Dual Behavior of Iodine Species in Condensation of Anilines and Vinyl Ethers Affording 2-Methylquinolines

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Abstract: A metal-free, mild and efficient method for the synthesis of 2-methylquinolines was successfully developed by condensation of anilines with vinyl ethers in the presence of catalytic amount of iodine. Modification of both pyridine and benzene moieties was easily achieved by changing only the vinyl ether and aniline. In this reaction, the iodine species was revealed to show dual behavior; molecular iodine serves as an oxidant, while its reduced form, hydrogen iodide, activates the vinyl ether. The redox reaction between these iodine species enables the use of a catalytic amount of iodine in this synthetic method.

Keywords: 2-methylquinoline; iodine-mediated reaction; aniline; vinyl ether; redox reaction

1. Introduction

Iodine-catalyzed reactions have attracted much attention as environmentally sustainable alternatives to transition metal catalysis in industrial chemistry for producing commodity and specialty chemicals, foods, medicines, and pharmaceuticals [1]. Iodine undergoes oxidative addition, ligand exchange, reductive elimination, and ligand coupling, playing a role similar to that of transition metal catalysts [2]. In contrast to poisonous and expensive transition metals, molecular iodine is an environmentally friendly, inexpensive, and readily available reagent. The mild Lewis acidity of iodine also facilitates its use in organic synthesis, from stoichiometric levels to catalytic amounts. Thus, iodine-mediated reactions have been explored as a powerful method for the synthesis of many organic compounds [3–8].

Meanwhile, the importance and usefulness of quinoline derivatives has considerably increased in the pharmaceutical industry. Among them, 2-methylquinoline derivatives have versatile pharmacological properties such as antibacterial [9], antimalarial [10,11], anti-tumor [12] and anti-HIV [13,14] properties, and can act as nociceptin receptor antagonists [15]. 2-Methylquinolines can also be used as precursors in the synthesis of styrylquinolines, which are potential inhibitors of HIV-1 integrase and the replication of HIV-1 in cell culture [16]. Various quinolines for the treatment of protozoal and retroviral co-infection are also synthesized from 2-methylquinoline [17]. Furthermore, the 7-methoxy derivative is known to be a non-peptide bradykinin B2 receptor antagonist [18], and the 8-methoxy derivative is used as a neuroprotegerative agent, a radioprotective [19] and an antibiotic against Staphylococcus aureus [20]. In addition to the aforementioned pharmaceutical uses,
substituted 2-methylquinolines are often employed as precursors for electronic and optoelectronic materials [21,22].

Despite their great importance, 2-methylquinolines are commonly prepared using traditional methods developed by Doebner-von Miller [23], Skraup [24], Conrad-Limpach-Knorr [25], Friedlaender [26] and Pfitzinger [27]. Unfortunately, these methods suffer from several disadvantages such as low yields due to side reactions; harsh reaction conditions, including the use of strong acids; multi-step reactions; and low regioselectivity. Although an acid-free approach using transition metal catalysts overcomes these disadvantages [28–30], an additional purification step is required to remove metal contaminants from the product. Furthermore, limited functional group tolerance diminishes the generality of this method [28–30]. Several researchers have reported synthetic methods using inexpensive Lewis acids such as iron(III) chloride, magnesium perchlorate, and zinc chloride [26,31–36]; however, these methods still have drawbacks, including the need for harsh reaction conditions, difficult work-up procedures, low yields, and high catalyst loadings.

Recently, an iodine-mediated reaction was applied to the synthesis of quinoline derivatives. Wang and co-workers reported a molecular iodine-catalyzed reaction for the synthesis of substituted quinolines from imines and aldehydes [37]. Furthermore, they reported the highly efficient multi-component synthesis of quinoline derivatives using catalytic amounts of molecular iodine [38–41]. Later, Wu et al. improved this method for the synthesis of quinolines and polycyclic quinolines [42]. Owing to the numerous advantages of molecular iodine over transition metals, an iodine-catalyzed quinoline synthesis was also reported in which anilines were condensed with cyclic vinyl ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2H-pyran [43]. In this reaction, iodine was reported as serving only as a Lewis acid. In contrast, we report here a metal-free and efficient method for the synthesis of substituted 2-methylquinolines using low toxicity, low cost, commercially available iodine, anilines, and acyclic ethers under mild reaction conditions. We also suggest that the molecular iodine serves as an oxidant, which has not been proposed previously. In addition, a reaction mechanism is proposed, which includes the dual behavior of iodine species.

