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Condensation of Diethyl Acetonedicarboxylate. IV.[1] Regioselective Reaction of Diethyl Acetonedicarboxylate-magnesium Complex

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The reactivity of diethyl acetonedicarboxylate (DADC)-magnesium complex (**1a, b**) was examined. The Michael reaction of **1a, b** gave the regioselectively monoalkylated derivative (**2** or **3**) of DADC.

Reaction of **1a** with nucleophilic reagents, $LiAlH_4$ or alkylamines, took place at the unchelated ethoxycarbonyl group and gave the single corresponding product (**7** or **9**) with regioselectivity.

Keywords——diethyl acetonedicarboxylate; magnesium; metal chelate complex; regioselectivity; Michael condensation; reduction; aminolysis; mass spectra

We have had a continuing interest in the reaction of diethyl acetonedicarboxylate (DADC)-magnesium complex, *i.e.*, $(DADC)_2Mg \cdot 2H_2O$ (**1a**)[2] or $(DADC)_2Mg$ (**1b**)[1] (Chart 1 and 2). In particular, our attention has centered on regioselective reactions of DADC-magnesium complex (**1a, b**) with various nucleophilic or electrophilic reagents. DADC has two active methylene and two active ethoxycarbonyl groups, but in the case of **1a, b**, one methine and one ethoxycarbonyl group form the chelate ring, and one methylene and one ethoxycarbonyl group are in the side chain of the chelate ring. Therefore, it was considered that the two types of groups should have different reactivities and that regioselective reactions might occur.

Muramoto *et al.* reported the regioselective alkylation of DADC in the presence of magnesium ethoxide and stated that the methine group in the chelate ring is inactive.[3,4] However, we previously found that the methine group in the chelate ring is sufficiently reactive to be acylated by acyl chloride or acyl anhydride to give a monoacylated product.[1]

We first examined the reactivity of the methine group in the chelate ring with α,β-unsaturated carbonyl compounds, socalled Michael acceptors, and found that ethyl 4-ethoxycarbonyl-3,7-dioxooctanate (**2**) was obtained in 93% yield by stirring **1a** with methyl vinyl ketone in THF at room temperature (Chart 1). Similarly, reflux of a mixture of **1a** and 2-cyclohexen-1-one in THF gave diethyl 3-oxo-2-(3-oxocyclohexyl)glutarate (**3**) in 93% yield. The complexes **1a** and **1b** showed the same reactivity in the Michael addition, but **1a, b** did not react with acrylonitrile, benzylideneacetone, and methyl acrylate.

In order to clarify whether the methylene or methine group of **1a** added to the Michael reagents, the magnesium complex (**5**) of diethyl 2-methylacetonedicarboxylate (**4**)[3] was prepared. In the nuclear magnetic resonance (NMR) spectrum of **5**, a doublet (J=7 Hz) of C_2-methyl protons at δ: 1.21, a methine proton quartet (J=7 Hz) at δ: 3.17, and a methine proton singlet at δ: 4.72 were observed. These results indicated that the C_2-methyl group was located at the methylenic carbon in the side chain of the chelate ring (Chart 1). Treatment of **5** with methyl vinyl ketone under the same conditions as used for **1a** to give **2** afforded ethyl 4-ethoxycarbonyl-2-methyl-3,7-dioxooctanate (**6**) in 71% yield. In the NMR spectrum of **6**, a doublet (J=7 Hz) of C_2-methyl protons at δ: 1.28 and a methine proton quartet (J=7 Hz) at δ: 3.78 were observed and the former signal collapsed to a sharp singlet on irradiation at the latter signal. These results showed that the Michael addition had occurred at the methine group in the chelate ring of **1a** or **5** to give the regioselectively monoalkylated derivative of DADC in high yield without addition of any other basic catalyst.

