## 2-ARYL-4-QUINOLONE SYNTHESIS USING THE THERMAL REARRANGEMENT OF IMINOCYCLOBUTENONES

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**Abstract** – 2-Aryl-4-quinolone synthesis is developed using the thermal rearrangement of iminocyclobutenones formed by a conjugate addition reaction of ketene silyl acetals to alkynyl imines.

Since the discovery of nalidixic acid as an antimicrobial agent in 1962, several 4-quinolone derivatives have been investigated as a chemotherapeutic agent. While 4-quinolone derivatives possessing a 3-carboxy group such as norfloxacin, ciprofloxacin, and levofloxacin have been introduced (Scheme 1),<sup>1</sup> 2-aryl-4-quinolones are also significant biologically active compounds because of antimitotic, antiplatelet, and antiviral activities. Therefore, numerous methods for the synthesis of 2-aryl-4-quinolone derivatives have been reported.<sup>2</sup>



Scheme 1. 4-Quinolone Antimicrobial Agents

Alkynyl imines are some of the most useful nitrogen-containing starting materials and extensively used in the synthesis of nitrogen-containing compounds including heterocycles.<sup>3</sup> We have been interested in the reactivity at the  $\beta$ -position of alkynyl imines as a Michael acceptor and developed efficient synthetic methods for several nitrogen containing heterocycles such as 2-pyridones,<sup>4</sup> bicyclo-pyridones,<sup>5</sup> iminopyridines,<sup>6</sup> and aminopyridines.<sup>6</sup> During these investigations, we have found that aluminum chloride promoted conjugate addition reactions of alkynyl imines **1** with ketene silyl acetals **2** proceed to give the iminocyclobutenones **3** in good yields. Furthermore, it has been also developed that

This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

chemoselective reduction of iminocyclobutenones **3** proceeds to give the aminocyclobutenones **4** in high yields, and the subsequent thermal rearrangement of aminocyclobutenone **4** in the presence of an appropriate amine affords either *cis*- or *trans*- $\beta$ -lactams **7** in good yields and with high diastereoselectivities (Scheme 2).<sup>7</sup> We propose a plausible reaction mechanism of the thermal rearrangement of aminocyclobutenones **4** via aminoketene **5**, which is considered to be one of the intermediates in the Kinugasa reaction.<sup>8</sup> Aminoketene **5** would be generated by ring opening reaction of aminocyclobutenone **4** and undergoes a cyclization to give the enol **6**. Protonation of the enol **6** and/or concomitant epimerization would occur in the presence of an appropriate amine to afford either *cis*- or *trans*- $\beta$ -lactams **7** with high diastereoselectivities.



Scheme 2. Diastereoselective Synthesis of  $\beta$ -Lactams 7 Using the Thermal Rearrangement of Aminocyclobutenones 4



Scheme 3. 2-Aryl-4-quinolone 10 Synthesis Using the Thermal Rearrangement of Iminocyclobutenones 3

We next envisioned that a ring opening reaction of iminocyclobutenone **3** followed by a cyclization of iminoketene **8'** would give 4-quinolone **10** via an intermediate **9** (Scheme 3). Although several 4-quinolone syntheses via iminoketene intermediates have already been reported, there still remain some drawbacks such as a limited substrate scope and/or forcing cyclization conditions at high temperatures.<sup>9</sup> Herein, this paper describes the 2-aryl-4-quinolone synthesis using the thermal rearrangement of iminocyclobutenones.<sup>10</sup>

OMe  $R^1$ toluene, reflux, time ОМе 3 10  $\mathbf{R}^2$  $\mathbf{R}^{3}$ 3  $\mathbf{R}^1$ 10 Time (h) Yield (%) Entry 94 1 3a Ph 2-thienyl Me 10a 3.0 2 Ph 10a 2.0 84 3a 2-thienyl Me 3 3a Ph 2-thienyl Me 10a 1.0 74 4 2-thienyl 10a 3a Ph Me 0.5 17 5 Ph **3b** Ph Me 10b 3.0 95 6 3c Ph 2-furyl Me 10c 3.0 91 7 Ph 2-naphthyl Me 10d 81 **3d** 3.0 8 3e 2-thienyl 2-naphthyl **10e** 3.0 76 Me 9 3f 2-naphthyl Ph **10f** 3.0 87 Me 10 2-thienyl Ph 3.0 91 Me 10g 3g  $68(29)^b$ 11 3h Ph Ph 10h 5.0 Et  $12^{c}$ Ph Ph 10h 3h Et 5.0 86

