

Synthesis of β -Lactams from Isocyanates and Vinyl Ethers under High Pressure

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The [2+2]cycloaddition of phenyl isocyanate to 2,3-dihydrofuran was appreciably accelerated by compression to produce a β -lactam ring; its apparent activation volume was estimated to be -28 ml mol^{-1} . Similar β -lactams were obtained under high pressure in the reaction of phenyl isocyanate with various vinyl ethers. Although the [2+2]cycloaddition of alkyl isocyanates to 2,3-dihydrofuran was also accelerated under high pressure to give β -lactams with good yields; the reactions of alkyl isocyanates with ethyl vinyl ether were slow, even at high pressure.

A large number of studies^{1,2)} have been undertaken to construct the β -lactam ring, because many antibiotics, such as Penicillin, Cephalosporin, and Thienamycin, have this ring system in the active center. Among the various synthetic methods for producing the β -lactam ring, [2+2]cycloadditions of isocyanates to olefins are interesting methods because of the one-step construction of the ring. We have recently reported on a facile synthesis of bicyclic β -lactams upon the reaction of aryl isocyanates with 2,3-dihydrofuran in excellent yields.³⁾ However, the [2+2]cycloadditions of alkyl isocyanates to 2,3-dihydrofuran, or of aryl isocyanates to other vinyl ethers, did not occur because of their low reactivity.³⁾

On the other hand, it has been reported that [2+2]cycloadditions are substantially accelerated by pressure, and have large negative activation volumes ($\Delta V^\ddagger = -20$ to -50 ml mol^{-1}).^{4,5)} The [2+2]cycloaddition of electrophilic isocyanates to glycols under high pressure has been investigated in the past,⁵⁾ and we have reported that the dimerization of isocyanates, a kind of [2+2]cycloaddition, was accelerated by compression.⁶⁾ Accordingly, we have expected that the reactions of various isocyanates with alkenes could be promoted by pressure.

In this paper, we will report on the pressure effect of the [2+2]cycloaddition of phenyl isocyanate to 2,3-dihydrofuran and the synthesis of various β -lactams by the reaction of aryl and alkyl isocyanates with vinyl ethers under high pressure.

Results and Discussion

It has been reported that the reaction of phenyl isocyanate (**1a**) with 2,3-dihydrofuran (**2**) at 100°C gave 7-phenyl-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (**3a**) in good yield (Chart 1).³⁾ Figure 1 shows the effect of pressure on the reaction of **1a** with **2** at low temperature (A, 40°C , 20 h; B, 30°C , 1 h). The yield of **3a** increased appreciably by adding pressure. The reaction is regarded as being a first order reaction with respect to **1a**, because large excess of **2**

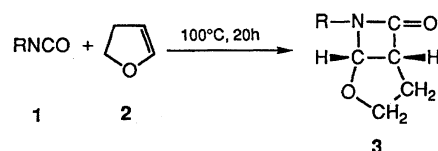


Chart 1.

was used. Therefore, the apparent reaction velocity constant (k) is given by Eq. 1, and calculated from the data given in Fig. 1. The activation volume ($\Delta V^\ddagger$) in the range from 0.1 MPa to 100 MPa (estimated by Eq. 2) is -28 ml mol^{-1} (both A and B). This result suggests that the reaction of isocyanate with vinyl ether is considerably accelerated by pressure.

$$kt = \ln \frac{a_0}{a} = \ln \frac{100}{100-x} \quad (1)$$

Where a is the concentration of **1a**, a_0 the initial concentration of **1a**, and x the yield of **3a**

$$\Delta V^\ddagger = -RT \left(\frac{\partial \ln k}{\partial P} \right)_T \quad (2)$$

Table 1 shows the reaction of alkyl and benzyl isocyanates with **2** under high pressure. Although [2+2]cycloaddition of alkyl isocyanate to **2** did not occur at atmospheric pressure,³⁾ the corresponding β -lactams, **3b–3f**, were obtained in good

Table 1. Reaction of Various Isocyanates with **2** under High Pressure^{a)}

Run	Isocyanate	R	Product	Yield/%
1	1b	CH ₃	3b	71
2	1c	C ₂ H ₅	3c	92
3	1d	<i>n</i> -C ₄ H ₉	3d	77
4	1e	Cyclohexyl	3e	68
5	1f	(CH ₃) ₃ C	3f	23
6	1g	PhCH ₂	3g	100

a) Isocyanate 3 mmol, **2** 15 mmol, 800 MPa, 100°C , 20 h, in a sealed Teflon[®] tube.

