presence of 5 mol% ANP, the yield of **6a** was heightened to 71% (entry 3 in Table 1). It can be seen in Table 1 that 10% of ANP loading afforded the best result (entry 4).

Catalytic activities of ANP (**5a**) derivatives, *threo*-(1S,2S)-2-dimethylamino-1-(4′-nitrophenyl)-1,3-propanediol (DMANP, **5b**), and *threo*-(1S,2S)-3-triphenylmethoxy-2-amino-1-(4′-nitrophenol)propanol (TPANP, **5c**) (Fig. 1) toward the reaction were compared. It was found that the modification of ANP could not improve the **6a** yield (Table 2).

In view of these results, ANP was used as catalyst for Hantzsch synthesis of hexahydroquinolines. A wide range of aromatic, heteroaromatic, and aliphatic aldehydes were subjected to this procedure. The results are shown in Table 3. All the products were characterized by infrared (IR), ^{1}H NMR, and ^{13}C NMR spectra, and **6b** was authorized by the single-crystal x-ray diffraction analysis (Fig. 2). It can be seen in Table 3 that under ANP catalysis, all the reactions furnished hexahydroquinolines in good yield; however, the attribute of aldehyde, the position and the electronic property of the substituent in the aromatic aldehydes, as well as the alkyl group of acetoacetic esters influence the selectivity of the reaction. In general, the aliphatic aldehyde (entry 14) and the α,β-unsaturated aldehyde (entry 13) furnished less of the desired products than the aromatic or heteroaromatic aldehydes; for the substituted benzaldehydes, the yields of the desired products from the reactions of the



Scheme 1. Synthesis of hexahydroquinolines through the Hantzsch reaction catalyzed by ANP.

Table 1. Dependence of Hantzsch synthesis of 1,4-dihydropyridines on ANP

Entry	Amount of ANP (mol %)	Time (h)	Yield[a] (%)
1	0	4	10
2	0	24	35
3	5	4	71
4	10	4	88
5	30	4	85

[a]Refers to isolated yield.

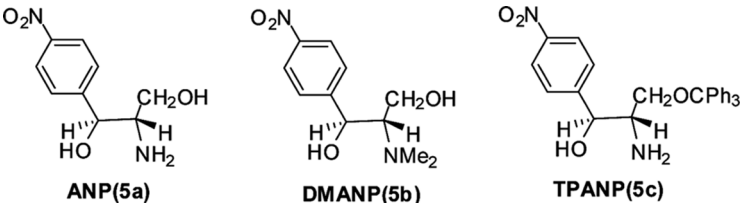


Figure 1. Catalysts used for Hantzsch reaction.

Table 2. Effect of the composition of catalyst on the yield of 1,4-dihydropyridine **6a**

Entry	Catalyst	Time	Yield[a]
2	5a	4	88
3	5b	4	85
4	5c	4	80

[a]Refers to isolated yield.

Table 3. ANP-catalyzed Hantzsch synthesis of 1,4-dihydropyridines

						Mp (°C)	
Entry	R_1	R_2	Time (h)	Product	Yield (%)[a]	Observed	Reported
1	C_6H_5	OC_2H_5	4	**6a**	88	203–205	202–204[7]
2	4-ClC_6H_4	OC_2H_5	4	**6b**	88	243–245	245–246[8]
3	4-BrC_6H_4	OC_2H_5	4	**6c**	92	255–257	253–255[7]
4	3-BrC_6H_4	OC_2H_5	4	**6k**	83	235–237	234–236[6]
5	2,6-$Cl_2C_6H_3$	OC_2H_5	4	**6f**	86	263–265	—
6	2,4-$Cl_2C_6H_4$	OC_2H_5	4	**6l**	95	242–244	241–244[7]
7	3-$NO_2C_6H_4$	OC_2H_5	5	**6g**	75	177–179	177–178[8]
8	4-$CH_3C_6H_4$	OC_2H_5	4	**6h**	82	261–263	260–261[7]
9	4-$CH_3OC_6H_4$	OC_2H_5	4	**6i**	87	257–259	257–259[7]
10	2-$CH_3OC_6H_4$	OC_2H_5	5	**6j**	78	194–196	193–195[7]
11	4-OHC_6H_4	OC_2H_5	4	**6d**	83	233–234	232–234[7]
12	4-$(CH_3)_2NC_6H_4$	OC_2H_5	4	**6e**	85	229–231	229–231[7]
13	$C_6H_5CH{=}CH$	OC_2H_5	5	**6m**	77	205–206	204–206[7]
14	$CH_3CH_2CH_2$	OC_2H_5	5	**6n**	75	147–148	147–148[7]
15	Fur-2-yl	OC_2H_5	4	**6o**	85	247–249	246–248[7]
16	C_6H_5	OBu^n	5	**6p**	76	223–224	222–223[8]

[a]Refers to isolated yield.