Table 1. Synthesis of 4-Quinolones 10 Using the Thermal Rearrangement of Iminocyclobutenones 3

<sup>a</sup>Isolated yield. <sup>b</sup>Yield of the recovered **3h** in parenthesis. <sup>c</sup>Reaction performed in xylenes.

We first examined reaction time in the thermal rearrangement of iminocyclobutenone **3a** in toluene at reflux. When the reaction was carried out for 3 h, the desired 4-quinolone **4a** was obtained in 94% yield (Table 1, entries 1-4).<sup>11</sup> Several iminocyclobutenones **3b**-h were subjected to the thermal rearrangement conditions. The reaction of diphenylated iminocyclobutenone **3b** gave the 4-quinolone **10b** in 95% yield (entry 5). The reaction of iminocyclobutenone **3c** having a 2-furyl group as a hetero aromatic group also

afforded 4-quinolone **10c** in 91% yield (entry 6). When iminocyclobutenones **3d** and **3e** possessing a 2-naphthyl group at the  $R^2$  moiety were used, both yields slightly decreased probably due to the steric bulkiness (entries 7 and 8). The reactions of the iminocyclobutenones **3f** and **3g** possessing a 2-thienyl or a 2-naphthyl group at the  $R^1$  moiety gave 4-quinolones **10e** and **10f** in high yields, respectively (entries 9 and 10). When the iminocyclobutenone **3h** having an ethyl group at the  $R^3$  moiety was carried out in toluene at reflux for 5 h, 4-quinolone **10h** was obtained in 68% yield along with the recovered iminocyclobutenone **3h** in 29% yield (entry 11). The reaction of **3h** was next carried out in xylenes at reflux for 5 h to consume the remaining iminocyclobutenone **3h**. The reaction proceeded to reach completion to afford 4-quinolone **10h** in 86% yield (entry 12).

We next examined the effects of the substituents on a phenyl group at the nitrogen atom, and Table 2 summarizes the results. The reactions of *N*-phenylated iminocyclobutenones **11a** and **11b** gave 4-quinolones **12a** and **12b** in 93% and 98% yields, respectively (entries 1 and 2). When *para*-halophenylated iminocyclobutenones **11c-e** were used, 4-quinolones **12c-e** were obtained in high yields irrespective of the kind of the halogen (entries 3-5). The reaction of *ortho*-methoxyphenylated iminocyclobutenone **11f** gave 4-quinolone **12f** in quantitatively yield (entry 6), whereas use of 2,4-disubstituted iminocyclobutenone **11g** decreased the yield (entry 7).

| Table 2. Ef | ffects of o | ortho, para- | Substituents | of Pheny | l Group | ps at the l | Nitrogen A | Atom |
|-------------|-------------|--------------|--------------|----------|---------|-------------|------------|------|
|             |             |              |              |          |         |             | <u> </u>   |      |

|       | Ph R <sup>1</sup> | $\mathbb{R}^{\mathbb{R}^2} - \mathbb{R}^3$ | oluene, reflux, 3 | $h$ $Ph$ $R^1$ | $ \begin{array}{c} 0\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$ |                |
|-------|-------------------|--|-------------------|----------------|---|----------------|
| Entry | 11                | R <sup>1</sup>                             | R <sup>2</sup>    | R <sup>3</sup> | 12  | Yield $(\%)^a$ |
| 1     | 11a               | Ph   | Н                 | Н              | 12a   | 93             |
| 2     | 11b               | 2-thienyl                                  | Н                 | Н              | 12b   | 98             |
| 3     | 11c               | 2-thienyl                                  | Н                 | F              | 12c   | 98             |
| 4     | 11d               | 2-thienyl                                  | Н                 | Br             | 12d   | 89             |
| 5     | 11e               | 2-thienyl                                  | Н                 | Cl             | 12e   | 87             |
| 6     | 11f               | Ph   | OMe               | Н              | 12f   | quant          |
| 7     | 11g               | 2-thienyl                                  | Cl                | OMe            | 12g   | 77             |

<sup>*a*</sup>Isolated yield.

