REACTION OF FORMYLATED ACETOPHENONES WITH DIMEDONE AND NH\(_4\)OAc ASSISTED BY KHSO\(_4\) IN AQUEOUS MEDIA: A FACILE ENVIRONMENT FRIENDLY ONE-POT TWO-STEP REGIOSELECTIVE SYNTHETIC STRATEGY FOR 2-ARYL-5-OXO-7,7-DIMETHYL-5,6,7,8-TETRAHYDROQUINOLINES

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Abstract
An efficient synthesis of substituted quinolines has been achieved in a one-pot two-step regioselective reaction from formylated acetophenones with dimedone and ammonium acetate assisted by KHSO\(_4\) in aqueous media. Synthetic protocol of 2-aryl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline9(a-f) described herein offers several advantages including high yields, short reaction times and a simple work-up procedure with a readily available acid like KHSO\(_4\) in aqueous media.

Keywords: Enaminone, regioselective, tetrahydroquinolines, microwave irradiation

Introduction
Compounds containing quinoline motif are most widely used as antimalarials,\(^{1-iii}\) antibacterials,\(^{iv-vii}\) antifungals\(^{viii,ix}\) and anticanter agents\(^{x,xi}\) etc. Quinoline is a ubiquitous subunit in many quinoline containing natural products with remarkable biological activities. Members of this family have wide applications in medicinal chemistry, being used as anti-inflammatory, anti-asthmatic, anti-hypertensive and tyrosine kinase inhibiting agents.\(^{xii,xiii}\) Because of their importance as substructures in a broad range of natural and synthetically designed products, significant efforts continue to be directed into the development of new quinoline-based structures.\(^{xiv}\)

Among quinoline derivatives, tetrahydroquinolines are important structural subunit of natural products and many tetrahydroquinoline derivatives exhibit interesting biological and pharmaceutical activities,\(^{xv,xvi}\) including anti-HIV\(^{xvii,xviii}\) anticancer\(^{xix}\) antimalarial\(^{xx}\) cholesteryl ester transfer protein inhibitors,\(^{xxi}\) anti-diabetic,\(^{xxii}\) etc.

Recently, 5,6,7,8-tetrahydroquinolines have drawn considerable attention due to their interesting pharmacological applications as RET tyrosine kinase inhibitors,\(^{xxiii}\) anti-HIV\(^{xvii,xviii,xxiv,xxv}\) antifungal\(^{xxvi}\) anti-cancer\(^{xxvii}\) and C5a receptor antagonists agents\(^{xxviii}\). Some examples of reported derivatives of 5,6,7,8-tetrahydroquinolines with their biological activities are shown in Fig. 1.

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Owing to the important biological properties of tetrahydroquinolines, several synthetic strategies have been reported. Some of the synthetic strategies for 5,6,7,8-tetrahydroquinolines reported in the literature involves the reaction of 5,6-dihydroquinoline with amines, N-alkylhydroxylamines, and O-alkylhydroxylamines\textsuperscript{xxx}, heating of alkynyl-substituted 1,2,4-triazine in refluxing bromobenzene\textsuperscript{xxx}, catalytic hydrogenation of acetamidoquinolines and acetamidoisoquinolines\textsuperscript{xxi}, palladium-catalyzed oxidation of hydroxy eniminones\textsuperscript{xxiii}. S. Kantevari et al. have reported\textsuperscript{xxv} the synthesis of 2,7,7-trisubstituted-5,6,7,8-tetrahydroquinoline-5-ones by the reaction of formylated methyl aromatic ketones with dimedone and NH\textsubscript{4}OAc in presence of K\textsubscript{3}CoW\textsubscript{12}O\textsubscript{40}.3H\textsubscript{2}O as catalyst. The same group has also reported\textsuperscript{xxiv} the same reaction under the influence of MW irradiation.

