

Nucleophilic Substitution Accompanying Carbon–Carbon Bond Cleavage Assisted by a Nitro Group

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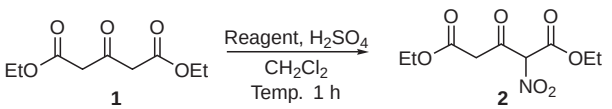
A 2-nitrated 3-oxoester reacted with amines or alcohols to afford unsymmetrical malonic acid derivatives as a result of nucleophilic substitution accompanying C–C bond cleavage. The 2-nitrated 3-oxoester easily formed ammonium salts with amines. When the amine is liberated from the salt under equilibrium, nucleophilic amine and electrophilic keto ester locate close to each other. This intimate pair effect causes a pseudo intramolecular reaction to occur, giving rise to effective substitution under mild conditions.

Introduction of three halogen atoms at the α-position activates a carbonyl group to cause nucleophilic substitution by hydroxide ion, which is well-known as the haloform reaction.[1] Similar activation of a carbonyl group can be achieved by introducing only one nitro group. Although some other deacylations are known,[2–5] the nucleophile has been limited to water, except for a few cases.[6,7] There are some reports on deacylation of 2-nitroketones giving carboxylic acids, though harsh conditions are necessary.[8,9] Deacylation is considered to proceed more easily if an additional electron-withdrawing group is introduced to the nitroketones. Indeed, during the course of our study on nitration of 1,3-dicarbonyl compounds, we have observed that 2-nitro-1,3-diketones are easily hydrolyzed by ambient moisture at room temperature.[10] We planned to exploit the present deacylation to organic synthesis, in which a 2-nitro-3-oxoester was used as a novel acylating agent of nucleophiles, such as amines and alcohols. In this work, our attention focused on unsymmetrical malonic acid derivatives, which are important synthetic intermediates for elaborate syntheses of polyfunctionalized systems.[11,12] In spite of their synthetic utility, they are not always readily available, because one of the two equivalent carbonyl groups of diethyl malonate must be selectively transformed.

Result and Discussion

Synthesis of the 2-nitro-3-oxoester, diethyl 2-nitro-3-oxopentanedioate (**2**), was performed by nitration of 3-oxoester **1** according to Laikhter's method using two phase reaction (dichloromethane–sulfuric acid).[9] In this nitration, controlling the reaction temperature was found to be crucial, and the yield of **2** was improved up to 86% after optimizing the reaction conditions (Table 1). The electron-withdrawing property of the nitro group of **2** prevents the formation of polynitrated keto esters during the nitration of **1**. Furthermore, nitrated compound **2** was easily isolated by separating the organic layer from the reaction mixture after nitration, because only **2** dissolved in the organic layer.

Table 1. Nitration of 3-Oxoester **1**



1 **2**

Run	Reagent	Temp/°C	Yield/%[b)]
1[a)]	fuming HNO_3	−10	48
2[a)]	fuming HNO_3	−5	86
3[a)]	fuming HNO_3	0	38[c),d)]
4	HNO_3	−5	59
5	NH_4NO_3	−5	57

a) Fuming HNO_3 ($d = 1.52$). b) Isolated yield. c) Mixture containing unidentified by-products. d) Yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

When a solution of 2-nitro-3-oxoester **2** and propylamine **3a** in dichloromethane was stirred at room temperature for 1 day, nucleophilic substitution proceeded quantitatively at the central carbonyl group to give amide ester **4a** together with ethyl nitroacetate **5**. Product **4a** was easily isolated by column chromatography on silica gel (Table 2, Run 1). Nitrated compound **2** could be employed for the subsequent reaction in a dichloromethane solution without concentration or further purification. Bulkier primary amines **3b** and **3c** and secondary amines **3d** and **3e** could be employed for the present acylation, and the corresponding amide esters **4b**–**4e** formed in moderate yields (Runs 2–5). In the case of morpholine **3e**, acylation proceeded even at room temperature. Functionalized amide ester **4f** was also prepared by using allylamine **3f** (Run 6). These results showed the present reaction was considerably affected by the bulkiness of amines, which prompted us to study the selective

