A Convenient Synthesis of 5-Oxoindolizine Derivatives

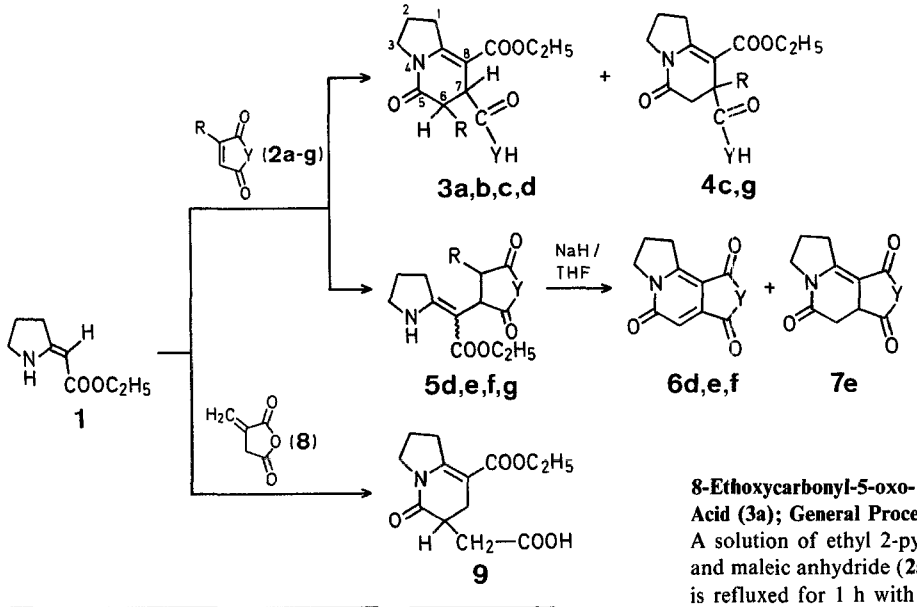
Tatsuo NAGASAKA*, Hitoshi INOUE, Mayumi ICHIMURA, Fumiko HAMAGUCHI

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Enamine ketones[1] and enamine esters[2] are versatile intermediates in organic synthesis. Enamine ester **1** (ethyl pyrrolidin-2-ylideneacetate) has been shown to be a promising starting material for the synthesis of fused heterocyclic compounds[3,4]. We have now investigated anellation reactions of **1** with some cyclic α,β-unsaturated anhydrides and imides and we report here a convenient, one-step (or two-step) synthesis of 5-oxo-1,2,3,5,6,7-hexahydroindolizine or 5-oxo-1,2,3,5-tetrahydroindolizine derivatives.

Treatment of **1** with maleic anhydride **(2a)** in boiling benzene leads to the formation of 8-ethoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine-7-carboxylic acid **(3a)** in quantitative yield. This reaction is exothermic and fast. The structure of **3a** is supported by the I.R., ^{1}H-, and ^{13}C-N.M.R. spectra[5]. The reaction of **1** with itaconic anhydride **(8)** also proceeds smoothly to give **9** in high yield. Similarly, the reactions with 2-substituted maleic anhydrides **(2b, c)** afford the indolizine derivatives (**3b**[6], **c**[7], **4c**[7]); however, longer reaction times and separation of products by chomatography[7] are necessary in these latter cases. On the other hand, the reactions of **1** with maleimides **(2d, e, f)** afford only Michael adducts **(5d, e, f)** in high yields, incapable to convert to indolizine **(3)** under the same conditions. These adducts **(5d, e, f)**, however, can be converted to indolizines **(3d, 6d, e, f, 7e)** as follows; **5d** is heated at 205 °C (m.p. of **5d**) to give the desired indolizine **(3d)** in 32% yield[8]. Treatment of adducts **(5e, f)** with sodium hydride in boiling tetrahydrofuran affords hexahydroindolizine **(7e)** and/or tetrahydroindolizines **(6e, f)**[9]. Similarly, **3d**

0039-7881/82/1032-0848 $ 03.00



2,3,4,5	R	Y		R	Y
a	H	O	e	H	N–CH_3
b	C_6H_5	O	f	H	N–C_6H_5
c	CH_3	O	g	CH_3	NH
d	H	NH			

6,7	Y
d	NH
e	N–CH_3
f	N–C_6H_5

cyclizes to the dehydrogenated **6d** under the conditions described above[10]. The reaction of **1** with 2-methylmaleimide **(2g)** gives only small amounts of the Michael adduct **(5g)** and the desired product **(4g)** upon refluxing for 10 days; the use of toluene or xylene instead of benzene did not improve the result, the reaction mixture becoming turbid and colored.