S. Kantevari et al. have reported\textsuperscript{xxv} an efficient cerium (III)-catalyzed protocol for one-pot regioselective synthesis of novel dihydrobenzofuran-tethered pyridines and dihydroquinolin-5(6H)-ones employing β-enaminones and acyclic and cyclic 1,3-dicarbonyls as novel variants of the Bohlmann-Rahtz substrate, and ammonium acetate in refluxing propan-2-ol. This strategy of Kantevari et al was very well exploited by reacting formylated ketones with a variety of diketones to give tetrahydroquinolines and related products.

However, these methods suffer from drawbacks like usage of heavy metal catalysts, high reaction temperatures, longer reaction time etc. Prompted by these facts and in continuation with our synthetic investigations involving formylated ketones assisted by KHSO\textsubscript{4} in aqueous media, we undertook this investigation and the results are reported herein.

Among various quinoline derivatives, 5,6,7,8-tetrahydroquinoline derivatives draw a special attention for their wide spectrum of biological activities and are extensively studied. The present study involves development of synthetic protocol for 2,7,7-trisubstituted-5,6,7,8-tetrahydroquinolines from formylated acetophenones\textsuperscript{xxvi} assisted by KHSO\textsubscript{4}\textsuperscript{xxvii,xxviii} in aqueous media. Enaminones\textsuperscript{xxix,xxi} being versatile substrates in the synthesis of heterocyclic compounds\textsuperscript{xli,xlii} and drug intermediates, were chosen as starting materials for the synthesis of 2,7,7-trisubstituted-5,6,7,8-tetrahydroquinoline-5-ones. The development of simple synthetic
routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Keeping in mind various biomedical applications and with a view to further assess the pharmacological profile of this class of compounds, we herein report the synthesis of 2-aryl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinolines from formylated acetophenones, ammonium acetate and dimeredone using KHSO₄ catalyst in aqueous media (Scheme 1).

**Results and Discussion**

Thus, a mixture of dimeredone and ammonium acetate was irradiated in microwave oven to give the condensation product (enaminone) which was subsequently reacted with formylated acetophenone (8a) in the presence KHSO₄ in aqueous ethanol at 60 °C to give a solid product 9a in 89% yield (Scheme 1). This product was identified as 2-phenyl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline on the basis of spectral and analytical data. Thus, the infrared spectra of 9a showed peaks at 1583, 1685 cm⁻¹ due to C=N and C=O groups respectively. The ¹H NMR spectra of the compound showed a signal at 1.14 ppm due to the two methyl groups. The protons CH₂ groups at positions 6 and 8 of the ring resonated at 3.14 and 2.63 ppm respectively while a multiplet for six aromatic protons was observed at 7.33-8.07 ppm. In addition, a doublet due to C₃-H was obtained with coupling constant 8.0 Hz. The mass spectra of 9a exhibited molecular ion peak at 252 due MH⁺. Under identical conditions, the products 9b was obtained as white solid in 88% yield. The IR spectra of 9b showed peaks at 1580 cm⁻¹ and 1686 cm⁻¹ due to the stretching vibrations of the C=N and C=O groups, respectively. Similarly, the ¹H NMR spectra of 9b showed a signal at 1.14 ppm due to the two methyl groups. The protons CH₂ groups at positions 6 and 8 of the ring resonated at 3.10 and 2.57 ppm respectively. This spectrum showed a signal at 2.42 ppm due to methyl group in the aromatic ring. The aromatic protons of 9b resonated as doublets at 7.30 ppm and 7.97 ppm with coupling constant 8.0 Hz. in the ¹H NMR spectra. While a doublet due to C₃-H appeared with coupling constant 8.0 Hz. The mass spectra of 9b showed molecular ion peak at 266 due MH⁺. The reaction of other formylated acetophenones 8(c-f) with dimeredone and ammonium acetate went smoothly under identical conditions giving the expected products 9(c-f) in excellent yields (87-92%).

