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

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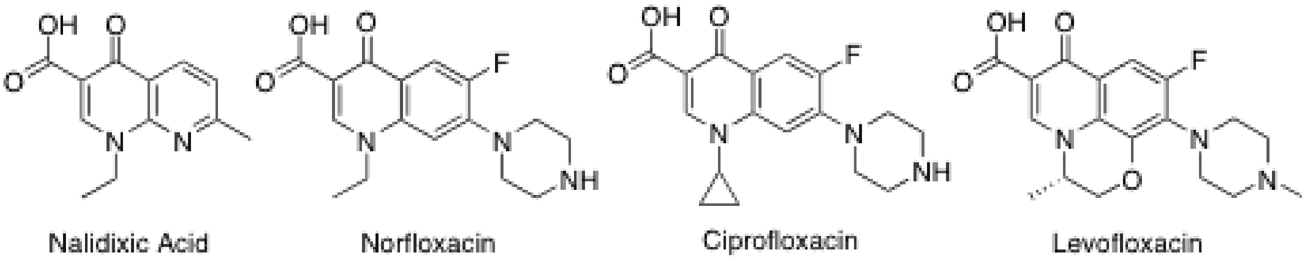
Abstract – 2-Aryl-4-quinolone synthesis is developed using the thermal rearrangement of iminocyclobutenones formed by a conjugate addition reaction of ketene silyl acetals to alkynyl imines.

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),[1] 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.[2]

