*International Journal of Organic Chemistry*, **2012, 2, 111-116**
http://dx.doi.org/10.4236/ijoc.2012.22017 Published Online June 2012 (http://www.SciRP.org/journal/ijoc)

# Three-Component Coupling Catalyzed by Phosphine: Preparation of $\alpha$-Amino $\gamma$-Oxo Acid Derivatives

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Received March 8, 2012; revised April 20, 2012; accepted April 23, 2012

## ABSTRACT

The three-component coupling reaction of ethyl propiolate (**1**), phthalimide (**2**), and aldehyde (**3**) catalyzed by triphenylphosphine, was developed. A solution of an equivalent amount of **1** and **2** in benzaldehyde (**3a**) in the presence of 30 mol% of $PPh_3$ was heated at 100˚C for 48 h to give *N*-(1-ethoxycarbonyl-3-oxo-3-phenylpropyl)phthalimide (**4a**) in 83% yield. This reaction was thought to proceed via vinylphosphonium salt formed from the reaction of ethyl propiolate (**1**) with triphenylphosphine *in situ*.

**Keywords:** Three-Component Coupling; Phosphine; 2-Amino-4-Oxocarboxylic Acid

## 1. Introduction

Phosphines have been the subject of great focus as catalysts for organic synthesis [1-10]. Especially, Morita-Baylis-Hillman reaction catalyzed by a phosphine has been paid much attention for constructing carbon-carbon frame work [11-14]. In these reactions, phosphine attacks electron-deficient carbon-carbon multiple bond, and then the anion in the produced zwitterionic intermediate attacks another molecule as a nucleophile. We have focused on the reactivity of vinylphosphonium salts, formed in situ from acetylenecarboxylates and phosphines instead of pre-prepared of them [15-18], for the reason of simple procedure [19-22]. That is, those [23,24] from dialkyl acetylenedicarboxylates or alkyl alkynoates and triphenylphosphine have been applied on the synthesis of various organic compounds [25-33].

In the course of our study for the reaction of acetylenecarboxylic esters in the presence of $PPh_3$, we found the efficient three-component coupling of acetylene carboxylic esters, phthalimide, and aldehyde catalyzed by phosphine. This three-component coupling reaction is an efficient way to construct a useful framework in a one-pot, and we wish to describe the detail here.

## 2. Results and Discussion

### 2.1. Reaction Conditions

The reaction of ethyl propiolate (**1**) with phthalimide (**2**) and *p*-nitrobenzaldehyde (**3c**) was performed in the presence of two equivalents of $Ph_3P$ in toluene (5 mL) (Equation (1)). From the reaction at 100˚C for 48 h, ethyl 4-oxo-4-(4-nitrophenyl)-2-phthalimidoylbutanoate (**4c**) was obtained in 15% yield accompanied by ethyl 2-phthalimidoyl-2-propenoate (**5**) in 19% yield (**Table 1**, entry 2). This product **4c** is not the desired compound by the intermolecular Wittig reaction, but the compound consisted of three components. The reaction conditions were then optimized (**Table 1**). At higher concentration, the yield of the product **4c** was improved. The reaction at room temperature or at reflux resulted a lower yield of **4c** (**Table 1**, entries 1 and 4). Employment of other solvents, such as $CH_2Cl_2$, $CHCl_3$, $CH_3CN$, resulted in a lower yield. Especially, when acetonitrile was used as the solvent, compound **5** was mainly obtained in 36% yield with a trace amount of **4c**. Finally, a mixture of **1** (1.0 mmol), **2** (1.0 mmol), and **3c** (2.0 mmol) in toluene (1.5 mL) in the presence of 2.0 mmol of $PPh_3$ was stirred at 100˚C for 48 h to give **4c** in 40% yield (**Table 1**, entry 3).

The effect of the catalyst was also examined (**Table 1**). Using $PBu_3$ instead of $PPh_3$ decreased the yield of the product (entry 9). Amines, such as $NEt_3$ and pyridine, did not catalyze this reaction at all. Triphenylphosphine was demonstrated not to be needed in a stoichiometric amount. That is, the use of 30 mol% of $Ph_3P$ was enough for this reaction (38% yield of **4c**, **Table 1**, entry 7).

