

Note

Synthesis of 4-aryl-5-oxo-1*H,4H*-5,6,7,8-tetrahydroquinoline and 4-aryl-5-oxo-1*H*-4,5,6,7-tetrahydrocyclopenteno[*b*]pyridine derivatives by ultrasound irradiation and by conventional methods

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Methyl 2-methyl-4-aryl-5-oxo-1*H,4H*-5,6,7,8-tetrahydroquinoline-3-carboxylates **4a-d** and methyl 2-methyl-4-aryl-5-oxo-1*H*-4,5,6,7-tetrahydrocyclopenteno[*b*]pyridine-3-carboxylates **6a-e** have been synthesized by the condensation of cyclic 1,3-diones with aromatic aldehydes and β -aminocrotonate using thermal and ultrasound irradiation methods.

Keywords: Quinolines, pyridines, ultrasound irradiation.

IPC: Int.Cl.⁷ C 07 D

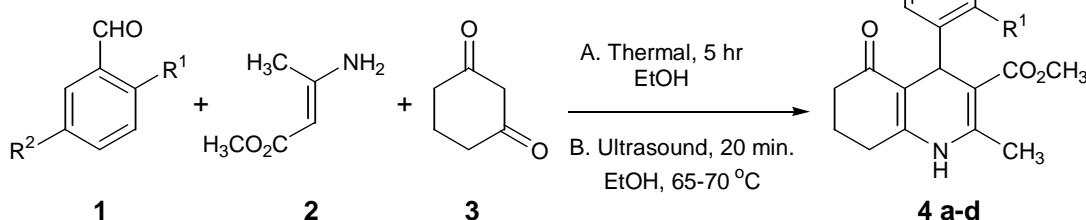
The ring system of 1,4-dihydropyridine analogues is generally considered to be one of the most broadly involved rings in heterocyclic compounds. Aryldihydropyridines, first synthesized by Hantzsch¹ and Eisner *et al.*², have played an important role in medicinal chemistry as vasodilators and anti-hypertensive agents³⁻⁵. Various aryldihydropyridines like Nifedipine and SKF 24260 have been found to be highly effective calcium antagonist and vasodilators⁶. Most of these aryldihydropyridine derivatives have been synthesized by the condensation of aromatic aldehydes with β -aminocrotonate and 1,3-diketones. Now a days, ultrasonication is a very convenient

energy source for synthetic organic chemistry^{7,8}. Concerning the ultrasound irradiation, most of the observed effects of ultrasound on chemical reactions can be attributed to cavitations, the formation and subsequent collapse of small micro bubble inside the liquid phase⁹. The pressure and temperature inside the micro bubbles are estimated to be \sim 1000 atmosphere and 4000~5000 K¹⁰. The high pressure is especially favourable for condensation reactions, since the product has a smaller volume than those of the reactants. The formation of micro cavitations is non selective. In this paper, we wish to report a very convenient, short time, high yield and low reaction cost one-pot synthesis of arylhexahydroquinoline and arylcyclopentenopyridine derivatives by conventional and ultrasound methods.

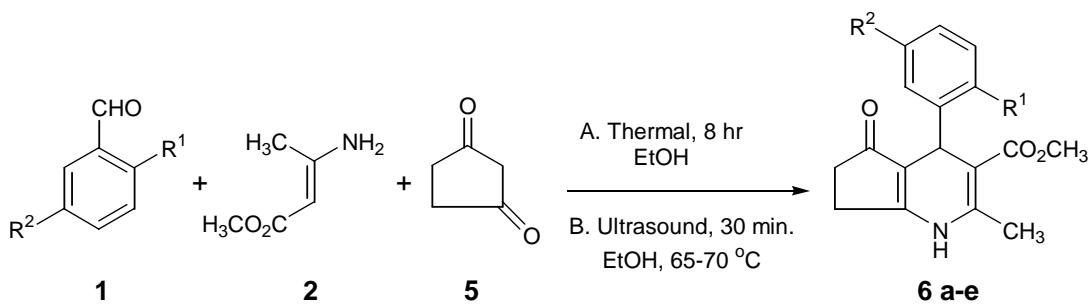
Results and Discussion

Condensation of substituted benzaldehydes **1** with β -aminocrotonate **2** and cyclohexane-1,3-dione **3** furnished the corresponding methyl 2-methyl-4-aryl-5-oxo-1*H,4H*-5,6,7,8-tetrahydroquinoline-3-carboxylates **4a-d** under thermal and ultrasound irradiation conditions in good yields (**Scheme I, Table I**).