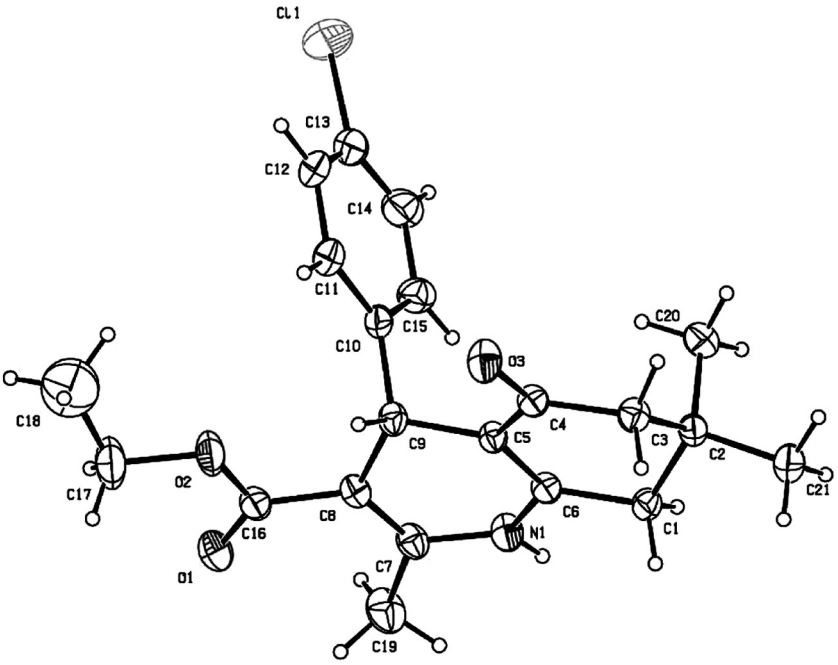
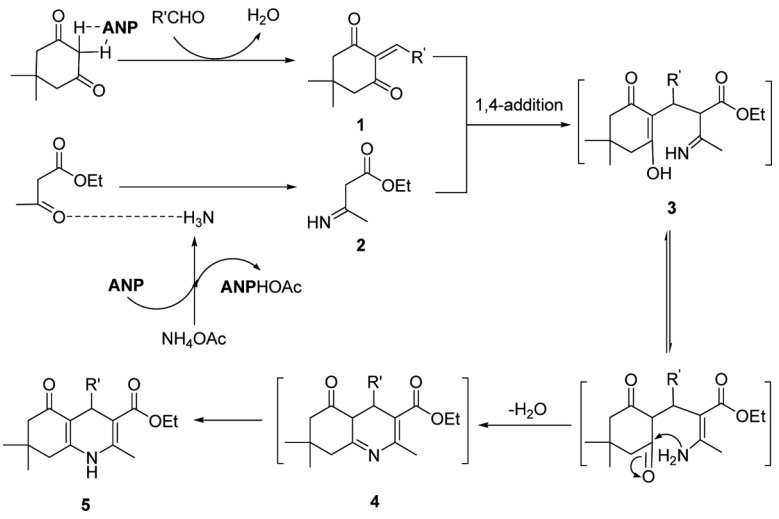


Figure 2. Showing the ORTEP diagram of **6b**.

4-substituted aromatic aldehydes are greater by nearly 10% than those of the 2- or 3-substituted ones (entries 3 and 4, 9 and 10, 5 and 6), and the longer chain alkyl group of acetoacetic ester is not beneficial for the reaction (entries 1 and 16).



Scheme 2. Possible mechanism for the formation of hexahydroquinolines in the presence of ANP.