Trost *et al*. reported that dehydroamino acid derivatives

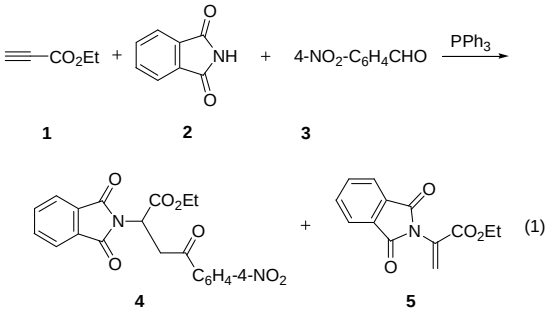
 

**Table 1. Reaction of ethyl propiolate (1), phthalimide (2), and 4-nitrobenzaldehyde (3c) [a].**

| Entry | Phosphine (equiv) | Solvent | Reaction Temp. (˚C) | Yield [b] of Products (%) | |
|---|---|---|---|---|---|
| | | | | **4c** | **5** |
| 1 [c] | $PPh_3$ (2.0) | $PhCH_3$ (5 mL) | rt | 7 | 8 |
| 2 | $PPh_3$ (2.0) | $PhCH_3$ (5 mL) | 100 | 15 | 19 |
| 3 | $PPh_3$ (2.0) | $PhCH_3$ (1.5 mL) | 100 | 40 | 17 |
| 4 | $PPh_3$ (2.0) | $CH_2Cl_2$ (1.5 mL) | reflux | 26 | 22 |
| 5 | $PPh_3$ (2.0) | $CHCl_3$ (1.5 mL) | reflux | 26 | 20 |
| 6 | $PPh_3$ (2.0) | $CH_3CN$ (1.5 mL) | reflux | trace | 36 |
| 7 | $PPh_3$ (0.3) | $PhCH_3$ (1.5 mL) | 100 | 38 | 15 |
| 8 | $PPh_3$ (0.1) | $PhCH_3$ (1.5 mL) | 100 | 18 | 10 |
| 9 | $PBu_3$ (2.0) | $PhCH_3$ (1.5 mL) | 100 | 10 | 0 |

[a] **2** (1.0 mmol), **3c** (1.0 mmol), $Ph_3P$ (2.0 mmol) were mixed in solvent at room temperature, then **1** (1.0 mmol) was added to the reaction mixture, and the resulting mixture was stirred for 48 h; [b] Isolated yield based on the amount of **2**; [c] The reaction was carried out for 96 h.

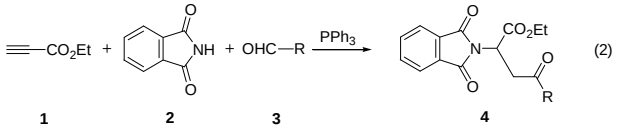
were efficiently formed in the mixture of toluene and buffer solution of acetic acid/sodium acetate [34]. Therefore, the same system was tried for this reaction. That is, the reaction of **1**, **2**, and **3c** in the presence of 2.0 equiv of $PPh_3$ in a mixture of toluene, acetic acid, and sodium acetate gave the product **4c** in 20% yield and **5** in 14% yield.




## 2.2. Using Various Aldehydes

The aldehyde was then changed for determining the scope and limitation of this reaction by using a catalytic amount of $PPh_3$ (**Table 2**). Based on above results, the reaction at a high concentration smoothly proceeds. Therefore, if the aldehyde was a liquid, excess aldehyde (1 mL) can be used without solvent. When the aldehyde is a solid, toluene was used as the solvent, and the yields were moderate to low (entries 3 and 7). Without solvent, good product yields were achieved using aromatic aldehydes. When using benzaldehyde (**3a**) as the aldehyde, **4a** was obtained in 83% yield. Introducing substituents on the benzaldehyde did not significantly affect the yield of the product. Heteroaromatic aldehydes, such as 2-furanecarbaldehyde (**3h**) and 2-pyridinecarbaldehyde (**3i**) (**Table 2**, entries 8 and 9), were also used for this reaction, while aliphatic aldehydes **3j**, **3k**, gave products in poor yields (**Table 2**, entries 10 and 11).