The IR spectrum of the compound **4a** showed a band at 3310 cm^{-1} due to NH stretching, two bands at 1710 and 1670 cm^{-1} due to ester and keto carbonyl groups, respectively, and two bands at 1525 and 1358 cm^{-1} due to nitro group. The ¹H NMR spectrum of the compound **4a** showed a multiplet at δ 1.68-2.15 due to C₇ and C₈-CH₂ protons, a singlet at δ 2.26 due to C₂-CH₃ protons, a multiplet at δ 2.44-2.48 due to C₆-CH₂ protons, a singlet at δ 3.41 due to OCH₃ protons, another singlet at δ 5.54 due to C₄-CH proton, a multiplet at δ 7.27-7.67 due to aromatic



Scheme I



Scheme II

Table I—Comparison of yields of **4a-d** and **6a-e** under thermal and ultrasound irradiation conditions

Products	R ¹	R ²	Reaction conditions			
			Thermal condition		Ultrasound irradiation	
			Time (min)	Yield (%)	Time (min)	Yield (%)
4a	NO ₂	H	5	85	20	85
4b	OH	NO ₂	5	80	20	82
4c	OH	H	5	78	20	76
4d	OH	Cl	5	81	20	79
6a	NO ₂	H	8	68	30	66
6b	OH	NO ₂	8	71	30	68
6c	OH	H	8	61	30	61
6d	H	H	8	75	30	70
6e	OH	Cl	8	60	30	66

protons and a singlet at δ 9.23 due to NH proton. In ¹³C NMR and DEPT spectra of the compound **4a**, it is observed that the C₂-CH₃ carbon appeared at δ 18.26, the C₆, C₇ and C₈-CH₂ carbons appeared at δ 20.67, 26.17 and 36.53, the C₄-CH appeared at δ 31.73, the OCH₃ carbon appeared at δ 50.57, the aromatic CH carbons appeared at δ 123.53, 126.94, 130.64 and 132.90, other olefinic and aromatic carbons appeared at δ 102.75, 110.93, 141.78, 145.89, 147.81 and 151.80, the ester carbonyl carbon appeared at δ 167.00 and the keto carbonyl carbon at δ 194.26.

Similarly, reaction of cyclopentane-1,3-dione **5** with substituted benzaldehydes **1** and β -aminocrotonate **2** afforded methyl 2-methyl-4-aryl-5-oxo-1*H*-4,5,6,7-tetrahydrocyclopenteno[*b*]pyridine-3-carboxylates **6a-e** under thermal and ultrasound irradiation conditions (Scheme II, Table I).

The IR spectrum of the compound **6a** showed a band at 3310 cm⁻¹ due to NH stretching, two bands at 1709 and 1674 cm⁻¹ due to ester and keto carbonyl groups, respectively, and two bands at 1524 and 1357 cm⁻¹ due to nitro group. In the ¹H NMR spectrum, a

multiplet appeared at δ 2.15-2.26 for C₇-CH₂ protons, a sharp singlet appeared at δ 2.28 for C₂-CH₃ protons, a multiplet at δ 2.56-2.59 for C₆-CH₂ protons and a singlet appeared at δ 3.35 for OCH₃ protons, a sharp singlet appeared at δ 5.49 for C₄-CH, another multiplet appeared at δ 7.31-7.76 for aromatic protons and a singlet appeared at δ 9.85 for NH proton. On the basis of ¹³C NMR, DEPT-90 and DEPT-135 spectra, the following signals were assigned: a peak appeared at δ 18.85 for C₂-CH₃ carbon, two peaks appeared at δ 23.80 and 33.34 for the C₆ and C₇-CH₂ carbons, a peak at δ 32.12 for the C₄-CH carbon and a peak at δ 50.72 for OCH₃ carbon appeared, aromatic CH carbons appeared at δ 123.57, 127.11, 130.98 and 133.22, aromatic and olefinic quaternary carbons appeared at δ 102.96, 115.44, 140.90, 147.07, 147.79 and 164.40 and two peaks appeared at δ 166.75 and 200.39 for ester and keto carbonyl carbons, respectively.

