# ADDITION OF TRIMETHYLSILYL ENOL ETHERS TO QUINOLINIUM SALTS: A FACILE SYNTHESIS OF METHYL 2-(2-OXOALKYL)-1,2-DIHYDROQUINOLINE-1-CARBOXYLATES AND THEIR CYCLIZATION

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Abstract— The addition of trimethylsilyl enol ethers (2) to 1-alkoxycarbonylquinolinium salts (1) afforded a mixture of 1-alkoxycarbonyl-2-(2-oxoalkyl or alkoxycarbonyl)-1,2-dihydroquinolines (3) and the corresponding 1,4-dihydroquinolines (4) in high total yield (85-99%). The regioselectivity ( 3/4 = 2.3-19 ) was examined carefully. The easily separated main products (3) were treated with sodium hydride to give the corresponding benzo[c]quinolizine derivatives (5).

It is well known that the reaction of 1-acylquinolinium salts with cyanide ion affords 1-acyl-2-cyano-1,2-dihydroquinolines, so-called Reissert compounds, and they are widely used in organic synthesis.[1] But ketones do not condense effectively with quinoline in the presence of acyl halides, and only under severe conditions, 2-keto derivatives of 1-acyl-1,2-dihydroquinoline are obtained in low yield.[2] As a further extension of our research on the regioselective introduction of substituents into heteroaromatics,[3] this paper describes an efficient method for introduction of 2-oxoalkyl groups into quinoline by the reaction of 1-alkoxycarbonylquinolinium salts (1) with trimethylsilyl enol ethers (2) prepared from ketones and esters.

First we examined the regioselectivity of this reaction with regard to the structure of the quaternizing agent by use of trimethylsilyl enol ethers of acetophenone (2b) and 3-pentanone (2d). The results are summarized in Table (Entry 1-6).

When methyl chloroformate was used, the ratio of attack at the 2-position was highest but almost the same selectivity was observed with ethyl chloroformate. The very high total yield and good selectivity encouraged us to examine the

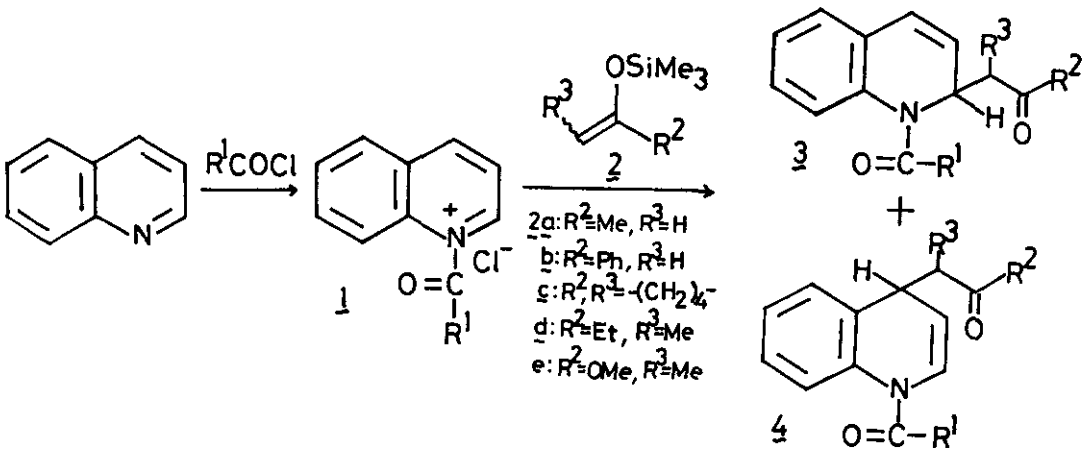



Table: Reaction of Quinolinium Salts with Trimethylsilyl Enol Ethers

| Entry | Compds 3 and 4 | $R^1$ | $R^2$ | $R^3$ | Yield(%)[a] 3 | Yield(%)[a] 4 | Ratio 3/4 | React. Cond.[b] Temp/°C | Time/h |
|---|---|---|---|---|---|---|---|---|---|
| 1 | a | Me | Ph | H | 51 | 12 | 4.3 | 0 | 3 |
| 2 | b | $CCl_3CH_2O$ | Ph | H | 69 | 8 | 8.6 | 0[c] | 3 |
| 3 | c | EtO | Ph | H | 78 | 8 | 9.8 | 0 | 3 |
| 4 | d | MeO | Ph | H | 78 | 7 | 11.3 | -20 | 10 |
| 5 | e | EtO | Et | Me | 79[d] | 18[d] | 4.3 | -20 | 10 |
| 6 | f | MeO | Et | Me | 81[d] | 18[d] | 4.6 | -20 | 10 |
| 7 | g | MeO | Me | H | 87 | 5 | 19.0 | -20 | 10 |
| 8 | h | MeO | $-(CH_2)_4-$ | | 85[d] | 12[d] | 7.1 | -20 | 11 |
| 9 | i | MeO | MeO | Me | 65[d] | 28[d] | 2.3 | -20 | 5 |

