Regio- and Stereoselective Addition of Ketene Silyl Acetals to Quinolinium Salts by Way of an Intramolecular C=O···Qu$^+$ or C=S···Qu$^+$ Interaction

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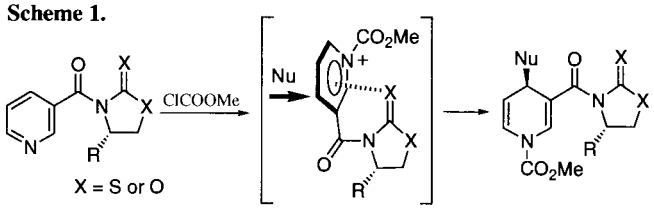
Chiral 1,4-dihydroquinolines were synthesized by the addition of ketene silyl acetals to quinolinium salts. The stereoselectivity was associated with the intramolecular interaction between the quinolinium and the carbonyl or thiocarbonyl groups, which was revealed by ^{1}H NMR spectroscopy and X-ray analysis.

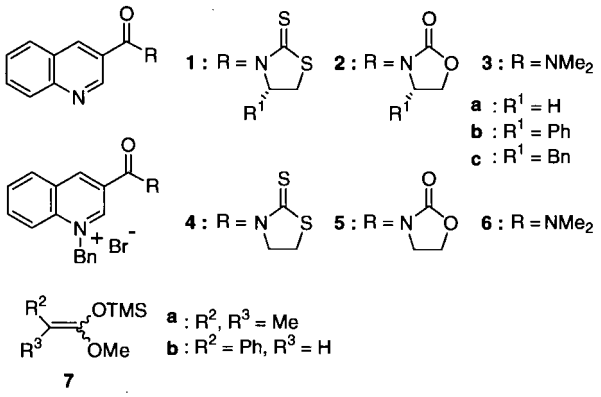
1,4-Dihydroquinolines have received great interest as NADH models[1] and as the precursor of 1,2,3,4-tetrahydroquinolines[2] that have a variety of biological activities. Although faceselective nucleophilic addition to pyridinium salts is a convenient method for the synthesis of chiral 1,4-dihydropyridines,[3] little has been known about applicability of the method to quinolinium salts[4] due to significant difference in the reactivity toward nucleophiles between a pyridinium and a quinolinium salt. Recently, Mangeney and his coworkers have reported[5] that the addition of organocopper reagents to a quinolinium salt gave 1,4-dihydroquinolines with unexpectedly lower regio- and stereoselectivities, which is in contrast to the high selectivities in the case of pyridinium derivatives[6].

Scheme 1.



Previously, we have reported regio- and stereoselective addition of organometallic reagents to the pyridinium salts possessing 1,3-thiazolidine-2-thiones,[7] where an intramolecular C=S···Py$^+$ interaction[8] plays a key role in the resulting stereoselectivity (Scheme 1). Here we report that addition of ketene silyl acetals to quinolinium salts bearing chiral auxiliaries afforded 1,4-dihydroquinolines via a C=S···Qu$^+$ or C=O···Qu$^+$ complex as a key intermediate.

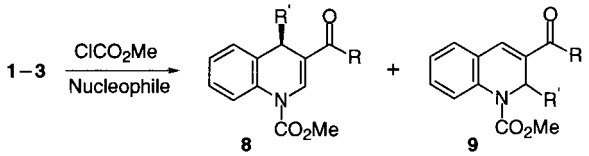
We employed 3-quinolinecarboxamides **1** and **2** possessing 1,3-thiazolidine-2-thiones and 1,3-oxazolidine-2-ones, respectively, and amide **3** as a standard. Attempts at the addition of PhCu to **1** and **2** under the reported conditions[5] resulted in no desired products. Then, we selected ketene silyl acetals as nucleophiles because they are scarcely used for the addition to quinolinium salts, although the reactions with pyridinium[9] and isoquinolinium[4b,10] salts have extensively been studied. 3-Qunolinecarboxamides **1a–1c**, **2a–2b** and **3**, activated by methyl chloroformate were allowed to react with ketene silyl acetals at r.t. for 6 h to give 1,4-adducts **8** and 1,2-adducts **9**. The results are summarized in Table 1. Addition of **7a** to **1a** and **2a** yielded **8a** and **8b** as major products with a small amount of **9a** and **9b**, respectively. Their regioselectivities were higher than in the case of **3**. The



regioisomer ratio was easily determined by ^{1}H NMR analysis based on the chemical shifts of H2 and H4 of **8** and **9**; for example, H2 and H4 of **8a** appeared at δ 8.03 and 4.25, whereas those of **9a** appeared at δ 5.85 and 7.37, respectively.