In a test run at ambient temperature in ultrasound irradiation condition, the reaction furnished only a small amount of the product in much lower yield. The effect of ultrasound on the synthesis of arylhexa-hydroquinoline and arylcyclopentenopyridine derivatives is more efficient by shortening the reaction time to 1/15 of the thermal condition.

Experimental Section

All melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8300 model and BOMEM (Hartmann and Braun). ¹H and ¹³C NMR spectra were recorded on Jeol GMX 400 MHz, Varian 400 MHz, Varian Unity Inova 500 MHz spectrometer using DMSO-*d*₆ as the solvent and TMS as the internal standard. HRMS (High Resolution Mass Spectra) data were recorded on Thermo Finnigan MAT 95XL mass spectrometer. The source of ultrasound is from Misonix XL2020 450 W Ultrasound cleaner bath at 65-70°C.

Typical procedure for the synthesis of arylhexa-hydroquinoline derivatives **4a-d and pentahydro-pyridine derivatives **6a-e****

Conventional method¹⁰

A mixture of substituted benzaldehyde (0.01 mole), methyl β -amino-crotonate (0.01 mole) and 1,3-dione (0.01 mole) was refluxed in ethanol (20 mL) for the time period indicated in **Table I**. Upon cooling the reaction mixture to room temperature, a yellow colour solid was obtained, which was filtered and recrystallized from a mixture of methanol-chloroform (1:1).

The synthesis of compound **4a** has been reported earlier.¹¹

Ultrasound irradiation method

A solution of substituted benzaldehyde (0.01 mole), methyl β -amino-crotonate (0.01 mole) and 1,3-dione (0.01 mole) in ethanol (20mL) was irradiated with ultrasound for the time periods indicated in **Table I**. After irradiation, the reaction mixture was cooled to room temperature and the separated solid was filtered and finally recrystallized from a mixture of methanol-chloroform (1:1).

Methyl 2-methyl-4-(2-nitrophenyl)-5-oxo-1H, 4H-5,6,7,8-tetrahydroquinoline-3-carboxylate 4a: m.p. 254-56°C (lit.¹¹ m.p. 250°C); IR (KBr): 3310, 1710, 1670, 1610, 1525, 1358 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): δ 1.68-2.15 (m, 4H, C₇ and C₈-CH₂), 2.26 (s, 3H, CH₃), 2.44-2.48 (m, 2H, C₆-CH₂), 3.41 (s, 3H, OCH₃), 5.54 (s, 1H, C₄-CH), 7.27-7.67 (m, 4H, Ar-H), 9.23 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO- d_6): δ 18.26, 20.67, 26.17, 31.73, 36.53, 50.57, 102.75, 110.93, 123.53, 126.94, 130.64, 132.90, 141.78, 145.89, 147.81, 151.80, 167.00, 194.26; ^{13}C NMR DEPT-90 (125 MHz, DMSO- d_6): δ 31.73, 123.53, 126.94, 130.64, 132.90 (all CH); ^{13}C NMR DEPT-135 (125 MHz, DMSO- d_6): δ 18.26 (\uparrow), 20.67 (\downarrow), 26.17 (\downarrow), 31.73 (\uparrow), 36.53 (\downarrow), 50.57 (\uparrow), 123.53 (\uparrow), 126.94 (\uparrow), 130.64 (\uparrow), 132.90 (\uparrow); HRMS: Calcd for C₁₈H₁₈N₂O₅: 342.1710. Found: 342.1721.

Methyl 2-methyl-4-(2-hydroxy-5-nitrophenyl)-5-oxo-1H, 4H-5, 6, 7,8-tetrahydro-quinoline-3-carboxylate 4b: m.p. 262-64°C; IR (KBr): 3308, 1710, 1668, 1610, 1520, 1355 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): δ 1.63-2.18 (m, 4H, C₇ and C₈-CH₂), 2.21 (s, 3H, CH₃), 2.41-2.49 (m, 2H, C₆-CH₂), 3.56 (s, 3H, OCH₃), 5.00 (s, 1H, C₄-CH), 7.09-7.68 (m, 3H, Ar-H), 9.45 (s, 1H, NH), 10.40 (bs, 1H, OH); HRMS: Calcd for C₁₈H₁₈N₂O₆: 358.1218. Found: 358.1209.

