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REACTION OF TRIMETHYLSILYL ENOL ETHERS WITH ISOQUINOLINIUM SALTS. A FACILE SYNTHESIS OF ETHYL 1-(2-OXOALKYL)-1, 2-DIHYDROISOQUINOLINE-2-CARBOXYLATES AND THEIR CYCLIZATION

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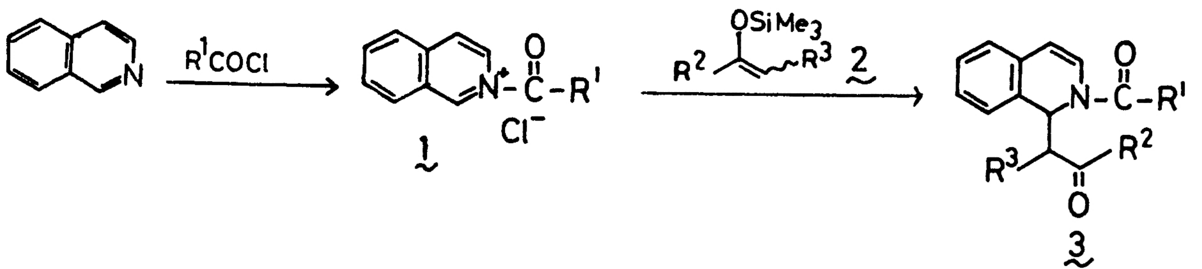
An efficient method is described for the synthesis of ethyl 1-(2-oxoalkyl)-1, 2-dihydroisoquinoline-2-carboxylates by C-C bond formation between 2-ethoxycarbonylisoquinolinium chloride and trimethylsilyl enol ethers. The products were treated with a few bases to afford the corresponding pyrido [2, 1-a] isoquinoline derivatives.

Recently, Yamanaka et al.[1] and Sheinkman et al.[2] reported the reaction of isoquinoline with methyl ketones in the presence of acetic anhydride or benzoyl chloride in order to introduce carbon-substituents having a β-carbonyl group into 1-position of the isoquinoline ring. These attempts are important, but should be improved essentially, because the reaction conditions are drastic and the yields are low. For this purpose, we have most recently described that ethyl 1-(2-oxoalkyl)-1, 2-dihydroisoquinoline-2-carboxylates (**3**) are synthesized efficiently in 64 - 98% yields under mild conditions by the reaction of boron enolates prepared from ketones[3] with isoquinolinium salts (**1**).[4]

This paper describes a more efficient and general method for introduction of a 2-oxoalkyl group into 1-position of isoquinoline in excellent yields by the reaction of **1** with trimethylsilyl enol ethers[5] (**2**) prepared from ketones,[6] aldehydes[6] and esters,[7] because it is still unable to prepare efficiently boron enolates from aldehydes or esters.



First we examined the reaction of 1 (R^1=OEt) with trimethylsilyl enol ether of acetophenone (2a) in ether at room temperature for 3 h. The yield of desired product (3a) was, however, only 40% yield and the original trimethylsilyl enol ether (2a) was recovered in a 58% yield. On the other hand, when the same reaction was attempted in acetonitrile at 0 °C for 1 h, 3a was obtained quantitatively. Thus, acetonitrile was found to be a superior solvent for C-C bond formation for this reaction. Trimethylsilyl enol ethers of ketones and an ester reacted smoothly with 1 to give 3 in quantitative yields. When trimethylsilyl enol ether of an aldehyde (2e) was

Table Syntheses of 1-(2-Oxoalkyl)-1, 2-dihydroisoquinolines (3)

Compound 3 [a]	R^1	R^2	R^3	Yield/% [b]	Reaction Conditions Temperature/°C	 Time/h
3a	OEt	Ph	H	98	0	1.0
3b	OEt	C_2H_5	CH_3	92[c]	0	1.5
3b	OEt	C_2H_5	CH_3	98[c]	r.t.	1.5
3b'	CH_3	C_2H_5	CH_3	98[c]	r.t.	1.5
3c	OEt	$-(CH_2)_4-$		88[c]	0	1.5
3d	OEt	OCH_3	Ph	94[c]	0	0.5
3d'	CH_3	OCH_3	Ph	97[c]	0	0.5
3e	OEt	H	$PhCH_2$	46[c]	0	1.5
3e	OEt	H	$PhCH_2$	50[c]	r.t.	5.0
3e	OEt	H	$PhCH_2$	63[c]	30 - 40	2.5

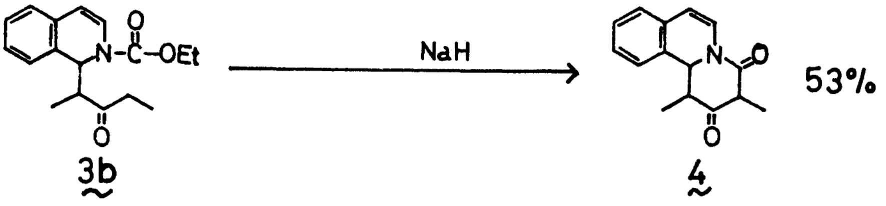
a) Satisfactory IR, NMR, MS, and elemental analyses were obtained for these compounds.

