A New Method for the Preparation of 2-Methyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines

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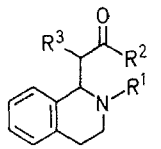
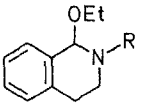
1-Ethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) has been prepared by the reaction of 2-methyl-3,4-dihydroisoquinolinium bromide (**7a**) with sodium ethoxide. A convenient method for the preparation of 2-methyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines **2** has been developed by utilizing the nucleophilic reaction of active methylene compounds with **3a**.

1-(2-Oxoalkyl)-1,2,3,4-tetrahydroisoquinolines **1** are very useful as intermediates of isoquinoline alkaloids. There are several methods for preparing **1**, which usually involve the reaction of 2-alkyl-[1-3] or 2-acyl-[4] isoquinolinium salts with ketones. Akiba et al. reported the reaction of 2-acylisoquinolinium salts with trimethylsilyl enol ethers.[5] Pelletier and Cava recently reported the synthesis of (1,2,3,4-tetrahydro-1-isoquinolyl)acetic acid by the reaction of 3,4-dihydroisoquinolines with malonic acid.[6] However, each of the above methods suffers from disadvantages, such as low yield, limited scope, or a difficult procedure.

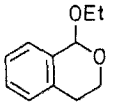
Herein we describe a new method for the preparation of 2-methyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines **2** by the reaction of 1-ethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) with active methylene compounds. We found that 1-ethoxyisochroman (**4**) undergoes nucleophilic substitution of active methylene compounds in the presence of the ether–boron trifluoride complex to give 1-(2-oxoalkyl)isochromans in excellent yields.[7] This finding led us to consider that 1-ethoxy-2-alkyl-1,2,3,4-tetrahydroisoquinolines **3**, regarded as *N,O*-acetals, might have reactivity similar to that of **4** and might be useful as synthetic intermediates in the preparation of **2**. Consequently, we selected 1-ethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) as a typical example and examined its reactivity towards active methylene compounds.



1
2 $R^1 = CH_3$



3a $R = CH_3$



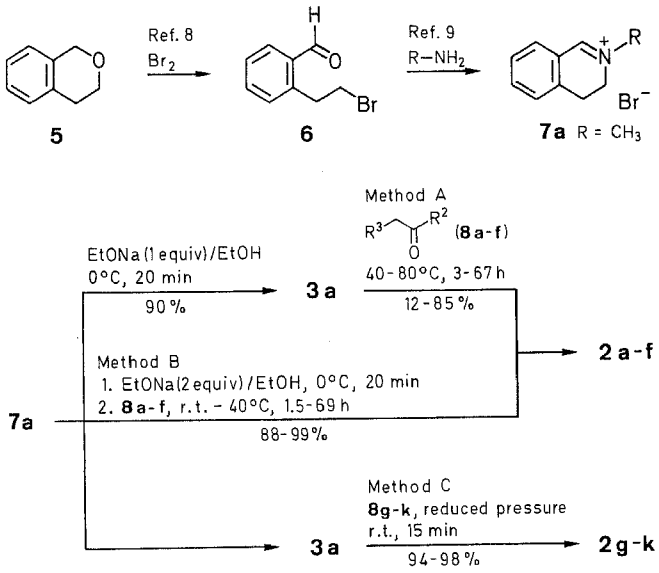
4

2	$-CH(R^3)COR^2$	**2**	$-CH(R^3)COR^2$
a	$-CH_2COPh$	**g**	$-CH(CO_2Et)_2$
b	2-tetralonyl	**h**	$-CH(CO_2Et)COCH_3$
c	$-CH_2COCH_3$	**i**	$-CH(CN)CO_2Et$
d	$-CH_2COCH(CH_3)_2$	**j**	$-CH(COCH_3)_2$
e	$-CH(CH_3)COCH_2CH_3$	**k**	4-hydroxy-2*H*-1-benzopyran-2-on-3-yl
f	2-cyclohexanonyl		

The synthesis of **3a** has not been hitherto reported, but it could be easily prepared from isochroman (**5**) as follows: Bromination of **5** followed by distillation gives 2-(2-bromoethyl)benzaldehyde (**6**),[8] which on treatment with amines, gives the corresponding 2-alkyl-3,4-dihydroisoquinolinium bromides **7**.[9] We found that the treatment of 2-methyl-3,4-dihydroisoquinolinium bromide[9] (**7a**) with sodium ethoxide gave **3a** in 90% yield.

The reaction of **3a** with a variety of active methylene compounds **8** was undertaken. When a mixture of **3a** with ketones **8a–f** was heated at 40–80 °C (Method A), the yields of **2** except **2a, b** are generally low. To improve the yields and to simplify the procedure, we tried a one-pot synthesis of **2** from **7a**. Compound **7a** was treated with two equivalents of sodium ethoxide for 20 min, and the mixture was then reacted with ketones **8a–f** at room temperature (Method B); **2a–f** were obtained in nearly quantitative yields. However, in the case of active methylene compounds **8g–k** having two electron-withdrawing groups, the desired **2g–k** could not be obtained by the methods A and B,

and the starting materials were recovered. Therefore, we explored other modifications of the reaction conditions. It was found that a mixture of **3a** and **8g–k**, after stirring at room temperature under reduced pressure with removal of the ethanol formed, gave **2g–k** in quantitative yield (Method C).



