Synthesis of 2-chloro 3-formyl quinoline Derivatives using Vilsemier-Hacck reagent and Ionic Liquid mediated under Ultrasound Irradiation

Quinolines\(^1\)^\(^-\)^\(^3\), are an important class of heterocyclic compounds. Several compounds of this class have been screened for biological activities such as bactericidal\(^4\), antitumor\(^5\), anti-inflammatory\(^6\), antimalarial\(^7\). Among quinolines, 2-chloroquinolin-3-carbaldehydes occupy a prominent position, as the latter are key intermediates for further annulations of a wide variety of ring and for various functional group interconversions\(^8\),\(^9\). It is earlier reported that the quinoline derivatives could be prepared via cyclization reaction under Vilsmieier-Hacck condition\(^10\). The Vilsmieier-Hacck (halomethyleneiminium salt) formed from the interaction of dialkyl formamide such as DMF with POCl\(_3\) has attracted the attention of synthetic organic chemists since its discovery in 1927\(^11\). It is one of the most commonly used reagent for introduction of aldehyde group into aromatic and heteroaromatic compound\(^12\). Rajanna et al\(^13\) reported that deactivating acetanilides, undergo Vilsmieier-Hacck cyclization in miceller media to afford 2-chloro-3-formyl quinoline derivatives. \(\alpha\)-hydroxyphosphonates, \(\alpha\)-acetyloxyphosphonates derived from 2-chloroquinolin-3-carbaldehyde showed good antibacterial activity\(^14\).

Recently, ionic liquids have been receiving a lot of attention as green catalyst and medium for variety of reactions\(^15\). Pyridinium salts have found use as acylating agents\(^16\), phase transfer catalysts,\(^17\) cationic surfactants. The 1-alkylpyridinium salts, which are liquid at rt., so-called ionic liquids, are potential new solvents for synthesis and catalysis,\(^18\) ionic liquid based p-toluenesulfonate anions are employed in few organic as well as electrochemical process. These are neutral ionic liquids, known to be electrochemically, chemically and thermally stable.\(^19\) Ultrasound has increasingly been used in organic synthesis in the past
three decades. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions, especially many metal-involved reactions, can be carried out in higher yields, shorter reaction times, and milder conditions under ultrasound irradiation.\textsuperscript{20,21,22}

**Present work**

Literature witness revealed that highly efficient method for synthesis 2-chloro-3-formyl quinoline derivatives. In continuation of our ongoing work on Vilsmeier Haack reaction, we wish to present the utilization of ultrasonic irradiation for the synthetic uses of Vilsmeier Cyclisation and Formylation reactions and demonstrate its activeness in relation to conventional thermal reactions. We focused our attention on the Cyclisation of acetanilide with Vilsmeier Haack reagent under ultrasound irradiation conditions. A solution of acetanilide (Entries 1–9) and Vilsmeier Haack adduct (formed from POCl\textsubscript{3}/DMF) and ionic liquid 1-alkylpyridinium sulfonates was immersed in an ultrasonic bath for 40-80 in at room temperature and the subsequent usual workup and purification gave the corresponding 2-chloro-3-formylquinolines (Entries 1-9) in excellent yield. In marked contrast, however, reaction under thermal condition resulted in formation of 2-chloro-3-formyl quinoline in (68\%) yields, and in most of the cases the intermediate formamidine is isolated in good yield. A similar tendency was also observed in the case of hydrocarbons (Entries 1–9) where the desired formylated product was obtained in 75–95 % yield under ultrasonic irradiation. The yield was significantly diminished under thermal conditions.
Scheme 1.

Experimental Section

All the reaction were carried out in Bandelin Sonorex (35Khz) ultrasonic bath and in domestic microwave oven model, BPL BMO 800T. Melting points were determined in open capillaries and are uncorrected. The progress of reaction was monitored on TLC, $^1$H NMR spectra were measured on Bruker Avance 400 (400 MHz) spectrometer using TMS as internal standard and CDCl$_3$ as solvent.

General Procedure

A mixture of DMF (0.12 mole, 9.13g) was cooled to 0 °C in a flask and POCl$_3$ (0.35mole,53.7g) was added drop wise with stirring and added IL (10 mol%) The mixture was irradiated in the ultrasonic bath at room temperature for the period as indicated in the Table-I. After completion of reaction, the reaction mixture was treated with ice-cold water. The solid separated was filtered and recrystallized from ethanol to obtain the pure product.
Table 1. Synthesis of 2-chloro 3-formyl quinoline Derivatives under Ultrasound Irradiation

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Yield</th>
<th>M.P. (°C)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>45</td>
<td>90</td>
<td>146-147</td>
</tr>
<tr>
<td>2</td>
<td>P-CH₃</td>
<td>40</td>
<td>92</td>
<td>123-125</td>
</tr>
<tr>
<td>3</td>
<td>M- CH₃</td>
<td>45</td>
<td>90</td>
<td>144-146</td>
</tr>
<tr>
<td>4</td>
<td>O- CH₃</td>
<td>50</td>
<td>90</td>
<td>135-37</td>
</tr>
<tr>
<td>5</td>
<td>P-OCH₃</td>
<td>45</td>
<td>95</td>
<td>148-50</td>
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<tr>
<td>6</td>
<td>M-OCH₃</td>
<td>50</td>
<td>85</td>
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<tr>
<td>7</td>
<td>O- OCH₃</td>
<td>60</td>
<td>90</td>
<td>190-92</td>
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<tr>
<td>8</td>
<td>P-Cl</td>
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<tr>
<td>9</td>
<td>M-Cl</td>
<td>80</td>
<td>75</td>
<td>156-58</td>
</tr>
</tbody>
</table>
\(^1\)H NMR Spectrum:

Entry 4:

- 10.6 δ Singlet 1H due to -CHO
- 8.6 δ Singlet 1H due to Ar-H
- 7.82-8.6 δ Multiplet 3H due to Ar-H
- 1.9 δ Singlet 3H due to Ar-H

Mass Spectrum:

- 193 m/z (Base peak and Molecular ion peak), 178, 158, 163, 105, 77.
References