A possible mechanism for ANP-catalyzed synthesis of hexahydroquinolines has been suggested (Scheme 2). ANP is a 1,3-dihydroxyl primary amine. The basic property of ANP determines that it is easy to accept the α acidic proton of dimedone and alkyl acetoacetates to form a carbon negative ion; on the other hand, it is also possible that the hydroxyl groups of ANP activated the carbonyls of dimedone and alkyl acetoacetates via the formation of H bonding. Namely, the existence of ANP strengthens the activity of dimedone and alkyl acetoacetates and lays a foundation for their reaction with other components. Furthermore, ANP can promote liberation of ammonia from NH_4OAc. Thus, in the presence of ANP, dimedone readily undergoes condensation with aldehyde to generate an alkylidenedimedone **1**, and the probability of the formation of amination product **2** of alkyl acetoacetates is increased. Under the experiment conditions, 1,4-addition of the β-imino ester **2** to the alkylidenedimedone **1** took place, forming intermediate **3**, which further dehydrated and cyclized into the desired hexahydroquinoline derivatives. The crystallographic analysis has shown that the hexahydroquinoline derivative **5** is the most stable form of the four-component Hantzsch reaction product.

In conclusion, we have successfully developed a convenient, efficient method for the synthesis of hexahydroquinolines via a one-pot, four-component reaction of dimedone, aldehydes, ethyl acetoacetate, and ammonium acetate in the presence of ANP. The major advantages of this method include mild conditions, simple experimental procedure, low cost, and excellent yield.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Testscan Shimadzu Fourier transform (FT)–IR 8000 in KBr. ^1H and ^{13}C NMR spectra were performed on a Varian Mercury VS 300, with δ values (ppm) relative to Me_4Si. Melting points were determined on a VEB Wagetechnik Rapio PHMK05 instrument and are uncorrected.

Typical Procedure

Aldehyde (2 mmol) and ammonium acetate (2 mmol) were added to a stirred mixture of dimedone (2 mmol), ethyl acetoacetate (2 mmol), and compound **5a** (0.042 g, 10 mol%) in ethanol (4 mL). The reaction mixture was stirred at room temperature for 4–5 h. The resulting yellow solid was filtered and treated by reflux in ethanol to give the pure hexahydroquinoline derivatives.

Ethyl 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6a)

^1H NMR (300 MHz, $CDCl_3$): δ 7.06–7.31 (m, 5H), 6.14 (s, 1H), 5.05 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 2.35 (s, 3H), 2.22 (s, 2H), 2.17 (s, 2H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 167.8, 163.9, 150.0, 147.4, 144.3, 128.2, 128.1, 126.2, 111.8 106.0, 77.5, 77.3, 77.1, 60.0, 51.0, 40.8, 36.9, 36.8, 32.8, 29.7, 27.3, 19.3, 19.2, 14.4. IR (KBr): (3289, 1689, 1611, 1484, 1382, 1211 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, $J = 9.0$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 2H), 6.52 (s, 1H), 5.01 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 2.34 (s, 3H), 2.26 (s, 2H), 2.20 (s, 2H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.05 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.7, 167.7, 148.1, 144.3, 135.6, 128.8, 128.1, 112.5, 106.4, 77.6, 77.2, 76.8, 60.0, 50.9, 41.3, 36.2, 32.9, 29.6, 27.4, 21.2, 19.6, 14.4. IR (KBr): (3274, 1706, 1605, 1496, 1382, 1214 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-bromophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6c)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 5.95 (s, 1H), 5.00 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 2.36 (s, 3H), 2.19 (s, 2H), 2.15 (s, 2H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.06 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 167.5, 148.9, 146.4, 144.1, 131.1, 130.1, 120.0, 111.8, 105.8, 60.1, 50.9, 41.1, 36.5, 32.9, 29.7, 27.3, 19.6, 14.4; IR (KBr): (3274, 1703, 1604, 1497, 1382, 1215 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-hydroxylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, $J = 8.1$ Hz, 2H), 6.64 (d, $J = 8.7$ Hz, 2H), 5.62 (s, 1H), 4.98 (s, 1H), 4.86 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 2.37 (s, 3H), 2.31 (s, 2H), 2.22 (s, 2H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 167.5, 148.9, 145.9, 144.1, 131.8, 129.7, 128.2, 111.9, 105.9, 60.1, 50.9, 41.1, 36.5, 32.9, 29.7, 27.3, 19.6, 14.5; IR (KBr): (3417, 3382, 1686, 1613, 1485, 1383, 1221 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-dimethylaminophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, $J = 8.7$ Hz, 2H), 6.59 (d, $J = 8.7$ Hz, 2H), 6.01 (s, 1H), 4.93 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 2.85 (s, 6H), 2.34 (s, 3H), 2.14–2.19 (s, 4H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.05 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 163.4, 145.6, 144.4, 139.3, 131.6, 124.1, 107.7, 107.1, 101.7, 55.2, 46.4, 36.1, 35.8, 30.9, 28.0, 25.1, 22.6, 14.5, 9.8; IR (KBr): (3206, 2956, 1701, 1606, 1489, 1381, 1221 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(2,6-dichlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 6.96 (t, $J = 8.1$ Hz, 1H), 5.91 (s, 1H), 5.86 (s, 1H), 4.02 (q, $J = 7.2$ Hz, 2H), 2.24 (s, 3H), 2.14 (s, 2H), 2.11 (s, 2H), 1.07–1.10 (m, 3H), 1.07 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 167.7, 151.0, 145.6, 139.5, 138.2, 136.2, 130.0, 128.4, 127.4, 109.0, 102.5, 59.9,