For the reaction of **1** with benzaldehyde (**3a**), using a large quantity of **3a** decreased the yield of **4a** to 35% (**Table 2**, entry 12). This result shows that the concentration of the alkynoate, $PPh_3$, and/or phthalimide is important for this reaction. Tributylphosphine instead of $PPh_3$ was not effective similar to that mentioned above (**Table 2**, entry 13).




Next, several alkynoates were examined for this coupling reaction without solvent. When ethyl 2-butynoate was used for this reaction, no three-component coupling product was obtained. Dimethyl butynedioate, which showed good reactivity for the preparation of heterocyclic compounds via the *in situ* vinylphosphonium intermediate, was allowed to be used for this three component coupling. Although various nucleophiles such as amines, amides, alcohols, and electrophiles, such as aldehydes, ketones, acid chlorides, were employed for this reaction, the desired product was not obtained, but only polymeric materials were formed.

Various nitrogen-containing nucleophiles having protonation ability were tested next. The primary amine, butylamine, directly reacted with propiolate to give mainly the Michael adducts. *N*-Tosylamide [34] was subjected to this reaction, but only a trace amount of the desired product was formed. Amides, such as caprolactam, *N*-acetylaniline, did not react with **1**. Pyrrole was employed for this reaction, but no reaction occurred as well.

## 2.3. Plausible Reaction Mechanism

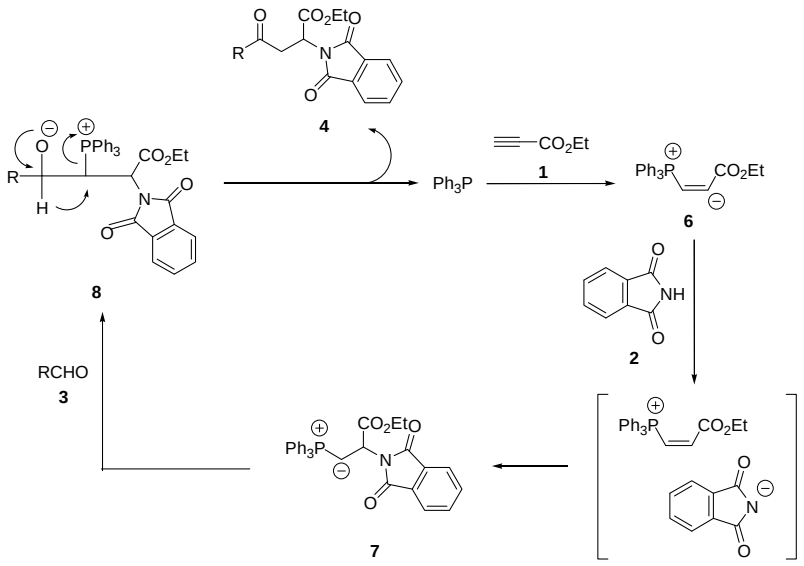
The reaction may occur in the following way (**Scheme 1**): (1) nucleophilic attack of $Ph_3P$ to ethyl propiolate (**1**) to

**Table 2. Reactions of ethyl propiolate (1), phthalimide (2), and various aldehydes (3) [a].**

| Entry | Aldehyde **3** | | Product **4** | |
|---|---|---|---|---|
| | | R= | | Yield [b] (%) |
| 1 | **3a** | Ph | **4a** | 83 |
| 2 | **3b** | 4-$FC_6H_4$ | **4b** | 81 |
| 3[c] | **3c** | 4-$NO_2C_6H_4$ | **4c** | 38 |
| 4 | **3d** | 4-$MeC_6H_4$ | **4d** | 68 |
| 5 | **3e** | 4-$MeOC_6H_4$ | **4e** | 70 |
| 6 | **3f** | 1-naphthyl | **4f** | 65 |
| 7 [c] | **3g** | 2-naphthyl | **4g** | 45 |
| 8 | **3h** | 2-furyl | **4h** | 51 |
| 9 | **3i** | 2-pyridyl | **4i** | 72 |
| 10 | **3j** | $(C_2H_5)_2CH$ | **4j** | 27 |
| 11 [d] | **3k** | $CH_3(CH_2)_2$ | **4k** | 25 |
| 12 [e] | **3a** | Ph | **4a** | 35 |
| 13 [f] | **3a** | Ph | **4a** | 21 |

