The effective reaction of 2-chloro-3-formylquinoline and acetic acid/sodium acetate under microwave irradiation

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Abstract

Pyrano[2,3-b]quinolin-2-ones have been synthesized efficiently from 2-chloro-3-formylquinolines in a single step by treating with sodium acetate and acetic acid under microwave irradiation. The structures of the compounds have been established by IR, NMR and mass spectral data. Unexpectedly, 3-formylquinolin-2(1H)-ones were exclusively formed in very high yields by changing the molar ratio of acetic acid and sodium acetate in just 1.5 to 2.5 min.

Keywords: pyrano, microwave, quinolines, solventless, acetic acid.

1. Introduction

The preparation of pyranoquinolines has received significant attention (Kamal et al., 2004; Yadav et al., 2002; Nagarajan et al., 2001) in previous years because of the broad spectrum of their biological properties such as psychotropic, antiallergic, anti-inflammatory and estrogenic activities (Yamada et al., 1992; Faber et al., 1984). In addition, pyranoquinoline derivatives are found to possess a wide range of pharmacological activity (Magesh et al., 2004). Further, several bioactive alkaloids which are widely distributed in nature contain a pyranoquinoline moiety (H.-Sheng Chen et al., 1997; Dagne et al., 1988). Among the pyranoquinolines, pyrano[2,3-b]quinolin-2-one systems are of interest because they are linear benzaza analogues of coumarins and they constitute the parent ring structures of pyranoquinoline alkaloids such as khaplofoline, which occurs in the rutaceae plant family (Michael 1995; Brader et al., 1996).

So far, only a few methods have been reported (Meth-Cohn et al., 1981; Tilakraj and Ambekar 1985) for the construction of pyrano[2,3-b]quinolin-2-ones, which generally involve 2-chloro-3-formylquinolines (1) as starting materials. In previous methods, (Sekar and Rajendra Prasad 1998) 2-chloro-3-formylquinolines (1) were converted into 3-formylquinolin-2(1H)-ones which on treatment with malonic acid followed by PPA cyclisation afforded pyrano[2,3-b]quinolin-2-ones. Later this method was modified by the condensation of 2-chloro-3-formylquinolines with acetic anhydride and sodium acetate in a single step to give pyrano[2,3-b]quinolin-2-ones. Similar methods of preparation of 4-methoxy-pyrano[2,3-b]quinolin-2-one and some 3-substituted-pyrano[2,3-b]quinolin-ones have also been reported (Narasimhan and Bhagwat 1979; Venkatesh Kumar and Rajendran 2003).

However, these methods have some disadvantages, which include multiple steps, longer reaction time, and use of toxic organic solvents, harsh reaction conditions and requirement of excess of reagents such as hydrochloric acid, acetic anhydride and polyphosphoric acid.

Microwave irradiation using commercial domestic oven has been recently used to accelerate organic reactions, the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction time (Jolivet et al., 1996). As a part of a research project to develop environmentally benign organic reactions, we have recently reported (Nadaraj et al., 2010; 2011) the synthesis of simple quinolines, pyrimido- and pyrazoloquinolines under microwaves. Hence, our new approach reported herein involves the use of microwave irradiation in the synthesis of pyrano[2,3-b]quinolin-2-ones under mild conditions and unexpected formation of 3-formylquinolin-2(1H)-ones as intermediates.
2. Materials and Method

Melting points (mp) were recorded on Boetius microheating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrophotometer. \(^1\)H NMR & \(^{13}\)C NMR spectra were recorded on Bruker AMX-500 (500 MHz) spectrophotometer, using TMS as an internal reference and Mass spectra were recorded at 70 eV on a Joel JMS-D-300 instrument. Microwave irradiations were carried out using a Kenstar, OM-20ESP, 2450 MHz, domestic microwave oven with adjustable irradiation power.

