A facile ultra sound assisted synthesis of quinoline derivatives

3.1. RESULTS AND DISCUSSION

Quinoline and their derivatives are biologically significant and many are drugs in clinical practice; quine, chlorquine and ciproflaxacine are the best examples. The literature states that, quinoline derivatives possess diverse applications in the design and synthesis of OLED materials, fluorescent sensors (Rouffet et al., 2010; Meng et al., 2012; Zhou et al., 2012).

Acridine/Dibenzo[\(b, e\)]pyridines are belong to the family of ‘anthracene’ of which one of the ‘-CH’ group is replaced by ‘Nitrogen’ atom. These acridines are having historical evidence that they can be used as bio-active agents. They are used as dyes and drugs (Denny, 2002). Proflavine is one of the best example for acridine analogue, which is used as a disinfectant against to gram positive bacteria and as DNA intercalating agent. Acridine orange base is a fluorescent dye used to study the cell cycle investigations.

![Important acridine based molecules](image)

Fig.3.1. Important acridine based molecules a) Proflavin; b) Acridine Orange Base.

So far the 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)ethanones and 7-chloro-3, 3-dimethyl-9-phenyl-3, 4-dihydro acridin-1(2\(H\))-ones were synthesized by adopting the conventional reflux conditions (high temperature and long reaction time), which are having the draw backs such longer reaction time and less yield. At the same time long reaction time would lead to decomposition of starting materials, reagents and formed products to side products. Often the scientists are moved to green techniques to synthesize the molecules which are difficult to produce by the conventional. By keeping all the above points we would like to attempt the synthesis under the sonication. By considering the synthesis of 3b from (2-amino-5-
chlorophenyl)(2-fluorophenyl)methanone and acety acetone as the representative reaction. The required reactants (2-amino-5-chlorophenyl)(2-fluorophenyl)methanone and acety acetone were taken in ethanol medium, sonicated to effect the conversions, but failed to afford the products. We have attempted the same reaction by varying the temperature and found that at 50 °C the reaction affords the maximum yield and hence the temperature was optimised as 50 °C. After optimizing the temperature the reaction was attempted by varying the solvent and found that ethanol is found to be suitable solvent (Table 3.1).

Scheme 3.1. Ultrasound assisted synthesis of some quinoline and acridine derivatives. Once the reaction conditions were optimised, to prove the generality of the reaction various substituted aminobenzophenones and various cyclic and acyclic diketones were employed under this protocol and found to afford the products 3a-g with satisfactory yield (45-92%).
Table 3.1. Solvent optimization for the synthesis of compound 3b under sonication (yield through the conventional reflux condition was included in parenthesis).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield( %)$^{b}$</th>
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<tbody>
<tr>
<td>Methanol</td>
<td>57 (15)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>92 (41)</td>
</tr>
<tr>
<td>IPA</td>
<td>52 (34)</td>
</tr>
<tr>
<td>n-Butanol</td>
<td>41 (trace)</td>
</tr>
<tr>
<td>DMF</td>
<td>No reaction (trace)</td>
</tr>
</tbody>
</table>

The formation of these compounds was confirmed through the $^1$H NMR, $^{13}$C NMR and mass spectral data. The compound 3b was considered as the representative example and its spectral characterization discussed as below. The ortep diagram of 3b was also represented which is isolated in ethylaacetate and ethanol mixture (2:1) is shown in Fig.3.6.

*Spectral confirmation of 3b:*

![Fig.3.2. Representation of atom positions of 3b.](image)

The proton NMR spectrum of 3b (Fig.3.3) reveals that, a singlet at $\delta$ 2.14 ppm is due to methyl group on aromatic ring labbled at 2' and another singlet at $\delta$ 2.71 ppm corresponds to a acetyl methyl group. A multiplet observed at $\delta$ 7.23-7.33 ppm belongs to three aromatic protons of phenyl ring at 4", 5" and 6". Two doubles of doublets at $\delta$ 7.55 (with coupling constants of 13.0 Hz and 6.6 Hz) ppm and $\delta$ 7.67 (8.8 Hz and 1.6 Hz ppm) are assigned to protons at 7' and 8' respectively. The doublet at $\delta$ 8.04 ppm ($J = 9.2$ Hz) is for 5' hydrogen. From $^{13}$C NMR spectrum (Fig.3.4) a signal at $\delta$ 23.76 ppm and $\delta$ 31.45 ppm belong to two methyl carbons at 2 and 2'.