When using **1b** and **1c** possessing chiral auxiliaries, the 1,4-adducts **8d** and **8e** were produced with good regio- and stereoselectivities. On the other hand, the stereoselectivity for **9d** and **9e** was very low, the ratio of which being about 2 : 1. X-ray analysis of **8d** proved the absolute configuration of the newly produced chiral center to be *R*.[11] The configuration of the other 1,4-adducts is tentatively assigned by analogy with **8d**.

Table 1. Nucleophilic addition of ketene silyl acetals to **1–3**[a]



R' = $C(CH_3)_2CO_2Me$ or $CHPhCO_2Me$

Amide	Nucleophile[b]	Products	Yield[c] /%	Ratio **8** : **9**	de of **8**[d] /%
1a	**7a**	**8a**, **9a**	71 (99)	95 : 5	—
2a	**7a**	**8b**, **9b**	73 (88)	90 : 10	—
3	**7a**	**8c**, **9c**	68 (83)	82 : 18	—
1b	**7a**	**8d**, **9d**	57 (92)	96 : 4	74 (*R*)
1c	**7a**	**8e**, **9e**	75 (97)	92 : 8	82 (*R*)
1b	**7b**[e]	**8g**, **9g**	68 (98)	95 : 5	90 (*S*)[f]
2b	**7a**	**8f**, **9f**	63 (99)	93 : 7	44 (*R*)
2b	**7b**[e]	**8h**, **9h**	86 (99)	99 : 1	64 (*S*)[g]

[a]CH_2Cl_2 was used as a solvent. [b]Two equiv of ketene silyl acetal was used unless otherwise noted. [c]Isolated yield. Conversion yields are indicated in parentheses. [d]Absolute configuration was indicated in parentheses. [e]Eight equiv of ketene silyl acetal was used. [f]The major diastereomer is a 84:16 mixture of syn-anti isomers. [g]The major diastereomer is a 92:8 mixture of syn-anti isomers.

Excellent regio- and stereoselectivities were obtained when using **7b** as a nucleophile. The diastereomer ratio with respect to the C4 of **8g** is 95 : 5, and the major isomer of which is an 86 : 14 mixture of syn-anti isomers based on the another chiral center next to C4, which were determined by ^{1}H NMR spectrum. These good selectivities would be attributable to intramolecular interaction between the quinolinium and the thiocarbonyl or carbonyl group, similar to our previous observations in the addition to pyridinium salts.[7] The addition to **2b** having 1,3-oxazolidine-2-one group gave similar results, but the stereoselectivities were lower than those in the case of **1b**.

Table 2. ^{1}H NMR chemical shifts of **1a**, **2a** and **3**–**6** and the Δδ values (ppm)[a]

Compd	δ_{H2}	δ_{H4}	$\Delta\delta_{H2}$[b]	$\Delta\delta_{H4}$[b]
1a	9.10	8.50	0.12	0.24
2a	9.11	8.51	0.13	0.25
3	8.98	8.26	—	—
4	11.69	9.07	1.54	0.02
5	11.98	9.17	1.83	0.12
6	10.15	9.05	—	—

[a]270 MHz in $CDCl_3$. [b]Δδ = δ1a or δ2a−δ3 for **1a** and **2a**, and Δδ = δ4 or δ5−δ6 for **4** and **5**.