The present methods are simple and will be applicable to the synthesis of a variety of 2-alkyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines **1**.

Melting points are uncorrected. Microanalyses were obtained with Yanaco CHN Corder MT-2 element analyser. IR spectra were recorded on Jasco A-102 spectrophotometer. ^{1}H-NMR spectra were recorded with a Hitachi R-24 spectrometer at 60 MHz. MS spectra were taken with a Shimadzu LKB 9000 spectrometer.

1-Ethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3a):
2-Methyl-3,4-dihydroisoquinolinium bromide[9] (**7a**; 0.2 g, 0.9 mmol) is added to a solution of EtONa (60 mg, 0.9 mmol) in EtOH (2 mL) at 0°C. The mixture is stirred for 20 min and evaporated to dryness under reduced pressure. The residue is dissolved in dry Et_2O (30 mL), and the Et_2O solution is filtered. The filtrate is concentrated, and the residue is distilled under reduced pressure to give the pure product **3a**; yield: 0.15 g (90%); bp 94–95°C/3 Torr; mp 83–84°C. Compound **3a** can be stored without decomposition in a refrigerator.

$C_{12}H_{17}NO$	calc.	C 75.35	H 8.96	N 7.32
(191.3)	found	75.49	9.01	7.38

MS (DEI): $m/z = 191$ (M^+).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.18$ (t, 3H, $J = 7$ Hz); 2.29 (s, 3H); 2.35–3.25 (m, 4H); 3.26–3.82 (m, 2H); 4.77 (s, 1H); 7.01–7.43 (m, 4H).

2-Methyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines 2; Typical Procedure:

Method A: A mixture of **3a** (0.12 g, 0.6 mmol) and acetophenone (**8a**; 0.15 g, 1.2 mmol) is heated at 50–60°C for 3 h under an argon atmosphere and extracted with 10% HCl (3 × 20 mL). The HCl solution is washed with Et_2O (3 × 10 mL) and made basic with 10% NaOH. The resultant mixture is extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 layer is washed with brine (2 × 20 mL), dried ($MgSO_4$), and evaporated. The residue is chromatographed on alumina (EtOAc/hexane, 1:8) to give the pure product **2a** as a viscous oil; yield: 0.12 g (72%) (Tables 1 and 2).

Method B: To a stirred solution of EtONa (600 mg, 9 mmol) in EtOH (10 mL) is added **7a** (1 g, 4.5 mmol) at 0°C, and stirring is continued for 20 min. Then acetophenone (**8a**; 1.1 g, 9 mmol) is added, and the mixture is stirred for 1.5 h at room temperature. A solution of 10% HCl (200 mL) is added, and the HCl solution is washed with Et_2O (3 × 20 mL) and made basic with 10% NaOH. The resultant mixture is extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layer is washed with brine (2 × 20 mL), dried ($MgSO_4$), and evaporated. The residue is chromatographed on alumina (EtOAc/hexane, 1:8) to give the pure **2a**; yield: 1.2 g (98%) (Tables 1 and 2).

Method C: A mixture of **3a** (1 g, 4.5 mmol) and ethyl acetoacetate (**8h**; 590 mg, 4.5 mmol) is stirred for 15 min under reduced pressure at room temperature, until the starting materials are consumed as indicated by TLC. The resultant crude product is recrystallized from EtOAc/hexane (1:6) to give the pure **2h**; yield: 1.2 g (97%); mp 70–72°C (Tables 1 and 2).

Table 1. Synthesis of 2-Methyl-1-(2-oxoalkyl)-1,2,3,4-tetrahydroisoquinolines **2**

Product	Method	Reaction Conditions		Yield (%)	mp (°C) (solvent)	Molecular Formula[a]
		Temperature (°C)	Time			
2a	A	50–60	3 h	72	oil[b]	$C_{18}H_{19}NO$ (265.3)
	B	r.t.	1.5 h	99		
2b	A	40	46 h	85	oil	$C_{20}H_{21}NO$ (291.4)
	B	r.t.	1.5 h	98		
2c	A	40	58 h	44	oil	$C_{13}H_{17}NO$ (203.3)
	B	r.t.	5 h	97		
2d[c]	A	80	10 h	12	oil	$C_{15}H_{21}NO$ (231.3)
	B	40	69 h	97		
2e	A	50	67 h	24	oil	$C_{15}H_{21}NO$ (231.3)
	B	r.t.	60 h	88		
2f	A	80	6 h	17	oil	$C_{16}H_{21}NO$ (243.3)
	B	r.t.	1.5 h	94		
2g	C	r.t.	15 min	98	oil	$C_{17}H_{23}NO_4$ (305.4)
2h	C	r.t.	15 min	97	70–72 (EtOAc/Hx,[d] 1:6)	$C_{16}H_{21}NO_3$ (275.3)
2i	C	r.t.	15 min	97	oil	$C_{15}H_{18}N_2O_2$ (258.3)
2j	C	r.t.	15 min	95	41–43 (EtOAc/Hx, 1:6)	$C_{15}H_{19}NO_2$ (245.3)
2k	C	r.t.	15 min	94	196–198 (EtOAc/Hx, 1:1)	$C_{19}H_{17}NO_3$ (307.3)