[a] Phthalimide (**2**, 1.0 mmol) and $Ph_3P$ (30 mol%) were mixed in the aldehyde (**3**, 1.0 mL) at room temperature, and then ethyl propiolate (**1**, 1.0 mmol) was added. The mixture was stirred at 100˚C for 48 h; [b] Isolated yield based on the amount of **2**; [c] Aldehyde (**3**, 1.0 mmol) and toluene (1.5 mL) were used; [d] The reaction was carried out at 65˚C; [e] Benzaldehyde (**3c**, 3 mL) was used; [f] $PBu_3$ was used instead of $PPh_3$.




**Scheme 1. Plausible mechanism.**

give zwitterionic intermediate (**6**), (2) protonation of the intermediate **6** by phthalimide, (3) Michael addition of phthalimidate anion to give ylide **7**, and (4) ylide attacks to aldehyde to give **8**. In the last step, the Wittig alkenylation does not proceed, and the $\gamma$-keto $\alpha$-amino acid derivative **4** is produced. Probably, the hydride shift occurred from the intermediate **8**. This type of hydride shift was suggested in the reaction of butanal with the butoxymethylenetriphenylphosphonium ylide forming 1-butoxy-2-pentanone [35]. In our reaction, the same hydride shift could proceed to give the product **4** in good yield. Alternatively, **7** undergoes intramolecular proton transfer, and elimination of the phosphine (by an E1cb mechanism). The phosphine may add to the aldehyde to generate an umpolung type intermediate, which would undergo conjugate addition to the acrylate (derived from **7**) to give an intermediate analogous to **8**, which can eliminate the phosphine to give **4** [36].

## 3. Conclusion

In conclusion, three-component coupling reaction of ace-

tylenic ester, phthalimide, and aldehyde was established. This reaction gives the $\gamma$-keto $\alpha$-amino acid derivatives in one-pot in up to 83% yield. The reaction seems to proceed through vinylphosphonium salts derived from acetylenic ester and phosphine, and via hydride transfer reaction. The application of this unique reaction is now underway.

## 4. Experimental

### 4.1. General

Proton nuclear magnetic resonance ($^1$H NMR) spectra were measured using a JEOL JNM A-400 (400 MHz) spectrometer using tetramethylsilane as the internal standard. IR spectra were measured on a Shimadzu IR-408 spectrometer. Mass spectral (GC-MS) data were recorded on a Shimadzu GP2000A instrument. Elemental analyses were performed at the Microanalytical Center of Kyoto University. High resolution mass spectra (FAB) were measured using a JEOL JMS-700 with *meta*-nitrobenzyl alcohol as the matrix. Melting points were measured on a Yanako Model MP and were not corrected. All substrates were purchased and used without further purification.

### 4.2. Typical Experimental Procedure

In an 80 mL-Schlenk tube were added phthalimide (**2**, 147 mg, 1.0 mmol), triphenylphosphine (79 mg, 30 mol%), aldehyde (**3**, 1.0 mL), and then ethyl propiolate (**1**, 98 mg, 1.0 mmol). The resulting mixture was heated at 100˚C for 48 h. Product was purified by column chromatogramphy (silica gel (200 - 400 mesh), hexane-ethyl acetate). When aldehydes were solid at room temperature, 1.0 mmol of aldehyde and 1.0 mL of toluene were used for the reaction.

