Strong Base-Induced Cycloaddition Reaction of Homophthalic Anhydride with Aldehydes

Ryuichi OKUNAKA, Takao HONDA, Maiko KONDO, Yasumitsu TAMURA, and Yasuyuki KITA*

Faculty of Pharmaceutical Sciences, Osaka University, 1–6, Yamada-oka, Suita 565, Japan. *Received October 17, 1990*

The reaction of homophthalic anhydride (1) and aldehydes in the presence of a strong base was studied. Reaction of 1 and benzaldehyde in the presence of NaH in anhydrous tetrahydrofuran (THF) at low temperature (0 °C—room temperature) followed by treatment with diazomethane gave the cycloadduct, *trans*-4-methoxycarbonyl-3-phenyl-3,4-dihydrocoumarin, and the reaction at 50 °C gave, after similar work-up, the C-4 methylene condensed product, methyl 2-(2-methoxycarbonylphenyl)-3-phenylacrylate, selectively. Treatment of homophthalic anhydride having a terminal aldehyde group in the side chain at the C-4 position with NaH in anhydrous THF at low temperature resulted in intramolecular cycloaddition in fair yield.

Keywords homophthalic anhydride; cycloaddition; sodium hydride; aldehyde; hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one

The fact that homophthalic anhydride (**1**) has two active sites (C-1 and C-3 positions) toward nucleophiles and one active site (C-4 position) toward electrophiles makes its chemical behavior of interest, and the anhydride is an important compound in organic synthesis. In view of these characteristics, **1** has been examined as a reactant for cycloaddition with polar double bonds (C=O[1] and C=N[2]), and used in the synthesis of natural products.[3] Previously, we reported[4] that heating of **1** with compounds containing carbon–carbon multiple bonds caused a cycloaddition reaction to give polycyclic *peri*-hydroxy aromatic compounds, and we also demonstrated[5] that a strong base such as sodium hydride (NaH) or lithium diisopropylamide (LDA) dramatically accelerated the cycloaddition reaction. The strong base-induced cycloaddition reaction of **1** with carbon–carbon multiple bonds was successively applied to syntheses of anthracyclines,[6] heteroanthracyclines,[7] SS-228R,[8] and other compounds.[9] We now report that the use of a strong base in the reaction of **1** with aldehydes is also effective for the cycloaddition reaction.

