REACTION OF 1-BENZYLINDOLE-2,3-DICARBOXYLIC ANHYDRIDE WITH WITTIG REAGENTS

Yasuyoshi Miki,* Hiroko Hachiken, Yoshiko Sugimoto, and Norihide Yanase Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577, Japan

Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with methylenetriphenylphosphorane (Ph₃P=CH₂) and carbethoxymethylenetriphenylphosphorane (Ph₃P=CHCOOEt) gave [2-(3-carboxyindol-2-yl)-2-oxoethylidene]triphenylphosphorane derivatives, which were converted to cyclopenta[*b*]indol-3-ones after decarboxylation and treatment with aldehydes. On the other hand, the anhydride reacted with carbethoxyethylidenetriphenylphosphorane (Ph₃P=C(Me)COOEt) to afford a mixture of two enol lactones.

We have shown that 1-benzylindole-2,3-dicarboxylic anhydride (1) is a useful synthon in the synthesis of natural products, murrayaquinone- A^1 and ellipticine.² Recently, we have reported that the reaction of 1 with phenylmagnesium bromide and methylmagnesium bromide gave 2-acylindole-3-carboxylic acids (2) as a sole product because a carbonyl group at the 2-position in 1 is more reactive toward Grignard reagents than a carbonyl group at the 3-position. Therefore, reactivity of the carbonyl group in 1 is governed by the nitrogen in an indole. However, the reaction of 1 with *tert*-butylmagnesium chloride afforded a mixture of 2 and 3-acylindole-2-carboxylic acid (3) due to the steric hindrance.³

Scheme 1



In the reaction of substituted phthalic anhydrides⁴ with Wittig reagents, the products were controlled by steric and electronic factors.⁵ However, in the reaction of pyridine-2,3-dicarboxylic anhydride⁶ and pyridine-3,4-dicarboxylic anhydride⁷ with $Ph_3P=CHCOOBu^t$, a nitrogen in the pyridine plays a significant

role in providing the product. In this paper, we report the reactivity of 1 toward Wittig reagents and a simple synthesis of cyclopenta[b]indoles.⁸

Reaction of 1-benzylindole-2,3-dicarboxylic anhydride (1) with $Ph_3P=CH_2$ gave a ylide (4) in 92% yield, but its isomer (5) was not isolated. Esterification of 4 by using methanol and 1-methyl-2-chloropyridinium iodide⁹ yielded a corresponding methyl ester (6) in 71% yield. Treatment of the ylide (6) with benzaldehyde in refluxing mesitylene gave an α,β -unsaturated ketone (7a) in 55% yield. In a similar manner, 7b and 7c were effected in 84% and 30% yields, respectively. 6 also reacted with acetaldehyde at room temperature to afford 7d in 31% yield, but with ketones the starting material was recovered.

Scheme 2



The structure of the ylide (4) was determined as follows: treatment of 4 with 20% hydrochloric acid gave a ylide (8)(74%), which reacted with benzaldehyde and acetaldehyde to give α,β -unsaturated ketones (9a) and (9b) in 97% and 88% yields, respectively. The (*E*) stereochemisty about the carbon-carbon bond in 9a was assigned on the basis of the large coupling constants (16 Hz) between the olefinic protons, but the stereochemistry of 9b was unclear. In ¹H-NMR, the proton of the 4-position (δ 7.60-7.79) in 9a appeared in higher field compared with the proton (δ 8.24-8.27) in 7a. Acid treatment of 9a and 9b with boron trifluoride etherate yielded cyclopenta[*b*]indol-3-ones (10a) and (10b) in 96% and 98% yields, respectively.





a: R = Ph, b: R = Me

A stabilized ylide (Ph₃P=CHCOOEt) reacted with a carbonyl group at the 2-position in 1 to give a ylide (11)(83%), which was converted by treatment with 20% hydrochloric acid to the ylide (8) in 89% yield, but its isomer (12) was not found. However, reaction of 1 with Ph₃P=C(Me)COOEt gave a mixture of two enol lactones (13) and (14) in 60% and 32% yields, respectively. 13 and 14 were converted to lactones (15) and (16) by catalytic hydrogenation over 5% palladium on activated carbon in 93% and 90% yields, respectively. The stereochemistry about the carbon-carbon bond in 14 was assigned on the basis that the proton of the 8-position (δ 8.24) in 14 appeared in lower field compared with the proton (δ 7.66) in 16.⁵ 13 was obtained as a single isomer, but its stereochemistry was ambiguous.

Scheme 4



EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ¹H-NMR spectra were determined on a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded on a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh). Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride prior to use.