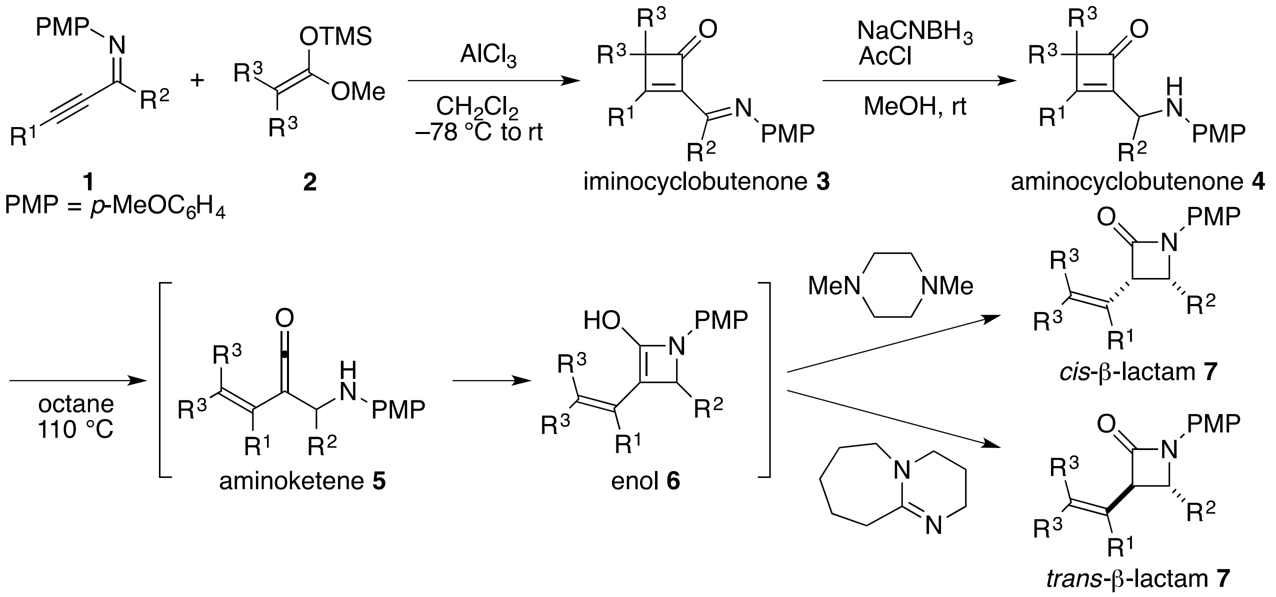


Scheme 1. 4-Quinolone Antimicrobial Agents

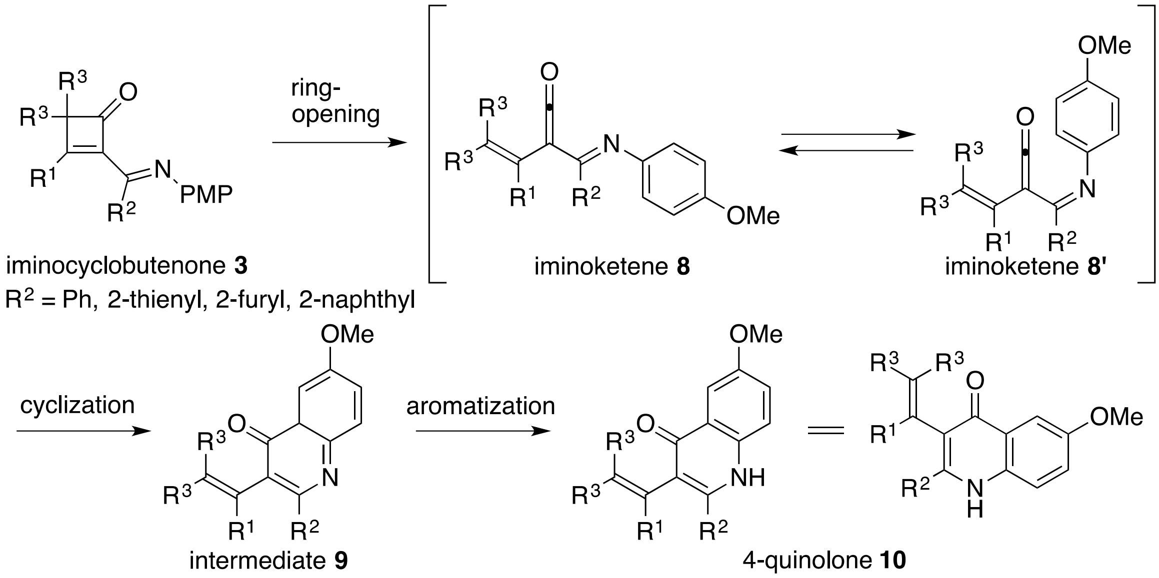
Alkynyl imines are some of the most useful nitrogen-containing starting materials and extensively used in the synthesis of nitrogen-containing compounds including heterocycles.[3] We have been interested in the reactivity at the β-position of alkynyl imines as a Michael acceptor and developed efficient synthetic methods for several nitrogen containing heterocycles such as 2-pyridones,[4] bicyclo-pyridones,[5] iminopyridines,[6] and aminopyridines.[6] 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*-β-lactams **7** in good yields and with high diastereoselectivities (Scheme 2).[7] 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.[8] 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*-β-lactams **7** with high diastereoselectivities.



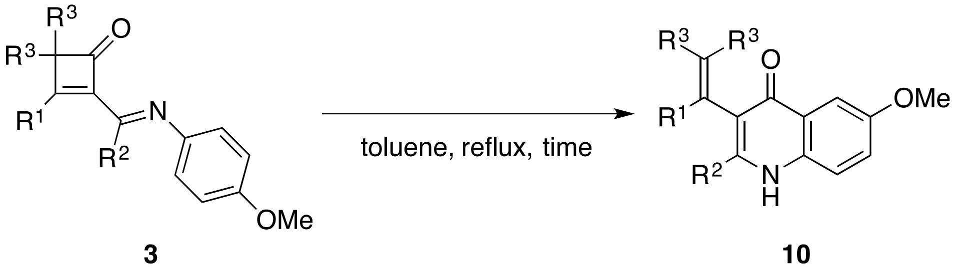
Scheme 2. Diastereoselective Synthesis of β-Lactams **7** Using the Thermal Rearrangement of Aminocyclobutenones **4**



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.[9] Herein, this paper describes the 2-aryl-4-quinolone synthesis using the thermal rearrangement of iminocyclobutenones.[10]

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



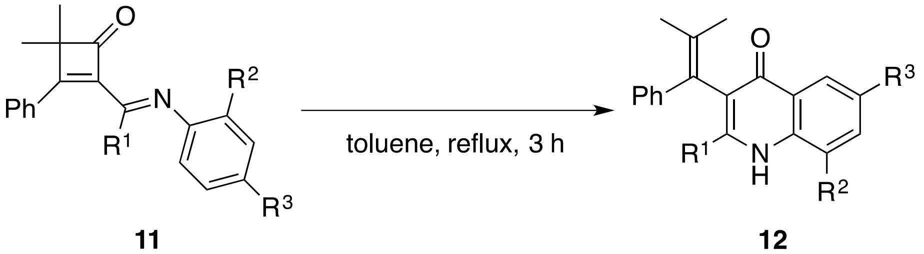
Entry	3	R^1	R^2	R^3	10	Time (h)	Yield (%)^a
1	**3a**	Ph	2-thienyl	Me	**10a**	3.0	94
2	**3a**	Ph	2-thienyl	Me	**10a**	2.0	84
3	**3a**	Ph	2-thienyl	Me	**10a**	1.0	74
4	**3a**	Ph	2-thienyl	Me	**10a**	0.5	17
5	**3b**	Ph	Ph	Me	**10b**	3.0	95
6	**3c**	Ph	2-furyl	Me	**10c**	3.0	91
7	**3d**	Ph	2-naphthyl	Me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

