A New Method for Preparation of Glutarimides from Glutaric Acid Diesters

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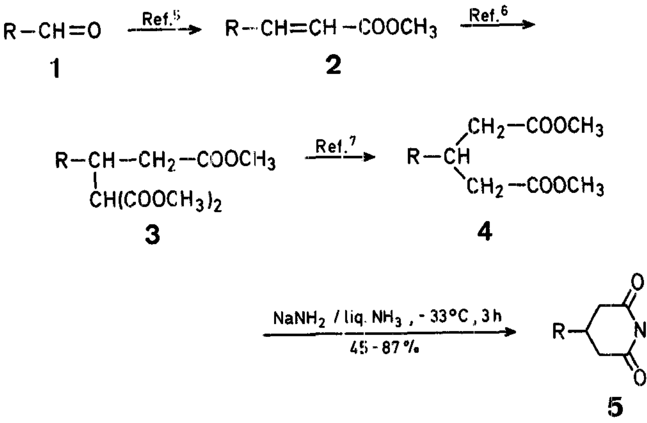
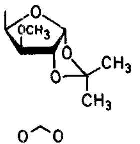
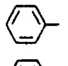
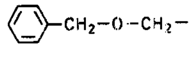
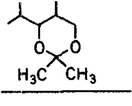
Several methods for the synthesis of cyclic carboxylic monoimides[1,2,3] are known, however, few general and versatile methods for the synthesis of glutarimides from glutaric acid diesters have been reported.

In the course of our synthetic work of sesbanimide[4], which is a potent antitumor compound containing a glutarimide ring, it was found that sodium amide/liquid ammonia system is an effective method for the preparation of glutarimides. We now report a convenient and efficient synthesis of some β-substituted glutarimides **5** from the corresponding glutaric acid diesters **4**. Generally, β-substituted glutaric acid diesters are easily derived from the appropriate aldehydes **1** via the following sequence of reactions: Wittig reaction[5] (→ **2**), Michael addition[6] (→ **3**), and dealkoxycarbonylation[7] (→ **4**). The best reaction conditions for the last step (**4** → **5**), adopted as a result of several examinations, are as follows: 3 equivalents of sodium amide in liquid ammonia at −33 °C for 3 h.



1-5	R	1-5	R
a	H	d	
b			
c			
		e	

Melting points were measured on a micro-hot stage and are uncorrected. Microanalyses were carried out on a Perkin-Elmer Model 240 elemental analyzer. ^1H- and ^{13}C-N.M.R. spectra were recorded on JEOL FX-100 spectrometer. Dimethyl glutarate (**4a**) is commercically available. Compounds **4b–e** were prepared from the corresponding aldehydes **1b–e** as described[5,6,7].

Table. Compounds **5a–e** prepared

Product	Yield [%][a]	m.p. [°C] (solvent)	$[\alpha]_D^{18}$ (c, CH_3OH)	Molecular Formula[b]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$) δ [ppm]
5a	45	152–153° (C_2H_5OH)	–	–[c]	2.00 (quint, 2H); 2.59 (t, 4H); 8.51 (br.s, 1H)	18.0 (t); 31.7 (t); 172.9 (s)
5b	61	179.5–180° (C_2H_5OH)	–	$C_{11}H_{11}NO_2$ (189.2)	2.67 (dd, 2H); 2.93 (dd, 2H); 3.42 (ddd, $J = 5.9$ Hz, $J = 10.0$ Hz, 1H); 7.25, 7.31 (5H); 8.80 (br.s, 1H)	35.7 (d); 38.8 (t); 126.4, 127.7, 129.2 (d); 140.5 (s); 172.3 (s)
5c	60	79–80° (hexane/C_2H_5OAc)	–	$C_{13}H_{15}NO_3$ (233.3)	2.53 (dd, $J = 12.0$ Hz, 4H); 2.56 (dd, $J = 6.0$ Hz, 1H); 3.41 (d, $J = 3.0$ Hz, 2H); 4.49 (s, 2H); 7.29 (s, 5H); 8.65 (br.s, 1H)	30.9 (d); 34.7 (t); 71.9 (t, $-C\underline{H}_2OCH_2C_6H_5$); 73.3 (t, $OC\underline{H}_2C_6H_5$); 127.5, 127.9, 128.5 (d); 137.7 (s); 172.5 (s)
5d	87	155–156° (hexane/C_2H_5OAc)	−61.7° (0.4)	$C_{13}H_{19}NO_6$ (285.3)	1.32, 1.48 (2s, 6H); 2.30–2.70 (m, 5H); 3.41 (s, 3H); 3.65 (d, $J = 3.2$ Hz, 1H, H-3); 3.88 (dd, $J = 7.0$ Hz, 1H, H-4); 4.59 (d, 1H, H-2); 5.88 (d, $J = 4.0$ Hz, 1H, H-1); 8.46 (br.s, 1H)	26.0, 26.7 (q); 29.7 (d); 34.1, 35.0 (t); 57.5 (q); 80.9 (d, C-2); 82.0 (d, C-4); 83.6 (d, C-3); 104.7 (d, C-1); 111.6 (s); 171.9, 172.1 (s)
5e	54	187–187.5° (hexane/C_2H_5OAc)	−31.7° (1.0)	$C_{13}H_{19}NO_6$ (285.3)	1.47 (s, 6H); 2.30–2.80 (m, 5H); 3.40 (d, $J = 7.0$ Hz, 1H); 3.46 (br.s, 1H); 3.73 (br.s, 1H); 3.88 (dd, $J = 12.5$ Hz, 1H); 4.02 (dd, $J = 2.0$ Hz, $J = 3.5$ Hz, 1H); 4.72 (d, $J = 6.4$ Hz, 1H); 5.19 (d, $J = 6.4$ Hz, 1H); 8.80 (br.s, 1H)	18.7, 29.0 (q); 30.2 (d); 33.0, 33.8 (t), 63.0 (t, C-4); 63.1 (d, C-2); 69.4 (d, C-3); 79.3 (d, C-1); 92.7 (t); 98.6 (s); 172.2, 172.6 (s)

[a] Yield of isolated pure products.

[b] The microanalyses were in satisfactory agreement with the calculated values; C ±0.04, H ±0.07, N ±0.06. Exception: **5e**, C −0.33, H +0.02, N −0.16.

[c] Lit.[8], m.p. 152 °C; Lit.[9], m.p. 145–146 °C.

β-Substituted Glutarimides (5); General Procedure:

To a stirred solution of sodium amide [3 mmol; prepared *in situ* from sodium metal (69 mg) and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia (30 ml)] is added a solution of the glutaric acid diester **4** (1 mmol) in dry tetrahydrofuran (10 ml) at −33 °C. After stirring for 3 h, ammonium chloride (500 mg) is added and the ammonia is allowed to evaporate. Water (10 ml) is added to the residue and the mixture is extracted with chloroform (3 x 20 ml). The extract is dried with sodium sulfate and concentrated to afford **5**. Crystalline products **5a** and **5d** are recrystallized, while **5b**, **5c**, and **5e** are separated by chromatography on silica gel with chloroform/acetone (9:1) and solidify on standing (Table).

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