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One-pot Multicomponent Synthesis Hexahydroquinoline Derivatives in Triton X-100 Aqueous micellar media

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Abstract: A facile and efficient synthesis of hexahydroquinoline derivatives (**5a-o**) was reported via four-component condensation reaction of aldehydes, dimedone, methyl aceto acetate and ammonium acetate in the presence of Triton X-100 in water at room temperature. The use of just 20 mol % of Triton X-100 in water solvent is sufficient. The FT-IR, ^{19}F-NMR, ^{1}H-NMR, ^{13}C-NMR spectra and elemental analysis confirm the structure of compounds.

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Keywords: Multicomponent reactions (MCRs); One-pot reaction; hexahydroquinolines; Triton X-100; Non ionic surfactant

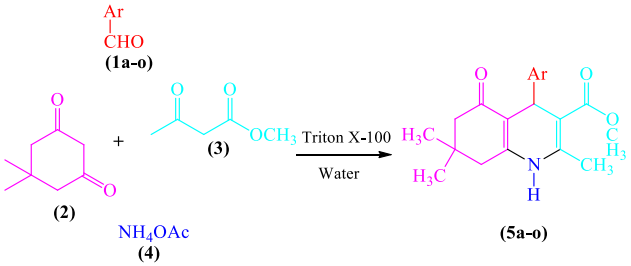
1. Introduction

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity [1]. Such processes are of great interest in diversity-oriented synthesis, especially to generate compound libraries for screening purposes. The Hantzsch reaction [2], and their products 1,4-dihydropyridines (DHP) have attracted immense attention of synthetic chemists due to their pharmacological properties [3,4].

In addition, the dihydropyridine unit has been widely employed as a hydride source for reductive amination [5]. Despite the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial, and synthetic point of view, [6-8] For these reasons, polyhydroquinoline compounds not only attract the attention of chemists to synthesize but also represent an interesting research challenge. The classical methods involve the three-component condensation of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol [9-11]. However, these methods suffer from drawbacks such as long reaction time, use of large quantities of organic solvents, lower product yields or harsh refluxing conditions. In recent years, several new efficient methods for the synthesis of polyhydroquinoline derivatives, which include the use of microwaves, [12] autoclave, [13] ionic liquids, [14] iodine, [15] metal triflate, [16] cerric ammonium nitrate, [17] L-proline, [18] PTSA-SDS, [19] BINOL-phosphoric acid, [20] $Hf(NPf_2)_4/C_{10}F_{18,}$ [21] and TFE. [22] In continuation of our studies in developing cheap and environmentally benign methodologies for organic synthesis, we turned our attention towards the synthesis of hexahydroquinoline derivatives. We report herein a practical synthesis of hexahydroquinoline derivatives in Triton X-100 aqueous micellar media at room temperature (Scheme 1).

2. Results and Discussion

We carried out the four component coupling reaction of dimedone, aldehyde, acetoacetic ester, and ammonium acetate using 20 mol % of Triton X-100 in water solvent (Scheme 1). In order to determine the scope of this reaction, we have synthesized differently substituted hexahydroquinoline by varying differently substituted aldehydes (**1a-o**) including both electron-donating and electron-withdrawing groups. It is observed that the reaction gave good yields of products with faster reaction rate when the aldehyde bearing electron-withdrawing group is used compared to the aldehydes with electron-donating groups. The corresponding results are tabulated in Table 1.



Scheme 1.

Table 1. Synthesis of hexahydroquinoline derivatives via Hantzsch reaction in Triton X-100 aqueous micellar media.

Entry	Ar	Product	Time (min)	Yield (%)[a]
1	C_6H_5	**5a**	60	97
2	4-BrC_6H_4	**5b**	90	94
3	2-BrC_6H_4	**5c**	100	93
4	4-$CH_3C_6H_4$	**5d**	120	92
5	2-$CH_3C_6H_4$	**5e**	130	91
6	4-$CH_3OC_6H_4$	**5f**	120	93
7	2-$CH_3OC_6H_4$	**5g**	110	92
8	4-$NO_2C_6H_4$	**5h**	30	98
9	2-$NO_2C_6H_4$	**5i**	35	96
10	4-FC_6H_4	**5j**	25	98
11	2-FC_6H_4	**5k**	30	98
12	4-$CF_3C_6H_4$	**5l**	30	97
13	4-$C_6H_5C_6H_4$	**5m**	30	90
14	1-Naphthyl	**5n**	65	89
15	2-Furyl	**5o**	85	87

[a]Isolated yields.