2. Results and Discussion

2.1. Iodine-Catalyzed Synthesis of 6-Substituted 2-Methylquinolines

Initially, the reaction of p-methoxyaniline 1a with ethyl vinyl ether 2a in dichloromethane was used as model reaction to optimize conditions (Table 1). The reaction did not proceed in the absence of iodine, with 88% of 1a recovered (entry 1). On the other hand, quinoline 3a [44] was successfully synthesized in 44% yield when the reaction was carried out in the presence of 5 mol % iodine, indicating that iodine was necessary for the construction of quinoline 3a (entry 2). Among the three solvents tested, benzene was found to be the most suitable for this reaction (entries 2–4). While 5 mol % iodine was enough for the reaction to operate efficiently, the yield of quinoline 3a decreased along with a 71% recovery of 1a, when the catalyst loading was reduced to 1 mol % (entries 4–6). Consequently, the reaction conditions used in entry 4 were determined to be the optimal conditions.

With the optimized conditions in hand, we applied the reaction to the syntheses of 2-methylquinolines 3b–h [29,45–50] using anilines 1b–h (Table 2). The reaction was influenced by substituents on the benzene ring. When m-methoxyaniline 1b and o-methoxyaniline 1c were used, the reactions proceeded in a similar fashion, affording corresponding quinolines 3b and 3c in lower yields, presumably due to the electron-withdrawing inductive effect and steric hindrance of the methoxy group (entries 2 and 3). In contrast, aniline possessing both o- and m-methoxy groups (1d) had a higher product yield, indicating that high electron density on the benzene ring overcomes the aforementioned disadvantages (entry 4). In the case of aminophenol 1e, no detectable 3e was produced due to side reactions, such as the oxidation of 1e (entry 5). Anilines connected to another electron-donating group, 1f and 1g, reacted efficiently to afford aminoquinoline 3f and methylquinoline 3g, respectively.
(entries 6 and 7). Unsubstituted aniline 1h was also a suitable substrate in this reaction, but with somewhat lower efficiency.

**Table 1. Synthesis of 6-methoxy-2-methylquinoline 3a.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>I$_2$/mol %</th>
<th>Solv.</th>
<th>Yield/%</th>
<th>Recovery of 1a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>CH$_2$Cl$_2$</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>MeCN</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>PhH</td>
<td>64</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>PhH</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>PhH</td>
<td>11</td>
<td>71</td>
</tr>
</tbody>
</table>

**Table 2. Modification of the benzene ring of quinoline 3.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>Product</th>
<th>Yield/%</th>
<th>Recovery of 1a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3a</td>
<td>64</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>3b</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3c</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3d</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>3e</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>3f</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>3g</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>3h</td>
<td>37</td>
<td>7</td>
</tr>
</tbody>
</table>
To further demonstrate the scope of this reaction, various vinyl ethers, 2a–f, were subjected to the reaction with p-methoxylaniline 1a (Table 3). Interestingly, quinoline 3a was produced despite the ether alkox group being changed from ethoxy to isobutoxy (entries 1 and 2), indicating that the pyridine moiety in quinolines 3 was derived from the vinyl group. Indeed, propenyl ether 2c afforded 2-ethyl-3-methylquinoline 4 [51] in good yield, which is employed in the preparation of metal acid corrosion inhibitors, sorbents, and cyanine dyes [52]. When 2,3-dihydrofuran 2d was used, a quinoline possessing acetal functions, 5, was synthesized (See the Supplementary Materials). Desired quinolines 6 and 7 were not detected when electron-poor vinyl ethers 2e and 2f were employed (entries 5 and 6).

Table 3. Modification of the pyridine ring of quinoline 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Vinyl Ether</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>2</td>
<td>MeO</td>
<td>3a</td>
<td>64 1</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>2</td>
<td>OMe</td>
<td>3a</td>
<td>54 1</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>14</td>
<td>MeO</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>2</td>
<td>OMe</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>2</td>
<td>MeO</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>14</td>
<td>MeO</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Recovery of 1a: Entry 1 (3%), Entry 2 (33%).

2.2. Study on the Mechanism

In the reaction of o-methoxylaniline 1d with vinyl ether 2a, several products were formed. In order to gain insight into the mechanism, the reaction mixture was subjected to column chromatography and the products were identified as 4-ethoxy-1,2,3,4-tetrahydro-8-methoxy-2-methylquinoline (8) as single diastereomer [53] and N-ethyl-2-methoxylaniline (9) [54] (Scheme 1). Although elucidation of the stereochemistry of compound 8 was attempted by 1H-NMR, it was not achieved due to two protons at the 3-position having the same coupling constant (12.0 Hz) with a proton at the 2-position. Considering steric repulsion, the stereochemistry was predicted to be the cis-isomer because the ethoxy and methyl groups are located at the equatorial position. Indeed, DFT calculation using B3LYP 6-31G(d,p) revealed that the cis-isomer was more stable than the trans-isomer, with 1.887 kcal/mol. Interestingly, tetrahydroquinoline 8 was converted to 3d in 77% yield by heating in the presence of
iodine. In contrast, no reaction was observed for 9 under the same conditions. These results suggest that 8 is an intermediate in the formation of 3d, and that N-alkylaniline 9 is a by-product (Scheme 1).