### 2.1 General procedure for the synthesis of pyrano[2,3-b]quinolin-2-ones (2a-j):

A mixture of 2-chloro-3-formylquinoline (0.5 mmol), glacial acetic acid (103 mmol) and sodium acetate (25 mmol) was taken in a closed Teflon vessel and irradiated in a microwave oven at power 320 W for the specified time (Table 2). After irradiation, the reaction mixture was poured into crushed ice. The precipitated product was filtered, washed with water, dried and recrystallized from ethyl acetate.

**Example**

A mixture of 2-chloro-3-formylquinoline (0.5 mmol), glacial acetic acid (87.5 mmol) and sodium acetate (25 mmol) was taken in an open Teflon vessel and irradiated in a microwave oven at power 320 W for the specified time (Table 2). After irradiation, the reaction mixture was poured into crushed ice. The precipitated product was filtered, washed, dried and recrystallized from ethyl acetate.

**Examples: 3-formylquinolin-2(1H)-one (2a-j):**

- **3-diformylquinolin-2-one (2a):** IR (KBr): \(\nu = 1621 \text{ cm}^{-1}, 1740 \text{ cm}^{-1} (C=O)\); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 6.56 (d, \ J (H,H) = 9 \text{ Hz}, 1H; C_3-H), 7.50-7.85 (m, 3H; C_7-H, C_8-H & C_9-H), 7.95 (d, 3H; C_5-H); 13C NMR (DMSO-\(d_6\)): \(\delta = 117.5, 122.5, 126.5, 132.3, 134.2, 136.8, 137.9, 140.5, 143.2, 146.2, 156.3, 162.3\); MS \(m/z\): 197 [M\(^+\)]; elemental analysis calcd (%) for C\(_{13}\)H\(_9\)NO\(_3\): C 68.72, H 3.99, N 6.16; found: C 68.70, H 4.00, N 6.13.

- **3-6-Methoxy-formylquinolin-2-one (2e):** IR (KBr): \(\nu = 1622 \text{ cm}^{-1}, 1735 \text{ cm}^{-1} (C=O)\); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta = 3.91 (s, 3H; C_6-OCH_3), 7.35 (d, 1H; C_8-H), 7.59 (d, 1H; C_7-H), 8.04 (s, 1H; C_5-H), 8.35 (s, 1H; C_4-H), 10.41 (s, 1H; CHO), 11.52 (s, 1H; NH)."

**Examples: 3-formylquinolin-2-one (2a-j):**

A mixture of 2-chloro-3-formylquinoline (0.5 mmol), glacial acetic acid (87.5 mmol) and sodium acetate (25 mmol) was taken in an open Teflon vessel and irradiated in a microwave oven at power 320 W for the specified time (Table 2). After irradiation, the reaction mixture was poured into crushed ice. The precipitated product was filtered, washed, dried and recrystallized from ethyl acetate.

2.2 General procedure for synthesis of 3-formylquinolin-2(1H)-ones (3a-j):

A mixture of 2-chloro-3-formylquinoline (0.5 mmol), glacial acetic acid (87.5 mmol) and sodium acetate (25 mmol) was taken in an open Teflon vessel and irradiated in a microwave oven at power 320 W for the specified time (Table 3). After irradiation, the reaction mixture was poured into crushed ice. The precipitated product was filtered, washed with water, dried and recrystallized from aqueous acetic acid.
3. Results and Discussion

To identify an efficient reagent/catalyst for the synthesis of pyrano[2,3-b]quinolin-2-one derivatives, we initially examined the reaction of 2-chloro-3-formylquinoline (1) with acetic acid and sodium acetate under microwave irradiation. Various parameters such as different molar ratio of acetic acid and sodium acetate, irradiation power and time and using closed or open Teflon vessel were studied and optimized (Table 1, Methods 1-5).

