NITRATION OF DIMETHYL 1-SUBSTITUTED INDOLE-2,3-DICARBOXYLATES: SYNTHESIS OF NITRO- AND AMINOINDOLE DERIVATIVES

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Abstract – The treatment of dimethyl indole-2,3-dicarboxylate with nitronium tetrafluoroborate in the presence of tin (IV) chloride produced dimethyl 5-nitroindole-2,3-dicarboxylate as the major product. In a similar manner, the dimethyl 1-benzyl- and 1-benzenesulfonylindole-2,3-dicarboxylates provided a mixture of the corresponding 4-nitro-, 5-nitro-, 6-nitro- and 7-nitroindole derivatives. However, dimethyl 5-bromoindole-2,3-dicarboxylate gave dimethyl 5-bromo-4-nitroindole-2,3-dicarboxylate as the sole product, which was converted to dimethyl 4-aminoindole-2,3-dicarboxylate.

The nitration of indoles is one of the useful reactions for introducing the nitrogen atom directly into indole rings, but indoles having an electron-donating group are unstable under the usual nitration conditions and also undergo undesirable oxidation and polymerization. However, indoles possessing an electron-withdrawing group such as acyl or ester group are relatively stable under severe nitration conditions. The aromatic nitro group is a useful functional group, which could be converted into various groups via an amino group by reduction. The nitration of ethyl indole-2-carboxylate afforded 4-nitroindole derivative in low yield as reported by Norland, and from methyl indole-3-carboxylate, a mixture of methyl 4-nitroindole-3-carboxylate (30%) and ethyl 6-nitroindole-3-carboxylate (30%) was obtained by Nakatsuka. Ottoni showed that 3-acetyl-5-nitroindole was obtained at low temperature by the nitration of 3-acetylindole with nitronium tetrafluoroborate (NO$_2$BF$_4$), but at 60° C, 3-acetyl-6-nitroindole was isolated as the sole product. Tobinaga reported the synthesis of chuangxinmycin from 3-acetyl-4-nitroindole, which was prepared by the nitration of 3-acetylindole in the presence of metal in low yield. We reported that dimethyl indole-2,3-dicarboxylates and indole-2,3-dicarboxylic anhydrides were useful synthons for the synthesis of pratosine, hippadine, murrayquinone-A, ellipticine, olivacine, and caulersin. Recently, we showed the selective bromination of the dimethyl indole-2,3-dicarboxylates and the synthesis of the dimethyl 5-bromo-
6-bromo-, and 5,6-dibromoindole-2,3-dicarboxylates because many bromoindole alkaloids have been isolated from various sources. In this study, we examine the nitration of the dimethyl 1-substituted indole-2,3-dicarboxylates (I) using NO₂BF₄ and trifluoroacetyl nitrate (TFAN, CF₃COONO₂) to enhance their utility as a synthon for the synthesis of the indole alkaloids.

The reaction of dimethyl indole-2,3-dicarboxylate (1a) (R = H) with NO₂BF₄ in the presence of tin (IV) chloride in dichloromethane at -20 °C gave dimethyl 5-nitroindole-2,3-dicarboxylate (3a) in 79% yield as a major product with a mixture of dimethyl 6-nitro- (4a) and 7-nitroindole-2,3-dicarboxylate (5a), in 4% and 13% yields, respectively, but with TFAN, 1a gave a mixture of dimethyl 4-nitroindole-2,3-dicarboxylate (2a), 3a, 4a, and 5a in 9%, 30%, 13%, and 9% yields, respectively. (Entries 1, 2) The nitration of dimethyl 1-benzylindole-2,3-dicarboxylate (1b) (R = CH₂Ph) with NO₂BF₄ resulted in a complex mixture, but with TFAN, a mixture of 2b, 3b, and 4b was obtained. (Entries 3, 4) The treatment of dimethyl 1-benzenesulfonylindole-2,3-dicarboxylate (1c) (R = SO₂Ph) with NO₂BF₄ or TFAN afforded an inseparable mixture of 2c, 3c, 4c, and 5c. (Entries 5, 6) (Table 1)

We also examined the nitration of the dimethyl 5-bromoindole-2,3-dicarboxylates (6a and 6b) because 6a and 6b were easily obtained by the bromination of dimethyl indole-2,3-dicarboxylate (1a) and (1b),

Scheme 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Condition</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>-20 °C 5 h</td>
<td>79 4 13  -</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>-78 °C 0.5 h</td>
<td>9 30 13 9 23</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>rt 3 h</td>
<td>- - - - -</td>
</tr>
<tr>
<td>4</td>
<td>b</td>
<td>-78 °C 2 h</td>
<td>16 35 19 - 16</td>
</tr>
<tr>
<td>5</td>
<td>c</td>
<td>rt 8 h</td>
<td>16 26 26 - -</td>
</tr>
<tr>
<td>6</td>
<td>c</td>
<td>-78 °C 3 h</td>
<td>30 28 24 15 -</td>
</tr>
</tbody>
</table>

1) SO₂Ph derivatives (2c, 3c, 4c, 5c) were isolated as NH derivatives (2a, 3a, 4a, 5a) by treatment with tetrabutylammonium fluoride.