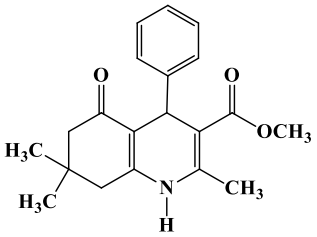
3. Experimental

Aldehydes were distilled before use. Melting points were determined using a Linkman HF591 heating stage, used in conjunction with a TC92 controller, and re uncorrected. NMR spectra were recorded using either a Brucker DRX500 machine at room temperature. ^1H and ^{13}C NMR spectra were measured using deuterochloroform as solvent and chemical shifts were measured relatives to residual solvent or $CFCl_3$ as an internal standard for $^{19}FNMR$ and are expressed in parts per million (δ). Mass spectra were obtained using a MicroMass LCT machine in ES or EI mode. Infrared spectra were measured on a Perkin Elmer Paragon 100 FT-IR spectrometer.

Typical experimental procedure of the hexahydroquinoline derivatives (5ao) (Scheme 1).

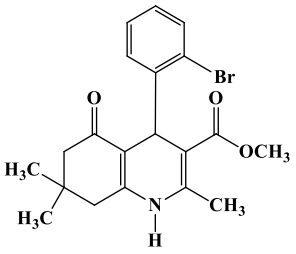
A mixture of aromatic aldehyde (**1a-o**), dimedone (**2**) (0.01 mol), methyl acetoacetate (**3**) (0.01 mol) and ammonium acetate (**4**) (0.01 mol) were taken in a mixture of Triton X-100 (5 mol%) and water (2 mL) in a round bottomed flask. The resulting mixture was vigorously stirred at room temperature until completion of the reaction as monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was poured onto crushed ice (70 g) with vigorous stirring. The precipitate obtained was filtered, washed with water, dried, and purified by column chromatography on silica gel (60-120 mesh, ethyl acetate/hexane, 1:3) to afford pure products. Structures of the all the products were confirmed by analytical and spectral data.

Methyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a).



0.315g (97%); white crystal; mp 262-264 °C. IR (KBr) (υ_{max}/cm^{-1}): γ =3513, 3098, 2989, 2893, 1721, 1703, 1556, 1445, 798, 745. ^1H NMR ($CDCl_3$, 500 MHz), δ, ppm, 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.28-2.31 (m, 4H, 2×CH_2), 2.39 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 5.06 (s, 1H, CH), 6.21 (s, 1H, NH), 7.10 (t, 1H, Ar-H), 7.20 (t, 2H, Ar-H), 7.29 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, δ 19.45, 26.30, 26.33, 26.60, 27.11, 29.33, 32.12, 36.25, 41.13, 50.44, 51.04, 106.06, 112.18, 1117.09, 127.78, 127.99, 143.58, 146.63, 167.79, 195.38. MS (EI), m/z (%) =326 (M^+, 25), 327 (5), 248 (37); HRMS (EI) Found: M^+, 325.1693. $C_{20}H_{23}NO_3$ requires M^+, 325.1702. Anal Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.76; H, 7.28; N, 4.43.

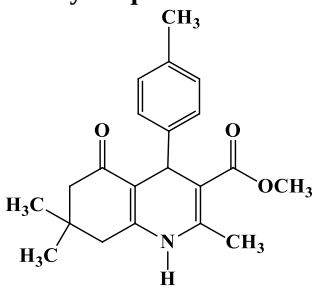
Methyl 4-(2-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5c).