Methyl 2-methyl-4-(2-hydroxyphenyl)-5-oxo-1H, 4H-5,6,7,8-tetrahydro-quinoline-3-carboxylate 4c: m.p. 247-49°C; IR (KBr): 3300, 1700, 1669, 1600 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 1.61-2.15 (m, 4H, C₇ and C₈-CH₂), 2.28 (s, 3H, CH₃), 2.39-2.46 (m, 2H, C₆-CH₂), 3.56 (s, 3H, OCH₃), 5.12 (s, 1H, C₄-CH), 7.18-7.62 (m, 4H, Ar-H), 9.20 (s, 1H, NH) 10.18 (s, 1H, OH); HRMS: Calcd for C₁₈H₁₉NO₄: 313.3524. Found: 313.3532.

Methyl 2-methyl-4-(2-hydroxy-5-chlorophenyl)-5-oxo-1H,4H-5,6,7,8-tetrahydroquinoline-3-carboxylate 4d: m.p. >270°C; IR (KBr): 3300, 1700, 1678, 1600 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 1.61-2.16 (m, 4H, C₇ and C₈-CH₂), 2.26 (s, 3H, CH₃), 2.41-2.45 (m, 2H, C₆-CH₂), 3.50 (s, 3H, OCH₃), 5.09 (s, 1H, C₄-CH), 7.16-7.80 (m, 3H, Ar-H), 9.48 (s, 1H, NH), 10.26 (bs, 1H, OH); HRMS: Calcd for C₁₈H₁₈NO₄Cl: 347.7775. Found: 347.7778.

Methyl 2-methyl-4-(2-nitrophenyl)-5-oxo-1H-4,5,6,7-tetrahydrocyclopenteno[b] pyridine-3-carboxylate 6a: m.p. 260-62°C; IR (KBr): 3310, 1709, 1674, 1600, 1524, 1357 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): δ 2.15-2.26 (m, 2H, C₇-CH₂), 2.28 (s, 3H, CH₃), 2.56-2.59 (m, 2H, C₆-CH₂), 3.35 (s, 3H, OCH₃), 5.49 (s, 1H, C₄-CH), 7.31-7.76 (m, 4H, Ar-H), 9.85 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO- d_6): δ 18.85, 23.80, 32.12, 33.34, 50.72, 102.96, 115.44, 123.57, 127.11, 130.98, 133.22, 140.90, 147.07, 147.79, 164.40, 166.75, 200.39; ^{13}C NMR DEPT-90 (125 MHz, DMSO- d_6): δ 32.12, 123.57, 127.11, 130.98, 132.22 (all CH); ^{13}C NMR DEPT-135 (125 MHz, DMSO- d_6): δ 18.85 (\uparrow), 23.80 (\downarrow), 32.12 (\uparrow), 33.34 (\downarrow), 50.72 (\uparrow), 123.57 (\uparrow), 127.11 (\uparrow), 130.98 (\uparrow), 133.22 (\uparrow); HRMS: Calcd for C₁₇H₁₆N₂O₅: 328.3238. Found: 328.3219.

Methyl 2-methyl-4-(2-hydroxy-5-nitrophenyl)-5-oxo-1H-4,5,6,7-tetrahydro-cyclopenteno[b]pyridine-3-carboxylate 6b: m.p. >270°C; IR (KBr): 3310, 1705, 1668, 1610, 1520, 1352 cm^{-1} ; ^1H NMR (500MHz, DMSO- d_6): δ 2.14-2.22 (m, 2H, C₇-CH₂), 2.26 (s, 3H, CH₃), 2.53-2.57 (m, 2H, C₆-CH₂), 3.49 (s, 3H, OCH₃), 5.42 (s, 1H, C₄-CH), 6.98-7.38 (m, 3H, Ar-H), 9.18 (s, 1H, NH), 10.07 (s, 1H, OH); HRMS: Calcd for C₁₇H₁₆N₂O₄: 344.3232. Found: 344.3222.