To elucidate the postulated intramolecular C=S···Qu$^+$ and C=O···Qu$^+$ interactions, ^{1}H NMR studies of **1a**, **2a** and **3** and their benzyl salts **4**–**6**, and X-ray analysis of **5** were carried out. Table 2 shows the δ_{H2} and δ_{H4} values and Δδ values that represent the difference from standards **3** or **6**. Remarkable is that the $\Delta\delta_{H2}$ of **4** and **5** are significantly larger than those of **1a** and **2a**. On the other hand, all the $\Delta\delta_{H4}$ values are very small. These results are comparable to our previous structural studies of pyridinium salts,[8] where H2 of the pyridinium significantly shifted to downfield, suggesting the intramolecular interaction of the C=S···Qu$^+$ and C=O···Qu$^+$.

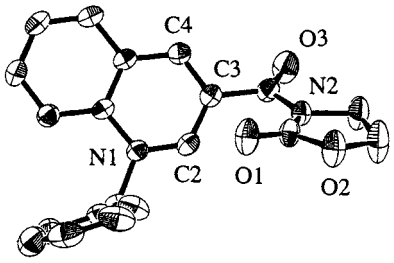


Figure 1. X-ray structure for **5**. The thermal ellipsoids are set at 50 % probability level. The hydrogen and bromine atoms are omitted for clarity. Selected interatomic distances (Å): O1···N1 3.607, O1···C2 2.731, O1···C3 2.856, O1···C4 3.294.

The X-ray structure of benzyl salt **5** strongly supports the existence of an intramolecular interaction between the quinolinium ring and the carbonyl group (Figure 1).[12] The carbonyl oxygen of the oxazolidinone moiety is close to C2 of the quinolinium ring; the 2.731 Å of the distance of which is much shorter than the sum of van der Waals radii of the carbon and oxygen atoms (3.22 Å). This structural feature of **5** is in agreement with that of a pyridinium salt having a thiazolidine-2-thione moiety.[8] The close contact of the O1 and C2 atoms can reasonably explain the unusual downfield shifts of H2 because it will make H2 lie in a deshielding area of the carbonyl group.

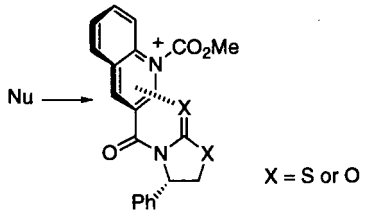


Figure 2. Working model for the faceselective addition of nucleophile to the C=X···Qu$^+$ complex.

A working model for the present stereoselective reactions is proposed as follows: Conversion of quinoline to quinolinium salt will cause an attractive intramolecular C=S···Qu$^+$ or C=O···Qu$^+$ interaction. The shielding of one side of the quinolinium face[13] enables nucleophiles to attack from the opposite side of the thiocarbonyl or carbonyl group, which would result in the chiral 1,4-dihydroquinolines (Figure 2).

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References and Notes

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11 Crystal data for **8d**: $C_{26}H_{26}N_2O_5S_2$, M_r = 510.61, monoclinic, space group $P2_1$, a = 11.0980(10), b = 22.154(3), c = 10.340(2) Å, β = 89.999(10)°, V = 2542.4(6) Å^3, T = 293 K, Z = 4, D_c = 1.334 g cm^{-3}, 6511 reflections measured (2θ < 136.0°), 4764 unique data (R_{int} = 0.0372), 4752 data with $I > 2\sigma(I)$, 632 refined parameters, Final $R_1(F^2)$ = 0.0533, wR_2 = 0.1878.
12 Crystal data for **5a** : $C_{20}H_{17}N_2O_3Br$, M = 413.27, monoclinic, $P2_1/n$; a = 14.024(2), b = 10.5067(14), c = 12.2905(11) Å, β = 102.578(8)°, V = 1767.6(3) Å^3, T = 293 K, Z = 4, D_c = 1.553 g cm^{-3}, 5416 reflections measured (2θ < 136.0°), 3227 unique data (R_{int} = 0.0495), 3220 data with $I > 2\sigma(I)$, 236 refined parameters, Final $R_1(F^2)$ = 0.0421, wR_2 = 0.1434.
13 RHF/3-21G* calculations for the intermediary *N*-methoxycarbonyl salt of **2b** predict that the conformer shown in Figure 2 is more stable than the conformer of which opposite face is shielded about 6 kcal/mol.