51.1, 41.0, 35.8, 32.4, 29.4, 27.7, 19.4, 144.4; IR (KBr): (3288, 1702, 1600, 1493, 1383, 1221 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 7.2$ Hz, 1H), 7.38 (t, $J = 7.2$ Hz, 1H), 6.55 (s, 1H), 5.16 (s, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 2.39 (s, 3H), 2.28 (s, 2H), 2.17 (s, 2H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.7, 167.2, 149.5, 149.2, 148.5, 144.8, 135.0, 128.8, 123.1, 121.5, 111.4, 105.3, 60.3, 50.8, 41.1, 37.2, 32.9, 31.2, 29.6, 27.3, 19.6, 14.4; IR (KBr): (3285, 1705, 1606, 1486, 1382, 1211 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, $J = 7.5$ Hz, 2H), 7.01 (d, $J = 7.5$ Hz, 2H), 6.12 (s, 1H), 5.01 (s, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 2.35 (s, 3H), 2.17–2.29 (m, 7H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 167.9, 158.0, 149.9, 144.1, 140.1, 129.1, 113.5, 111.9, 106.3, 60.0, 55.3, 51.1, 45.8, 40.8, 36.0, 32.8, 29.7, 27.3, 19.3, 14.5; IR (KBr): (3275, 1702, 1605, 1496, 1383, 1216 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6i)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, $J = 2.1$ Hz, 2H), 6.73 (d, $J = 8.7$ Hz, 2H), 6.40 (d, $J = 10.8$ Hz, 1H), 4.99 (s, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 2.20 (s, 2H), 2.18 (s, 2H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 152.8, 143.3, 138.3, 134.7, 124.0, 108.3, 107.3, 101.3, 54.8, 50.1, 45.8, 36.0, 30.7, 27.7, 26.0, 24.5, 22.2, 14.4, 9.3; IR (KBr): (3276, 1702, 1605, 1497, 1382, 1215 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(2-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6j)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.08 (s, 1H), 6.80 (m, 2H), 6.04 (s, 1H), 5.26 (m, 2H), 4.01 (m, 2H), 3.80 (s, 3H), 2.29 (s, 3H), 2.12–2.16 (m, 4H), 1.18 (m, 3H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 167.0, 156.5, 149.1, 149.1, 143.5, 134.3, 130.1, 126.0, 118.8, 109.9, 108.9, 102.9, 58.2, 54.4, 49.9, 33.0, 31.9, 28.7, 25.7, 17.65, 13.3; IR (KBr): (3284, 1689, 1487, 1215 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(3-bromophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6k)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.21–7.27 (m, 2H), 7.04–7.09 (m, 1H), 6.96 (s, 1H), 5.02 (s, 1H), 4.06–4.10 (m, 2H), 2.33 (m, 3H), 2.13–2.28 (m, 4H),