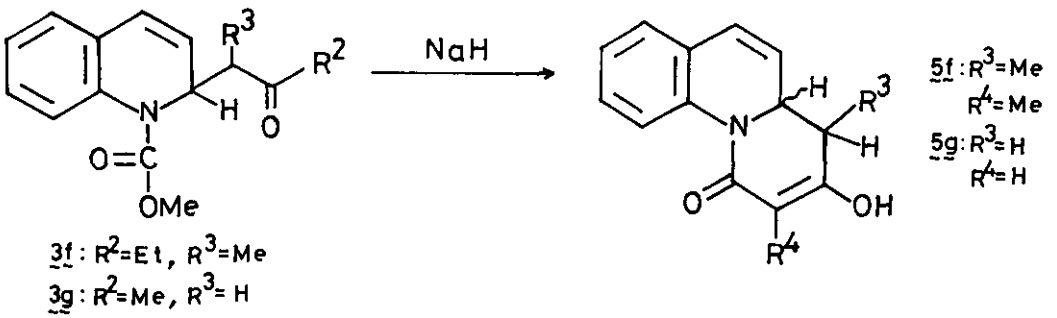
a) Isolated yield by flash column chromatography ($SiO_2$, hexane:$CH_3CO_2Et$=8:2-9:1). b) Acetonitrile was used as a solvent. c) Dichloromethane was used as a solvent. d) A mixture of diastereomers.

effect of the structure of silyl enol ethers using methyl chloroformate as a quaternizing agent. As is evident from the Table (Entry 4,6,7-9), when $R^2$, $R^3$ disubstituted trimethylsilyl enol ethers (2c,2d) and ketene silyl acetal (2e) were employed, the selectivity was lower than that with 2a and 2b. Such regioselectivity can be understood by considering the softness of the silyl enol ethers and quinolinium salts. The ratio of attack at 4-position increased with $R^2$, $R^3$ disubstituted trimethylsilyl enol ethers and a ketene silyl acetal, which are softer and more electron-donating than 2a and 2b. It is also accepted that

4-position of quinolinium salt is softer than 2-position.[4] The same trend was observed by our previous work on the reaction of pyridinium salts with silyl enol ethers.[5]

Irrespective of the selectivity, 3 and 4 were separated easily by flash column chromatography, therefore, good yields of 3 were at hand in every case. A typical procedure of the reaction is as follows: Quinolinium salt (1, $R^1$=OMe) was prepared in situ from quinoline (0.24 ml, 2 mmol) and methyl chloroformate (0.19 ml, 2.5 mmol) in 5 ml of $CH_3CN$ at -20 °C under an atmosphere of nitrogen. To this solution was added trimethylsilyl enol ether of 3-pentanone (2d, 449 mg, 2.7 mmol) through a syringe and the reaction mixture was stirred for 10 h at -20 °C. The resulting reaction mixture was treated with aq. HCl (ca. 1M, 20 ml), then extracted with $Et_2O$ (20 mlx3). The crude product was subjected to flash column chromatography (hexane:$CH_3CO_2Et$=9:1) and diastereomers of 3f were obtained in 52 and 29 % yields, respectively, and a mixture of diastereomers of 4f (1:1) was obtained in 18 % yield. $^1$H NMR ($CDCl_3$): Major isomer of 3f; δ 0.96 (t,3H,J=7 Hz), 1.03 (d,3H,J=7 Hz), 2.2-2.8 (m,3H), 3.75 (s,3H), 5.24 (dd,1H,J=6, 9 Hz), 6.02 (dd,1H,J=6, 9 Hz), 6.47 (d,1H,J=9 Hz), 6.9-7.7 (m,4H). 4f; δ 0.75-1.15 (m,6H), 2.0-2.9 (m,3H), 3.55 (dd,J=6, 9 Hz)+3.71 (t,J=6 Hz)(1H), 3.88 (s,3H), 5.29 (t, J=6 Hz)+5.37 (t,J=6 Hz)(1H), 6.9-7.4 (m,4H), 7.8-8.1 (m,1H).

Next we effected cyclization of the adduct (3) to afford benzo[c]quinolizine derivative (5). By treatment of 3f and 3g with sodium hydride in refluxing benzene for 15 h under nitrogen, 5f and 5g were obtained in 20 and 39 % yields, respectively. $^1$H NMR showed that these compounds exist in enol form as was observed previously in isoquinoline analogues.[6] $^1$H NMR ($CDCl_3$): 5f; δ 1.38 (d,3H,J=7 Hz), 1.58 (s,3H), 3.10 (dq,1H,J=10, 7 Hz), 4.35 (dt,1H,J=10, 1 Hz), 5.90 (dd,1H,J=9, 1 Hz), 6.56 (dd,1H,J=9, 1 Hz), 7.0-8.0 (m,5H). 5g; 2.87 (d,1H,J=7 Hz), 3.54 (d,1H,J=8 Hz), 4.2-5.0 (m,2H), 5.68 (dd,1H,J=10, 2 Hz), 6.45



(dd,1H,J=10, 2 Hz), 6.9-8.3 (m,5H).

Thus, it was found that the adduct (3) was an effective precursor for cyclization to form the third ring to quinoline skeleton.

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7. Satisfactory IR, NMR, and MS data were obtained for 3, 4, and 5(f,g), and correct elemental analyses (or high resolution MS) were obtained for 3a-3g, 3i, 4a-4f, 4i, and 5f.

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