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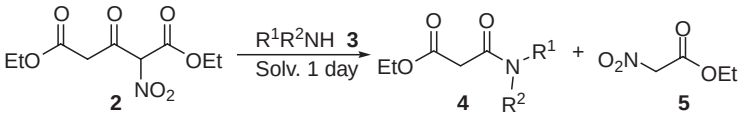
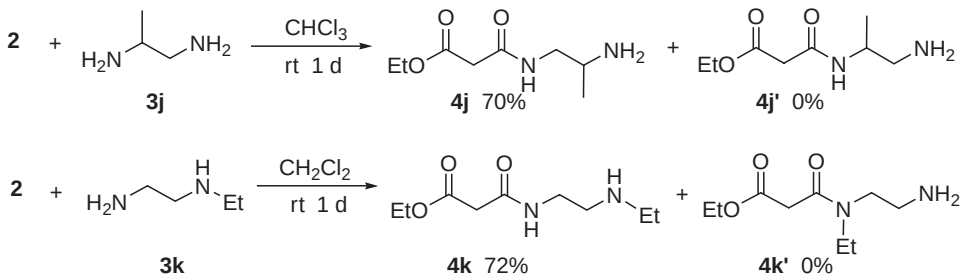
Table 2. Synthesis of Unsymmetrical Amide Esters **4**



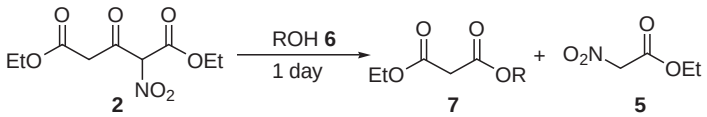
Run	R^1	R^2	Solv.	Temp/°C	Yield of **4**[a)]/%
1	Pr	H	**a** CH_2Cl_2	rt	quant.
2	*i*-Pr	H	**b** CH_2Cl_2	40	62
3	*t*-Bu	H	**c** CH_2Cl_2	40	41
4[b)]	Et	Et	**d** $CHCl_3$	60	50
5	$(CH_2)_2O(CH_2)_2$		**e** $CHCl_3$	rt	68
6	$CH_2{=}CHCH_2$	H	**f** $CHCl_3$	rt	80
7	Ph	H	**g** CH_2Cl_2	40	45
8	*p*-$NO_2C_6H_4$	H	**h** $CHCl_3$	60	55
9	*p*-$MeOC_6H_4$	H	**i** CH_2Cl_2	rt	quant.

a) All of products **4** except for **4h** have been reported in Refs. 6, 13, and 14. b) Reaction time: 2 days.



Scheme 1. Chemoselective modification of 1,2-diamines **3j** and **3k**.

Table 3. Acylation of Alcohols



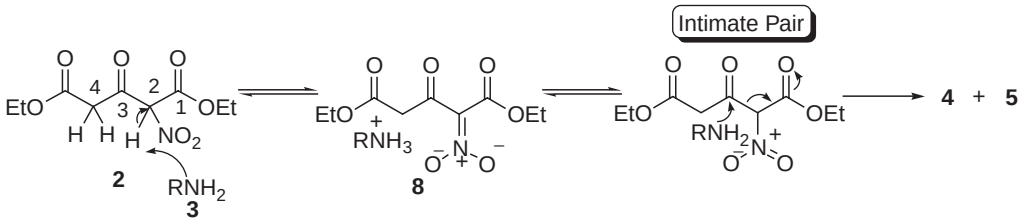
Run	ROH	(molar amount)	Temp/°C	Yield of **7**[d)]/%
1	MeOH	(solv.)	**a** rt	92
2[a)]	MeOH	(20)	**a** 60	99
3[a)]	MeOH	(5)	**a** 60	89
4	*i*-PrOH	(solv.)	**b** 65	59
5[b)]	*t*-BuOH	(solv.)	**c** 80	38[c)]

a) Chloroform was used as the solvent. b) 1 molar amount of $KOBu^t$ was added. c) Yield based on ^{1}H NMR. d) Ref. 16.

acylation of diamines **3j** and **3k**. When diamine **3j** was acylated by using commercially available ethyl chloroformylacetate[15] in the presence of triethylamine, the difference in bulkiness between the two amino groups was not recognized, and both **4j** and **4j′** were afforded in 50% yield.[6] In the acylation of diamine **3k** by ethyl chloroformylacetate, a mixture of **4k** and the double-acylated product was produced. On the other hand, nitrated keto ester **2** acylated exclusively less hindered primary amino groups of **3j** and **3k** without any modification of the bulky amino group leading to **4j** and **4k**, respectively (Scheme 1).