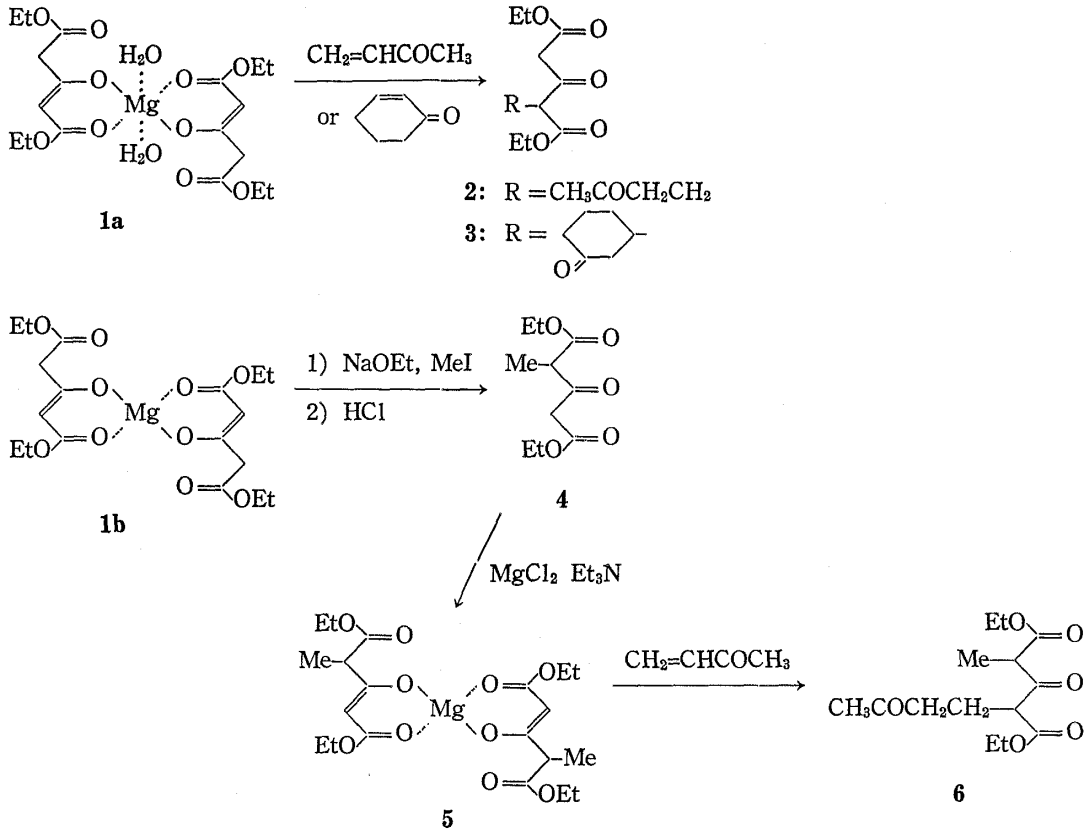


Chart 1

In an attempt to examine the reactivity of the ethoxycarbonyl group of **1a** with nucleophilic reagents, first of all, **1a** was reduced with lithium aluminum hydride ($LiAlH_4$). Although the reduction of **1a** with $LiAlH_4$ in THF took place smoothly and the reduction mixture gave essentially only a single spot corresponding to that of ethyl 5-hydroxy-3-oxopentanate (**7**) on a thin-layer chromatogram, the isolated yield of **7** was 34% (Chart 2). The reason for this low isolated yield of **7** seemed to be its hydrophilicity.

Compound **5** was reduced with $LiAlH_4$ to examine whether the ethoxycarbonyl group of the chelate ring or that of the side chain of **1a** was reduced. The reduction product (obtained in 62% yield) was established to be ethyl 5-hydroxy-4-methyl-3-oxopentanate (**8**) by NMR spectroscopy. In the NMR spectrum of **8**, a pair of triplet-quartet patterns (J=7 Hz) at δ: 1.23 and 4.30 due to ethoxycarbonyl protons and a singlet at δ: 3.63 due to C_2-methylene protons were observed. In addition, a doublet (J=7 Hz) at δ: 1.37 due to the C_4-methyl protons, a multiplet at δ: 2.85—3.18 due to the C_4-methine proton, a doublet (J=7 Hz) at δ: 3.80 due to the C_5-methylene protons, and a broad peak at δ: 2.40—2.80 due to the C_5-hydroxyl proton showed the hydroxymethyl group to be adjacent to the methylated methine group. Based on these results, it was concluded that the ethoxycarbonyl group in the side chain of **1a** or **5** was reduced.