Table 1. 5-Oxo-1,2,3,5,6,7-hexahydroindolizines or 5-Oxo-1,2,3,5-tetrahydroindolizines

Product	Reaction time [h]	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (M^+)
3a	1	97	148–150° (benzene)	$C_{12}H_{15}NO_5$ (253.2)	253
3b	24	60	178–181° (benzene)	$C_{18}H_{19}NO_5$ (329.3)	329
3c[c]	96	53	119–153° (diisopropyl ether)	$C_{13}H_{17}NO_5$ (267.3)	267
3d	3	32	149–151° (ethanol)	$C_{12}H_{16}N_2O_4$ (252.3)	252
4c	96	22	oil	$C_{13}H_{17}NO_5$ (267.1105)	267.1094[d]
4g	240	3	148–150° (ethyl acetate)	$C_{13}H_{18}N_2O_4$ (266.3)	266
6d	1.5	22	292° (dec.) (acetone)	$C_{10}H_8N_2O_3$ (204.2)	204
6e	3	16	265–267° (dec.) (ethanol)	$C_{11}H_{10}N_2O_3$ (218.2)	218
6f	24	26	280° (dec.) (ethanol)	$C_{16}H_{12}N_2O_3$ (280.3)	280
7e	31	27	160–162° (isopropyl ether)	$C_{11}H_{12}N_2O_3$ (220.2)	220
9	1	92	108–111° (benzene)	$C_{13}H_{17}NO_5$ (267.3)	267

[a] Yields of isolated product of >95% purity as determined by ^{1}H-N.M.R. spectrometry.
[b] All crystalline products gave satisfactory microanalysis: C, ±0.32; H, ±0.26; N, ±0.22. Exception: **4g**; C, −0.67.
[c] *cis/trans* Mixture (1/1).
[d] High-resolution M.S.

8-Ethoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine-7-carboxylic Acid (3a); General Procedure for 3a–c, 4, 5, 9:
A solution of ethyl 2-pyrrolidinylideneacetate (**1**; 1.5 g, 9.67 mmol) and maleic anhydride (**2a**; 0.948 g, 9.67 mmol) in dry benzene (15 ml) is refluxed for 1 h with stirring. The crystalline product **3a** (1.04 g; m.p. 147–149 °C) formed upon cooling of the solution is collected by filtration. The filtrate is evaporated in vacuo and the residue is submitted to column chromatography on silica gel (40 g) using chloroform as eluent to give a further 1.35 g (m.p. 145 °C) of **3a** as colorless needles; total yield: 2.39 g (97%); m.p. 148–150 °C (benzene).

8-Ethoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine-7-carboxamide (3d):
Ethyl succinimido-2-(2-pyrrolidinylidene)-acetate (**5d**; 3.7 g) is heated at 205 °C for 3 h with stirring. After cooling, the solid mass is chromatographed on silica gel (80 g) using chloroform/acetone (10/1) as eluent to give **3d** as yellow needles from ethanol; yield: 1.185 g (32%); m.p. 149–151 °C.

5-Oxo-1,2,3,5-tetrahydroindolizine-*N*-methyl-7,8-dicarboximide (6e) and 5-Oxo-1,2,3,5,6,7-hexahydroindolizine-*N*-methyl-7,8-dicarboximide (7e); General Procedure for 6,7:
A suspension of ethyl *N*-methylsuccinimido-2-(2-pyrrolidinylidene)-acetate (**5e**; 266 mg, 1 mmol) and sodium hydride (50%; 66 mg, 1.3 mmol) in tetrahydrofuran (18 ml) is refluxed with stirring till disappearance of **5e** on thin layer chromatography (silica gel; chloroform/acetone 1/1) (3–4 h). After removal of excess sodium hydride by filtration, the filtrate is evaporated to give a yellow powder (139 mg), which is separated by high-resolution chromatography (Iatrobeads 6 RS-8060; chloroform/acetone 1/1): compound **7e** from former fractions; yield: 44 mg (27%); m.p. 160–162 °C; compound **6e** from latter fractions; yield: 34 mg (16%); m.p. 265–267 °C.