Less nucleophilic aromatic amines **3g–3i** similarly reacted with **2** to afford anilide esters **4g–4i**, respectively. In the case of aniline **3g**, the yield of **4g** was low owing to the complication of the reaction mixture (Table 2, Run 7). Quite different reactivities were observed between substituted anilines **3h** and **3i**. Whereas aniline **3h** with an electron-withdrawing group afforded anilide ester **4h** in a moderate yield under heated conditions (Run 8), aniline **3i**, which was substituted with an electron-donating group, underwent acylation to give **4i** in quantitative yield even at room temperature (Run 9). These results show that electronic property of amines is an important factor for the present reaction.

Alcohols were also usable as nucleophiles for this reaction. When a solution of nitrated compound **2** in methanol **6a** was stirred at room temperature, unsymmetrical diester **7a** was obtained in a high yield (Table 3, Run 1). The amount of methanol **6a** could be decreased to 5 molar amounts by conducting



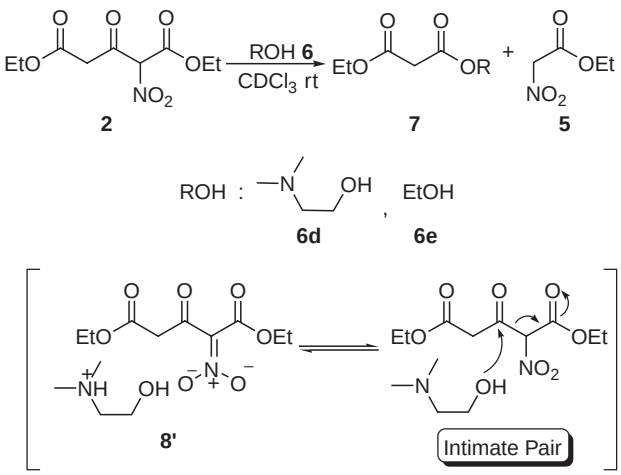
Scheme 2. A plausible mechanism for the reaction of **2** with an amine.

the reaction in a chloroform solution under reflux conditions (Runs 2 and 3). Furthermore, sterically hindered isopropanol **6b** and *tert*-butyl alcohol **6c** could be employed giving diesters **7b** and **7c** in moderate yields, though the addition of potassium *tert*-butoxide was necessary in the latter case (Runs 4 and 5).

To clarify the reaction mechanism, we monitored the reactions of **2** and propylamine **3a** or methanol **6a** by ^{1}H NMR using chloroform-*d* as a solvent at room temperature. The signals for the diastereotopic protons at the 4-position of **2** were observed separately. In the reaction with propylamine **3a**, these signals became equivalent immediately after the addition of **3a** to a solution of **2**, and the signals of *N*-methylene protons of **3a** shifted to 3.0 from 2.6 ppm. These changes indicate that amine **3a** removes a hydrogen at the 2-position of **2** to form **8**. Then, signals of **4a** and **5** gradually increased as those of **8** decreased, and **8** was completely consumed within 3 h. It is noteworthy that the reaction quantitatively proceeded without formation of any detectable by-products. In the reaction of **2** with methanol **6a**, however, the diastereotopic methylene signals did not change, indicating that a nitroalkanide corresponding to **8** does not form. Furthermore, 30 h were required for consumption of **2**.

On the basis of above the results, a plausible mechanism is proposed in Scheme 2. The key step of the present reaction is the formation of ammonium nitroalkanide **8**, which involves the removal of the hydrogen at the α-position of the nitro group. Because the 2-position is connected with a nitro and two carbonyl groups, the hydrogen at this position is acidic enough for the formation of nitroalkanide **8**. When the amine is liberated from **8** under equilibrium, the nucleophile and the electrophile, namely, the amine and **2**, are located close to each other, which is called an intimate pair. Nucleophilic substitution by the amine easily occurs at the 3-position to afford amide ester **4a** accompanied by elimination of nitroacetate **5** as a result of C2–C3 bond cleavage assisted by the electron-withdrawing property of the nitro group. Because of this intimate pair effect, the reaction process is thought to be a pseudo intramolecular one, thus, acylation of the amine occurs without by-products under mild conditions. On the other hand, the reaction of **2** with methanol **6a** is considerably slower, since less basic methanol does not form the corresponding intimate pair. However, the lower nucleophilicity of methanol is another reason for the slow reaction.