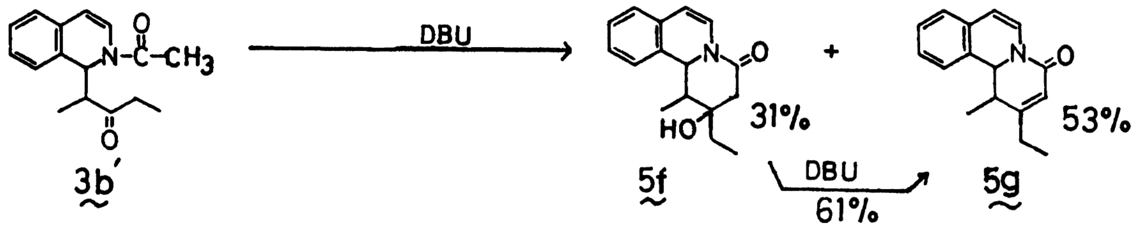
b) Isolated yield by flash column chromatography (SiO_2, hexane-ethyl acetate).

c) A mixture of diastereoisomers. The ratio could not be determined because of difficulty in their quantitative separation by flash column chromatography and instability of the products under the conditions of GC analysis.

used, however, **3e** was obtained in only ca. 60% yield probably due to lower nucleophilicity of **2e**. Some of the results are summarized in the Table.

A typical procedure of the reaction is as follows : Isoquinolinium salt (**1**, R^1=OEt) was prepared *in situ* from isoquinoline (0.387 g, 3 mmol) and ethyl chloroformate (0.326 g, 3 mmol) in 10 ml of CH_3CN at 0 °C. To this solution was added trimethylsilyl enol ether of acetophenone (**2a**, 0.576 g, 3 mmol) through a syringe under an atmosphere of nitrogen and the reaction mixture was stirred for 1 h at 0 °C. The resulting reaction mixture was treated with H_2O (20 ml), then the product was extracted with Et_2O (10 ml × 3). After drying the ether layer over anhydrous $MgSO_4$, the solvent was evaporated *in vacuo*. The crude product was purified on flash column chromatography with hexane : CH_3COOEt = 9 : 1 as eluent to afford **3a** (0.945 g) in a 98% yield.[4]





Next, we prepared cyclic compounds (**4** and **5**) to demonstrate synthetic application of this reaction. In the previous paper, we have already reported that **3b** was cyclized to give **4** in the presence of EtONa.[4] Also **4** was obtained in a 53% yield when **3b** was treated with NaH in refluxing benzene for 2.5 h. In a similar fashion, treatment of **3b'** with 2.4 equivalents of NaOEt in refluxing Et_2O for 4 h gave the expected product (**5g**) in a 23% yield accompanied with a decomposition product, *i.e.*, isoquinoline (31% yield). **5g** :[8] m.p. 106 - 108 °C (recrystallized from petroleum ether). ^{1}H NMR ($CDCl_3$) : δ 1.05 (d, 3H, J=7 Hz), 1.17 (t, 3H, J=7 Hz), 2.35 (dq, 2H, J=0.8, 7 Hz), 2.75 (dq, 1H, J=3, 7 Hz), 5.47 (d, 1H, J=3 Hz), 5.55 (d, 1H, J=8 Hz), 5.80 (t, 1H, J=0.8 Hz), 6.75 - 7.50 (m, 4H), 7.35 (d, 1H, J=8 Hz). IR (KBr) : 1670, 1630 cm^{-1}. MS (m/e) : 239 (M$^+$, 23%), 130 (100).

On the other hand, when **3b**' was treated with 3 equivalents of DBU in dimethylformamide at 100 °C for 4 h, **5f** and **5g** were obtained in 31 and 53% yields, respectively. **5f**:8) m.p. 204 - 206 °C (recrystallized from ethyl acetate-hexane). ^{1}H NMR (CD_3OD) : δ 1.02 (t, 3H, J=7.5 Hz), 1.30 (d, 3H, J=6 Hz), 1.75 (q, 2H, J=7.5 Hz), 2.48 (dq, 1H, J=11, 6 Hz), 2.52 (s, 2H), 4.20 (d, 1H, J=11 Hz), 4.51 (s, 1H), 6.26 (d, 1H, J=7.5 Hz), 7.0 - 7.4 (m, 5H). IR (KBr) : 3370, 1640, 1625 cm^{-1}. MS (m/e): 257 (M$^+$, 29%), 143 (100), 130 (92), 171 (58).

5f was converted into **5g** in a 61% yield by heating with DBU (DMF, 100 °C, 1.5 h).

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

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8) Correct elemental analyses were obtained for **5f** and **5g**.

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