Method A: NO₂BF₄ (2.2 eq) and Sn (IV)Cl₄ (5 eq) in CH₂Cl₂.

Method B: NH₄NO₃ (1.2 eq) and (CF₃COO)₂O (10 eq) in CH₂Cl₂.
respectively. A complex mixture was obtained from the reaction of dimethyl 5-bromoindole-2,3-dicarboxylate (6a) (R = H) with TFAN, but dimethyl 5-bromo-4-nitroindole-2,3-dicarboxylate (7a) was isolated as the sole product in 83% yield by treatment with NO₂BF₄. (Entries 1, 2) However, the treatment of 6b with TFAN provided an inseparable mixture of dimethyl 5-bromo-4-nitro-(7b) and 5-bromo-4-nitroindole-2,3-dicarboxylate (8b), which were isolated as 7a and 8a by treatment of tetrabutylammonium fluoride in 60% and 35% yields, respectively. (Entry 3) (Table 2)

![Scheme 2](image)

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>6</th>
<th>R</th>
<th>Nitrating agent</th>
<th>Condition</th>
<th>Yield(%)</th>
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<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>TFAN (3 eq)</td>
<td>-20 °C 0.5 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>H</td>
<td>NO₂BF₄ (2.2 eq)</td>
<td>0°C 0.5 h</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>SO₂Ph</td>
<td>TFAN (3 eq)</td>
<td>-20 °C 0.5 h</td>
<td>60</td>
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</table>

1) SO₂Ph derivatives (7b and 8b) were isolated as NH derivatives (7a and 8a) by treatment with tetrabutylammonium fluoride.

Finally, we examined the conversion of the nitro group in dimethyl 5-nitroindole-2,3-dicarboxylate (3a) and dimethyl 5-bromo-4-nitroindole-2,3-dicarboxylate (7a) to an amino group in them. (3a) was treated with ammonium formate in the presence of 10% Pd-C in hot MeOH to give a corresponding dimethyl 5-aminoindole-2,3-dicarboxylate (9) in 88% yield. (Scheme 3)

![Scheme 3](image)

The reduction of 7a with ammonium formate in the presence of 10% Pd-C in hot MeOH provided dimethyl 4-aminoindole-2,3-dicarboxylate (10) in 85% yield, but dimethyl 5-bromo-4-aminoindole-2,3-dicarboxylate (11) was not isolated. (Entry 1) The treatment of 7a with sodium borohydride in the
presence of tin (II) chloride resulted in a low yield. (Entry 2) However, 7a was treated with tetra-n-butylammonium borohydride (3 eq) in the presence of tin (II) chloride in tetrahydrofuran to give dimethyl 4-amino-5-bromoindole-2,3-dicarboxylate (11) in 45% yield and 7a was also recovered in 42% yield, but in the presence of excess tetra-n-butylammonium borohydride (6 eq), a mixture of 10 and 11 was obtained in 42% and 58% yields, respectively. (Entries 3, 4) (Scheme 4) (Table 3)

Scheme 4

Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing agent</th>
<th>Solvent</th>
<th>Condition</th>
<th>10</th>
<th>11</th>
<th>Recovered</th>
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<tr>
<td>1</td>
<td>HCO₂NH₄ (3 eq) / 10% Pd-C</td>
<td>MeOH</td>
<td>reflux 2 h</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄ (1.5 eq) / SnCl₂ (5 eq)</td>
<td>MeOH</td>
<td>reflux 9 h</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu₄NBH₄ (3 eq) / SnCl₂ (5 eq)</td>
<td>THF</td>
<td>rt 3 d</td>
<td>-</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu₄NBH₄ (6 eq) / SnCl₂ (5 eq)</td>
<td>THF</td>
<td>rt 10 min</td>
<td>42</td>
<td>58</td>
<td>-</td>
</tr>
</tbody>
</table>

EXPERIMENTAL

Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. The ¹H-NMR spectra were determined by a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded using a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded by a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh).