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.31, N ± 0.25.
[b] The oily compounds are purified by alumina chromatography (EtOAc/hexane).
[c] The structure of **2d** was determined to be 1-(3-methyl-2-oxobutyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline based on its ^{1}H-NMR spectrum.
[d] Hx = hexane.

Table 2. Spectral Data of Compounds **2**

Compound	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	1680	2.42 (s, 3H); 2.57–3.10 (m, 4H); 3.11 (dd, 1H, J = 5, 16); 3.60 (dd, 1H, J = 6, 16); 4.58 (dd, 1H, J = 5, 6); 7.07 (s, 4H); 7.30–7.63 (m, 3H); 7.99 (dd, 2H, J = 2, 8)
2b[a]	1679	0.97–2.25 (m, 2H); 2.31 (s, 3 × 0.23H); 2.56 (s, 3 × 0.77H); 2.67–3.39 (m, 7H); 4.56 (d, 0.23H, J = 2); 4.78 (d, 0.77H, J = 2); 6.92–7.62 (m, 7H); 8.14 (dd, 1H, J = 2, 7)
2c	1710	2.14 (s, 3H); 2.43 (s, 3H); 2.59–3.28 (m, 6H); 4.20 (t, 1H, J = 6); 7.13 (s, 4H)
2d	1710	1.04 (d, 3H, J = 7); 1.08 (d, 3H, J = 7); 2.40 (s, 3H); 2.50–3.07 (m, 5H); 3.12 (dd, 2H, J = 6, 7); 4.23 (t, 1H, J = 6); 7.07 (s, 4H)
2e[a]	1710	0.93 (d, 3 × 0.5H, J = 8.8); 0.95 (d, 3 × 0.5H, J = 7); 1.05 (t, 3H, J = 7); 2.36 (s, 3 × 0.5H); 2.38 (s, 3 × 0.5H); 2.14 (q, 2H, J = 7); 2.47–3.53 (m, 5H); 3.77 (d, 0.5H, J = 8.8); 3.79 (d, 0.5H, J = 7); 6.90–7.40 (m, 4H)
2f[a]	1707	1.41–2.21 (m, 6H); 2.22–3.01 (m, 6H); 3.22 (d, 0.79H, J = 6); 3.31 (d, 0.21H, J = 5); 4.27 (d, 0.21H, J = 5); 4.31 (d, 0.79H, J = 6); 7.09 (s, 4H)
2g	1760, 1730	1.04 (t, 3H, J = 7); 1.22 (t, 3H, J = 7); 2.42 (s, 3H); 2.45–3.05 (m, 4H); 3.20 (d, 1H, J = 9); 3.98 (q, 2H, J = 7); 4.21 (q, 2H, J = 7); 4.41 (d, 1H, J = 9); 7.09 (s, 4H)
2h[a]	(Nujol) 1740, 1710	1.15 (t, 3 × 0.64H, J = 7.2); 1.33 (t, 3 × 0.36H, J = 7.6); 2.23 (s, 3 × 0.36H); 2.28 (s, 3 × 0.64H); 2.41 (s, 3 × 0.64H); 2.47 (s, 3 × 0.36H); 2.55–3.48 (m, 4H); 3.68 (d, 0.64H, J = 10); 3.85 (d, 0.36H, J = 6); 4.04 (q, 2 × 0.64H, J = 7.2); 4.25 (q, 2 × 0.36H, J = 7.6); 4.38 (d, 0.36H, J = 6); 4.41 (d, 0.64H, J = 10); 7.04 (s, 4H)
2i[a]	2260, 1746	1.25 (t, 3H, J = 7); 2.46 (s, 3H); 2.61–3.25 (m, 4H); 3.73 (d, 1H, J = 6); 4.15 (q, 2H, J = 7); 4.21 (d, 1H, J = 6); 7.01 (s, 4H)
2j	(Nujol) 1695	1.75–2.29 (m, 6H); 2.30 (s, 3H); 2.45–3.31 (m, 4H); 4.13 (s, 1H); 7.06 (s, 4H); 17.38 (br s, 1H)
2k[b]	(Nujol) 1660, 1640	2.95 (s, 3H); 3.08–4.00 (m, 4H); 4.50 (s, 1H); 5.80 (s, 1H); 7.00–7.72 (m, 7H); 7.98 (dd, 1H, J = 2, 8)

[a] Mixture of diastereoisomers.
[b] NMR solvent: $CDCl_3$/CD_3OD.

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