To confirm the acceleration effect by forming the intimate pair, we monitored the reaction of 2-dimethylaminoethanol **6d** (124 mmol dm^{-3}) and ethanol **6e** (124 mmol dm^{-3}) by ^{1}H NMR using chloroform-*d* as the solvent at 24 °C. Both nucleophiles underwent O-acylation with **2** to give the corresponding diesters **7d** and **7e**, respectively. In the case of **6d**,



Scheme 3. Comparison of the reactivity between alcohols **6d** and **6e**.

salt **8′** formed just after addition of aminoethanol **6d**. Significant difference in the reactivity between alcohols **6d** and **6e** was observed. Although the reaction of **6d** with **2** afforded **7d** in 90% yield after 2 h, **7e** was obtained in only 6% yield after the same reaction period. The reactivity of **6e** did not increase even when triethylamine was added to a reaction mixture. These results support that the reaction of **6d** proceeds by a pseudo intramolecular process in which an intimate pair is formed after the deprotonation of **2** with the dimethylamino group (Scheme 3). Furthermore, whether the reaction proceeded in the pseudo intramolecular process or the intermolecular process was determined by the experimental results under dilute conditions. When the concentration of both **2** and **6e** (62.5 mmol dm^{-3}) was decreased to the half of original, the conversion giving **7e** substantially decreased from 17% to 3% after 6 h, which suggests the reaction is an intermolecular process. On the other hand, aminoalcohol **6d** (62.5 mmol dm^{-3}) was similarly converted to **7d** (90% after 2 h) in spite of the dilute conditions, supporting the pseudo intramolecular process.

We have previously observed an intimate pair effect in the reaction of 2-aryl-3-oxoesters with amines, in which the acidity of the hydrogen at the 2-position is promoted by bulkiness of an aryl group, forming the intimate pair after forming ammonium enolate.[6] However, the acidity of the hydrogen at 2-position is promoted by a nitro group in 2-nitro-3-oxoester **2** in the present reaction. The strong electron-withdrawing effect of a nitro group prevents multiple nitration of **1**, whereas a complex mixture is sometimes observed due to polyarylation in the case of 2-aryl-3-oxoester. Moreover, the electrophilicity

of the carbonyl group is considerably increased by an adjacent nitro group, which enables substitution with an alcohol under milder conditions than those employed in the case of 2-aryl-3-oxoester.

Conclusion

We demonstrated 2-nitro-3-oxoester could be used as acylating reagents by introducing a nitro group at the α-position. Unsymmetrical malonic acid derivatives, amide esters **4** and diesters **7** were easily prepared upon treatment of diethyl 2-nitro-3-oxopentanedioate **2** with various amines and alcohols in moderate to high yields under mild conditions without any special reagents. In the present reaction, the nitro group plays the following roles: it (a) increases the acidity of the hydrogen at 2-position, which enables the formation of ammonium nitroalkanides **8** to cause the pseudo intramolecular process, (b) improves the electophilicity of the adjacent carbonyl group, and (c) assists C–C bond cleavage to release the ester function as nitroacetate **5**. Consequently, this work provided new aspects in the chemistry of 3-oxoesters, which have been studied for a long time.

Experimental

Melting points were determined on a Yanaco micro-melting-point apparatus and are uncorrected. All reagents and solvents were commercially available and used as received. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 at 400 MHz and at 100 MHz, respectively, with TMS as an internal standard. Assignments of ^{13}C NMR spectra were performed by DEPT experiments and are indicated as p (primary), s (secondary), t (tertiary), and q (quaternary). IR spectra were recorded on a Horiba FT-200 IR spectrometer. Mass spectra were recorded on a JEOL JMS-AX505HA. Elemental microanalyses were performed using a Yanaco CHN corder.