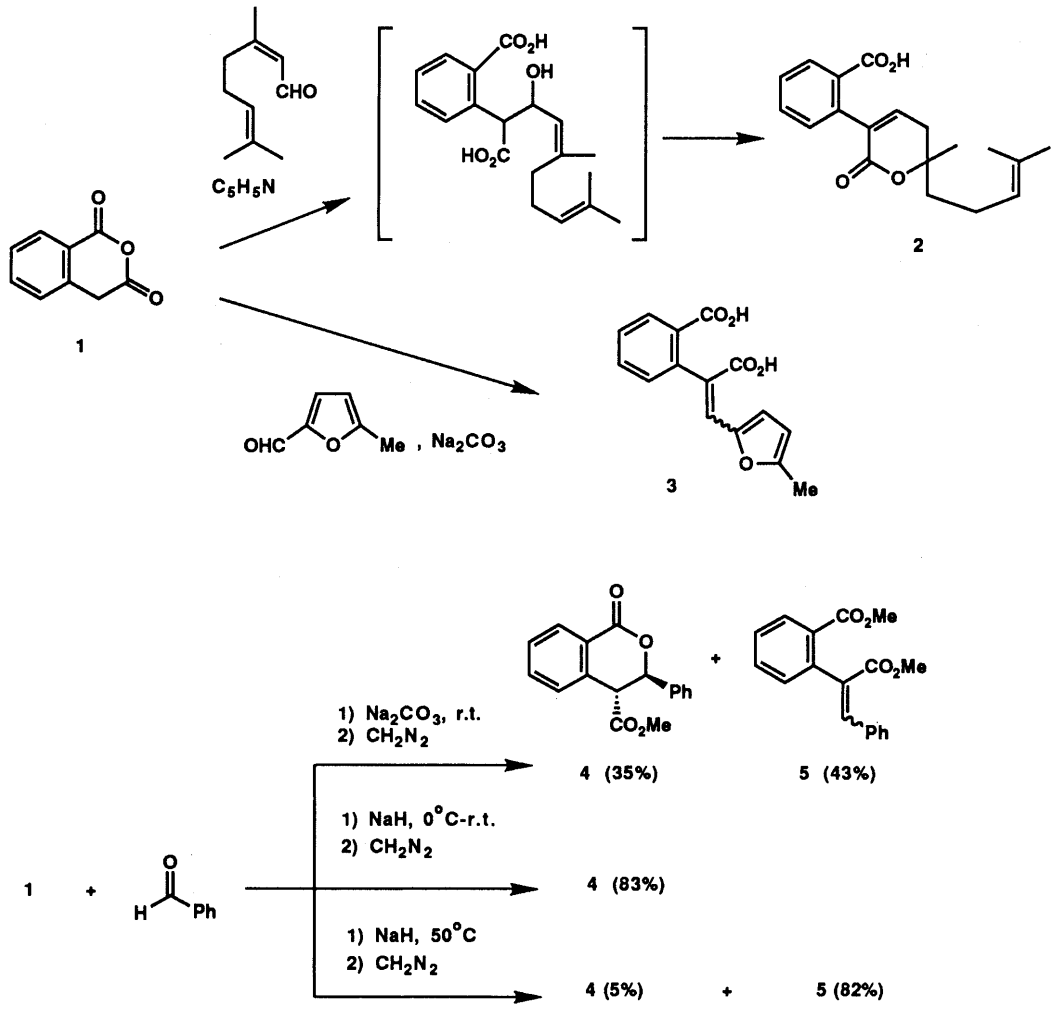


Chart 1

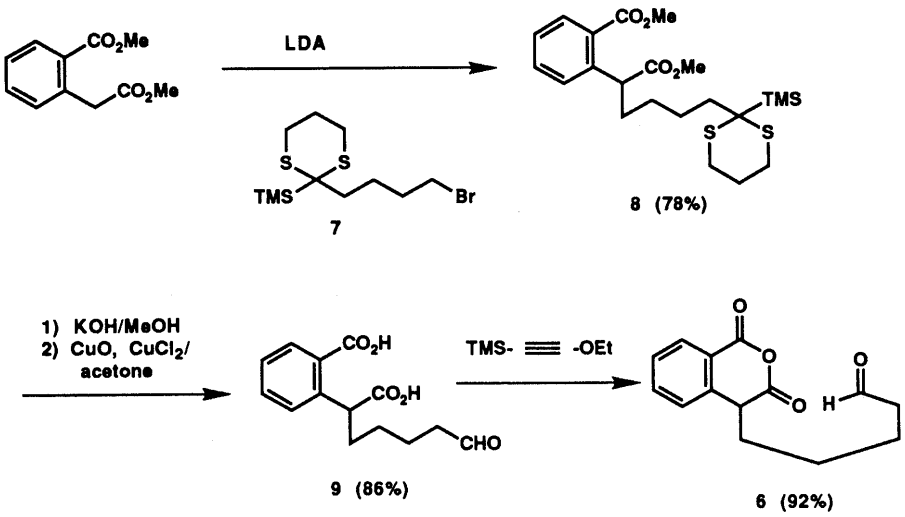


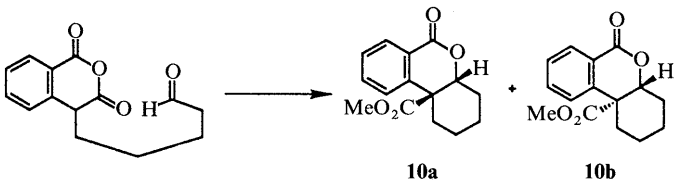
Chart 2

Reaction of **1** with some aldehydes, citral[1b] and furfural[1c] in the presence of pyridine and sodium carbonate (Na_2CO_3) is known to yield the C-4 methylene condensed products (**2** and **3**, respectively). 8-Hydroxy- and 8-methoxyhomophthalic anhydrides were reported to react with benzaldehyde in the presence of Na_2CO_3 to give the cycloadducts in moderate yield.[1d] Homophthalic anhydride (**1**), however, reacted with benzaldehyde under the same conditions to give the cycloadduct and the C-4 methylene condensed product, respectively, which were isolated as the methyl esters (**4** and **5**) after treatment with diazomethane. Although reaction of **1** with aldehydes under weakly basic conditions has been examined extensively, there has been no report on the reaction under strongly basic conditions utilizing NaH or LDA. We have now found that reaction of **1** and benzaldehyde in the presence of NaH in anhydrous tetrahydrofuran (THF) at low temperature (0 °C—room temperature) followed by treatment with diazomethane gave the cycloadduct (**4**) in 83% yield as a single product and the reaction at 50 °C gave, after similar work-up, the C-4 methylene condensed product (**5**) (82%), selectively. Therefore, it is presumed that the initially formed cycloadduct is a kinetically controlled product and the C-4 methylene condensed product is a thermodynamically controlled product.

Next, we investigated the intramolecular version of the reaction. The starting homophthalic anhydride (**6**) having a terminal aldehyde group in the side chain at the C-4 position was prepared as shown in Chart 2. Dimethyl homophthalate was treated with the bromothioacetal (**7**) to give