The reaction of 1a with vinyl ether 2a was monitored by 1H-NMR (Figure 1). As starting material 1a was consumed, product 3a formed. Just after the reaction started, the formation of 10 [55] was observed, which gradually decreased over time. In addition, a small amount of 11 [54] was formed, but the amount was unchanged, even after 72 h. Thus, it was confirmed that 10 was a reaction intermediate and 11 was a by-product.

Scheme 1. Reactions of by-products 8 and 9 with iodine under the same conditions.

![Scheme 1](image)

Figure 1. Monitoring the reaction of 1a and 2a by 1H-NMR.

In addition, hydriodic acid and p-toluenesulfonic acid were employed as catalysts in this reaction instead of iodine (Scheme 2). Hydriodic acid catalyzed this reaction, but gave a lower yield of 3a. p-Toluenesulfonic acid did not catalyze the reaction at 80 °C, and it was necessary to heat at 120 °C. Although the reaction proceeded in the presence of an acid catalyst, iodine was necessary to accelerate the reaction smoothly under milder conditions.
Based on these experimental results, the reaction mechanism in Scheme 3 was proposed. At first, iodine generates a trace amount of hydrogen iodide by reacting with water present in the reaction mixture [56], initiating the reaction. Aniline 1h attacks the activated vinyl group of 2a, leading to an N,O-acetal, from which ethanol is eliminated to afford iminium intermediate 12. Iminium 12 is considered a common intermediate for both N-ethylaniline 14 and tetrahydroquinoline 15. Tetrahydroquinoline 15 is formed by the attack of another molecule of 2a to iminium ion 12 followed by intramolecular cyclization, while dihydroquinoline 16 is obtained as a result of ethanol elimination. Oxidation of 16 by iodine affords the final product, quinoline 3h. In this process, iodine is reduced to hydrogen iodide, which then returns to iodine upon contact with air. Indeed, when the reaction was conducted under Ar atmosphere, the product was obtained in lower yield. Thus, oxygen may assist the reaction. Therefore, a catalytic amount of iodine is enough to produce this reaction. In contrast, when intermediate 12 is reduced by dihydroquinoline 16, N-alkylaniline 14 is formed as a by-product.

Scheme 3. A plausible mechanism.

3. Materials and Methods

3.1. General Information

All the reagents and solvents were commercially available and used as received. The $^1$H-NMR spectra were measured on a Bruker Ascend-400 (Bruker, Billerica, MA, USA) at 400 MHz with TMS as an internal standard. The $^{13}$C-NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of $^{13}$C-NMR spectra were performed by DEPT experiments. The high resolution mass spectra were measured on a AB SCIEX Triple TOF 4600 (AB Sciex, Framingham, MA, USA).
3.2. Procedures

Iodine-Mediated Synthesis of 2-Methylquinolines 3

To a solution of vinyl ether 2a (192 µL, 2 mmol) in benzene (10 mL), were added p-methoxyaniline (1a, 123.2 mg, 1 mmol) and iodine (12.7 mg, 0.05 mmol), and the resultant mixture was heated at 80 °C for 2 h. The reaction mixture was washed with saturated sodium thiosulfate solution (1 x 10 mL) to remove unreacted iodine, and dried over magnesium sulfate. After removal of solvent, the residue was subjected to silica gel column chromatography (eluent: hexane/ethyl acetate = 95/5) to afford 3a (110.7 mg, 0.64 mmol, 64%).

The reactions of the aniline 1 with other vinyl ether 2 were performed in a similar manner.

3.3. Compound Characterizations

6-Methoxy-2-methylquinoline (3a) [44]: 1H-NMR (400 MHz, CDCl3): δ 7.94 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.33 (dd, J = 9.1, 2.8 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 3.91 (s, 3H), 2.70 (s, 3H).

7-Methoxy-2-methylquinoline (3b) [45]: 1H-NMR (400 MHz, CDCl3): δ 7.95 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.37 (s, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 2.71 (s, 3H).