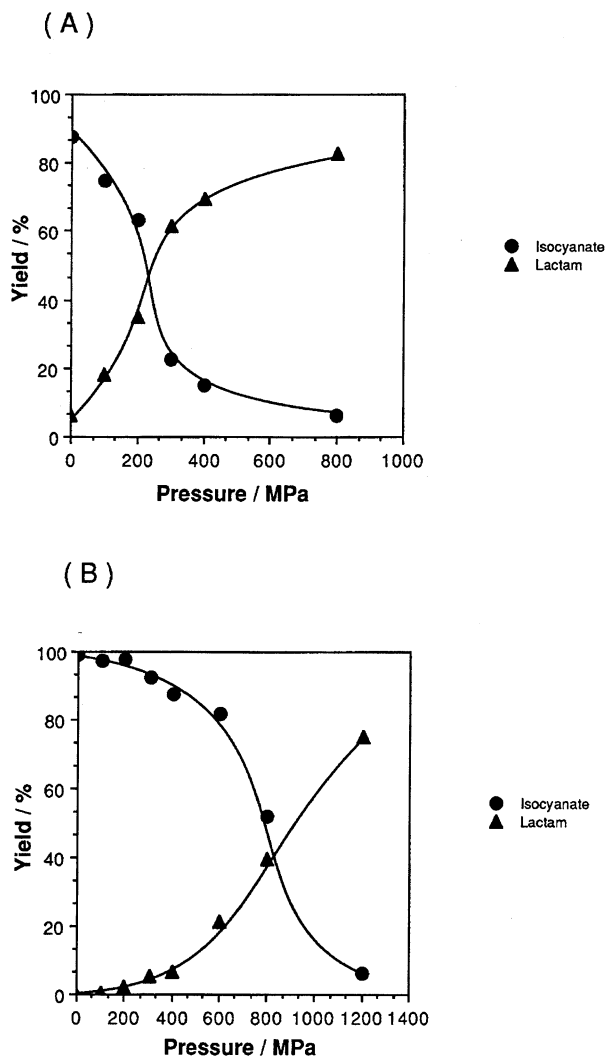


Fig. 1. Effect of pressure on the cycloaddition of **1a** to **2**. **1a** 3 mmol, **2** 15 mmol, in a sealed Teflon[®] tube. (A): reaction temperature 40 °C, reaction time 20 h, (B): reaction temperature 30 °C, reaction time 1 h, ●: **1a**, ▲: **3a**.

yields at 800 MPa. The IR, ¹H and ¹³C NMR spectra of **3b**–**3g** greatly resemble those of **3a**. The reaction of benzyl isocyanate (**1g**) with **2** gave **3g** quantitatively. Even *t*-butyl isocyanate **1f**, which has a lower reactivity because of its bulkiness, reacted with **2** to give a 23% yield of **3f**.

Table 2 shows the reaction of **1a** with various vinyl ethers under high pressure. Ethyl vinyl ether, 2-ethylhexyl vinyl ether, and 3,4-dihydro-2*H*-pyran reacted with **1a** to give the corresponding β -lactam, **4a**–**4c**, in high yield at 800 MPa. If the reaction of 3,4-dihydro-2-methoxy-2*H*-pyran was carried out under the same reaction conditions, a small amount of β -lactam isomers, **4d** and **4e**, were obtained, and the cyclic trimer of **1a** was formed as a main product in 26% yield (Run 4). The trimerization of **1a** in a polar solvent is known to be accelerated by pressure.⁷⁾ When the reaction was carried out in toluene, **4d** and **4e** were obtained in good yields (Run 5). This result suggests that the [2+2]cycloaddition of isocyanate to vinyl ether is strongly affected by