the C-2 alkylated compound (**8**) in 78% yield. After hydrolysis of **8** with potassium hydroxide in methanol, the resulting dicarboxylic acid was dethioacetalized with copper(II) oxide-copper(II) chloride in acetone[10] to give the formyldiacid (**9**) in 86% yield. The diacid (**9**) was dehydrated with (trimethylsilyl)ethoxyacetylene[11] to give the anhydride (**6**) having a terminal aldehyde in the side chain.

Treatment of **6** with NaH in anhydrous THF at low temperature (0 °C—room temperature) for 10 min gave a 58% yield of the *cis*-cycloadduct (**10a**) and *trans*-cycloadduct (**10b**) in a 32:26 ratio. Although LDA gave the same cycloadducts (**10a** and **10b**) from **6** in approximately the same yield, the use of Na_2CO_3 or heating in a sealed tube provided the mixture of cycloproducts (**10a** and **10b**) in only 29 and 21% yields, respectively.

TABLE I.



10a **10b**

Entry	Reaction conditions	Yield (%)	Ratio **10a : 10b**
1	NaH, 0 °C—r.t., 10 min	58	32:26
2	LDA, −78 °C, 1 h and r.t., 30 min	53	26:27
3	Na_2CO_3, r.t., 65 h	29	14:15
4	200 °C in a sealed tube, 24 h	21	14: 7

The strong base-induced cycloaddition of homophthalic anhydride was found to be quite useful to lead aldehydes to 4-carboxy-3,4-dihydrocoumarins.

Experimental

All boiling and melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on Hitachi R-600 (60 MHz), R-22 (90 MHz), and JEOL JNM-GX500 (500 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution MS were obtained on ESCO EMD-05A and JEOL JMS-D300 mass spectrometers. E. Merck Silica gel 60 (70—230 mesh ASTM) for column chromatography and E. Merck precoated TLC plates, Silica gel F_{254} for preparative thin layer chromatography (TLC) were used. Organic layers were dried with anhydrous $MgSO_4$. THF was distilled from the sodium benzophenone dianion under nitrogen.