[2-(1-Benzyl-3-carboxyindol-2-yl)-2-oxoethylidene]triphenylphosphorane (4)

A solution of 1-benzylindole-2,3-dicarboxylic anhydride (1)(0.83 g, 3 mmol) in THF (30 mL) was added to a solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (3.24 g, 9.1 mmol) and *n*-butyllithium (5.8 mL of a 1.56 M *n*-hexane solution, 9 mmol) at rt for 20 min] in THF (15 mL) at 0°C and the mixture was stirred for 1 h. The reaction mixture was acidified with 10% hydrochloric acid and extracted with CH₂Cl₂. The organic extracts were washed with water, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography (CHCl₃ : MeOH = 50 : 1) to give **4** (1.53 g, 92%) as a pale yellow solid: mp 192-193°C (*n*-hexane-CHCl₃). IR (nujol) 1679, 1500 cm⁻¹; ¹H-NMR (CDCl₃) δ 5.76 (2H, s, CH₂Ph), 7.09-7.64 (26H, m, aromatic protons), 8.62-8.68 (1H, m, H-4). HRMS *m*/z (M⁺) calcd for C₃₆H₂₉NO₃P: 554.1885. Found: 554.1887.

[2-(1-Benzyl-3-methoxycarbonylindol-2-yl)-2-oxoethylidene]triphenylphosphorane (6) To a solution of 4 (1.44 g, 2.6 mmol) and triethylamine (0.90 mL, 6.5 mmol) in MeOH (0.32 mL, 7.9

mmol) and CH₂Cl₂ (26 mL) was added 2-chloro-1-methylpyridinium iodide (0.73 g, 2.9 mmol) and the reaction mixture was stirred for 17 h under argon. The solvent was evaporated off to give a residue, which was purified by column chromatography (CH₂Cl₂ : AcOEt = 10 : 1) to give **6** (1.05 g, 71%), mp 164-165°C (*n*-hexane-CH₂Cl₂). IR (nujol) 1692, 1527 cm⁻¹; ¹H-NMR (CDCl₃) δ : 3.86 (3H, s, OCH₃), 4.08 (1H, d, J = 24 Hz, CHPPh₃), 5.50 (2H, s, CH₂Ph), 7.00-7.70 (23H, m, aromatic protons), 8.22 (1H, dt, J = 8, 1 Hz, H-4). Anal. Calcd for C₃₇H₃₀NO₃P: C, 78.29; H, 5.33; N, 2.47. Found: C, 78.15; H, 5.47; N, 2.60.

Reaction of 6 with Aldehydes: Synthesis of α,β -Unsaturated Ketones (7) (General Procedure)

A solution of the ylide (6) (0.1 mmol) and benzaldehyde (0.1 mmol) in mesitylene (2 mL) was refluxed under argon. The solvent was evaporated off to afford a residue, which was purified by column chromatography (*n*-hexane or CH_2Cl_2 : AcOEt = 5 : 1) to give 7.

(E)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-phenyl-2-propen-1-one (7a)

7a; mp 140-143°C (MeOH). IR (nujol) 1692, 1655 cm⁻¹; ¹H-NMR (CDCl₃) δ : 3.83 (3H, s, OCH₃), 5.39 (2H, s, CH₂Ph), 7.03 (1H, d, J = 16 Hz, COCH=CHPh), 7.08-7.44 (14H, m, COCH=CHPh and

aromatic protons), 8.24-8.27 (1H, m, H-4). Anal. Calcd for C₂₆H₂₁NO₃: C, 78.97; H, 5.35; N, 3.54. Found: C, 79.05; H, 5.45; N,3.51.

(E)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-(4-nitrophenyl)-2-propen-1-one (7b)

7b; mp 187-188°C (AcOMe). IR (nujol) 1680, 1665, 1514, 1347 cm⁻¹; ¹H-NMR (CDCl₃) δ : 3.86 (3H, s, OCH₃), 5.42 (2H, s, CH₂Ph), 7.04-7.58 (12H, m, COCH=CHPh and aromatic protons), 8.16-8.28 (3H, m, aromatic protons). *Anal.* Calcd for C₂₆H₂₀N₂O₅: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.75; H, 4.68; N, 6.27.