Methyl 2-methyl-4-(2-hydroxyphenyl)-5-oxo-1H-4,5,6,7-tetrahydrocyclo-penteno[b]pyridine-3-carboxylate 6c: m.p. >270°C; IR (KBr): 3310, 1708, 1661, 1600 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 2.11-2.25 (m, 2H, C₇-CH₂), 2.27 (s, 3H, CH₃), 2.56-

2.59 (m, 2H, C₆-CH₂), 3.47 (s, 3H, OCH₃), 5.33 (s, 1H, C₄-CH), 6.80-7.15 (m, 4H, Ar-H), 8.97 (s, 1H, NH), 10.22 (bs, 1H, OH); HRMS: Calcd for C₁₇H₁₇NO₄: 299.3256. Found: 299.3262.

Methyl 2-methyl-4-phenyl-5-oxo-1*H*-4, 5, 6, 7-tetrahydrocyclopenteno[*b*]pyridine-3-carboxylate

6d: m.p. >270°C; IR (KBr): 3300, 1710, 1660, 1600 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 2.11-2.25 (m, 2H, C₇-CH₂), 2.27(s, 3H, CH₃), 2.56-2.59 (m, 2H, C₆-CH₂) 3.45 (s, 3H, OCH₃), 5.48 (s, 1H, C₄-CH), 7.10-7.40 (m, 5H, Ar-H), 9.19 (s, 1H, NH); HRMS: Calcd for C₁₇H₁₇NO₃: 283.3262. Found: 283.3258.

Methyl 2-methyl-4-(2-hydroxy-5-chlorophenyl)-5-oxo-1*H*-4,5,6,7-terahydro-cyclopenteno[*b*]pyridine-3-carboxylate 6e: m.p. >270°C; IR (KBr): 3310, 1710, 1660, 1600 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.11-2.25 (m, 2H, C₇-CH₂), 2.27(s, 3H, CH₃), 2.56-2.59 (m, 2H, C₆-CH₂), 3.40 (s, 3H, OCH₃), 5.48 (s, 1H, C₄-CH), 6.91-7.81 (m, 3H, Ar-H), 9.19 (s, 1H, NH), 10.31 (bs, 1H, OH); HRMS: Calcd for C₁₇H₁₆NO₄Cl: 333.7707. Found: 333.7711.

Conclusion

In summary, a facile and high yield one-pot synthesis of arylhexahydroquinoline and arylcyclopentenopyridine derivatives is reported. It is also evident from the comparison of products yield and reaction time period that the ultrasound irradiation method is more convenient and requiring less reaction time than the conventional thermal method.

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References

- 1 Hantzsch A, *Ann Chem*, 1, **1882**, 215.
- 2 Eisner U & Kuthan J, *Chem Rev*, 72, **1972**, 1.
- 3 Moiseur I K, Zemtsova M N & Trakhtenberg P L, *Chem Abstr*, 110, **1989**, 147183k.
- 4 Awad Ibrahim M A, Abdel Rahmann Abda E & Bahlite Ehify A, *Coll Czech Chem Commun*, 56, **1991**, 1749; *Chem Abstr*, 115, **1991**, 232110g.
- 5 Fadda A A, *Indian J Chem*, 30B, **1991**, 28.
- 6 Sorkin E M, Clissold S P & Brogden R N, *Drugs*, 30, **1985**, 182.
- 7 Iwanami M, Shibanume I, Fujimoto M, Kawai K & Tamazawa K, *Chem Pharm Bull*, 27, **1979**, 1426.
- 8 a) Suslick K S, *Ultrasound: Its Chemical, Physical and Biological effects*, (VCH Publishers, New York), **1988**.
b) Suslick K S, *Science*, 247, **1990**, 1439.
- c) Suslick K S & Othmer K, *Encyclopedia of Chemical Technology*, 4th Edn. (John Wiley, New York), **1998**, p 517.
- d) Einhorn C, Einhorn J & Luche J L, *Synthesis*, **1989**, 787.
- e) Mason T J, *Chem Soc Rev*, 26, **1997**, 443.
- f) Mason T J & Luche J L, *Chemistry under extreme or non-classical conditions*, edited by R Van Eldick and C D Hubbard, (John Wiley, New York), **1997**, p 317.
- 9 Hilgenfeldt S, Grossmann S & Liphse D, *Nature*, 398, **1999**, 402.
- 10 a) Ahluwalia V K & Goyal B, *Indian J Chem*, 35B, **1996**, 1021.
b) Ahluwalia V, K, Goyal B & Das U, *J Chem Res*, **1997**, 266.
- 11 Bayer A G, *US Pat*, **1970**, DE2003148.