***trans*-4-Methoxycarbonyl-3-phenyl-3,4-dihydroisocoumarin (4) and Methyl 2-(2-Methoxycarbonylphenyl)-3-phenylacrylate (5)** [Entry 1]: A mixture of **1** (50 mg, 0.309 mmol), benzaldehyde (0.048 ml, 0.463 mmol), Na_2CO_3 (65.5 mg, 0.618 mmol), and dry benzene (5 ml) was stirred at room temperature for 24 h. The reaction mixture was quenched with aqueous NH_4Cl. The obtained carboxylic acid was extracted with 10% NaOH solution, and the aqueous layer was acidified (pH = 3) with 10% HCl and extracted with Et_2O. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with AcOEt and treated with a Et_2O solution of diazomethane, which was obtained from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. The mixture was stirred

at 0 °C for 1 h. The excess diazomethane was trapped with acetic acid and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 10 : 1) to give the esterified cycloproducts, **4** (30.8 mg, 35%) and **5** (39.0 mg, 43%). **4**: Colorless crystals, mp 129—132 °C (hexane–CH_2Cl_2). IR ($CHCl_3$) ν: 3030, 3000, 2950, 1735, 1725, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (s, 3H, OCH_3), 4.35 (d, 1H, J=8 Hz, CH), 5.86 (d, 1H, J=8 Hz, CH), 7.09—7.60 (m, 8H, ArH × 8), 8.17 (dd, 1H, J=7, 2 Hz, ArH). Exact MS Calcd for $C_{17}H_{14}O_4$: 282.0891. Found: 282.0891. *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.24; H, 4.88. **5**: A colorless viscous oil. IR ($CHCl_3$) ν: 2950, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.84—7.47 (m, 8H, ArH and vinyl H), 7.78 (s, 1H, ArH), 8.04—8.15 (m, 1H, ArH). Exact MS Calcd for $C_{18}H_{16}O_4$: 296.1048. Found: 296.1048.

[Entry 2]: An anhydrous THF solution (3 ml) of **1** (100 mg, 0.617 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 27.2 mg, 0.679 mmol) in anhydrous THF (2 ml) at 0 °C under nitrogen. The mixture was stirred for 30 min, then a solution of benzaldehyde (0.0630 ml, 0.617 mmol) in anhydrous THF (3 ml) was added dropwise at the same temperature. The reaction mixture was stirred at room temperature for 24 h and then worked up in a similar manner to that described above. Purification by column chromatography on silica gel (hexane : AcOEt = 10 : 1) gave **4** (144 mg, 83%).

[Entry 3]: A mixture of **1** (100 mg, 0.617 mmol), benzaldehyde (0.0630 ml, 0.617 mmol), NaH (60% in mineral oil, 27.2 mg, 0.679 mmol), and anhydrous THF (9 ml) was stirred for 33 h at 50 °C. The reaction mixture was worked up in a similar manner to that described above. Purification by column chromatography on silica gel (hexane : AcOEt = 10 : 1) gave **4** (8.9 mg, 5%) and **5** (150.3 mg, 82%).

2-(4-Bromobutyl)-2-trimethylsilyl-1,3-dithiane (7) *n*-BuLi (1.6 N in hexane, 1.77 ml, 2.86 mmol) was added dropwise to a THF (7 ml) solution of 2-trimethylsilyl-1,3-dithiane (500 mg, 2.60 mmol) at −50 °C under nitrogen, and the solution was stirred for 30 min under the same conditions. The anion solution was added dropwise to a THF (17 ml) solution of 1,4-dibromobutane (1.56 ml, 13.0 mmol) at the same temperature, and the mixture was stirred at −50 °C for 2 h and then at room temperature for 1 h. The reaction was quenched with aqueous saturated NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 10 : 1) to give **7** (569 mg, 67%) as a pale yellow oil. IR ($CHCl_3$) ν: 2970, 2920, 1430, 1250, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.20 (s, 9H, $Si(CH_3)_3$), 1.53—2.64 (m, 8H, CH_2 × 4), 2.82—3.22 (m, 4H, CH_2 × 2), 3.46 (t, 2H, J=7 Hz, $BrCH_2$). Exact MS Calcd for $C_{11}H_{23}BrS_2Si$: 326.0195. Found: 326.0201; and Calcd for $C_{11}H_{23}Br^*S_2Si$: 328.0175. Found: 328.0197.