1.19–1.24 (m, 3H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 167.5, 149.7, 149.6, 144.5, 131.3, 129.7, 129.4, 127.1, 122.3, 111.5, 105.6, 60.2, 51.0, 41.0, 36.9, 32.9, 29.7, 27.4, 19.5, 14.4; IR (KBr): (3273, 1702, 1604, 1489, 1211 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(2-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6l)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.7$ Hz, 1H), 7.24 (s, 1H), 7.09 (d, $J = 8.7$ Hz, 1H), 5.33 (s, 1H), 4.01–4.05 (m, 2H), 2.11–2.30 (m, 7H), 1.14–1.19 (3 m, H), 1.04 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 167.5, 149.5, 144.4, 143.0, 134.1, 133.1, 132.3, 129.5, 126.8, 110.9, 104.9, 60.1, 50.9, 41.1, 36.0, 32.7, 29.6, 27.4, 19.5, 14.5; IR (KBr): (3283, 1706, 1609, 1495, 1381, 1213 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-styryl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6m)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.28 (m, 5H), 7.02 (s, 1H), 6.20–6.22 (m, 2H), 4.69 (d, $J = 3.9$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.35 (s, 3H), 2.19–2.28 (m, 4H), 1.24–1.29 (m, 3H), 1.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 150.0, 144.8, 137.7, 132.0, 128.6, 128.3, 126.8, 126.1, 109.5, 103.5, 59.8, 50.8, 40.8, 33.2, 32.6, 29.3, 27.4, 19.2, 14.4; IR (KBr): (3438, 3292, 2188, 1674, 1635 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-propyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylate (6n)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H), 4.16–4.17 (m, 2H), 4.02 (s, 1H), 2.32–2.34 (m, 5H), 2.25 (s, 2H), 1.26–1.31 (m, 4H), 1.09 (s, 6H), 0.83 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6, 168.4, 151.3, 145.1, 111.0, 105.3, 59.8, 51.2, 41.0, 39.1, 32.7, 30.1, 30.0, 27.3, 19.2, 18.5, 14.6; IR (KBr): (3293, 2962, 1699, 1604, 1487, 1216 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(furan-2-yl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylate (6o)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (s, 1H), 6.20 (d, $J = 2.1$ Hz, 1H), 6.01 (m, 2H), 5.25 (s, 1H), 4.15 (m, 2H), 2.36 (s, 3H), 2.26 (s, 2H), 1.62 (s, 2H), 1.26 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 172.4, 163.8, 155.8, 150.8, 145.3, 115.1, 113.6, 109.3, 101.8, 64.4, 55.8, 37.4, 35.0, 34.6, 31.8, 23.7, 19.4; IR (KBr): (3285, 3220, 1676, 1606, 1220 cm^{-1}.

Ethyl 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3- Carboxylate (6p)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08–7.31 (m, 5H), 6.93 (s, 1H), 5.04 (s, 1H), 3.99–4.05 (m, 2H), 2.10–2.32 (m, 7H), 1.52–1.57 (m, 2H), 1.18–1.30 (m, 2H), 1.05 (s, 3H), 0.91 (s, 3H), 0.84–0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1,

167.9, 149.2, 147.4, 144.2, 128.2, 128.1, 126.2, 112.1, 106.1, 64.0, 51.0, 41.0, 36.8, 32.9, 30.9, 29.6, 27.3, 19.4, 13.9.

Crystallography of Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6b)

Procedure. Compound **6b** was dissolved in hot ethanol and then cooled slowly to furnish a crystal suitable for crystallographic analysis, 0.42 mm × 0.33 mm × 0.31 mm.

Crystallographic data. $C_{21}H_{24}ClNO_3$, M 373.86, orthorhombic, space group *Pbcn, a* 18.1554 (12) ?, *b* 15.5900 (10) ?, *c* 14.2034 (9) ?, $V = 4020.2(4)$?^{3}, Z 8, μ(Mo Kα) 0.71073 mm^{-1}, absorption coefficient (μ), 0.209 mm^{-1}; index ranges: $-22 < h < 21$, $-18 < k < 19$, $-17 < 1 < 17$; $F(000)$ 1584, GOF 0.993, T 273(2) K, 23080 reflections, 4164 independent ($R_{int} = 0.0223$), R_1 0.0746 ($I > 2ó(I)$) and wR_2 (all data) 0.1973.

Supplementary data. Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 693368. The crystallographic information file can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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