When we irradiated (Method 1) 0.5 mmol of 2-chloro-3-formylquinoline (1a) with 123 mmol of acetic acid and 50 mmol of sodium acetate in a closed Teflon vessel, for 5 min at power 320 W, pyrano[2,3-b]quinolin-2-one (2a) was formed in good yield (92%) (Scheme 1).

\[1a \rightarrow 2a\]

Table 1. Microwave irradiation of 2-chloro-3-formylquinoline (1a) with acetic acid and sodium acetate under different conditions

<table>
<thead>
<tr>
<th>Methods</th>
<th>Reagent/Catalyst</th>
<th>Molar ratio (mmol)</th>
<th>Irradiation Power (W)</th>
<th>Time (min)</th>
<th>Product formed</th>
<th>Yield (%)</th>
<th>Teflon Vessel type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH/NaOAc</td>
<td>123 and 50</td>
<td>320</td>
<td>5.00</td>
<td>2a</td>
<td>92</td>
<td>Closed</td>
</tr>
<tr>
<td>2</td>
<td>AcOH/NaOAc</td>
<td>87.5 and 25</td>
<td>320</td>
<td>2.20</td>
<td>3a</td>
<td>98</td>
<td>Open</td>
</tr>
<tr>
<td>3</td>
<td>AcOH</td>
<td>175</td>
<td>480</td>
<td>15.00</td>
<td>2a</td>
<td>67</td>
<td>Open or Closed</td>
</tr>
<tr>
<td>4</td>
<td>NaOAc</td>
<td>50</td>
<td>480</td>
<td>10.00</td>
<td>3a</td>
<td>80</td>
<td>Open</td>
</tr>
<tr>
<td>5</td>
<td>AcOH/NaOAc</td>
<td>123 and 50</td>
<td>320</td>
<td>5.00</td>
<td>2a &amp; 3a</td>
<td>-</td>
<td>Open</td>
</tr>
</tbody>
</table>

The above reaction has also been tried out with lesser amount of acetic acid and sodium acetate (87.5 mmol and 25 mmol) in an open Teflon vessel, at power 320 W (Method 2). When the irradiation time was 2.20 min, we got a single product (3a) in 98% yield but different from pyranoquinoline 2a. IR spectrum of 3a showed absorption at 1680 cm\(^{-1}\) corresponding to free aldehyde group. The spectral (\(^1\)H-NMR & Mass) and analytical data attested the compound 3a to be 3-formylquinolin-2(1H)-one, which is also a good intermediate in the synthesis of other quinoline heterocycles (Rajendran and Vijayalakshmi 1994, 1998) (Scheme 1).

Then 2-chloro-3-formylquinoline (1a) irradiated with acetic acid alone in either closed or open vessel (Table 1, Method 3). The target product pyranoquinoline 2a was obtained in lesser yield (67%). But, this method required more amount of acetic acid (175 mmol) and high irradiation power and time.

The solid-state condition was also checked for the reaction: Irradiation with only sodium acetate failed to give pyrano[2,3-b]quinolin-2-one but afforded 3-formylquinolin-2(1H)-one (3a) in 80% yield. This reaction also required high irradiation power and more time for complete conversion (Table 1, Method 4).

When method 1 was repeated in an open vessel, (Table 1, Method 5), a mixture of 2a and 3a was formed. Hence, with all these trials, we have found that, methods 1 and 2 are efficient ways to synthesize pyrano[2,3-b]quinolin-2-one (2a) and 3-formylquinolin-2(1H)-one (3a) respectively. To establish the generality and applicability of these methods, various substituted 2-chloro-3-formylquinolines (1b-j) were subjected to the same reaction conditions (Methods 1 and 2) to furnish the corresponding quinolines 2b-j and 3b-j in good yields (Tables 2 and 3).

All the yields were calculated from crystallized products and the products were identified by comparison of analytical data (mp, mmp, IR, NMR, and Mass) with those reported or with authentic samples prepared by the conventional methods (Meth-Cohn et al., 1981). Some new derivatives (2e,g,h & 3e,g,h) were also prepared and reported.
Table 2. Microwave Synthesis of 2-oxo-2H-pyrano[2,3-b]quinolines (2a-j)