Table 2. Reactions of **1** with Maleimides **(2d–g)**: Michael Adducts

Product	Reaction time [h]	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (M^+)
5d	10	92	205–207° (ethyl acetate)	$C_{12}H_{16}N_2O_4$ (252.3)	252
5e	16	97	127–128° (ethyl acetate)	$C_{13}H_{18}N_2O_4$ (266.3)	266
5f	24	93	141–143° (ethyl acetate/ diisopropyl ether)	$C_{18}H_{20}N_2O_4$ (328.4)	328
5g	240	8	148–152° (ethyl acetate)	$C_{13}H_{18}N_2O_4$ (266.3)	266

[a] Yields of isolated product of >95% purity as determined by ^{1}H-N.M.R. spectrometry.
[b] All crystalline products gave satisfactory microanalysis: C, ±0.32; H, ±0.26; N, ±0.22.

Table 3. Spectral Data of Compounds **3, 4, 6, 7** and **9**

Compound	I.R. (KBr) ν [cm^{-1}] (C=O, C=C)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
3a	1725, 1690, 1620	1.32 (t, 3H, J=8 Hz); 2.00 (quin, 2H, J=7 Hz); 2.5–3.2 (m, 2H); 3.20 (t, 2H, J=7 Hz); 3.8 (m, 3H); 4.24 (q, 2H, J=8 Hz); 8.9 (br, 1H)
3b	1720, 1695, 1670, 1640	1.27 (t, 3H, J=8 Hz); 2.05 (m, 2H); 3.25 (t, 2H, J=8 Hz); 3.83 (t, 2H, J=8 Hz); 3.98 (s, 2H); 4.23 (q, 2H, J=8 Hz); 7.33 (br, 1H); 7.36 (s, 5H)
3c	1710, 1690, 1630	1.30 (t, 3H); 1.35 (d, 2H, J=6.7 Hz); 2.0 (m, 2H); 2.4–3.3 (m, 3H); 3.75 (m, 3H); 4.25 (q, 2H); 7.0 (br, 1H)
3d	1705, 1680, 1645, 1615	1.35 (t, 3H, J=7.5 Hz) 2.0 (quin, 2H, J=7.5 Hz); 2.4–3.1 (m, 2H); 3.18 (t, 2H, J=7.5 Hz); 3.67–3.87 (m, 3H); 4.30 (q, 2H, J=7.5 Hz); 6.0 (br, 1H); 6.55 (br, 1H)
4c	1700, 1665, 1625[a]	1.30 (t, 3H, J=6.7 Hz); 1.36 (s, 3H); 2.43 (m, 2H); 2.97 (t, 2H, J=8 Hz); 3.0 (q, 2H, J_{AB}=18 Hz); 3.63 (t, 2H, J=8 Hz); 4.23 (q, 2H, J=8 Hz); 6.66 (br, 1H)
4g	1720, 1685, 1630	1.30 (t, 3H, J=8 Hz); 1.35 (s, 3H); 2.35 (m, 2H); 2.82 (q, 2H, J_{AB}=18 Hz); 2.9 (m, 2H); 3.60 (t, 2H, J=8 Hz); 4.17 (q, 2H, J=8 Hz); 5.5 (br, 2H)
5d	1760, 1700, 1650 1585	1.20 (t, 3H, J=8 Hz); 2.1 (m, 2H); 2.4–3.1 (m, 4H); 3.55 (m, 3H); 4.10 (q, 2H, J=8 Hz); 8.43 (br, 2H)
5e	1760, 1720, 1685, 1650, 1575	1.12 (t, 3H, J=8 Hz); 2.1 (m, 2H); 2.4–3.0 (m, 4H); 3.02 (s, 3H); 3.45 (q, 1H); 3.60 (t, 2H, J=7 Hz); 4.05 (q, 2H, J=8 Hz); 8.45 (br, 1H)
5f	1770, 1700, 1650, 1570	1.16 (t, 3H, J=8 Hz); 2.03 (quin, 2H, J=8 Hz); 2.5–3.3 (m, 4H); 3.6 (m, 3H); 4.15 (q-d, 2H); 7.4 (m, 5H); 8.5 (br, 1H)
5g	1770, 1710, 1650, 1580	1.23 (t, 3H, J=8 Hz); 1.35 (d, 3H, J=8 Hz); 2.1 (m, 2H); 2.5–3.1 (m, 4H); 3.60 (t, 2H, J=8 Hz); 4.10 (q, 2H, J=8 Hz); 8.0 (br, 1H); 8.5 (br, 1H)
6d	1755, 1720, 1665, 1605	[in d_6-DMSO] 2.32 (quin, 2H, J=7.5 Hz); 3.42 (t, 2H, J=7.5 Hz); 4.12 (t, 2H, J=7.5 Hz); 6.62 (s, 1H)
6e	1755, 1710, 1675, 1620	2.33 (quin, 2H, J=7.5 Hz); 3.13 (s, 3H); 3.45 (t, 2H, J=7.5 Hz); 4.17 (t, 2H, J=7.5 Hz); 6.80 (s, 1H)
6f	1765, 1710, 1680, 1620	2.33 (quin, 2H, J=7.5 Hz); 3.48 (t, 2H), J=7.5 Hz); 4.18 (t, 2H, J=7.5 Hz); 6.90 (s, 1H); 7.40 (m, 5H)
7e	1755, 1710, 1680	2.10 (quin, 2H, J=7.5 Hz); 2.37–2.66 (m, 1H); 3.10 (s, 3H); 2.93–3.20 (m, 3H); 3.16–4.0 (m, 3H)
9	1700, 1670, 1625	1.33 (t, 3H, J=8 Hz); 2.03 (quin, 2H, J=8 Hz); 2.3–3.3 (m, 7H); 3.77 (t-d, 2H, J=8 Hz, J=2 Hz); 4.20 (q, 2H, J=8 Hz); 9.66 (br, 1H)