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Fig.3.3. $^1$H NMR spectrum of 1-(6-chloro-4-(2-fluorophenyl)-2-methyl quinolin-3-yl) ethanone (3b).

Fig.3.4. $^{13}$C NMR spectrum of 1-(6-chloro-4-(2-fluorophenyl)-2-methyl quinolin-3-yl) ethanone (3b).
Fig. 3.5. GC-MS spectrum of 1-(6-chloro-4-(2-fluorophenyl)-2-methyl quinolin-3-yl) ethanone (3b).

Fig. 3.6. ORTEP diagram of compound 3b.

The rest of the chemical shifts values are assigned as follows: δ 116.33 ppm (3"-C), δ 24.54 ppm (5'a-C), δ 124.90 ppm (5'-C), δ 125.87 ppm (5"-C), δ 130.54 ppm (3'-C), δ 131.27 ppm (6'-C), δ 131.76 ppm (8'-C), δ 132.09 ppm (6"-C), δ 132.87 ppm (4"-C), δ 136.32 ppm (1'-C), δ 137.53 ppm (7'-C), δ 145.59 ppm (4'-C), δ 153.91 ppm (8'a-C), δ 158.11 ppm (2'-C), δ 160.58 ppm (2"-C) carbon atoms and the aliphatic carbonyl carbon appeared at δ 204.39 ppm. The molecular ion peak at 313.2 (M+) in GC-MS further confirmed the formation of compound 3b.
3.2. EXPERIMENTAL SECTION

MATERIALS AND METHODS

The reagents (2-amino-5-chlorophenyl) (phenyl) methanone and (2-amino-5-chlorophenyl)(2-fluorophenyl) methanone, acetyl acetone, cyclohexanone, 1, 3-dicyclocloxanone, 5, 5-dimethyl cyclohexane-1, 3-dione were purchased from Aldrich; the commercially available ethanol and ortho-phosphoric acid were purchased and used as such. Solvents were removed under reduced pressure on a rotovapour. Organic extracts were dried with anhydrous Na$_2$SO$_4$. Silica gel 60F$_{254}$ aluminum sheets were used in analytical thin-layer chromatography (TLC) and silica gel for column chromatography purification (230-400 mesh). Visualization of spots on TLC plates was effected by UV illumination, exposure to iodine vapor and heating the plates dipped in KMnO$_4$ stain.

3.3. GENERAL PROCEDURE FOR THE SYNTHESIS OF 3-ACETYL-4-PHENYL QUINOLINES/ACRIDINES THROUGH ULTRA SONICATION

The reagents substituted 2-amino-benzophenone (1eq), aliphatic diketone/cyclic diketone (e.g. acetyl acetone (1eq) and 1.5 eq of H$_3$PO$_4$ were charged in a container with 5 mL of absolute ethanol. The reaction mixture was sonicated at 50-60 °C for about 35-45 minutes. After the completion of reaction the product extracted with ethyl acetate and recrystallization from chloroform and ethanol (5:1). Yield = 62-75 %.

3.3.1. Synthesis of compound 3a:

Yield = 75 % (0.095 g); mp = 153-155 °C; $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 1.98 (s, 3H, CH$_3$), 2.66 (s, 3H, CH$_3$), 7.31-7.34 (m, 2H, ArH), 7.52 (dd, 3H, $J_{1,2} = 6.2$ Hz and 3.0 Hz, ArH), 7.56 (t, 1H, $J = 2.4$ Hz, ArH), 7.99 (dd, 1H, $J_{1,2} = 8.8$ Hz and 3.6 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 23.83, 31.83, 124.93, 125.89, 128.95, 129.24, 129.94, 130.55, 130.99, 132.49, 134.50, 135.51, 143.11, 145.93, 153.97, 205.25.