the polarity of the solvent. Aromatic vinyl ethers, furan and benzofuran, did not react with **1a**, even at 800 MPa (Runs 6 and 7). Compounds with an unsaturated 5-membered ring, such as 2,5-dihydrofuran and cyclopentene, or a vinyl ester, such as vinyl acetate, did not react with **1a**, even at 800 MPa. Although no [2+2]cycloaddition of **1a** to alkenes, such as styrene, cyclohexene or 1-decene occurred, some interaction of **1a** and alkene was considered to be present because the dimer of **1a** was produced in high yield (Chart 2). The dimer was hardly obtained in a reaction of only **1a** in the absence of catalyst.⁶⁾

Table 3 shows the reaction of methyl isocyanate (**1b**) with vinyl ethers, except for **2**, under high pressure. The corresponding β -lactams were obtained, though the yields were not very high. Compound **1b** had a lower reactivity to vinyl ethers than did aryl isocyanates. This tendency agrees with the fact that a [2+2]cycloaddition of alkyl isocyanate to **2** does not occur at ambient pressure.

Table 4 shows the [2+2]cycloaddition of various isocyanates to ethyl vinyl ether. Although these reactions were considerably slow compared with the case of **1a** to ethyl vinyl ether (Table 2: Run 1), butyl, cyclohexyl, and benzyl isocyanates gave the corresponding β -lactams under high pressure. No β -lactam was obtained by the reaction of *t*-butyl isocyanate with ethyl vinyl ether, even at 1200 MPa. These results suggest that these reactions are highly influenced by the electrophilicity and bulkiness of the isocyanates used.

Two reaction mechanisms, a concerted process and a step-wise process, are possible upon [2+2]cycloaddition.^{4,5)} Upon the [2+2]cycloaddition of aryl isocyanate to **2**, a concerted mechanism is conceivable because neutral nonpolar conditions gave good results (Chart 3).³⁾ It is also considered that a concerted mechanism is more reasonable upon the [2+2]cycloaddition of isocyanates to vinyl ethers under high pressure, because good yields of β -lactams were obtained in a nonpolar solvent (Table 2: Run 5).

Many novel β -lactams could be obtained upon the [2+2]cycloaddition of aryl and alkyl isocyanates to vinyl ethers under high pressure. Most of these β -lactams are stable at

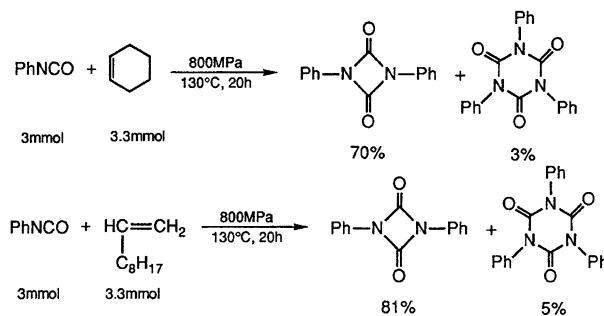


Chart 2.

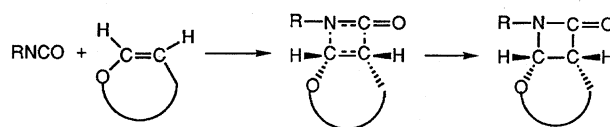
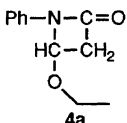
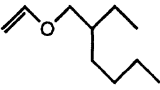
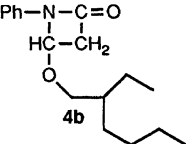
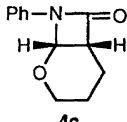
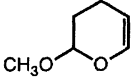
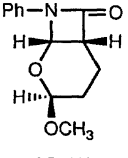
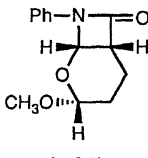
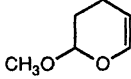
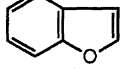


Chart 3.