[a] In $CHCl_3$ solution.

Received: December 15, 1981

* Address for correspondence.

1 H. Iida, Y. Yuasa, C. Kibayashi, *J. Am. Chem. Soc.* **100,** 3598 (1978).

2 J. B. Patrick, E. K. Saunders, *Tetrahedron Lett.* **1979,** 4009.

3 Y. Yamada, M. Matsui, *Agr. Biol. Chem.* **35,** 282 (1971).

4 J.-P. Célérier, C. Eskénazi, G. Lhommet, P. Maitte, *J. Heterocycl. Chem.* **16,** 953 (1979).

5 In the ^{13}C-N.M.R. spectrum, the three carbonyl groups give signals at δ=173.5 (carboxy), 167.0, and 165.6 (amide and ester) ppm. This fact excludes the presence of the regioisomeric ketone; see R. W. McCabe, D. W. Young, *J. Chem. Soc. Chem. Commun.* **1981,** 395.

6 Two methin moieties at the 6- and 7-positions of **3b** show signals at δ=47.3 (d) and 49.3 (d) ppm in the ^{13}C-N.M.R. spectrum and at 3.98 (s) ppm in the ^{1}H-N.M.R. spectrum; the regioisomer **4b** could not be isolated from the oily products obtained together with **3b**.

7 A mixture of **3c** (*cis*/*trans* = 1/1) and **4c** is separable by high-resolution chromatography (Iatrobeads 6 RS-8060, chloroform/acetone 10/1).

8 Heating of **5e** and **5f** at melting points afforded only tarry products.

9 The Michael adducts **(5e, f)** are completely converted into a mixture of **6** and **7** under this condition, but isolation of them is rather difficult because of the small solubility of **6** and **7** in organic solvents.

10 Product **6d** could not be obtained directly from **5d** by treatment with base.

0039-7881/82/1032-0850 $ 03.00