Cyclization of 1-Benzyl-1,2-dihydro-2-(substituted methylene)quinolines to Pyrrolo[1,2-a]quinoline Derivatives

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1-Alkyl-2-alkythioquinolinium salts were prepared from 1-alkyl-2(1H)-quinolones via 1-alkyl-2(1H)-thioquinolones in two steps. Under mild conditions, the reaction of 1-alkyl-2-alkythioquinolinium iodides with active methylene compounds in the presence of sodium hydride afforded 1-alkyl-1,2-dihydro-2-(substituted methylene)quinolines in good yields. The cyclization of 1-benzylquinolines using acetic anhydride produced the corresponding pyrrolo[1,2-a]quinoline derivatives.

Key words 1-benzyl-2(1H)-thioquinoline; dimethyl malonate; cyclization; pyrrolo[1,2-a]quinoline; 2-methylthioquinolinium iodide

Previously we reported a new method for the formation of a carbon–carbon bond at the 2-position of a quinoline ring using the reaction of 1-methyl-2-methylthioquinolinium iodide with active methylene compounds.1) Excellent yields were obtained as shown in Chart 1. Various methods for the synthesis of the pyrrolo[1,2-a]quinoline skeleton have also been reported.2—7) The conventional methods for preparing the substituted pyrrolo[1,2-a]quinoline derivatives typically involve reactions of 2-substituted quinolines having a phenacyl group with acetic anhydride.5,7) Recently, Komatsu and co-workers reported synthesis of the pyrrolo[1,2-a]quinoline by cycloaddition of quinolinium methylide at 180 °C for 6 h in 84% yield.8) Further, Weaver et al. reported synthesis of indolizines and pyrrolo[2,1-a]-isoquinolines using cycloaddition of pyridinium-1- and isoquinolinium-2-yl-methylene compounds with 1,1-diiodo-2,2-dinitroethylene in 17—43% yields. But, they did not report synthesis of pyrrolo[1,2-a]quinolines.9) Therefore, 2-substituted quinolines having a benzyl group would be extremely useful as an intermediate for the synthesis of the pyrrolo-fused heterocycles. Herein, we report a new method for the synthesis of a pyrrolo[1,2-a]quinoline skeleton using the cyclization of 1-benzyl-1,2-dihydro-2-(substituted methylene)quinolines, which were easily prepared from the reaction of 1-benzyl-2-methylthioquinolinium iodides with active methylene compounds, and the reaction of 1-methyl-2-alkythioquinolinium salts with cyclic active methylene compounds.

Reaction of 2-Alkylthioquinolinium Salts with Active Methylene Compounds

First, the reaction of 1-benzylquinolinium iodide (5) having a methylthio group as a leaving group at the 2-position with active methylene compounds (6a—g) was examined under mild conditions in the presence of sodium hydride (Chart 2, Table 1). 1-Benzyl-2(1H)-thioquinoline (3) was readily prepared from 2(1H)-quinolone (1) via 1-benzyl-2(1H)-quinolone (2) in two steps. The reaction of 3 with methyl iodide (4a) afforded 1-benzyl-2-methylthioquinolinium iodide (5) in 72% yield. The reaction of quinolinium iodide (5) with active methylene compounds (6a—e) in the presence of sodium hydride at room temperature for 2 h in tetrahydrofuran (THF) afforded 2-(substituted methylene)quinolines (7a, 91%; 7b, 97%; 7c, 76%; 7d, 63%; 7e, 62%; entries 1—5, respectively), as listed in Table 1. Furthermore, studies using cyclic active methylene compounds have shown that the reaction between 6f and 5 at room temperature for 6 h in dimethylformamide (DMF) afforded 2-(substituted methylene)quinolines (7f and 7g, 75% and 73%, respectively, entries 6 and 7).

Table 1. Reactions of 5 with 6a—g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>a 91</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>b 97</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>c 76</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>d 63</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>e 62</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>r.t.</td>
<td>2</td>
<td>THF</td>
<td>f 22</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>r.t.</td>
<td>2</td>
<td>DMF</td>
<td>f 26</td>
</tr>
<tr>
<td>8</td>
<td>g</td>
<td>90</td>
<td>6</td>
<td>DMF</td>
<td>g 75</td>
</tr>
<tr>
<td>9</td>
<td>g</td>
<td>90</td>
<td>6</td>
<td>DMF</td>
<td>g 73</td>
</tr>
<tr>
<td>10</td>
<td>a</td>
<td>90</td>
<td>6</td>
<td>DMF</td>
<td>a 86</td>
</tr>
</tbody>
</table>

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Chart 1

Chart 2

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temperature for 2 h in either THF or DMF gives 2-(substituted methylene)quinoline (7f) in poor yields (entries 6, 7). In contrast, the reaction of 6f with 5 at 90 °C for 6 h in DMF gave 7f in 75% yield (entry 8). Interestingly, the reaction of 6g with 5 at 90 °C for 6 h in THF resulted in two products (entry 9): 2-(substituted methylene)quinoline (7g, 73%) and 4-(substituted methylene)quinoline (7h, 18%). However, the reaction of 6a with 5 at 90 °C for 6 h afforded only one product: 2-(substituted methylene)quinoline (7a, entry 10).