3.3.2. Synthesis of compound 3b:

Yield = 70 % (0.08 g); mp = 162-164 °C; $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 2.14 (s, 3H, CH$_3$), 2.71 (s, 3H, CH$_3$), 7.23-7.34 (m, 3H, ArH), 7.39 (s, 1H, ArH), 7.55 (dd, 1H, $J_{1,2} = 13.0$ Hz and 6.6 Hz, ArH), 7.67 (dd, 1H, $J_{1,2} = 8.8$ Hz and 1.6 Hz, ArH),
8.04 (d, 1H, J = 9.2 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 23.76, 31.45, 116.33, 124.54, 124.90, 125.87, 130.54, 131.27, 131.76, 132.09, 132.87, 136.32, 137.53, 145.59, 153.91, 158.11, 160.58, 204.39.

### 3.3.3. Synthesis of compound 3c:

Yield = 62 % (0.08 g); mp = 208-210 °C; $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 1.21 (s, 6H, 2 × -CH$_3$), 2.66 (s, 2H, -CH$_2$), 3.83 (s, 2H, -CH$_2$), 7.18 (d, 2H, J = 6.4 Hz), 7.60 (t, 4H, J = 2.0 Hz, ArH), 7.95 (t, 1H, J = 6.6 Hz, ArH), 9.06 (t, 1H, J = 9.6 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 30.94, 32.74, 42.27, 53.61, 123.46, 124.42, 127.46, 127.66, 128.84, 129.13, 129.64, 133.84, 136.56, 136.60, 136.87, 137.82, 158.43, 159.56, 193.21.

### 3.3.4. Synthesis of compound 3d:

Yield = 60 % (0.08 g); $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 1.24 (s, 6H, 2 × CH$_3$), 2.66 (d, 1H, J = 16.4 Hz, CH$_2$), 2.73 (d, 1H, J = 16.4 Hz, CH$_2$), 3.86 (s, 2H, CH$_2$), 7.20 (t, 1H, J = 7.2 Hz, ArH), 7.30 (t, 1H, J = 9.2 Hz, ArH), 7.42 (t, 1H, J = 7.4 Hz, ArH), 7.64 (dd, 2H, J$_{1,2}$ = 13.6 Hz and 6.8 Hz, ArH); 8.01 (d, 1H, J = 8.8 Hz, ArH), 9.14 (d, 1H, J = 8.8 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 28.14, 32.59, 42.22, 53.20, 116.09, 116.30, 121.46, 121.62, 123.79, 124.70, 124.74, 124.97, 126.93, 128.81, 129.32, 129.34, 132.06, 132.14, 136.95, 137.05, 138.18, 151.64, 157.41, 159.36, 159.86, 193.14.

### 3.3.5. Synthesis of compound 3e:

Yield = 68 % (0.07 g); mp = 160-162 °C; $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 1.75-1.8 (m, 2H, CH$_2$), 1.93-1.99 (m, 2H, CH$_2$), 2.59 (t, 2H, J = 6.4 Hz, CH$_2$), 3.17 (t, 2H, J = 6.4 Hz, CH$_2$), 7.21 (d, 2H, J = 7.2 Hz, ArH), 7.28 (d, 1H, J = 2.0 Hz, ArH), 7.46-7.55 (m, 4H, ArH), 7.94 (d, 1H, J = 8.8 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 28.10, 30.92, 34.21, 124.56, 127.42, 128.06, 128.83, 129.03, 129.24, 129.46, 130.08, 131.15, 136.41, 144.72, 145.74, 159.52.