Dimethyl 2′-(5,5-Propylenedithio-5-trimethylsilyl)pentylhomophthalate (8) A THF (5.5 ml) solution of dimethyl homophthalate (208 mg, 1.00 mmol) was added dropwise at −78 °C under nitrogen to a THF (5.5 ml) solution of LDA, which had been prepared from diisopropylamine (0.154 ml, 1.10 mmol) and *n*-BuLi (1.6 N in hexane, 0.680 ml, 1.10 mmol), and the mixture was stirred at the same temperature for 30 min. To this anion solution, hexamethylphosphoric triamide (HMPA) and a THF (5.5 ml) solution of **7** (327 mg, 1.00 mmol) were added continuously, and the mixture was stirred at −78 °C for 1.5 h and at room temperature for 2 h. The reaction was quenched with aqueous saturated NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 10 : 1) to give **8** (355 mg, 78%) as a pale yellow oil. IR ($CHCl_3$) ν: 2950, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.16 (s, 9H, $Si(CH_3)_3$), 1.25—2.41 (m, 8H, CH_2 × 4), 2.41—2.60 (m, 2H, CH_2), 2.80—3.20 (m, 4H, CH_2 × 2), 3.65 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.46 (t, 1H, J=7 Hz, COCH), 7.20—7.58 (m, 3H, ArH × 3), 7.89 (m, 1H, ArH). Exact MS Calcd for $C_{22}H_{34}O_4S_2Si$: 454.1667. Found: 454.1667. *Anal.* Calcd for $C_{22}H_{34}O_4S_2Si$: C, 58.11; H, 7.53. Found: C, 57.68; H, 7.41.

2′-(4-Formylbutyl)homophthalic Acid (9) A solution of **8** (198 mg, 0.436 mmol) and KOH (244 mg, 4.36 mmol) in MeOH (17 ml) and H_2O (3.7 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure, then the residue was diluted with brine and washed with AcOEt. The aqueous layer was acidified (pH = 3) with 10% HCl and extracted with AcOEt; the extract was dried and concentrated under reduced pressure. Recrystallization of the crude product gave pure 2′-(5,5-propylenedithiopentyl)homophthalic acid as colorless crystals (147 mg, 96%), mp 137—139 °C (hexane–CH_2Cl_2). IR ($CHCl_3$) ν: 2940, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.87 (m, 8H, CH_2 × 4), 1.94—2.11 (m, 2H, CH_2), 2.74—2.96 (m, 4H, CH_2 × 2), 4.07 (t, 1H, J=7 Hz, SSCH), 4.78 (t, 1H, J=7 Hz, COCH), 7.20—7.57 (m, 3H, ArH × 3), 7.98 (m, 1H, ArH). Exact MS Calcd for $C_{17}H_{22}O_4S_2-H_2O$: 336.0852. Found: 336.0746.

A suspension of 2′-(5,5-propylenedithiopentyl)homophthalic acid (35.0 mg, 0.0990 mmol), $CuCl_2$ (27.0 mg, 0.198 mmol), CuO (31.0 mg, 0.396 mmol) and acetone (2 ml) was stirred at room temperature for 3 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with aqueous saturated NH_4Cl and washed with Et_2O. The aqueous layer was acidified (pH = 3) with 10% HCl and extracted with Et_2O; the extract was dried and concentrated under reduced pressure to give **9** (23.4 mg, 90%) as a colorless oil. IR ($CHCl_3$) ν: 3020, 2940, 1720, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25—2.82 (m, 8H, CH_2 × 4), 4.71 (t, 1H, J=7 Hz, COCH), 7.19—7.60 (m, 3H, ArH × 3), 8.01 (d, 1H, J=7 Hz, ArH), 9.75 (t, 1H, J=1 Hz, CHO), 10.57 (br s, 2H, OH). Exact MS Calcd for $C_{14}H_{16}O_5$: 264.0998. Found: 264.1020.