![Scheme 1](image)

Scheme 1

The structures of these compounds 9(a-f) were very well established with the help of spectral and analytical data and by comparison with those reported in the literature. Spectra of 7,7-dimethyl-2-aryl-5,6,7,8-tetrahydroquinoline-5-ones (9a) are shown in figures 2, 3 & 4. The results are compared with those already reported and summarized in Table I.
Table 1: Synthesis of 7,7-dimethyl-2-aryl-5,6,7,8-tetrahydroquinoline-5-ones assisted by KHSO₄ in aqueous media

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>R</th>
<th>Reaction (hr)</th>
<th>Yield (%)</th>
<th>Mp (°C)/Lit.(mp)xxiii</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>2.5</td>
<td>89</td>
<td>69/67</td>
</tr>
<tr>
<td>9b</td>
<td>4-CH₃C₆H₄</td>
<td>CH₃</td>
<td>3</td>
<td>88</td>
<td>120-121/120</td>
</tr>
<tr>
<td>9c</td>
<td>4-CH₃OC₆H₄</td>
<td>CH₃</td>
<td>3</td>
<td>87</td>
<td>126/125</td>
</tr>
<tr>
<td>9d</td>
<td>4-NO₂C₆H₄</td>
<td>CH₃</td>
<td>2</td>
<td>92</td>
<td>179-180/182</td>
</tr>
<tr>
<td>9e</td>
<td>4-ClC₆H₄</td>
<td>CH₃</td>
<td>3</td>
<td>91</td>
<td>107-108/105</td>
</tr>
<tr>
<td>9f</td>
<td>4-BrC₆H₄</td>
<td>CH₃</td>
<td>3</td>
<td>90</td>
<td>133-134/132</td>
</tr>
</tbody>
</table>

A plausible mechanism for the formation 9 has been proposed hereunder (Scheme 2).

Scheme 2: A plausible mechanism for the formation of quinolines
Figure 2: IR spectrum of compound 9b.
Figure 3: $^1$H NMR spectrum of compound 9b
Experimental
Melting points were recorded by open capillary method and are uncorrected. The infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm$^{-1}$. High resolution $^1$H NMR spectra was recorded on Bruker Avance II-400 spectrometer using CDCl$_3$ as the solvent. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to TMS as internal reference. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All reactions were monitored by tlc using precoated aluminum sheets (Silica gel 60/Kieselguhr F$_{254}$). Column chromatographic separations were carried out using SRL silica gel (60–120 mesh) and EtOAc-hexane (1:9). Formylated acetophenones (8) were synthesized by our previously reported procedure. xxxvi
**General Procedure**

A mixture of dimedone (7) (1 mmol) and NH₄OAc (2 mmols) was irradiated under MW at 850W for 4 minutes and the mixture was sucked dry under reduced pressure. To this was then added formylated acetophenone (8) (1 mmol), KHSO₄ (2 mmol) and 5 mL of a mixture of water-ethanol (1:1) and the resulting mixture was heated with stirring at 60°C for 2-3 hours. The progress of the reaction was monitored by tlc and on completion, the precipitated product was collected by filtration, washed with a mixture of ethanol and water (1:1) and then dried to give practically pure product, 9. Subsequent purification for analytical purposes was effected by column chromatography (silica gel, EtOAc-hexane, 1:9).

2-phenyl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9a):

![Chemical Structure](image)

This compound was obtained as pale yellow solid in 89% yield, mp 69°C; IR (KBr): 1583, 1685 cm⁻¹; ¹H NMR (CDCl₃): δ 1.14 (s, 6H), 2.63 (s, 2H), 3.14 (s, 2H), 7.33-8.07 (m, 6H), 8.32 (d, 1H, J = 8 Hz); MS: m/z 251, 252 (MH⁺). *Anal. Caled for C₁₇H₁₇NO (251): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.29; H, 6.79; N, 5.62%.