Table 2. The Reaction of **1a** with Vinyl Ethers under High Pressure^{a)}

Run	Alkene	Temp/°C	Conv./%	Products
1		70	93	 4a 90%
2		100	97	 4b 87%
3		70	88	 4c 82%
4		100	85 ^{b)}	 4d 5%  4e 2%
5 ^{c)}		130	100	4d 59% 4e 30%
6		100	8	— 0
7		70	11	— 0

a) **1a** (3 mmol) and vinyl ether (15 mmol) in a Teflon[®] tube were heated at 100 °C in 20 h under 800 MPa. b) The trimer of **1a** was obtained with 26% yield. c) **1a** (3.1 mmol) and vinyl ether (3.6 mmol) in toluene (2 ml) were used.

room temperature for one month. The facile preparation and stability of these β -lactams would open new applications of a β -lactam as sources of polyamides and various organic compounds.

Experimental

Apparatus. The apparatus used for the high-pressure reaction was the same as that described previously.⁸⁾

Measurement. GLC was carried out using a Shimadzu GC-14A chromatograph with a capillary column (Frontier Lab Ultra ALLOY-1). ¹H and ¹³C NMR spectra were measured in CDCl₃ using a Bruker Aux500 (500 MHz) and a Bruker AC200 (200 MHz) spectrometer. The mass spectra were measured using a Shimadzu QP 2000 GC-MS spectrometer. IR spectra were obtained using a JASCO A-302 spectrophotometer.

Reaction of Isocyanates with 2 under High Pressure. The typical procedure was as follows. A homogeneous mixture of **1b** (3 mmol) and **2** (15 mmol) in a sealed Teflon[®] tube was compressed to 800 MPa, heated at 100 °C, and maintained for 20 h in a high-pressure apparatus. The resulting mixture was subjected to evaporation, and **3b** was purified from the residue by column chromatography on silica gel using a mixture of hexane and ethyl acetate (2 : 1 v/v)

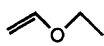
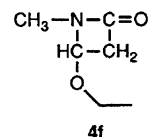
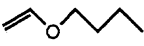
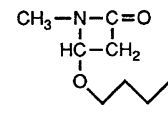
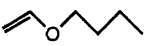
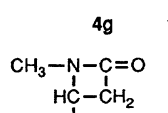
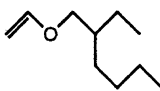
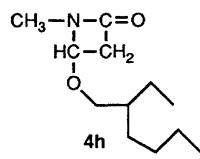
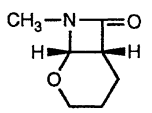
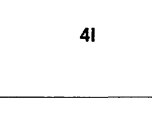
as an eluent (yield 71%).

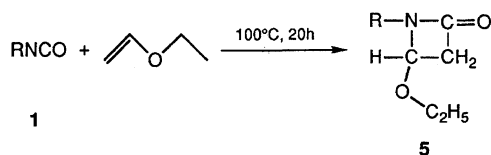
3b: IR (neat) 1757 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 1.67–1.83 (m, 1H, one proton of CH₂), 2.06–2.15 (dd, J =5.4, 13.0 Hz, 1H, one proton of CH₂), 2.74 (s, 3H, CH₃), 3.65 (dd, J =2.6, 8.4 Hz, 1H, COCH), 3.74–3.87 (m, 1H, one proton of OCH₂), 4.18 (t, J =9.0 Hz, 1H, one proton of OCH₂), 5.46 (d, J =2.8 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ = 167.83, 86.72, 66.04, 55.85, 25.09, 24.76. Found: m/z 127.0636. Calcd for C₆H₉NO₂: M, 127.0633.

3c: IR (neat) 1757 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 1.20 (t, J =7.4 Hz, 3H, CH₃), 1.68–1.85 (m, 1H, one proton of CH₂), 2.17 (dd, J =5.6, 13.3 Hz, 1H, one proton of CH₂), 3.15–3.28 (m, 2H, CH₂), 3.63 (dd, J =2.8, 8.5 Hz, 1H, COCH), 3.83–3.94 (m, 1H, one proton of OCH₂), 4.20 (t, J =8.8 Hz, 1H, one proton of OCH₂), 5.53 (d, J =2.8 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ = 167.82, 86.00, 66.51, 55.72, 34.82, 25.07, 13.18. Found: m/z 142.0850. Calcd for C₇H₁₂NO₂: (M+¹H), 142.0866.