(E)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-(4-methoxyphenyl)-2-propen-1-one (7c)

7c; mp 185-186°C (AcOMe-MeOH). IR (nujol) 1688, 1647 cm⁻¹; ¹H -NMR (CDCl₃) δ : 3.82 (6H, s, OCH₃x2), 5.37 (2H, s, CH₂Ph), 6.80-6.90 (2H, m, aromatic protons), 6.93 (1H, d, J = 16 Hz, COCH=CHPh), 7.08-7.42 (11H, m, COCH=CHPh and aromatic protons), 8.22-8.28 (1H, m, aromatic protons). Anal. Calcd for C₂₇H₂₃NO₄: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.02; H, 5.56; N, 3.25.

(E)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-2-buten-1-one (7d)

A solution of the ylide (6) (397 mg, 0.7 mmol) in acetaldehyde (8 mL) was stirred for 16 h under argon. The reaction mixture was evaporated off to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **7d** (73 mg, 31%), mp 106-109 °C (MeOH). IR (nujol) 1699, 1656 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.75 (3H, dd, J = 7, 1 Hz, CH₃), 3.86 (3H, s, OCH₃), 5.32 (2H, s, CH₂Ph), 6.41 (1H, dq, J = 16, 1 Hz, COCH=CHCH₃), 6.56 (1H, dq, J = 16, 7 Hz, COCH=CHCH₃), 7.03-7.37 (8H, m, aromatic protons), 8.14-8.25 (1H, m, aromatic protons). Anal. Calcd for C₂₁H₁₉NO₃: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.60; H, 5.88; N, 4.23.

[2-(1-Benzylindol-2-yl)-2-oxoethylidene]triphenylphosphorane (8)

1) from The Ylide (4)

A suspension of the ylide (4) (3.32 g, 6 mmol) in 20% hydrochloric acid (120 mL) was refluxed for 2 h. The reaction mixture was made alkaline by 10% sodium hydroxide solution, and extracted with CH₂Cl₂. The organic extracts were washed with water, dried over Na₂SO₄, and concentrated to give a residue, which was purified by column chromatography (CH₂Cl₂ : MeOH = 50 : 1) to yield 8 (2.25 g, 74%), mp 234-235 °C (*n*-hexane-CH₂Cl₂) as a pale yellow solid. IR (nujol) 1529 cm⁻¹; ¹H-NMR (CDCl₃) δ : 4.39 (1H, d, J = 24 Hz, CHPPh₃), 5.98 (2H, s, CH₂Ph), 7.00-7.70 (25H, m, aromatic protons). HRMS *m/z* (M⁺) calcd for C₃₅H₂₈NOP: 509.1908. Found: 509.1927.

2) from The Ylide (11)

Using a procedure similar to that described for the preparation of 8 from the ylide (4), 8 (89%) was obtained from 11.

(E)-1-(1-Benzylindol-2-yl)-3-phenyl-2-propen-1-one (9a)

A solution of the ylide (8) (51 mg, 0.1 mmol) and benzaldehyde (12 μ L, 0.12 mmol) in benzene (1 mL) was refluxed for 2 h under argon. The solvent was evaporated off and the residue was purified by column

chromatography (*n*-hexane : AcOEt = 10 : 1) to give **9a** (33 mg, 97%), mp 94-96°C (*n*-hexane). IR (nujol) 1654 cm⁻¹; ¹H-NMR (CDCl₃) δ : 5.95 (2H, s, CH₂Ph), 7.06-7.45 (11H, m, aromatic protons), 7.53 (1H, s, H-3), 7.58 (1H, d, J = 16 Hz, COCH=CHPh), 7.60-7.79 (3H, m, aromatic protons), 7.79 (1H, d, J = 16 Hz, COCH=CHPh). Anal. Calcd for C₂₄H₁₉NO: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.39; H, 5.80; N, 4.23.

1-(1-Benzylindol-2-yl)-2-buten-1-one (9b)

A suspension of the ylide (8) (509 mg, 1.0 mmol) in acetaldehyde (10 mL) was stirred for 1 h at 0°C under argon. The reaction mixture was evaporated off and the residue was purified by column chromatography (*n*-hexane : AcOEt = 20 : 1) to give **9b** (241 mg, 88%), mp 69-70°C (*n*-hexane). IR (nujol) 1661 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.98 (3H, dd, J = 6, 1 Hz, CH₃), 5.90 (2H, s, CH₂Ph), 6.91-7.40 (11H, m, aromatic protons), 7.72 (1H, dt, J = 8, 1 Hz, H-4). Anal. Calcd for C₁₉H₁₇NO: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.86; H, 6.38; N, 5.06.