Aminolysis of **1a** with methylamine or benzylamine was carried out as an example of nucleophilic reactions, and 4-ethoxycarbonyl-N-methyl-3-oxobutyramide (**9a**) or N-benzyl-4-ethoxycarbonyl-3-oxobutyramide (**9b**) was obtained in 59 or 92% yield, respectively (Chart 3). Furthermore, aminolysis of **5** with methylamine or benzylamine gave 4-ethoxycarbonyl-2,N-dimethyl-3-oxobutyramide (**10a**) or N-benzyl-4-ethoxycarbonyl-2-methyl-3-oxobutyramide (**10b**) in 44 or 21% yield, respectively. These structures of **10a** and **10b** were established from the mass spectral data. Namely, the fragmentation patterns of **10a**, **b** were similar to those of **9a**, **b** (Table I) and the mass spectrum of **10a** or **10b** showed a characteristic fragment ion

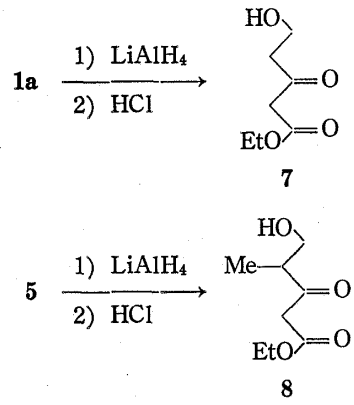


Chart 2

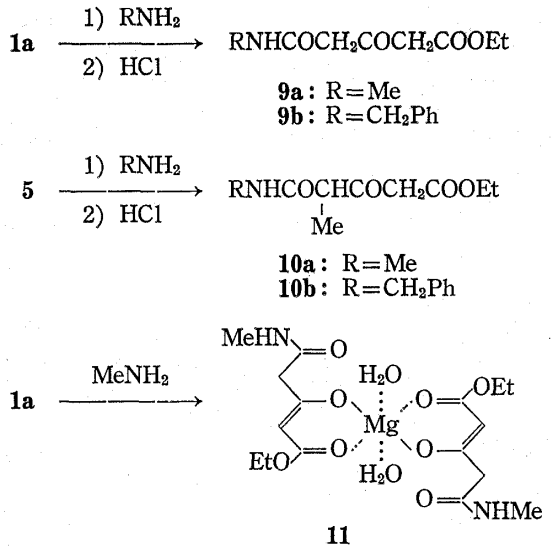


Chart 3

TABLE I.

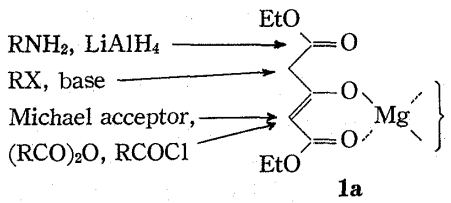
$EtOOCCH_2COCHCONHR_2$
R_1

Compd. No.	R_1	R_2	Molecular and fragment ions (m/e)					
			M^+	M^+-OEt	M^+-EtOH	M^+-CH_2COOEt	$R_1CH_2CONHR_2^{\dagger+}$	$R_1\overset{+}{H}CONHR_2$
9a	H	Me	187	142	141	100	73	—
9b	H	CH_2Ph	263	218	217	176	—	148
10a	Me	Me	201	156	155	114	87	86
10b	Me	CH_2Ph	277	232	231	—	163	162

at m/e: 87 or 163 which was assignable to $CH_3CH_2CONHCH_3$ or $CH_3CH_2CONHCH_2C_6H_5$, respectively. These findings showed that the methylated methine gorup of **10** was adjacent to the carbamoyl group. Thus, it appears that the aminolysis of **1a** or **5** took place selectively at the ethoxycarbonyl group in the side chain of the chelate ring, and that the ethoxycarbonyl and carbonyl groups in the chelate ring were both unreactive.