(a) acetic acid (123 mmol), sodium acetate (50 mmol), mw, 320W

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product R 1 R 2 R 3</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (Lit.mp) °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a H H H</td>
<td>5.00</td>
<td>92</td>
<td>243-244 (243)</td>
</tr>
<tr>
<td>2</td>
<td>2b CH3 H H</td>
<td>6.20</td>
<td>95</td>
<td>245-247 (240)</td>
</tr>
<tr>
<td>3</td>
<td>2c H CH3 H</td>
<td>6.50</td>
<td>81</td>
<td>273-275 (274)</td>
</tr>
<tr>
<td>4</td>
<td>2d H H CH3</td>
<td>6.40</td>
<td>86</td>
<td>231-232 (230)</td>
</tr>
<tr>
<td>5</td>
<td>2e OCH3 H H</td>
<td>5.00</td>
<td>78</td>
<td>224-225</td>
</tr>
<tr>
<td>6</td>
<td>2f H OCH3 H</td>
<td>5.00</td>
<td>81</td>
<td>226-227 (225)</td>
</tr>
<tr>
<td>7</td>
<td>2g H H OCH3</td>
<td>6.00</td>
<td>89</td>
<td>260-262</td>
</tr>
<tr>
<td>8</td>
<td>2h Br H H</td>
<td>9.00</td>
<td>70</td>
<td>262-264</td>
</tr>
<tr>
<td>9</td>
<td>2i Cl H H</td>
<td>8.20</td>
<td>75</td>
<td>210-212 (215)</td>
</tr>
<tr>
<td>10</td>
<td>2j H Cl H</td>
<td>8.50</td>
<td>76</td>
<td>282-283 (280)</td>
</tr>
</tbody>
</table>

Table 3. Microwave Synthesis of 2(1H)-quinolinone-3-carboxaldehydes (3a-j)

(a) acetic acid (87.5 mmol), sodium acetate (25 mmol), mw, 320W

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product R 1 R 2 R 3</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (Lit.mp) °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a H H H</td>
<td>2.20</td>
<td>98</td>
<td>304-305 (298)</td>
</tr>
<tr>
<td>2</td>
<td>3b CH3 H H</td>
<td>2.00</td>
<td>94</td>
<td>272-274 (275)</td>
</tr>
<tr>
<td>3</td>
<td>3c H CH3 H</td>
<td>2.00</td>
<td>93</td>
<td>296-297 (294)</td>
</tr>
<tr>
<td>4</td>
<td>3d H H CH3</td>
<td>1.80</td>
<td>96</td>
<td>285-287 (284)</td>
</tr>
<tr>
<td>5</td>
<td>3e OCH3 H H</td>
<td>1.50</td>
<td>98</td>
<td>275-276</td>
</tr>
<tr>
<td>6</td>
<td>3f H OCH3 H</td>
<td>1.70</td>
<td>97</td>
<td>265-267 (263)</td>
</tr>
<tr>
<td>7</td>
<td>3g H H OCH3</td>
<td>1.50</td>
<td>97</td>
<td>260-262</td>
</tr>
<tr>
<td>8</td>
<td>3h Br H H</td>
<td>2.50</td>
<td>72</td>
<td>&gt;300 (342-344)</td>
</tr>
<tr>
<td>9</td>
<td>3i Cl H H</td>
<td>2.20</td>
<td>87</td>
<td>&gt;300 (357-358)</td>
</tr>
<tr>
<td>10</td>
<td>3j H Cl H</td>
<td>2.50</td>
<td>75</td>
<td>&gt;300 (340)</td>
</tr>
</tbody>
</table>
4. Conclusion

The procedures described above provide a useful, clean, fast and efficient alternative for the preparation of both pyrano[2,3-b]quinolin-2-ones and 3-formylquinolin-2(1H)-one. Prominent among the advantages of these new methods are operational simplicity, good yield in a very short reaction time, solvent-free conditions, very inexpensive, easily available reagent and catalyst and easy workup procedure employed.

Acknowledgement

The author VN is grateful to Director of Collegiate Education, Govt. of Tamilnadu, India, for financial support. Author thank to Research centre, Indian Institute of Science, Bangalore, INDIA for providing 1H NMR spectral data.

References


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Received March 2011
Accepted July 2011
Final acceptance in revised form July 2011