To investigate the influence of steric or ionic effect, reactions of 1-methylquinolinium salts (9a–c) bearing methylthio, ethylthio, or isopropylthio group at the 2-position with quinolines was carried out (Chart 3, Table 2). The reaction of 1-methyl-2(1H)-thioquinolinone (8) with alkyl iodides (4a–c) proceeded smoothly to produce the corresponding 1-methyl-2-alkylthioquinolinium iodides (9a–c) in high yields (Chart 3). The reactions of 9a–c with 6a at room temperature for 0.5 h gave 2-(substituted methylene)quinoline (10a) in 95%, 82%, and 66% yields, respectively (entries 1—3). Similar reactions of 9b, c with 6f afforded 10a in 79% and 78% yields (entries 4, 5). The reactions of 9a–c with 6f in DMF gave 2- (substituted methylene)quinoline (10b) in 81%, 28% and 24% yields at room temperature for 2 h (entries 6—8), and 85%, 75% and 76% at 90 °C for 6 h (entries 9—11), respectively. The reaction of 9a with 6g gave two products: 2- and 4-(substituted methylene)quinolines (10g, 10h). Reaction at room temperature (entry 12) afforded products (10g, 40%; 10h, 15%), whereas reaction at 90 °C (entry 15) resulted in 10g (82%) and 10h (17%). However, the reactions of 9b and 9c with 6g at room temperature and at 90 °C afforded only the 2-(substituted methylene)quinoline (10g) (entries 13, 14, 16, 17). These results indicate that at room temperature, a bulky group on the sulfur atom interfere the interaction between the carbanion arisen from 6a, f, g and the carbocation on the 2-position of the quinolines ring and tends to reduce the yields of product (Table 2, entries 6—8, 12—14). In addition, a bulky substituent on the nitrogen atom can affect the reaction of 5 with 6f at room temperature, while at 90 °C it can not affect the reaction (Table 1, entries 6—8). Further the steric interaction between hydrogens on the 4- and 5-positions of quinoline ring is known. It can be presumed that as 6g is smaller size than 6f, the carbanion arising from 6g can reacted with the carbocation on the 4-position of 5 and 9a. On the other hand, as the carbanion arising from 6g would be a soft base (Lewis base) than the carbanion arising from 6a, it can be assumed that the carbanion arising from 6g reacted with the soft acid (Lewis acid) on the 4-position.

The structures of 2-(substituted methylene)quinolines (7a—g, 10a, f, g) and 4-substituted quinolines (7h, 10h) were determined from 1H-NMR spectra studies as follows. For the 2-(substituted methylene)quinolines, the signals due to the alkylthio group disappeared with replacement of the alkylthio group by the active methylene compounds. In contrast, for 4-(substituted methylene)quinolines (7h, 10h), a signal due to the methylthio group at 2.83 ppm and a singlet signal due to H-3 at 8.40 ppm were observed.

Spectroscopic studies of compounds (7c, d) showed nuclear Overhauser and exchange spectroscopy (NOE) correlations between the methyl of the ester (3.80, 3.69 ppm) and the proton (8.28, 8.06 ppm) at the 3-position, and therefore these configuration are suggested to be cis. The reaction described herein can be regarded as a promising method for carbon–carbon bond formation at the 2- and 4-positions in the quinoline ring.

**Cyclizations of 1-Benzylquinoline Compounds in Acetic Anhydride**

Next, we attempted the cyclizations of 1-benzylquinoline compounds (7a, d, e) in acetic anhydride to provide the corresponding functionalized pyrrolo[1,2-
a|quinoline derivatives (Chart 4). Refluxing of 7a-e in acetic anhydride for 4 h afforded the corresponding pyrrolo[1,2-
|quinolines (11a, 65% and 11e, 86%, respectively). The cy-
|clication of 7d, which has an ester and acetyl groups, pro-
|ceeded smoothly to afford 11d (75%) and 12d (21%). Unfor-
|tunately, the cyclization of 7b and 7c was unsuccessful with-
|out the recovery of the starting materials. The structures of 
|11a, d, e and 12d were determined from the 1H-NMR spectra for 11a, d, e and 12d, which showed that the signals (5.50—
|9.2 ppm) due to the methylene proton of benzyl groups in 
|11a and 12d disappeared by dehydration and condensa-
|tion.

