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

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Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with methylene-triphenylphosphorane (Ph₃P=CH₂) and carbethoxymethylene triphenylphosphorane (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-A¹ 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 Ph₃P=CHCOOBu⁴, 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 Ph3P=CH2 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

![Scheme 2 diagram]

Table 1

<table>
<thead>
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<tr>
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<td>55</td>
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<tr>
<td>b</td>
<td>4-NO2-Ph</td>
<td>3</td>
<td>84</td>
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<tr>
<td>c</td>
<td>4-MeO-Ph</td>
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</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>6</td>
<td>31</td>
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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) stereochemistry 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 stabilized ylide (Ph$_3$P=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 Ph$_3$P=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 ($\delta$ 8.24) in 14 appeared in lower field compared with the proton ($\delta$ 7.66) in 16.$^5$ 13 was obtained as a single isomer, but its stereochemistry was ambiguous.
EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The $^1$H-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 (CH$_2$Cl$_2$) 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 CH$_2$Cl$_2$. The organic extracts were washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography (CHC$_3$ : MeOH = 50 : 1) to give 4 (1.53 g, 92%) as a pale yellow solid: mp 192-193°C (n-hexane-CHCl$_3$). IR (nujol) 1679, 1500 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 5.76 (2H, s, CH$_2$Ph), 7.09-7.64 (26H, m, aromatic protons), 8.62-8.68 (1H, m, H-4). HRMS m/z (M$^+$) calcd for C$_{36}$H$_{29}$N$_3$O$_3$P: 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 CH$_2$Cl$_2$ (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 (CHC$_3$ : MeOH = 10 : 1) to give 6 (1.05 g, 71%), mp 164-165°C (n-hexane-CHCl$_3$). IR (nujol) 1692, 1527 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 3.86 (3H, s, OCH$_3$), 4.08 (1H, d, $J = 16$ Hz, COCH=CHPh), 7.00-7.44 (14H, m, aromatic protons). Anal. Calcd for C$_{37}$H$_{30}$N$_3$O$_3$P: 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 $\alpha,\beta$-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$_2$Cl$_2$ : 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$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 3.83 (3H, s, OCH$_3$), 5.39 (2H, s, CH$_2$Ph), 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 C_{26}H_{21}NO_{3}: 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 C_{26}H_{20}N₂O₅: 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, OCH₃×₂), 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 (1H, m, COCH=CHPh and aromatic protons), 8.22-8.28 (1H, m, aromatic protons).  
*Anal.* Calcd for C_{27}H_{23}N₂O₄: 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 C_{21}H₁₉NO₃: 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 with 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 (n-hexane : 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 C_{35}H_{28}NOP: 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 µL, 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 (1H, 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 FL, 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, 85.39; H, 5.80; N, 4.23.

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 carboxethoxymethylenetriphenylphosphorane (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 CH$_2$Ph), 7.41-7.83 (25H, m, aromatic protons), 8.29 (1H, d, J = 8 Hz, H-4). HRMS m/z (M$^+$) calcd for C$_{39}$H$_{33}$N$_2$O$_5$P: 626.2097. Found: 626.2104.

**Ethyl 2-(4-Benzyl-1,3-dihydro-1-oxo-4H-furo[3,4-b]indol-3-ylidine)propionate (13)** and **Ethyl (E)-2-(4-Benzyl-1,3-dihydro-3-oxo-4H-furo[3,4-b]indol-1-ylidine)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-butan: CH$_2$Cl$_2$ = 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$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 1.14 (3H, t, J = 7 Hz, CH$_2$CH$_3$), 2.21 (3H, s, CH$_3$), 4.00 (2H, q, J = 7 Hz, CH$_2$CH$_3$), 5.57 (2H, s, CH$_2$Ph), 6.86-7.38 (8H, m, aromatic protons), 7.92-7.99 (1H, m, H-4). Anal. Calcd for C$_{22}$H$_{19}$N$_2$O$_4$: 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$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 1.40 (3H, t, J = 7 Hz, CH$_2$CH$_3$), 2.25 (3H, s, CH$_3$), 4.41 (2H, q, J = 7 Hz, CH$_2$CH$_3$), 5.57 (2H, s, CH$_2$Ph), 7.20-7.42 (8H, m, aromatic protons), 8.24 (1H, dt, J = 8, 1 Hz, H-4). Anal. Calcd for C$_{22}$H$_{19}$N$_2$O$_4$: C, 73.12; H, 5.30; N, 3.89. 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 (CH$_2$Cl$_2$: AcOEt = 30:1) to yield 15 (135 mg, 93%), mp 157-158°C (n-hexane:AcOEt). IR (nujol) 1748 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 0.95 (3H, t, J = 7 Hz, CHCH$_3$), 1.19 (3H, d, J = 7 Hz, CHCH$_3$), 3.10-3.20 (IH, m, CHCH$_3$), 3.79-4.01 (2H, m, CH$_2$CH$_3$), 5.30 (1H, d, J = 17 Hz, one of CH$_2$Ph), 5.53 (1H, d, J = 17 Hz, one of CH$_2$Ph), 5.56 (1H, d, J = 3 Hz, CHCHCH$_3$), 7.04-7.40 (8H, m, aromatic protons), 7.88-7.96 (1H, m, H-4). Anal. Calcd for C$_{22}$H$_{21}$N$_2$O$_4$: 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$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$: 1.21 (3H, d, J = 7 Hz, CHCH$_3$), 1.29 (3H, t, J = 7 Hz, CHCH$_3$), 3.12 (1H, dq, J = 7, 6 Hz, CHCH$_3$), 4.27 (2H, q, J = 7 Hz, CH$_2$CH$_3$), 5.55 (2H, s, CH$_2$Ph), 5.97 (1H, d, J = 6 Hz, CHCHCH$_3$), 7.16-7.45 (8H, m, aromatic protons), 7.66 (1H, dt, J = 8, 1 Hz, H-4). HRMS m/z (M$^+$) calcd for C$_{22}$H$_{21}$NO$_4$: 363.1471. Found: 363.1449.

**REFERENCES**


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