Preparation of Diethyl 2-Nitro-3-oxopentanedioate (2). Nitration was conducted according to modified Laikhter's method.[9] Mixed acid was prepared by slowly adding fuming nitric acid (0.45 mL, 10 mmol, $d = 1.52$) to 18 M sulfuric acid (1.9 mL, 34 mmol) at $-10\,^\circ$C in an ice-salt bath. To a solution of diethyl 3-oxopentanedioate (**1**) (1.3 mL, 10 mmol) in dichloromethane (7 mL), the mixed acid was slowly dropped with vigorously stirring over 30 min at $-5\,^\circ$C, and the mixture was stirred at the same temperature for further 1 h. After addition of cold dichloromethane (10 mL), the organic layer was immediately separated, dried over $MgSO_4$, and concentrated to give nitrated 3-oxoester **2** as a yellow oil (2.12 g, 86%). IR (neat) 3200–3400 br (OH), 1747 (CO), 1668 (C=C), 1569 and 1373 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (t, $J = 6.9$ Hz, 3H, OCH_2CH_3), 1.34 (dd, $J = 7.1$, 7.1 Hz, 3H, OCH_2CH_3), 3.74 (d, $J = 17.2$ Hz, 1H, COC*H*HCO), 3.84 (d, $J = 17.2$ Hz, 1H, COCH*H*CO), 4.22 (q, $J = 6.9$ Hz, 2H, OCH_2CH_3), 4.35–4.41 (m, 2H, OCH_2CH_3), 5.39 (s, 1H, C*H*NO_2); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.6 (p), 13.7 (p), 46.6 (s), 62.0 (s), 63.7 (s), 92.8 (t), 159.7 (q), 165.9 (q), 186.5 (q). In the NMR spectrum of **2**, signals due to two kinds of enol forms were also observed, which were too small to be assigned. Satisfactory elemental analysis and mass spectroscopy could not be performed because of its instability. Nitrated 3-oxoester **2** was used for the subsequent acylation immediately after work up.

Preparation of Ethyl 3-Propylamino-3-oxopropanoate (4a).[6] To a solution of 2-nitrated 3-oxoester **2** (358 mg, 1.45 mmol) in dichloromethane (1.5 mL), propylamine **3a** (119 µL, 1.45 mmol) was added, and the resultant mixture was stirred for 1 day at room temperature. After concentration under reduced pressure, the residue was subjected to chromatography on silica gel affording **4a** as a dark yellow oil (eluted with AcOEt, 246 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.94 (t, $J = 7.3$ Hz, 3H, $NHCH_2CH_2CH_3$), 1.29 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.56 (tq, $J = 7.1$, 7.3 Hz, 2H, $NHCH_2CH_2CH_3$), 3.25 (dt, $J = 6.5$, 7.1 Hz, 2H, $NHCH_2CH_2CH_3$), 3.31 (s, 2H, $COCH_2CO$), 4.20 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 7.10–7.20 (br t, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 11.4 (p), 14.2 (p), 22.6 (s), 41.4 (s), 41.7 (s), 61.8 (s), 165.3 (q), 169.5 (q). Other amide esters **4** and diesters **7** were prepared in the same way.

Ethyl 3-Allylamino-3-oxopropanoate (4f).[14] Yellow oil, IR (neat) 3083sh (NH), 1741 (CO), 1664 (CO) 1645 (C=C), 1553 and 1332 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.30 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.34 (s, 2H, $COCH_2CO$), 3.91–3.94 (m, 2H, $NHCH_2$), 4.21 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 5.15 (dd, $J = 1.4$, 10.2 Hz, 1H, $CH_2CH{=}CHH$), 5.22 (dd, $J = 1.4$, 17.1 Hz, 1H, $CH_2CH{=}CHH$), 5.87 (ddt, $J = 5.5$, 10.2, 17.1 Hz, 1H, $CH_2CH{=}CHH$), 7.2–7.3 (br, 1H, N*H*): ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.1 (p), 41.0 (s), 41.9 (s), 61.7 (s), 116.4 (s), 133.7 (t), 164.8 (q), 169.9 (q); MS (EI) (m/z) 171 (M^+, 15%), 126 (15), 56 (100).

Ethyl 3-(*p*-Nitroanilino)-3-oxopropanoate (4h). Yellow powder, mp 104–105 °C; IR (neat) 3313 (NH), 1725 (CO), 1695 (CO), 1556 and 1305 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.35 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.52 (s, 2H, $COCH_2CO$), 4.29 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 7.75 (d, $J = 9.2$ Hz, 2H, aromatic), 8.23 (d, $J = 9.2$ Hz, 2H, aromatic), 9.85 (s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.4 (p), 41.7 (s), 62.7 (s), 119.9 (t), 125.4 (t), 143.6 (q), 144.1 (q), 163.9 (q), 170.3 (q). MS (FAB) (m/z) 253 ($M^+ + 1$, 100%); Found: C, 52.18; H, 4.48; N, 10.94%. Calc. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11%.