4-Benzyl-1-phenyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[b]indole (10a)

A mixture of the ketone (9a) (135 mg, 0.4 mmol) and boron trifluoride etherate (49 µL, 0.4 mmol) in CH₂Cl₂ (12 mL) was refluxed for 2 h under argon. The reaction mixture was neutralized with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts were washed with water, dried over Na₂SO₄, and evaporated off. The residue was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 10 : 1) to give **10a** (133 mg, 96%), mp 182-183°C (AcOEt). IR (nujol) 1678 cm⁻¹; ¹H-NMR (CDCl₃) δ : 2.91 (1H, dd, J = 18, 2 Hz), 3.54 (1H, dd, J = 18, 7 Hz), 4.67 (1H, dd, J = 7, 2 Hz), 5.58 (1H, d, J = 18 Hz, one of CH₂Ph), 5.62 (1H, d, J = 18 Hz, one of CH₂Ph), 7.00-7.40 (14H, m, aromatic protons). Anal. Calcd for C₂₄H₁₉NO: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.40; H, 5.84; N, 4.10. **4-Benzyl-1-methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta**[b]indole (10b)

Using a procedure similar to that described for the preparation of **10a**, **10b** (98%) was obtained from **9b**, mp 83-84°C (*n*-hexane). IR (nujol) 1681 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.50 (3H, d, J = 7 Hz, CH₃), 2.57 (1H, dd, J = 18, 2 Hz, one of CH₂), 3.25 (1H, dd, J = 18, 7 Hz, one of CH₂), 3.56 (1H, double of quintet, J = 7, 2 Hz), 5.49 (1H, d, J = 18 Hz, one of CH₂Ph), 5.56 (1H, d, J = 18 Hz, one of CH₂Ph), 7.12-7.37 (8H, m, aromatic protons), 7.73 (1H, dt, J = 8, 1 Hz, H-4). Anal. Calcd for C₁₉H₁₇NO: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.01; H, 6.29; N, 4.85.

[2-(1-Benzyl-3-carboxyindol-2-yl)-1-ethoxycarbonyl-2-oxoethylidene]triphenylphosphorane (11)

A solution of 1 (277 mg, 1 mmol) and carbethoxymethylenetriphenylphosphorane (348 mg, 1 mmol) in benzene (10 mL) was refluxed for 2 h under argon. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (CH₂Cl₂ : MeOH = 20 : 1) to give 11 (518 mg, 83%), mp 205-206°C (*n*-hexane-CHCl₃). IR (nujol) 1680, 1656, 1542, 1519 cm⁻¹; ¹H-NMR (CDCl₃) δ : 0.48 (3H, t, J = 7 Hz, CH₂CH₃), 3.62 (2H, q, J = 7 Hz, CH₂CH₃), 5.28 (1H, d, J = 17 Hz, one of CH₂Ph),

5.56 (1H, d, J = 17 Hz, one of CH₂Ph), 7.11-7.83 (25H, m, aromatic protons), 8.29 (1H, d, J = 8 Hz, H-4). HRMS m/z (M⁺) calcd for C₃₉H₃₃NO₅P: 626.2097. Found: 626.2104.

Ethyl 2-(4-Benzyl-1,3-dihydro-1-oxo-4*H*-furo[3,4-*b*]indol-3-ylidene)propionate (13) and Ethyl (*E*)-2-(4-Benzyl-1,3-dihydro-3-oxo-4*H*-furo[3,4-*b*]indol-1-ylidene)propionate (14) A solution of 1 (277 mg, 1.0 mmol) and carbethoxyethylidenetriphenylphosphorane (398 mg, 1.1 mmol) in benzene (10 mL) was stirred for 2 days under argon. The reaction mixture was evaporated off and the residue was purified by column chromatography (*n*-hexane : $CH_2Cl_2 = 5 : 1$) to afford 13 (218 mg, 60%) and 14 (114 mg, 32%).

13; mp 121-122°C (*n*-hexane-AcOEt). IR (nujol) 1773, 1700, 1647 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.14 (3H, t, J = 7 Hz, CH₂CH₃), 2.21 (3H, s, CH₃), 4.00 (2H, q, J = 7 Hz, CH₂CH₃), 5.57 (2H, s, CH₂Ph), 6.86-7.38 (8H, m, aromatic protons), 7.92-7.99 (1H, m, H-4). Anal. Calcd for C₂₂H₁₉NO₄: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.09; H, 5.40; N, 3.89.