This regioselective aminolysis was further confirmed by isolation of the magnesium chelate complex (**11**) of 4-ethoxycarbonyl-N-methyl-3-oxobutyramide (**9a**). Complex **11** was obtained in 97% yield by removal of the solvent from a reaction mixture of **1a** with methylamine. The infrared (IR) spectrum of **11** showed peaks at 1660 and 1640 cm^{-1} in the carbonyl region, while the IR spectrum of **1a** showed two peaks at 1735 and 1650 cm^{-1}.

The regioselective reactivities of **1a** were concluded to be as follows (Fig. 1).



Fig, 1

1) Electrophilic Reaction: The Michael reaction of **1a**, **b** with α,β-unsaturated carbonyl compounds or acylation[1] of **1a**, **b** with acyl anhydride and acyl chloride occurs at the methine group in the chelate ring of **1a**; however, alkylation of **1a** with alkyl halide in the presence of an excess molar amount of magnesium ethoxide or sodium ethoxide takes place at the methylene group in the side chain.[3,4]

2) Nucleophilic Reaction: Reduction of **1a** with an excess molar amount of $LiAlH_4$, or amination of **1a** with amines, takes place at the ethoxycarbonyl group in the side chain.

Experimental

Melting points are uncorrected. NMR spectra were taken with a Hitachi R-22 FTS spectrometer (90 MHz), with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu-LKB 9000 spectrometer, and IR spectra were recorded on a Nipponbunko A-102 spectrometer.

Ethyl 4-Ethoxycarbonyl-3,7-dioxooctanate (**2**)——A solution of **1a** (1 g, 2.15 mmol) and methyl vinyl ketone (0.38 g, 6.48 mmol) in dry THF was stirred for 5 h at room temperature. The reaction mixture was then acidified with dil. HCl and extracted with AcOEt. The AcOEt layer was washed with 10% $KHCO_3$ solution and H_2O, and the solvent was evaporated off. The residue was distilled under reduced pressure to give 1.11 g (93%) of **2** as an oil, bp 135—140°C (0.15 mmHg). *Anal.* Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.63; H, 7.15. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1720, 1685, 1625. NMR (CCl_4) δ: 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.02 (3H, s, C_8–H), 2.00—2.53 (5H, m, C_5–H, C_6–H, and C_3-enolic OH), 3.25—3.66 (1H, m, C_4–H), 4.26 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.31 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.35 (1H, s, C_2–H). MS *m/e*: 272 (M^+), 227 (M^+-OEt).

Diethyl 3-Oxo-2-(3-oxocyclohexyl)glutarate (**3**)——A solution of **1a** (2 g, 4.32 mmol) and cyclohexen-1-one (0.82 g, 8.62 mmol) in dry THF was refluxed for 24 h. The reaction mixture was treated as described for the synthesis of **2** to give 2.36 g (93%) of **3** as an oil, bp 80°C (6×10^{-4} mmHg). *Anal.* Calcd for $C_{15}H_{22}O_6$: C, 60.49; H, 7.43. Found: C, 59.97; H, 8.07. NMR (CCl_4) δ: 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.49—1.95 (5H, m, $C_{1'}$–H, $C_{5'}$–H, and $C_{6'}$–H), 2.15—2.68 (5H, m, $C_{2'}$–H, $C_{4'}$–H, and C_3-enolic OH), 3.05—3.18 (1H, m, C_2–H), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.29 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.32 (1H, s, C_4–H). MS *m/e*: 298 (M^+), 253 (M^+-OEt), 252 (M^+-EtOH), 211 (M^+-CH_2COOEt).