3d: IR (neat) 1759 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 0.93 (t, J =7.2 Hz, 3H, CH₃), 1.26–1.85 (m, 5H, 2CH₂, one proton of CH₂), 2.17 (dd, J =5.4, 13.1 Hz, 1H, one proton of CH₂), 3.06–3.19 (m, 2H, CH₂), 3.64 (dd, J =2.9, 8.6 Hz, 1H, COCH), 3.81–3.95 (m, 1H, one proton of OCH₂), 4.19 (t, J =9.1 Hz, 1H, one proton of OCH₂), 5.49 (d, J =2.9 Hz, 1H, NCHO); ¹³C NMR (50

Table 3. The Reaction of **1b** with Vinyl Ethers under High Pressure^{a)}

Run	Vinyl ether	Temp/°C	Press/MPa	Product	
1		100	800		21%
2		100	800		20%
3		100	1200		31%
4		100	1200		12%
5		100	800		12%
6		100	1200		33%

a) **1b** 3 mmol, vinyl ether 15 mmol, 20 h.Table 4. Reaction of Various Isocyanates with Ethyl Vinyl Ether under High Pressure^{a)}

Run	Isocyanate	R	Press/MPa	Product	Yield/%
3	1d	<i>n</i> -C ₄ H ₉	800	5d	8
3	1d	<i>n</i> -C ₄ H ₉	1200	5d	14
4	1e	Cyclohexyl	1200	5e	4
5	1f	(CH ₃) ₃ C	1200	None	0
6	1g	PhCH ₂	800	5g	42

a) Isocyanate 3 mmol, ethyl vinyl ether 6 mmol, 800 MPa, 100 °C, 20 h, in a sealed Teflon[®] tube.

MHz, CDCl₃) δ =168.16, 86.36, 66.59, 55.73, 39.93, 30.14, 25.05, 20.34, 13.64. Found: m/z 169.1112. Calcd for C₉H₁₅NO₂: M, 169.1102.

3e: IR (neat) 1755 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ =1.04—1.68 (m, 11H, C₅H₁₀, CH), 2.15 (dd, J =5.4, 13.0 Hz, 1H, one proton of CH₂), 3.36—3.47 (m, 1H, NCH), 3.55 (dd, J =2.9, 8.6 Hz, 1H, COCH), 3.85—3.98 (m, 1H, one proton of OCH₂), 4.16 (t, J =8.9 Hz, 1H, one proton of OCH₂), 5.55 (d, J =3.0 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ =167.23, 85.22, 66.30, 54.99, 51.27, 31.51, 30.43, 25.25, 25.05, 24.99 (2C). Found: m/z 195.1242. Calcd for C₁₁H₁₇NO₂: M, 195.1258.

3f: IR (neat) 1750 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ =1.36 (s, 9H, 3CH₃), 1.61—1.82 (m, 1H, one proton of CH₂), 2.17 (dd, J =5.4, 13.0 Hz, 1H, one proton of CH₂), 3.51 (dd, J =3.0, 8.6 Hz, 1H,

COCH), 3.87—4.00 (m, 1H, one proton of OCH₂), 4.17 (t, J =8.7 Hz, 1H, one proton of OCH₂), 5.56 (d, J =3.1 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ =167.24, 85.28, 66.07, 54.30, 53.29, 27.92 (3C), 25.14. Found: m/z 170.1181. Calcd for C₉H₁₆NO₂: (M+¹H), 170.1180.

3g: IR (neat) 1755 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ =1.61—1.82 (m, 1H, one proton of CH₂), 2.15 (dd, J =5.4, 13.1 Hz, 1H, one proton of CH₂), 3.62 (dd, J =2.9, 8.5 Hz, 1H, COCH), 3.70—3.83 (m, 1H, one proton of OCH₂), 4.11 (d, J =14.9 Hz, 1H, one proton of PhCH₂), 4.12 (t, J =8.7 Hz, 1H, one proton of OCH₂), 4.46 (d, J =15.0 Hz, one proton of PhCH₂), 5.40 (d, J =2.9 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ =167.96, 135.82, 128.71 (2C), 128.31 (2C), 127.66, 86.02, 66.53, 55.96, 43.89, 25.21. Found: m/z 203.0912. Calcd for C₁₂H₁₃NO₂: M, 203.0946.