8-Methoxy-2-methylquinoline (3c) [46]: 1H-NMR (400 MHz, CDCl3): δ 8.00 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.4, 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.08 (s, 3H), 2.80 (s, 3H).

5,8-Dimethoxy-2-methylquinoline (3d) [47]: 1H-NMR (400 MHz, DMSO): δ 7.45 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 6.8 Hz, 1H), 6.66 (d, J = 6.8 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 2.68 (s, 3H).

6-(N,N-dimethylamino)-2-methylquinoline (3f) [49]: 1H-NMR (400 MHz, DMSO): δ 7.98 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 9.2, 2.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 2.97 (s, 6H), 2.56 (s, 3H).

2,6-Dimethoxy-3-methylquinoline (4) [27]: 1H-NMR (400 MHz, CDCl3): δ 7.91 (d, J = 9.2 Hz, 1H), 7.69 (s, 1H), 7.25 (dd, J = 9.2, 2.8 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 3.87 (s, 3H), 2.94 (q, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H).

Compound 5: 1H-NMR (400 MHz, CDCl3): δ 7.89 (d, J = 9.2 Hz, 1H), 7.81 (s, 1H), 7.27 (d, J = 9.2 Hz, 1H), 6.99 (s, 1H), 5.14 (t, J = 2.0 Hz, 2H), 4.01—3.93 (m, 1H), 3.91 (s, 3H), 3.88–3.67 (m, 6H), 3.54–3.46 (m, 1H), 3.07–3.00 (m, 4H), 2.13–2.06 (m, 2H), 2.03–1.78 (m, 8H). 13C-NMR (100 MHz, CDCl3): 23.4 (CH2), 29.3 (CH2), 32.1 (CH2), 32.3 (two CH2 signals overlapped), 32.4 (CH2), 55.4 (CH3), 66.8 (four CH2 signals overlapped), 103.8 (CH), 103.9(CH), 104.7 (CH), 121.0 (CH), 127.9 (C), 130.0 (CH), 130.9 (C), 134.6 (CH), 142.8 (C), 157.2 (C), 158.9 (C). HRMS Calcd for C23H31NO5: 402.2275. Found: 402.2272.

Cis-4-Ethoxy-1,2,3,4-tetrahydro-8-methoxy-2-methylquinoline (8) [29]: 1H-NMR (400 MHz, CDCl3): δ 7.00 (dd, J = 4.8, 4.8 Hz, 1H), 6.64 (d, J = 4.8 Hz, 2H), 4.70 (dd, J = 10.4, 5.6 Hz, 1H), 4.1 (br, 1H), 3.82 (s, 3H), 3.69–3.55 (m, 1H), 3.51 (dq, J = 9.2, 7.2 Hz, 2H), 2.21 (dd, J = 12.0, 5.6, 2.4 Hz, 1H), 1.70 (ddd, J = 12.0, 10.4, 2.4 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.27 (dd, J = 7.2, 7.2 Hz, 3H).
N-Ethyl-2-methoxyaniline (9): $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.87 (dd, $J$ = 7.6, 7.6 Hz, 1H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.65 (dd, $J$ = 7.6, 7.6 Hz, 1H), 6.60 (d, $J$ = 7.6 Hz, 1H), 4.08 (br s, 1H), 3.84 (s, 3H), 3.16 (q, $J$ = 7.2 Hz, 2H), 1.28 (t, $J$ = 7.2 Hz, 3H).

4. Conclusions

In conclusion, we have successfully developed an environmentally benign and efficient method for the construction of quinolines 3 from substituted anilines 1 and vinyl ethers 2 in the presence of an iodine catalyst. This protocol can be performed with simple manipulations in one step under mild conditions for both the reaction and work-up. Furthermore, no transition metals are used, which eliminates the need for a product decontamination step, thus considerably reducing the cost. Hence, this is a new synthetic method for quinoline derivatives that can be applied in various fields.

Furthermore, the roles of iodine species were also studied, finding that the iodine species had dual behavior, with molecular iodine serving as an oxidant, and its reduced form, hydrogen iodide, activating the vinyl ether. The redox reaction between these iodine species enables the use of a catalytic amount of iodine in this reaction.

Supplementary Materials: Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/21/7/827/s1.

Author Contributions: Le, S.T. wrote the draft and measured HRMS and did a part of experiments; Yasuoka, C. designed experiments; Asahara, H. performed DFT calculation; Asahara, H. and Nishiwaki, N. analyzed data and discussed with other authors; all authors contributed to the revision.

Conflicts of Interest: The authors declare no conflicts of interest.

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**Sample Availability:** Not available.

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