2′-(4-Formylbutyl)homophthalic Anhydride (6) The dicarboxylic acid **9** (81.0 mg, 0.307 mmol) was treated with (trimethylsilyl)ethoxyacetylene (0.0900 ml, 0.307 mmol) in dry CH_2Cl_2 (4 ml) at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give **6** (69.5 mg, 92%), which was used for the next reaction without further purification. IR ($CHCl_3$) ν: 3030, 2970, 1795, 1755, 1725, 1605 cm^{-1}.

***cis*-10*b*-Methoxycarbonyl-1,2,3,4,4*a*,10*b*-hexahydro-6*H*-dibenzo[*b*,*d*]-pyran-6-one (10a) and *trans*-10*b*-Methoxycarbonyl-1,2,3,4,4*a*,10*b*-hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one (10b)** [Entry 1]: An anhydrous THF solution (1 ml) of **6** (25.2 mg, 0.102 mmol) was added dropwise at 0 °C under nitrogen to a suspension of NaH (60% in mineral oil, 4.50 mg, 0.113 mmol) in anhydrous THF (0.5 ml). After being stirred at room temperature for 10 min, the reaction mixture was worked up in a similar manner to that described above. Purification by preparative TLC (hexane : AcOEt = 5 : 1) gave **10a** (8.4 mg, 32%) and **10b** (6.9 mg, 26%). **10a**: Colorless crystals, mp 95—97 °C (hexane–CH_2Cl_2). IR ($CHCl_3$) ν: 2960, 1730, 1720, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.35 (m, 8H, CH_2 × 4), 3.77 (s, 3H, OCH_3), 5.09 (dd, 1H, J=6, 2 Hz, CH), 7.25 (dd, 1H, J=7.9, 1.2 Hz, ArH), 7.44 (td, 1H, J=7.9, 1.2 Hz, ArH), 7.59 (td, 1H, J=7.9, 1.2 Hz, ArH), 8.17 (dd, 1H, J=7.9, 1.2 Hz, ArH). Exact MS Calcd for $C_{15}H_{16}O_4$: 260.1022. Found: 260.1034. *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 68.53; H, 6.38. **10b**: Colorless crystals, mp 148—150 °C (hexane–CH_2Cl_2). IR ($CHCl_3$) ν: 2970, 1730, 1725, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42—2.17 (m, 8H, CH_2 × 4), 3.63 (s, 3H, OCH_3), 4.34 (dd, 1H, J=12, 4 Hz, CH), 7.29 (dd, 1H, J=7.3, 1.2 Hz, ArH), 7.45 (td, 1H, J=7.3, 1.2 Hz, ArH), 7.59 (td, 1H, J=7.3, 1.2 Hz, ArH), 8.12 (dd, 1H, J=7.3, 1.2 Hz, ArH). Exact MS Calcd for $C_{15}H_{16}O_4$: 260.1022. Found: 260.1034. *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 68.88; H, 6.24.

[Entry 2]: An anhydrous THF (1.5 ml) solution of **6** (25.2 mg, 0.102 mmol) was added dropwise at −78 °C under nitrogen to an anhydrous THF (1 ml) solution of LDA, obtained from diisopropylamine (0.0160 ml, 0.112 mmol) and *n*-BuLi (0.0700 ml, 0.112 mmol). The mixture was stirred at −78 °C for 1 h and at room temperature for 30 min. The reaction mixture was worked up in a similar manner to that described above. Purification by preparative TLC (hexane : AcOEt = 5 : 1) gave **10a** (6.8 mg, 26%) and **10b** (7.3 mg, 27%).

[Entry 3]: A mixture of **6** (69.5 mg, 0.283 mmol) and anhydrous Na_2CO_3 (36.0 mg, 0.339 mmol) in dry benzene (8 ml) was stirred at room temperature for 65 h. The reaction mixture was worked up in a similar manner to that described above. Purification by preparative TLC (hexane : AcOEt = 5 : 1) gave **10a** (10.2 mg, 14%) and **10b** (11.2 mg, 15%).