Reaction of 1a with Various Vinyl Ethers under High Pressure. The typical procedure was as follows. A homogeneous mixture of **1a** (3 mmol) and ethyl vinyl ether (15 mmol) in a sealed Teflon[®] tube was compressed to 800 MPa, heated at 100 °C, and maintained for 20 h in a high-pressure apparatus. After the resulting mixture was subjected to evaporation, **4a** was purified from the residue by column chromatography on silica gel using a mixture of hexane and ethyl acetate (2 : 1 v/v) as an eluent. The spectra of **4a** resemble those of **1a** very closely. Although a spin-spin coupling of the methyne of the lactam ring was detected as a triplet at 200 MHz in the ¹H NMR spectrum, a dd spin-spin coupling was obtained in a 500 MHz ¹H NMR measurement.

4a: IR (neat) 1763 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ =1.22 (t, J =7.0 Hz, 3H, CH₃), 2.84—3.13 (m, 2H, COCH₂), 3.45—3.69 (m, 2H, OCH₂), 5.37 (t, J =1.6 Hz, 1H, NCHO), 7.09 (t, J =7.3 Hz, 1H, *p*-), 7.32 (t, J =8.0 Hz, 2H, *m*-), 7.51 (d, J =8.2 Hz, 2H, *o*-); ¹H NMR (500 MHz, CDCl₃) δ =1.23 (t, J =7.0 Hz, 3H, CH₃), 3.01 (dd, J =1.5, 15.3 Hz, 1H, one proton of CH₂), 3.12 (dd, J =4.0, 15.3

Hz, 1H, one proton of CH₂), 3.54—3.67 (m, 2H, OCH₂), 5.44 (dd, *J*=1.5, 3.9 Hz, 1H, NCHO), 7.08 (t, 1H, *p*-), 7.31 (t, 2H, *m*-), 7.47 (d, 2H, *o*-); ¹³C NMR (50 MHz, CDCl₃) δ=163.16, 137.61, 129.05 (2C), 124.08, 116.69 (2C), 80.05, 61.02, 43.59, 15.06. Found: *m/z* 191.0943. Calcd for C₁₁H₁₃NO₂: M, 191.0946.

4b (Mixture of Diastereomers): IR (neat) 1767 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=0.80—0.93 (m, 6H, 2CH₃), 1.24—1.53 (m, 9H, 4CH₂, CH), 2.97—3.17 (m, 2H, COCH₂), 3.36—3.51 (m, 2H, OCH₂), 5.44 (t, *J*=1.0 Hz, 1H, NCHO), 7.07 (t, *J*=7.3 Hz, 1H, *p*-), 7.26—7.34 (m, 2H, *m*-), 7.44—7.50 (m, 2H, *o*-); ¹³C NMR (50 MHz, CDCl₃) δ=163.21, 137.57, 129.04 (2C), 124.24, 116.81 (2C), 80.28, 67.27 (0.5C), 67.17 (0.5C), 43.17 (0.5C), 43.11 (0.5C), 39.52, 30.41 (0.5C), 30.32 (0.5C), 29.01 (0.5C), 28.92 (0.5C), 23.71, 23.00, 14.07, 11.05. Found: *m/z* 275.1868. Calcd for C₁₇H₂₅NO₂: M, 275.14.

4c: IR (neat) 1755 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.61—2.06 (m, 4H, 2CH₂), 3.24—3.30 (m, 1H, COCH), 3.65—3.80 (m, 2H, OCH₂), 5.53 (d, *J*=4.8 Hz, 1H, NCHO), 7.02—7.10 (m, 1H, *p*-), 7.28 (t, *J*=6.6 Hz, 2H, *m*-), 7.52 (d, *J*=3.3 Hz, 2H *o*-); ¹³C NMR (50 MHz, CDCl₃) δ=166.73, 137.75, 128.87 (2C), 124.16, 117.24 (2C), 78.20, 60.02, 46.22, 19.66, 17.64. Found: *m/z* 203.0938. Calcd for C₁₂H₁₃NO₂: M, 203.0946.