Diethyl 2-Methylacetonedicarboxylate-Mg Complex (**5**)——Et_3N (1 g, 10 mmol) was added to a mixture of diethyl 2-methylacetonedicarboxylate[3] (2 g, 9.2 mmol) and $MgCl_2$ (0.44 g, 4.6 mmol) in dry benzene, and the mixture was refluxed for 1 h with stirring and concentrated *in vacuo*. The residue was extracted with dry Et_2O and the solvent was evaporated off to give **5** as a viscous oil in quantitative yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1735, 1640, 1550, 1510. NMR ($CDCl_3$) δ: 1.18 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.21 (6H, d, J=7 Hz, C_2–CH_3), 1.31 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.17 (2H, q, J=7 Hz, C_2–H), 3.98 (4H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.09 (4H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.72 (2H, s, C_2–H).

Ethyl 4-Ethoxycarbonyl-2-methyl-3,7-dioxooctanate (**6**)——A solution of **5** (7.6 g, 16.7 mmol) and methyl vinyl ketone (4 g, 68.2 mmol) in dry THF (50 ml) was stirred for 7 h at room temperature. The reaction mixture was then acidified with dil. HCl and extracted with Et_2O. The Et_2O layer was washed with 10% $KHCO_3$ solution and H_2O, and the solvent was evaporated off. The residue was column-chromatographed on silica gel (AcOEt: petr. ether=1: 2) to give 6.8 g (71%) of **6** as an oil, bp 115—116°C (0.05 mmHg). *Anal.* Calcd for $C_{14}H_{22}O_6$: C, 58.73, H, 7.75. Found: C, 58.85; H, 7.69. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1775, 1735, 1710, 1685. NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.28 (3H, d, J=7 Hz, C_2–CH_3), 1.34 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.90—2.20 (3H, m, C_5–H and C_3-enolic OH), 2.46 (2H, t, J=6 Hz, C_6–H), 3.78 (1H, q, J=7 Hz, C_2–H), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.18 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$). MS *m/e*: 286 (M^+).

Ethyl 5-Hydroxy-3-oxopentanate (**7**)——A solution of **1a** (10 g, 21.6 mmol) in dry THF was added to a solution of $LiAlH_4$ (3 g, 79.0 mmol) in dry THF and the mixture was stirred for 7 h at room temperature. The remaining $LiAlH_4$ was decomposed with H_2O, and then the mixture was acidified with dil. H_2SO_4 and extracted with AcOEt. The aqueous layer was further extracted with AcOEt using a continuous extractor. Both the AcOEt layers were combined and the solvent was evaporated off. The residue was distilled under reduced pressure to give 2.42 g (34%) of **7** as an oil, bp 95—105°C (1.5 mmHg). *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.75; H, 7.33. IR $\nu_{max}^{liq.}$ cm^{-1}: 3520, 1740, 1720, 1660. NMR (CCl_4) δ: 1.39 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.79 (2H, t, J=6 Hz, C_4–H), 3.57 (2H, s, C_2–H), 3.89 (2H, t, J=6 Hz, C_5–H), 3.26—4.12 (1H, b, OH), 4.26 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$). MS *m/e*: 160 (M^+), 142 (M^+-H_2O).

Ethyl 5-Hydroxy-4-methyl-3-oxopentanate (**8**)——A solution of **5** (2.5 g, 5.4 mmol) in dry THF was added to a solution of $LiAlH_4$ (0.34 g, 8.9 mmol) in dry THF and the mixture was stirred for 5 h at room temperature, then acidified with dil. H_2SO_4 and extracted with Et_2O. The Et_2O layer was washed with H_2O and the solvent was evaporated off. The residue was distilled under reduced pressure to give **8** (1.17 g, 62%) as an oil, bp 98—102°C (1.5 mmHg). *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.59; H, 8.03. NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.37 (3H, d, J=7 Hz, C_4–CH_3), 2.40—2.80 (1H, b, OH), 2.85—3.18 (1H, m, C_4–H), 3.64 (2H, s, C_2–H), 3.80 (2H, d, J=7 Hz, C_5–H), 4.30 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$). MS *m/e*: 174 (M^+), 156 (M^+-H_2O).