[Entry 4]: A mixture of **6** (17.5 mg, 0.0711 mmol) and *o*-dichlorobenzene (2 ml) was heated in a sealed tube at 200 °C for 24 h. The reaction mixture was worked up in a similar manner to that described above. Purification by preparative TLC (hexane : AcOEt = 5 : 1) gave **10a** (2.6 mg, 14%) and **10b** (1.3 mg, 7%).

References

1) *a*) S. Y. Dike and J. R. Merchant, *Heterocycles*, **12**, 253 (1979); *b*) H. Kaji, M. Yamada, K. Nozawa, K. Kawai, and S. Nakajima, *Org. Prep. Proced. Int.*, **18**, 253 (1986); *c*) K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai, and S. Nakajima, *Chem. Pharm. Bull.*, **29**, 3486 (1981).

2) *a*) M. A. Haimova, M. M. Mollov, S. C. Ivanova, A. I. Dimitrova, and V. I. Ognyanov, *Tetrahedron*, **33**, 331 (1977) and references cited therein; *b*) M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*,

42, 1111 (1977).
3) M. Cushman and E. Madaj, *J. Org. Chem.*, **52**, 907 (1987) and references cited therein.
4) *a*) Y. Tamura, A. Wada, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, **22**, 4283 (1981); *b*) *Idem*, *Chem. Pharm. Bull.*, **31**, 2691 (1983).
5) Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi, and Y. Kita, *J. Org. Chem.*, **49**, 473 (1984).
6) *a*) Y. Tamura and Y. Kita, *Yuki Gousei Kagaku Kyokai Shi*, **46**, 205 (1988); *b*) T. Izawa, Z.-q. Wang, Y. Nishimura, S. Kondo, and H. Umezawa, *Chem. Lett.*, **1987**, 1655; *c*) F. Matsuda, M. Kawasaki, M. Osaki, K. Yamada, and S. Terashima, *ibid.*, **1988**, 653; *d*) Y. Tamura, S. Akai, H. Kishimoto, M. Sasho, M. Kirihara, and Y. Kita, *Chem. Pharm. Bull.*, **36**, 3897 (1988); *e*) H. Fujioka, H. Yamamoto, H. Kondo, H. Annoura, and Y. Kita, *J. Chem. Soc., Chem. Commun.*, **1989**, 1509.
7) *a*) Y. Tamura, M. Kirihara, J. Sekihachi, R. Okunaka, S. Mohri, T. Tsugoshi, S. Akai, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, **28**, 3971 (1987); *b*) Y. Tamura, M. Kirihara, M. Sasho, S. Akai, J. Sekihachi, R. Okunaka, and Y. Kita, *J. Chem. Soc., Chem. Commun.*, **1987**, 1474; *c*) Y. Kita, M. Kirihara, Y. Fujii, R. Okunaka, S. Akai, H. Maeda, and Y. Tamura, *ibid.*, **1990**, 136.
8) Y. Tamura, F. Fukata, M. Sasho, T. Tsugoshi, and Y. Kita, *J. Org. Chem.*, **50**, 2273 (1985).
9) *a*) M. Watanabe, M. Date, and S. Furukawa, *Chem. Pharm. Bull.*, **37**, 292 (1989); *b*) A. P. Marchand, P. Annapurna, W. H. Watson, and A. Nagl, *J. Chem. Soc., Chem. Commun.*, **1989**, 281; *c*) H. Ohmori, H. Maeda, C. Ueda, and M. Masui, *ibid.*, **1988**, 874.
10) K. Narasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 3724 (1972).
11) *a*) Y. Kita, S. Akai, M. Yoshigi, Y. Nakajima, H. Yasuda, and Y. Tamura, *Tetrahedron Lett.*, **25**, 6027 (1984); *b*) Y. Kita, S. Akai, N. Ajimura, M. Yoshigi, T. Tsugoshi, H. Yasuda, and Y. Tamura, *J. Org. Chem.*, **51**, 4150 (1986); *c*) Y. Kita, S. Akai, M. Yamamoto, M. Taniguchi, and Y. Tamura, *Synthesis*, **1989**, 334.