In conclusion, we have developed a methodology for the 
|pyrrolo-fused heterocycles. Thus, the reactions between ac-
|cylation and dehydration of the intermediate 1-benzyl-1,2-
|dihydro-2-[bis-(methoxycarbonyl)methylene]quinoline 
|(4a) (1.24 g, 10 mmol) was gently refluxed for 6 h. The resulting yellow 
|precipitate was collected by filtration then recrystallized from methanol to give 1-benzyl-2-methylthioquino-
|linium iodide (5, 0.57 g, 72%). Reactions of 8 with 4b, c were carried out under similar conditions to give 2-
|ethylthioquinolinium iodide (9b, 100%) and 1-methyl-2-isopropyloquino-
|linium iodide (9c, 80%), respectively.

5. Yellow crystalline powder (methanol), mp 109—110 °C. IR (CHCl3) 
|cm⁻¹: 1597, 770, 753. 1H-NMR (DMSO-d₆) δ: 3.03 (3H, s, Me), 6.28 (2H, s, CH₂), 7.23 (2H, m, H-Ph), 7.36—7.42 (7H, m, H-Ph), 7.92 (1H, dd, J=0.6, 7.8, 8.4 Hz, H-aromatic), 8.11 (1H, dd, J=1.5, 7.8, 9.1 Hz, H-aromatic), 8.20 (1H, d, J=9.0 Hz, H-3), 8.30 (1H, dd, J=0.6, 9.1, H-aromatic), 8.42 (1H, dd, J=1.5, 8.4, H-aromatic), 4.90 (1H, d, J=9.0 Hz, H-4). 13C-NMR (CDCl3) δ: 15.88, 54.55, 117.68, 120.75, 127.72, 127.89, 128.94, 132.87 (C2), 131.22, 132.12, 133.46, 134.90, 140.55, 185.43. MS m/z: 251 (M⁺), 218, 91. HR-MS Calcd for C₂₄H₂₃N₂O, 251.0769. Found: 251.0750.

**General Procedure for the Syntheses of 1-Alkyl-2-alkylthioquinolino-
|lum Iodides (5, 9b, c)** A benzene solution of 3 (0.5 g, 2 mmol) and
7e: Yellow plates (methanol), mp 171–172°C. IR (KBr cm⁻¹): 2817, 1618, 164, 284, 750, 736. ¹H-NMR (CDCl₃): δ = 3.80 (3H, s, OMe), 5.70 (2H, s, CH₃), 6.94 (2H, d, J = 6.6 Hz, H aromatic), 7.19–7.32 (4H, m, H aromatic), 7.41–7.42 (2H, m, H aromatic), 7.60 (1H, d, J = 7.7 Hz, H aromatic), 7.74 (1H, d, J = 9.5 Hz, H-4), 8.28 (1H, d, J = 9.5 Hz, H-3). ¹³C-NMR (CDCl₃): δ = 51.69, 58.27, 101.44, 113.70, 119.17, 118.91, 123.89, 123.95, 124.59, 125.45, 127.39, 128.51, 128.60, 128.63, 129.08 (C2), 132.75, 133.31, 138.47, 166.90, 192.12. MS m/z: 343 (M⁺), 301, 286. HR-MS-Calcd for C₁₂H₁₀NO, 329.1416. Found: 329.1398.

7f: Yellow needles (acetone), mp 270–275°C. IR (KBr cm⁻¹): 1620, 1566, 757, 718. ¹H-NMR (CDCl₃): δ = 1.97–2.16 (2H, m, CH₂), 2.48–2.57 (4H, m, COCH₂), 5.92 (2H, s, NCH₂), 6.86 (2H, dd, J = 1.6, 6.9 Hz, H-Ph), 7.13–7.23 (2H, m, H-Ph), 7.50 (1H, d, J = 9.5 Hz, H-5). ¹³C-NMR (CDCl₃): δ = 28.64, 51.60, 100.51, 115.92, 117.77, 118.91, 123.89, 123.95, 124.59, 125.45, 127.39, 128.51, 128.60, 128.63, 129.08 (C2), 132.75, 133.31, 138.47, 166.90, 192.12. MS m/z: 343 (M⁺), 301, 286. HR-MS-Calcd for C₁₂H₁₀NO, 329.1416. Found: 329.1398.