^{a}Isolated yield. ^{b}Yield of the recovered **3h** in parenthesis. ^{c}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).[11] 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. Effects of *ortho*, *para*-Substituents of Phenyl Groups at the Nitrogen Atom

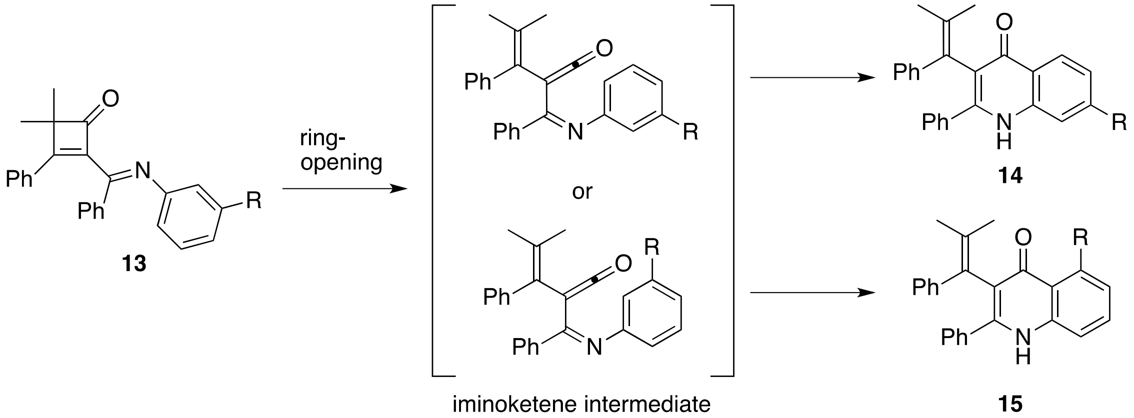


Entry	**11**	**R^1**	**R^2**	**R^3**	**12**	Yield (%)^a
1	**11a**	Ph	H	H	**12a**	93
2	**11b**	2-thienyl	H	H	**12b**	98
3	**11c**	2-thienyl	H	F	**12c**	98
4	**11d**	2-thienyl	H	Br	**12d**	89
5	**11e**	2-thienyl	H	Cl	**12e**	87
6	**11f**	Ph	OMe	H	**12f**	quant
7	**11g**	2-thienyl	Cl	OMe	**12g**	77

^{a}Isolated yield.

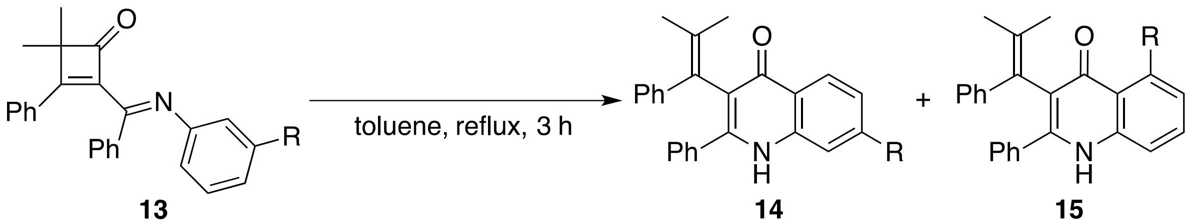
We next examined the thermal rearrangement of iminocyclobutenones **13** having *meta*-substituents on a phenyl group at the nitrogen atom. These iminocyclobutenones have two reaction sites on the phenyl moiety to form 4-quinolones **14** or **15** (Scheme 4).

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



entry	13	R	Yield (%)[a] 14	15
1	**13a**	F	74 (**14a**)	24 (**15a**)
2	**13b**	Br	69 (**14b**)	29 (**15b**)
3	**13c**	Me	38 (**14c**)	57 (**15c**)

[a] 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.

ACKNOWLEDGEMENTS

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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.

11. **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_2Cl_2/MeOH = 19/1 as an eluent) to give 4-quinolone **10a** (36.2 mg, 94%). Yellow white solid; Mp 279-280 °C; ^{1}H NMR (500 MHz, $CDCl_3$-$(CD_3)_2SO$ (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); ^{13}C NMR (126 MHz, $CDCl_3$-$(CD_3)_2SO$) 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^{-1}; HRMS (EI): Calcd for $C_{24}H_{21}NO_2S$ $(M)^+$ 387.1293, found 387.1308.