0.379g (94%); yellow solid; mp 252-254°C; IR (KBr) (υ_{max}/cm^{-1}): γ = 3539, 3109, 2978, 2798, 1731, 1709, 1545, 1465, 787, 732. ^1H NMR ($CDCl_3$, 500 MHz), δ, ppm, 0.95 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.32-2.36 (m, 4H, 2×CH_2), 2.78 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 5.10 (s, 1H, CH), 6.33 (s, 1H, NH), 7.34 (t, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.73 (t, 1H, Ar-H),

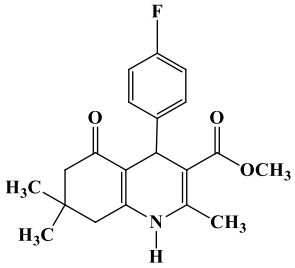
7.89 (d, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, 20.21, 27.31, 27.78, 28.66, 29.01, 30.13, 33.14, 38.25, 44.63, 52.44, 55.04, 103.26, 110.88, 118.69, 129.08, 130.93, 141.78, 145.62, 165.99, 193.68. MS (EI), m/z (%) =407 (M^+, 2), 405 (20), 248 (35). HRMS (EI) Found: M^+, 403.0812. $C_{20}H_{22}BrNO_3$ requires M^+, 403.0801. Anal Calcd for $C_{20}H_{22}BrNO_3$ C, 59.42; H, 5.48; N, 3.46. Found: C, 59.76; H, 5.28; N, 3.65.

Methyl 2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5d).



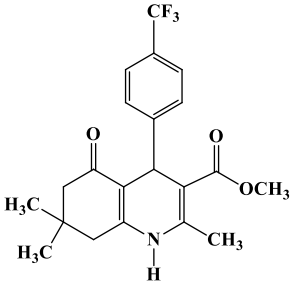
0.311g (92%); pale yellow solid; mp 257-259 °C. IR (KBr) (υ_{max}/cm^{-1}): γ =3496, 3069, 2893, 2798, 1718, 1709, 1525, 1429, 767, 737. ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm, 1.07 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.18-2.30 (m, 4H, 2×CH_2), 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.21 (s, 1H, CH), 6.11 (s, 1H, NH), 7.33 (t, 2H, Ar-H), 7.57 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, 21.15, 27.33, 26.33, 28.60, 28.91, 31.03, 33.42, 34.75, 40.83, 45.48, 50.54, 108.66, 114.98, 131.29, 134.58, 138.79, 143.68, 144.63, 166.89, 192.48. MS (EI), m/z (%) =339 (M^+, 15), 324 (5), 248 (57); HRMS (EI) Found: M^+, 340.1008. $C_{21}H_{25}NO_3$ requires M^+, 339.1809. Anal Calcd for $C_{20}H_{23}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.47; H, 7.38; N, 4.09.

Methyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j).



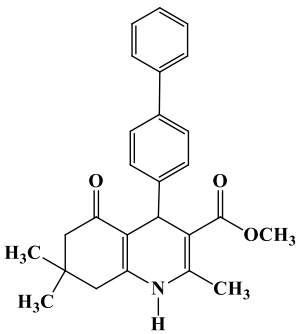
0.336g (98%); white solid; mp 243-245 °C. IR (KBr) (υ_{max}/cm^{-1}): γ =3534, 3075, 2968, 2859, 1730, 1711, 1543, 1438, 778, 735. ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm, 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.28-2.31 (m, 4H, 2×CH_2), 2.39 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 5.06 (s, 1H, CH), 6.21 (s, 1H, NH), 7.20 (t, 2H, Ar-H), 7.29 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, 21.46, 23.78, 25.34, 27.80, 28.81, 30.47, 31.14, 38.55, 43.14, 48.94, 50.54, 115.66, 120.68, 125.49, 129.10 (d, $^1J_{CF}$=250.3 Hz), 132.39, 140.53, 144.67, 163.59, 192.35.^{19}F NMR ($CDCl_3$, 470 MHz), δ, ppm, -60.1. MS (EI), m/z (%) =343 (M^+, 5), 324 (5), 248 (25); HRMS (EI) Found: M^+, 343.1653. $C_{20}H_{22}FNO_3$: requires M^+, 343.1602. Anal Calcd for $C_{20}H_{22}FNO_3$: C, 69.95; H, 5.53; N, 4.08. Found: C, 70.16; H, 5.68; N, 4.03.

Methyl 2,7,7-trimethyl-5-oxo-4-(4-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5l).