We next examined the thermal rearrangement of iminocyclobutenones **13** having *meta*-substituents on a phenyl group at the nitrogen atom. These iminocyclobutenones have two reaction sites on the phenyl moiety to form 4-quinolones **14** or **15** (Scheme 4).

Table 3 summarizes the results. The reaction of iminocyclobutenones **13a** and **13b** having an electron-withdrawing group such as fluoro or bromo group afforded a mixture of 4-quinolones **14** and **15** in high yields and with a moderate preference of 7-substituted-4-quinolone **14** (entries 1 and 2). On the other hand, use of iminocyclobutenone **13c** having an electron-donating group such as a methyl group gave a mixture of 4-quinolones **14c** and **15c** in high yields and with a slight 5-substituted-4-quinolone **15** selectivity (entry 3). The reason of the reversal of the selectivity is not yet clear at the present stage.



Scheme 4. Thermal Rearrangement of Iminocyclobutenones 13

Table 3. Effects of *meta*-Substituents of Phenyl Groups at the Nitrogen Atom



<sup>a</sup>Isolated yield.

In conclusion, we have developed a 2-aryl-4-quinolone synthesis using the thermal rearrangement of iminocyclobutenones. The present 2-aryl-4-quinolone synthesis is an attractive alternative method because iminocyclobutenones are readily available using a conjugate addition reaction of ketene silyl acetals to alkynyl imines and thermal rearrangements occur under mild reaction conditions to afford the corresponding 2-aryl-4-quinolones in high yields.

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- 10. Iminocyclobutenones were prepared using conjugate addition reactions of alkynyl imines with ketene silyl acetals according to the literature method in reference 7.
- Typical procedure (Table 1, entry 1): A solution of iminocyclobutenone 3a (38.7 mg, 0.0999 mmol) in toluene (1.0 mL) was stirred at reflux for 3 h. After cooling to room temperature, the solvent was removed in vacuo and then the residue was purified by preparative TLC on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 19/1 as an eluent) to give 4-quinolone 10a (36.2 mg, 94%). Yellow white solid; Mp 279-280 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>-(CD<sub>3</sub>)<sub>2</sub>SO (9:1)) δ 1.72 (s, 3H), 1.80 (s, 3H), 3.86 (s, 3H), 6.99-7.07 (m, 5H), 7.11 (dd, *J* = 3.1, 5.5 Hz, 1H), 7.19 (dd, *J* = 3.1, 9.2 Hz, 1H), 7.40 (d, *J* = 3.1 Hz, 1H), 7.58 (d, *J* = 5.5 Hz, 1H), 7.62 (d, *J* = 3.1 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 11.4 (s, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>-(CD<sub>3</sub>)<sub>2</sub>SO) δ 20.1, 21.1, 53.8, 102.9, 118.7, 120.3, 120.8, 124.0, 124.0, 125.1, 125.6, 127.4, 127.6, 128.0, 133.2, 133.9, 134.2, 139.2, 140.8, 154.2, 173.8; IR (KBr) 3160, 3060, 2997, 2966, 2927, 2848, 1614, 1571, 1540, 1491, 1436, 1369, 1342, 1291, 1258, 1228, 1164, 1113, 1029, 1053, 832, 794, 765, 735, 694 cm<sup>-1</sup>; HRMS (EI): Calcd for C<sub>24</sub>H<sub>21</sub>NO<sub>2</sub>S (M)<sup>+</sup> 387.1293, found 387.1308.