4-Ethoxycarbonyl-N-methyl-3-oxobutyramide (**9a**)——A solution of **1a** (2 g, 4.32 mmol) and excess methylamine in EtOH was stirred for 4 h at room temperature, acidified with dil. HCl, and extracted with AcOEt. The AcOEt layer was washed with H_2O and the solvent was evaporated off. The residue was purified by column chromatography on silica gel (petr. ether: AcOEt=2: 1) to give **9a** (0.96 g, 59%) as an oil. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1735, 1720, 1650. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.82 (3H, d, J=6 Hz, $NHC\underline{H}_3$), 3.52 (2H, s, C_2–H), 3.60 (2H, s, C_4–H), 4.13 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.94—7.41 (1H, b, NH).

N-Benzyl-4-ethoxycarbonyl-3-oxobutyramide (**9b**)——A solution of **1a** (3 g, 6.48 mmol) and excess benzylamine in EtOH was stirred for 2 h at room temperature, and then the reaction mixture was treated

as described for the synthesis of **9a** to give 3.16 g (92%) of **9b** as an oil. *Anal.* Calcd for $C_{14}H_{17}O_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.64; H, 6.21; N, 4.90. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 1740, 1720, 1650, 1605. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.51 (2H, s, C_2–H), 3.56 (2H, s, C_4–H), 4.19 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.43 (2H, d, J=6 Hz, $C\underline{H}_2Ph$), 7.12—7.58 (1H, b, NH), 7.31 (5H, s, Ph).

4-Ethoxycarbonyl-2,N-dimethyl-3-oxobutyramide (**10a**)—A solution of **5** (2 g, 4.4 mmol) and excess methylamine in EtOH was stirred for 48 h at room temperature, then treated as described for the synthesis of **9a**. The crude product was recrystallized from petr. ether–CH_2Cl_2 to give 0.78 g (44%) of **10a**, mp 67—67.5°C. *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.73; H, 7.51; N, 6.96. Found: C, 53.47; H, 7.45, N, 6.90. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1735, 1720, 1640. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.36 (3H, d, J=7 Hz, C_2–CH_3), 2.80 (3H, d, J=6 Hz, $NHC\underline{H}_3$), 3.58 (1H, q, J=7 Hz, C_2–H), 3.59 (2H, s, C_4–H), 4.16 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.42—6.81 (1H, b, NH).

N-Benzyl-4-ethoxycarbonyl-2-methyl-3-oxobutyramide (**10b**)——A solution of **5** (5 g, 11.0 mmol) and excess benzylamine in EtOH was stirred for 7 days at room temperature, and then treated as described for the synthesis of **9a** to give 1.3 g (21%) of **10b** as an oil. *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.23; H, 6.74; N, 5.05. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 1740, 1720, 1650, 1590. NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.40 (3H, d, J=7 Hz, C_2–CH_3), 3.57 (2H, s, C_4–H), 3.62 (1H, q, J=7 Hz, C_2–H), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.42 (2H, d, J=6 Hz, $C\underline{H}_2Ph$), 5.60—6.03 (1H, b, NH), 7.30 (5H, s, Ph).

4-Ethoxycarbonyl-N-methyl-3-oxobutyramide-Mg Complex (**11**)——A solution of **1a** (10 g, 21.6 mmol) and excess methylamine in EtOH was stirred for 4 h at room temperature, and the solvent was evaporated off. The residue was recrystallized from EtOH–H_2O to give **11** (7.8 g, 97%), mp 135—137°C. *Anal.* Calcd for $C_{16}H_{28}MgN_2O_{10}$: C, 44.41; H, 6.52; N, 6.47. Found: C, 44.61; H, 6.60; N, 6.22. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1660, 1640, 1620, 1530. NMR (DMSO-d_6) δ: 1.19 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.55 (6H, d, J=6 Hz, $NHC\underline{H}_3$), 2.80 (4H, s, H_2O), 3.38 (4H, s, C_4–H), 3.89 (4H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.55 (2H, s, C_2–H), 7.40—7.91 (2H, b, NH).

References and Notes

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