Hydrochloride of Ethyl 3-(2-Dimethylaminoethoxy)-3-oxopropanoate (7d). When oxoester **2** (672 mg, 2.73 mmol) was allowed to react with dimethylaminoethanol **6d** (275 µL, 2.73 mmol) in dichloromethane (3 mL) according to the general procedure, O-acylation proceeded to afford **7d**. However, it was difficult to isolate **7d**, since this product gradually formed a salt with ethyl nitroacetate **5**, a by-product of the reaction. Hence, diester **7d** was isolated as its hydrochloride. After addition of 1 M (=mol dm^{-3}) hydrochloric acid (2.73 µL, 2.73 mmol) to the reaction mixture, the aqueous solution was washed once with benzene (20 mL) to remove liberated ethyl nitroacetate. Then, the aqueous layer was evaporated to afford **7d** as the hydrochloride (385 mg, 60%).

The salt consists of two isomers **A** and **B**, of which the structures were not assigned. The ratio **A**/**B** was variable depending on the solvent (**A**/**B** = 1/2 in $CDCl_3$, 4/1 in CD_3CN, and 1/1 in DMSO-d_6). In the ^{1}H NMR spectrum, the integrals of isomers **A** and **B** are indicated as H_A and H_B, respectively. The presence of chloride in **7d** was confirmed by using both a Beilstein test and qualitative analysis using silver nitrate. Satisfactory elemental analysis was not obtained because it was hygroscopic.

Colorless oil, IR (neat) 1747 (CO), 1728 cm^{-1} (CO); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (t, $J = 7.1$ Hz, $3H_A$, OCH_2CH_3), 1.33 (t, $J = 6.9$ Hz, $3H_B$, OCH_2CH_3), 2.87–2.98 (br s, $6H_A$ + $6H_B$, NCH_3), 3.31–3.39 (br, $2H_A$ + $2H_B$, NCH_2CH_2), 3.42 (s, $2H_B$, $COCH_2CO$), 3.51 (s, $2H_A$, $COCH_2CO$), 4.20 (q, $J = 7.1$ Hz, $2H_A$, OCH_2CH_3), 4.25 (q, $J = 6.9$ Hz, $2H_B$, OCH_2CH_3), 4.6–4.75

(br, $2H_A + 2H_B$, OCH_2CH_2), 12.4–12.8 (br, $1H_A + 1H_B$, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 15.9 (p, C_A), 16.0 (p, C_B), 42.8 (s, C_A), 43.1 (s, C_B), 45.5 (p, C_A), 45.7 (p, C_B), 57.9 (s, C_A), 58.0 (s, C_B), 61.2 (s, C_A), 63.4 (s, C_A), 63.6 (s, C_B), 66.7 (s, C_B), 167.8 (q, C_A), 168.2 (q, C_A), 169.3 (q, C_B), 170.1 (q, C_B); MS (EI) (m/z) 203 ($M^+ - 1$, 65%), 158 (100).

The Comparison of the Reaction Rates Using Propylamine and Methanol. To a solution of 2-nitro-3-oxoester **2** (24.7 mg, 0.100 mmol) and 1,1,2,2-tetrachloroethane (internal standard, 9.0 μL) in $CDCl_3$ (300 μL), propylamine **3a** (8.2 μL, 0.10 mmol), or methanol **6a** (4.1 μL, 0.10 mmol) was added. The reaction mixtures were stood at room temperature, and the ^1H NMR spectra were measured at appropriate intervals. The amounts of amide ester **4a** and diester **7a** were determined by comparing their peak integrals with that of the internal standard.

The Comparison of the Reaction Rates Using 2-Dimethylaminoethanol 6d and Ethanol 6e. To a solution of 2-nitro-3-oxoester **2** (12.4 mg, 0.050 mmol) and 1,1,2,2-tetrachloroethane (internal standard, 9.0 μL) in $CDCl_3$ (300 μL), aminoethanol **6d** (5.0 μL, 0.05 mmol) or ethanol **6e** (3.0 μL, 0.05 mmol) was added. The reaction mixtures were stood at room temperature, and the ^1H NMR spectra were measured at appropriate intervals. The amounts of malonates **7d** and **7e** were determined by comparing their peak integrals with that of the internal standard.

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Supporting Information

Spectral data of **4b**–**4e**, **4g**, **4i**–**4k**, and **7a**–**7c**. This material is available free of charge on the Web at: http://www.csj.jp/journals/bcsj/.

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