0.381g (97%); yellow solid; mp 248-250 °C; IR (KBr) (υ_{max}/cm^{-1}): γ = 3485, 3089, 2968, 2865, 1723, 1711, 1556, 1476, 779, 738; ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm, 1.19 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.47-2.65 (m, 4H, 2×CH_2), 2.85 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.06 (s, 1H, CH), 6.30 (s, 1H, NH), 7.54 (t, 2H, Ar-H), 7.79 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm, 22.54, 25.36, 26.26, 27.12, 28.16, 31.32, 32.56, 35.23, 40.18, 45.44, 53.54, 107.66, 111.28, 121.32, 131.09, 132.56, 134.89, 134.33 (q, $^1J_{CF}$=252.3 Hz, CF_3), 143.64, 164.73, 194.33.^{19}F NMR ($CDCl_3$, 470 MHz), δ, ppm, -110.5. MS (EI), m/z (%) =393 (M^+, 7), 324 (5), 248 (54).HRMS (EI) Found: M^+, 393.1601. $C_{21}H_{22}F_3NO_3$ requires M^+, 393.1612. Anal Calcd for $C_{21}H_{22}F_3NO_3$: C, 64.11; H, 5.64; N, 3.56. Found: C, 73.76; H, 7.28; N, 4.43.

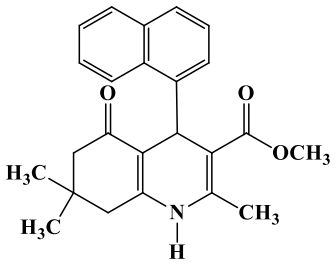
Methyl 4-(biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5m).



0.360g (90%); pale yellow solid; mp 267-269 °C; IR (KBr) (υ_{max}/cm^{-1}): γ = 3531, 3079, 2976, 2881, 1731, 1710, 1536, 1443, 776, 734; ^{1}H NMR ($CDCl_3$, 500

MHz), δ, ppm, 1.07 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.34-2.56 (m, 4H, 2×CH_2), 2.67 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 5.23 (s, 1H, CH), 6.35 (s, 1H, NH), 7.14 (t, 1H, Ar-H), 7.17 (d, 2H, Ar-H), 7.24 (d, 2H, Ar-H), 7.14 (t, 2H, Ar-H), 7.54 (d, 1H, Ar-H), 8.02 (d, 1H, Ar-H),. ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, 19.45, 26.30, 26.33, 26.60, 27.11, 29.33, 32.12, 36.25, 41.13, 50.44, 51.04, 106.06, 112.18, 114.23, 116.65, 116.98, 118.76, 119.98, 121.65, 124.65, 129.09, 127.78, 127.99, 143.58, 146.63, 167.79, 195.38. MS (EI), m/z (%) =401 (M^+, 12), 274 (5), 215 (32). HRMS (EI) Found: M^+, 401.2102. $C_{26}H_{27}NO_3$ requires M^+, 401.2014. Anal Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.85; H, 6.84; N, 3.56.

Methyl 2,7,7-trimethyl-4-(naphthalen-1-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5n).



0.337g (89%); pale yellow solid; mp 263-265 ºC. IR (KBr) (υ_{max}/cm^{-1}): γ =3523, 3080, 2979, 2879, 1736, 1712, 1539, 1438, 789, 747. ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm, 0.93 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.31-2.45 (m, 4H, 2×CH_2), 2.54 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.12 (s, 1H, CH), 6.17 (s, 1H, NH), 7.38-7.67 (m, 7H, Ar-H), 7.29 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm, 19.06, 23.32, 25.34, 25.66, 27.67, 28.93, 33.14, 38.28, 47.13, 55.44, 58.98, 108.76, 119.98, 120.76, 121.67, 123.65, 126.89, 128.09, 129.78, 129.99, 139.57, 143.33, 162.72, 192.28. MS (EI), m/z (%) =326 (M^+, 25), 327 (5), 248 (37). HRMS (EI) Found: M^+, 375.1903. $C_{24}H_{25}NO_3$ requires M^+, 375.1812. Anal Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 7704; H, 6.68; N, 3.87.

4. Conclusion

In summary, we have described herein an efficient methodology for Hantzsch reaction using various electronically and structurally divergent aldehydes to give the product in excellent isolated yields. In contrast to the existing methods using potentially hazardous catalysts/additives, this new method offers the following competitive advantages: (i) avoiding the use of any base, metal or Lewis acid catalyst (ii) short reaction time, (iii) ease of product isolation/purification by non-aqueous work-up, (iv) high chemo selectivity, (v) no side reaction, and (vi) low costs and simplicity in process and handling.

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