### 3.3.6. Synthesis of compound 3f:

Yield = 66 % (0.08 g); mp = 185-187 °C; $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 2.37 (t, 2H, J = 5.8 Hz, CH$_2$), 2.83 (t, 2H, J = 5.8 Hz, CH$_2$), 3.97 (t, 2H, J = 5.4 Hz, -CH$_2$),
7.21 (d, 2H, J = 6.0 Hz, ArH), 7.61 (s, 4H, ArH), 7.96 (d, 1H, J = 8.8 Hz, ArH), 9.01 (d, 1H, J = 9.2 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 20.23, 29.29, 39.81, 123.31, 125.34, 127.39, 127.67, 128.80, 129.23, 129.58, 133.97, 136.47, 136.88, 137.39, 158.84, 160.73, 193.05.

3.3.7. Synthesis of compound 3g:

Yield = 60 % (0.07 g); $^1$H NMR (400 MHz, CDCl$_3$, δ (ppm)): 1.84-1.78 (m, 2H, CH$_2$), 1.97 (t, 2H, J = 6.0 Hz, CH$_2$), 2.61 (dd, 2H, $J_{1,2}$ = 14.6 Hz and 7.0 Hz, CH$_2$), 3.19 (d, 2H, J = 2.4 Hz), 7.19 (t, 1H, J = 8.0 Hz, ArH), 7.26 (t, 2H, J = 8.0 Hz, ArH), 7.32 (t, 1H, J = 8.0 Hz, ArH), 7.48-7.56 (m, 2H, ArH), 7.98 (d, 1H, J = 8.0 Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$, δ (ppm)): 22.71, 27.61, 34.04, 76.75, 77.06, 77.38, 116.16, 116.37, 123.46, 123.64, 123.98, 124.61, 124.65, 127.23, 129.48, 130.13, 130.51, 130.59, 130.64, 131.15, 131.19, 131.58, 139.81, 144.56, 158.25, 159.44, 160.70.

3.4. SPECTRAL EVIDENCES

![NMR Spectrum](image)

Fig.3.7. $^1$H NMR spectrum of 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3a)
Fig. 3.8. $^{13}$C NMR spectrum of 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3a).

Fig. 3.9. GCMS spectrum of 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3a).
Fig.3.10. $^1$H NMR spectrum of 7-chloro-3, 3-dimethyl-9-phenyl-3, 4-dihydroacridin-1(2H)-one (3c).

Fig.3.11. $^{13}$C NMR spectrum of 7-chloro-3, 3-dimethyl-9-phenyl-3, 4-dihydroacridin-1(2H)-one (3c).
Fig. 3.12. $^1$H NMR spectrum of 7-chloro-9-(2-fluorophenyl)-3, 3-dimethyl-3, 4-dihydroacridin-1(2H)-one (3d).

Fig. 3.13. $^{13}$C NMR spectrum of 7-chloro-9-(2-fluorophenyl)-3, 3-dimethyl-3, 4-dihydroacridin-1(2H)-one (3d).
Fig. 3.14. GC-MS spectrum of 7-chloro-9-(2-fluorophenyl)-3, 3-dimethyl-3, 4-dihydroacridin-1(2H)-one (3d).

Fig. 3.15. $^1$H NMR spectrum of 7-chloro-9-(2-fluorophenyl)-3, 3-dimethyl-3, 4-dihydroacridin-1(2H)-one (3e).
Fig. 3.16. $^{13}$C NMR spectrum of 7-chloro-9-(2-fluorophenyl)-3,3-dimethyl-3,4-dihydroacridin-1(2H)-one (3e):

Fig. 3.17. $^1$H NMR spectrum of 7-chloro-9-phenyl-1, 2, 3, 4-tetrahydroacridine (3f).
Fig. 3.18. $^{13}$C NMR spectrum of $7$-chloro-$9$-phenyl-$1$, $2$, $3$, $4$-tetrahydroacridine (3f).

Fig. 3.19. $^1$H NMR spectrum of $7$-chloro-$9$-(2-fluorophenyl)-3, 4-dihydroacridin-1(2$\text{H}$)-one (3g).
Fig.3.20. $^{13}$C NMR spectrum of 7-chloro-9-(2-fluorophenyl)-3, 4-dihydroacridin-1(2)-one (3g).

Fig.3.21. GC-MS spectrum of 7-chloro-9-(2-fluorophenyl)-3, 4-dihydroacridin-1(2)-one (3g).