### 4.3. Identification of the Products

***N*-(1-Ethoxycarbonyl-3-oxo-3-phenylpropyl)phthalimide (4a):** Light yellow solid, mp. 122˚C - 123˚C; $^1$H NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.83 (m, 2H), 7.72 (m, 2H), 7.44 - 7.58 (m, 3H), 4.92 (dd, *J* = 9.0, 5.6 Hz, 1H), 4.46 (dd, *J* = 14.0, 9.0 Hz, 1H), 4.23 (dd, *J* = 14.0, 5.6 Hz, 1H), 4.10 (m, 2H), 1.11 (t, *J* = 6.8 Hz, 3H); IR (KBr) 3500, 3000, 1770, 1710, 1595, 1460, 1435, 1395, 1350, 1290, 1170, 980, 883, 722 cm$^{-1}$; FAB-MS (m/z) 352 ($M^+$), 306 ($M^+$-OEt). Anal. calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.38; H, 4.72; N, 3.99.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(4-fluorophenyl)propyl]phthalimide (4b):** White solid, mp. 93˚C - 94˚C; $^1$H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.83 (m, 2H), 7.73 (m, 2H), 7.12 (m, 2H), 4.91 (dd, *J* = 9.4, 6.0 Hz, 1H), 4.46 (dd, *J* = 14.4, 9.4 Hz, 1H), 4.22 (dd, *J* = 14.4, 6.0 Hz, 1H), 4.11 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3450, 3100, 2900, 1767, 1700, 1590, 1505, 1465, 1390, 1348, 1305, 1220, 1156, 1108, 1030, 970, 857, 720 cm$^{-1}$; Anal. calcd for $C_{20}H_{16}FNO_5$: C, 65.04; H, 4.37; N, 3.79. Found: C, 65.08; H, 4.24; N, 3.79.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(4-nitrophenyl)propyl]phthalimide (4c):** Light yellow crystal, mp. 113˚C - 115˚C; $^1$H NMR ($CDCl_3$) δ 8.31 (m, 2H), 8.15 (m, 2H), 7.84 (m, 2H), 7.74 (m, 2H), 4.94 (dd, *J* = 8.6, 6.0 Hz, 1H), 4.46 (dd, *J* = 14.4, 8.6 Hz, 1H), 4.26 (dd, *J* = 14.4, 6.0 Hz, 1H), 4.11 (m, 2H), 1.12 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 191.6, 167.8, 167.2, 150.6, 140.1, 134.3, 131.7, 129.6, 123.9, 123.5, 62.4, 52.5, 36.6, 13.7; IR (KBr) 3000, 1772, 1710, 1600, 1525, 1395, 1347, 1288, 1110, 1030, 970, 855, 750, 720 cm$^{-1}$; FAB-MS (m/z) 397 ($M^+$), 351 ($M^+$-OEt). Anal. calcd for $C_{20}H_{16}N_2O_7$: C, 60.61; H, 4.07; N, 7.07. Found: C, 60.69; H, 3.96; N, 6.96.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(4-methylphenyl)propyl]phthalimide (4d):** Light yellow solid, mp. 85˚C - 87˚C; $^1$H NMR ($CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.82 (m, 2H), 7.72 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.90 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.45 (dd, *J* = 14.0, 9.0 Hz, 1H), 4.21 (dd, *J* = 14.0, 6.0 Hz, 1H), 4.09 (m, 2H), 2.38 (s, 3H), 1.11 (t, *J* = 6.8 Hz, 3H); IR (KBr) 2900, 1768, 1700, 1600, 1462, 1390, 1350, 1300, 1220, 1110, 1022, 963, 893, 822, 800 cm$^{-1}$; Anal. calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.96; H, 5.04; N, 3.84.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(4-methoxyphenyl)propyl]phthalimide (4e):** Light yellow solid, mp. 82˚C - 83˚C; $^1$H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.83 (m, 2H), 7.72 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.90 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.45 (dd, *J* = 14.4, 9.2 Hz, 1H), 4.20 (dd, *J* = 14.4, 6.0 Hz, 1H), 4.09 (m, 2H), 3.85 (s, 3H), 1.12 (t, *J* = 6.8 Hz, 3H); IR (KBr) 2900, 2250, 1770, 1710, 1670, 1590, 1510, 1463, 1395, 1355, 1260, 1228, 1170, 1028, 910, 845 cm$^{-1}$; Anal. calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.25; H, 4.82; N, 3.58.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(1-naphthyl)propyl]phthalimide (4f):** Light yellow solid, mp. 98˚C - 101˚C; $^1$H NMR ($CDCl_3$) δ 8.60 (d, *J* = 8.8 Hz, 1H), 7.44 - 7.96 (m, 10H), 5.07 (dd, *J* = 8.6, 6.4 Hz, 1H), 4.41 (m, 2H), 4.00 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3000, 1771, 1715, 1678, 1393, 1357, 1215, 1031, 970, 720 cm$^{-1}$; Anal. calcd for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 72.01; H, 4.53; N, 3.56.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(2-naphthyl)propyl]phthalimide (4g):** Light yellow solid, mp. 91˚C - 92˚C; $^1$H NMR ($CDCl_3$) δ 8.53 (d, *J* = 1.6 Hz, 1H), 7.51 - 8.04 (m, 10H), 5.09 (dd, *J* = 9.0, 5.8 Hz, 1H), 4.51 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.28 (dd, *J* = 14.4, 5.8 Hz, 1H), 4.10 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3000, 1771, 1715, 1505, 1465, 1430, 1395, 1355, 1300, 1215, 1123, 1087, 1025, 760 cm$^{-1}$; HRMS calcd for $C_{24}H_{19}NO_5$ 402.1341,