2-(4-methylphenyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9b):

![Chemical Structure](image)

This compound was obtained as white solid in 88% yield, mp 120-121°C; IR (KBr): 1580, 1686 cm⁻¹; ¹H NMR (CDCl₃): δ 1.14 (s, 6H), 2.42 (s, 3H), 2.57 (s, 2H), 3.10 (s, 2H), 7.30 (d, 2H, J = 8 Hz), 7.69 (d, 1H, J = 8 Hz), 7.97 (d, 2H, J = 8 Hz), 8.29 (d, 1H, J = 8 Hz); MS: m/z 265, 266 (MH⁺). *Anal. Caled for C₁₈H₁₉NO (265): C, 81.47; H, 7.22; N, 5.28. Found: C, 81.56; H, 7.25; N, 5.26%.

2-(4-methoxyphenyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9c):

![Chemical Structure](image)

This compound was obtained as pale yellow solid in 87% yield, mp 126°C; IR (KBr): 1580, 1605, 1676 cm⁻¹; ¹H NMR (CDCl₃): δ 1.14 (s, 6H), 2.56 (s, 2H), 3.08 (s, 2H), 3.88 (s, 3H), 7.01 (d, 2H, J = 8.8 Hz), 7.65 (d, 1H, J = 8 Hz), 8.04 (d, 2H, J = 8.8 Hz), 8.27 (d, 1H, J = 8.4 Hz); MS: m/z 281, 282 (MH⁺). *Anal. Caled for C₁₈H₁₉NO₂ (281): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.77; H, 6.78; N, 4.97%.
2-(4-nitrophenyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9d):

![Chemical Structure]

This compound was obtained as pale yellow solid in 92% yield, mp 179-180°C; IR (KBr): 1515, 1579, 1687 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.16 (s, 6H), 2.61 (s, 2H), 3.14 (s, 2H), 7.80 (d, 1H, J = 8 Hz), 8.25 (d, 2H, J = 9.2 Hz), 8.34-8.40 (m, 3H); MS: m/z 297 (MH\(^+\)). Anal. Calcd for C\(_{17}\)H\(_{16}\)N\(_2\)O (296): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.75; H, 5.41; N, 9.48%.

2-(4-chlorophenyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9e):

![Chemical Structure]

This compound was obtained as off white solid in 91% yield, mp 107-108°C; IR (KBr): 1585, 1685 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.14 (s, 6H), 2.58 (s, 2H), 3.10 (s, 2H), 7.47 (d, 2H, J = 8.8 Hz), 7.66 (d, 1H, J = 8 Hz), 8.02 (d, 2H, J = 8.4 Hz), 8.32 (d, 1H, J = 8.4 Hz); MS: m/z 286 (MH\(^+\)). Anal. Calcd for C\(_{17}\)H\(_{16}\)ClNO (285): C, 71.45; H, 5.64; N, 4.90. Found: C, 71.38; H, 5.60; N, 4.93%.

2-(4-bromophenyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (9f):

![Chemical Structure]

This compound was obtained as pale yellow solid with 90% yield, mp 133-134°C; IR (KBr): 1582, 1681 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.14 (s, 6H), 2.57 (s, 2H), 3.10 (s, 2H), 7.50 (d, 2H, J = 8.8 Hz), 7.66 (d, 1H, J = 8 Hz), 7.95 (d, 2H, J = 8.4 Hz), 8.28 (d, 1H, J = 8.4 Hz); MS: m/z 331 (MH\(^+\)). Anal. Calcd for C\(_{17}\)H\(_{16}\)BrNO (330): C, 61.83; H, 4.88; N, 4.24. Found: C, 61.77; H, 4.91; N, 4.30%.

**Conclusion**

Thus, we have developed a facile environment-friendly one-pot two-step regioselective synthetic strategy for 2-aryl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinolines in very good yields. This method offers several advantages including high yields, short reaction times and a simple work-up procedure with a readily available acid like KHSO\(_4\) in aqueous media.
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References


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