Reaction of 1a with 3,4-Dihydro-2-methoxy-2H-pyran in Toluene under High Pressure. A homogeneous mixture of **1a** (3.1 mmol), 2,3-dihydro-2-methoxy-4H-pyran (3.6 mmol), and toluene (2 ml) in a sealed Teflon[®] tube was compressed to 800 MPa, heated at 130 °C, and maintained for 20 h in a high-pressure apparatus. After the resulting mixture was subjected to evaporation, **4d** and **4e** were isolated, respectively, from the residue by column chromatography on silica gel using a mixture of hexane and ethyl acetate (2 : 1 v/v) as an eluent. Although the ¹H NMR spectrum of **4d** was similar to that of **4e**, the chemical shift of the methyl protons of the methoxy group of **4d** was higher than that of **4e** (0.25 ppm). This difference in the chemical shift was considered to be caused because the methyl protons of **4d** were shielded by phenyl group, and the structures of **4d** and **4e** were determined.

4d: IR (neat) 1757 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.64—1.74 (m, 1H, one proton of CH₂), 1.92—2.14 (m, 3H, CH₂, one proton of CH₂), 3.39—3.47 (m, 1H, COCH), 3.47 (s, 3H, CH₃), 4.82—4.85 (m, 1H, CH), 5.62 (d, *J*=4.6 Hz, 1H, CH), 7.06—7.15 (m, 1H, *p*-), 7.26—7.38 (m, 2H, *m*-), 7.50—7.56 (m, 2H, *o*-); ¹³C NMR (50 MHz, CDCl₃) δ=166.15, 137.19, 129.17 (2C), 124.32, 116.88 (2C), 98.04, 75.97, 55.70, 47.71, 25.91, 14.98. Found: *m/z* 233.1056. Calcd for C₁₃H₁₅NO₃: M, 233.1051.

4e: IR (neat) 1761 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.66—1.90 (m, 2H, CH₂), 2.00—2.20 (m, 2H, CH₂), 3.40—3.47 (m, 1H, COCH), 3.22 (s, 3H, CH₃), 4.77—4.84 (m, 1H, CH), 5.61 (d, *J*=4.9 Hz, 1H, CH), 7.05—7.14 (m, 1H, *p*-), 7.27—7.38 (m, 2H, *m*-), 7.51—7.56 (m, 2H, *o*-); ¹³C NMR (50 MHz, CDCl₃) δ=165.69, 137.31, 128.94 (2C), 124.15, 116.91 (2C), 99.34, 77.58, 55.51, 48.10, 25.87, 16.02. Found: *m/z* 233.1055. Calcd for C₁₃H₁₅NO₃: M, 233.1051.

4f: IR (neat) 1755 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.26 (t, *J*=7.0 Hz, 3H, CH₃), 2.81 (dd, *J*=1.1, 16.2 Hz, 1H, one proton of COCH₂), 2.85 (s, 3H, CH₃), 3.04 (dd, *J*=3.6, 14.3 Hz, 1H, one proton of COCH₂), 3.50—3.74 (m, 2H, OCH₂), 4.93 (dd, *J*=1.3, 3.6 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=166.36, 82.29, 63.11, 44.51, 27.05, 15.27. Found: *m/z* 129.0821. Calcd for C₆H₁₁NO₂: M, 129.0790.

4g: IR (neat) 1767 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=0.94 (t, *J*=7.0 Hz, 3H, CH₃), 1.24—1.67 (m, 4H, 2CH₂), 2.81 (d, *J*=14.4 Hz, 1H, one proton of COCH₂), 3.02 (dd, *J*=3.2, 14.0 Hz, 1H, one

proton of COCH₂), 3.44—3.61 (m, 2H, OCH₂), 4.91 (d, *J*=3.6 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=166.42, 82.42, 67.23, 44.36, 31.79, 27.06, 19.24, 13.82. Found: *m/z* 157.1105. Calcd for C₈H₁₅NO₂: M, 157.1102.