found 402.1325.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(2-furyl)propyl]phthalimide (4h):** White solid, mp. 105˚C - 106˚C; $^1$H NMR ($CDCl_3$) δ 7.68 - 7.84 (m, 4H), 7.56 (d, *J* = 1.2 Hz, 1H), 7.32 (d, *J* = 3.6 Hz, 1H), 6.54 (q, *J* = 1.6 Hz, 1H), 4.65 (dd, *J* = 8.2, 6.8 Hz, 1H), 4.40 (dd, *J* = 14.4, 8.2 Hz, 1H), 4.25 (dd, *J* = 14.4, 6.8 Hz, 1H), 4.13 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3000, 1770, 1715, 1672, 1563, 1460, 1390, 1360, 1300, 1213, 1025, 968, 755, 720 cm$^{-1}$; Anal. calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.29; H, 4.17; N, 4.38.

***N*-[1-Ethoxycarbonyl-3-oxo-3-(2-pyridyl)propyl]phthalimide (4i):** White solid, mp. 112˚C - 113˚C; $^1$H NMR ($CDCl_3$) δ 8.55 (m, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.69 - 7.86 (m, 5H), 7.43 (m, 1H), 4.96 (dd, *J* = 8.3, 6.8 Hz, 1H), 4.45 (dd, *J* = 14.4, 8.3 Hz, 1H), 4.33 (dd, *J* = 14.4, 6.8 Hz, 1H), 4.09 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3450, 2900, 1770, 1700, 1610, 1580, 1462, 1390, 1350, 1317, 1220, 1118, 1032, 963, 895, 800, 720 cm$^{-1}$; Anal. calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.73; H, 4.36; N, 7.71.

***N*-[1-Ethoxycarbonyl-4-ethyl-3-oxo-hexyl]phthalimide (4j):** Light yellow solid, mp. 55˚C - 56˚C; $^1$H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.72 (m, 2H), 4.06 - 4.27 (m, 5H), 2.60 (m, 1H), 1.66 (m, 2H), 1.46 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.83 (m, 6H); IR (KBr) 2900, 1772, 1715, 1610, 1463, 1430, 1390, 1362, 1295, 1215, 1130, 1034, 970, 755, 720 cm$^{-1}$; Anal. calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.89; H, 6.67; N, 3.83.

***N*-[1-Ethoxycarbonyl-3-oxo-hexyl]phthalimide (4k):** Light yellow oil; $^1$H NMR ($CDCl_3$) δ 7.72 - 7.85 (m, 4H), 4.04 - 4.26 (m, 5H), 2.62 (m, 1H), 2.51 (m, 1H), 1.62 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); IR (NaCl) 2900, 1773, 1720, 1610, 1462, 1430, 1391, 1365, 1290, 1193, 1035, 970, 885, 790, 720 cm$^{-1}$; HRMS calcd for $C_{17}H_{20}NO_5$ 318.1341, found 318.1324.

## 5. Acknowledgements

We thank Dr. Takayuki Yamashita for the helpful discussions during the course of this work and the undergraduate project students Takeyuki Takizawa and Nahoko Sugioka. This work was partially supported by a research fund from Kyoeisha Chemical Co., Ltd., Doshisha University's Research Promotion Fund, and a grant to RCAST at Doshisha University from the Ministry of Education, Japan.

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