14; mp 142-143°C (*n*-hexane-AcOEt). IR (nujol) 1765, 1719, 1632 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.40 (3H, t, J = 7 Hz, CH₂CH₃), 2.25 (3H, s, CH₃), 4.41 (2H, q, J = 7 Hz, CH₂CH₃), 5.57 (2H, s, CH₂Ph), 7.20-7.42 (8H, m, aromatic protons), 8.24 (1H, dt, J = 8, 1 Hz, H-4). Anal. Calcd for C₂₂H₁₉NO₄: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.08; H, 5.40; N, 3.93.

Ethyl 2-(4-Benzyl-1,3-dihydro-1-oxo-4H-furo[3,4-b]indol-3-yl)propionate (15)

A suspension of 13 (144 mg, 0.4 mmol) and 5% palladium on activated carbon (14 mg) in AcOEt (8 mL) was stirred for 1 day under hydrogen. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by column chromatography (CH₂Cl₂ : AcOEt = 30 : 1) to yield 15 (135 mg, 93%), mp 157-158°C (*n*-hexane-AcOEt). IR (nujol) 1748 cm⁻¹; ¹H-NMR (CDCl₃) δ : 0.95 (3H, t, J = 7 Hz, CHCH₃), 1.19 (3H, d, J = 7 Hz, CHCH₃), 3.10-3.20 (1H, m, CHCH₃), 3.79-4.01 (2H, m, CH₂CH₃), 5.30 (1H, d, J = 17 Hz, one of CH₂Ph), 5.56 (1H, d, J = 3 Hz, CHCHCH₃), 7.04-7.40 (8H, m, aromatic protons), 7.88-7.96 (1H, m, H-4). Anal. Calcd for C₂₂H₂₁NO₄: C, 72.21; H, 5.82; N, 3.85. Found: C, 72.50; H, 5.82; N, 3.72.

Ethyl 2-(4-Benzyl-1,3-dihydro-3-oxo-4H-furo[3,4-b]indol-1-yl)propionate (16)

Using a procedure similar to that described for the preparation of **15**, **16** (90%) was obtained as an oil from **14** by using 10% palladium on activated carbon and eluent solvent (*n*-hexane : AcOEt = 5 : 1). IR (neat) 1758 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.21 (3H, d, J = 7 Hz, CHCH₃), 1.29 (3H, t, J = 7 Hz, CHCH₃), 3.12 (1H, dq, J = 7, 6 Hz, CHCH₃), 4.27 (2H, q, J = 7 Hz, CH₂CH₃), 5.55 (2H, s, CH₂Ph), 5.97 (1H, d, J = 6 Hz, CHCHCH₃), 7.16-7.45 (8H, m, aromatic protons), 7.66 (1H, dt, J = 8, 1 Hz, H-4). HRMS *m/z* (M⁺) calcd for C₂₂H₂₁NO₄: 363.1471. Found: 363.1449

REFERENCES

- 1. Y. Miki and H. Hachiken, Synlett, 1993, 333.
- 2. Y. Miki, Y. Tada, N. Yanase, H. Hachiken, and K. Matsushita, Tetrahedron Lett., 1996, 37, 7753.

- 3. Y. Miki, H. Hachiken, and I. Yoshikawa, Heterocycles, 1997, 45, 1143.
- 4. P. J. Murphy and J. Brennan, Chem. Soc. Rev., 1988, 17, 1.
- A. Allahdad and D. W. Knight, J. Chem. Soc., Perkin Trans. 1, 1982, 1855; L. Breau and M. M. Kayser, Can. J. Chem., 1989, 67, 569; M. M. Kayser, K. L. Hatt, and D. L. Hooper, Can. J. Chem., 1992, 70, 1985; M. M. Kayser, K. L. Hatt, H. Yu, and D. L. Hooper, Can. J. Chem., 1993, 71, 1010.
- B. L. Mylari, W. J. Zembrowski, T. A. Beyer, C. E. Aldinger, and T. W. Siegel, J. Med. Chem., 1992, 35, 2155.
- 7. H. H. Wasserman and G.-H. Kuo, Tetrahedron, 1992, 48, 7071.
- K. F. Jennings, J. Chem. Soc., 1957, 497; J. Bergman, L. Venemalm, and A. Gogoll, Tetrahedron, 1990, 46, 6067; M. Ishikura and M. Terashima, J. Org. Chem., 1994, 59, 2634; C.-A. Harrison, R. Leineweber, C. J. Moody, and J. M. J. Williams, J. Chem. Soc., Perkin Trans. 1, 1995, 1127; C.-A. Harrison, P. M. Jackson, C. J. Moody, and J. M. J. Williams, J. Chem. Soc., Perkin Trans. 1, 1995, 1131.
- 9. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1975, 1045.

Received, 9th June, 1997