4h: IR (neat) 1769 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=0.85—0.93 (m, 6H, 2CH₃), 1.29—1.52 (m, 9H, 4CH₂, CH), 2.80 (dd, *J*=0.7, 15.7 Hz, 1H, one proton of COCH₂), 2.84 (s, 3H, CH₃), 3.01 (dd, *J*=3.3, 14.1 Hz, 1H, one proton of COCH₂), 3.34—3.46 (m, 2H, OCH₂), 4.91 (dd, *J*=0.9, 3.3 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=166.42, 82.53, 69.87, 44.20, 39.72, 30.40, 29.06, 27.06, 23.71, 23.03, 14.09, 11.05. Found: *m/z* 214.1811. Calcd for C₁₂H₂₄NO₂: (M+¹H), 214.1806.

4i: IR (neat) 1757 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.61—2.15 (m, 4H, 2CH₂), 2.82 (s, 3H, CH₃), 3.17—3.24 (m, 1H, COCH), 3.73—3.80 (m, 2H, OCH₂), 5.09 (d, *J*=4.3 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=169.86, 79.27, 60.10, 46.63, 26.36, 19.94, 17.69. Found: *m/z* 142.0871. Calcd for C₇H₁₂NO₂: (M+¹H), 142.0867.

5d: IR (neat) 1765 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=0.93 (t, *J*=7.2 Hz, 3H, CH₃), 1.25 (t, *J*=7.0 Hz, 3H, CH₃), 1.30—1.65 (m, 4H, 2CH₂), 2.79 (d, *J*=14.5 Hz, 1H, one proton of COCH₂), 3.01 (dd, *J*=3.7, 14.7 Hz, 1H, one proton of COCH₂), 3.09—3.29 (m, 2H, NCH₂), 3.52—3.63 (m, 2H, OCH₂), 4.98 (dd, *J*=1.2, 3.6 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=166.17, 81.10, 62.67, 43.95, 40.57, 30.12, 20.26, 15.25, 13.64. Found: *m/z* 171.1261. Calcd for C₉H₁₇NO₂: M, 171.1258.

5e: IR (neat) 1759 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.10—2.03 (m, 10H, 5CH₂), 1.24 (t, *J*=7.0 Hz, 3H, CH₃), 2.77 (dd, *J*=1.3, 14.6 Hz, 1H, one proton of COCH₂), 2.93 (dd, *J*=3.6, 14.7 Hz, 1H, one proton of COCH₂), 3.35—3.67 (m, 3H, OCH₂, NCH), 5.05 (dd, *J*=1.3, 3.6 Hz, 1H, NCHO); ¹³C NMR (50 MHz, CDCl₃) δ=165.48, 79.82, 61.52, 51.81, 43.21, 31.75, 30.36, 25.32, 25.19 (2C), 15.24. Found: *m/z* 197.1412. Calcd for C₁₁H₁₉NO₂: M, 197.1415.

5g: IR (neat) 1761 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ=1.12 (t, *J*=7.0 Hz, 3H, CH₃), 2.83 (d, *J*=14.7 Hz, 1H, one proton of COCH₂), 3.02 (dd, *J*=3.7, 14.8 Hz, 1H, one proton of COCH₂), 3.35—3.50 (m, 2H, OCH₂), 4.19 (d, *J*=15.3 Hz, 1H, one proton of PhCH₂), 4.57 (d, *J*=15.2 Hz, 1H, one proton of PhCH₂), 4.85 (dd, *J*=1.4, 3.7 Hz, 1H, NCHO), 7.23—7.38 (m, 5H, aromatic); ¹³C NMR (50 MHz, CDCl₃) δ=166.20, 135.78, 128.76 (2C), 128.57, 128.20 (2C), 80.85, 63.22, 44.69, 15.10. Found: *m/z* 205.1097. Calcd for C₁₂H₁₅NO₂: M, 205.1102.

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