Nitration of Dimethyl Indole-2,3-dicarboxylates (1): General Procedure

By Using Nitronium Tetrafluoroborate (Method A)

To a mixture of dimethyl indole-2,3-dicarboxylates (1) (1 mmol) in CH₂Cl₂ (1 mL) was added 1M tin (IV) chloride in a CH₂Cl₂ solution, then the nitronium tetrafluoroborate (1–3 mmol) and the reaction mixture was stirred at rt. Water was added to the mixture and the mixture was extracted with CHCl₃ : MeOH (10 : 1). The extracts were washed with water, dried over Na₂SO₄, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on silica gel (n-hexane : AcOEt = 3 : 1 - 2 : 3) to give the dimethyl 4-nitro- (2), 5-nitro (3), 6-nitro- (4), and...
7-nitroindole-2,3-dicarboxylate (5). These reaction conditions and results are shown in Tables 1 and 2.

Using Trifluoroacetyl Nitrate (TFAN) (Method B)
The dimethyl indole-2,3-dicarboxylates (1) (1 mmol) were added to trifluoroacetyl nitrate (prepared from ammonium nitrate (1-3 mmol) and trifluoroacetic anhydride (5-10 mmol) in CH$_2$Cl$_2$ (1 mL)), stirring for 1 h at rt) and the mixture was stirred. The reaction mixture was added to water and the mixture was extracted with CH$_2$Cl$_2$. The extracts were washed with water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on silica gel (n-hexane : AcOEt = 3 : 1 - 2 : 3) to give the dimethyl 4-nitro- (2), 5-nitro (3), 6-nitro- (4), and 7-nitroindole-2,3-dicarboxylate (5). These reaction conditions and results are shown in Tables 1 and 2.

Debenzensulfonylation of Dimethyl 1-Benzensulfonylnitroindole-2,3-dicarboxylates (2c, 3c, 4c, 5c) and Dimethyl 1-Benzensulfonyl-5-bromo-nitroindole-2,3-dicarboxylates (7, 8) : General Procedure for Preparation of Dimethyl Nitroindole-2,3-dicarboxylates
To a solution of an inseparable mixture of dimethyl nitroindole-2,3-dicarboxylates (2c, 3c, 4c, 5c) (40 mg, 0.1 mmol) in THF (1 mL), a 1.0 M solution of tetrabutylammonium fluoride in THF (0.1 mL, 0.1 mmol) was added at -20 °C, and the mixture was stirred for 30 min. The reaction mixture was neutralized with 1% hydrochloric acid, and the aqueous mixture was extracted with CHCl$_3$. The extracts were washed with water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on silica gel.

Dimethyl 4-Nitroindole-2,3-dicarboxylate (2a); mp 241 °C (MeOH). IR (Nujol) cm$^{-1}$: 1679, 1519. 
$^1$H-NMR (CDCl$_3$): $\delta$: 3.99, 4.05 (6H, s, 2xCO$_2$CH$_3$), 7.60 (1H, t, $J = 8$ Hz, H-6), 7.78 (1H, d, $J = 8.5$ Hz, H-7), 8.05 (1H, d, $J = 8.5$ Hz, H-5), 9.30 (1H, br s, H-1). Anal. Calcd for C$_{12}$H$_{10}$N$_2$O$_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.70; H, 3.70; N, 10.11.

Dimethyl 5-Nitroindole-2,3-dicarboxylate (3a); mp 213-214 °C (MeOH). IR (Nujol) cm$^{-1}$: 1737, 1525. 
$^1$H-NMR (CDCl$_3$): $\delta$: 4.04 (6H, s, 2xCO$_2$CH$_3$), 7.54 (1H, d, $J = 9$ Hz, H-7), 8.27 (1H, dd, $J = 9$, 2 Hz, H-6), 9.02 (1H, d, $J = 2$ Hz, H-4), 9.64 (1H, br s, H-1). Anal. Calcd for C$_{12}$H$_{10}$N$_2$O$_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.89; H, 3.67; N, 10.10.

Dimethyl 6-Nitroindole-2,3-dicarboxylate (4a); mp 214 °C (MeOH). IR (Nujol) cm$^{-1}$: 1678, 1518. 
$^1$H-NMR (DMSO-d$_6$): $\delta$: 3.87, 3.95 (6H, s, 2xCO$_2$CH$_3$), 8.07 (1H, dd, $J = 8$, 1.5 Hz, H-5), 8.12 (1H, d, $J = 8$ Hz, H-4), 8.38 (1H, d, $J = 1.5$ Hz, H-7), 13.30 (1H, br s, H-1). HRMS (EI) m/z: Calcd for C$_{12}$H$_{10}$N$_2$O$_6$: 278.0564. Found: 278.0439. Anal. Calcd for C$_{12}$H$_{10}$N$_2$O$_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.82; H, 3.60; N, 10.16.

Dimethyl 7-Nitroindole-2,3-dicarboxylate (5a); mp 120 °C (n-hexane). IR (Nujol) cm$^{-1}$: 1707, 1544. 
$^1$H-NMR (CDCl$_3$): $\delta$: 4.01, 4.05 (6H, s, 2xCO$_2$CH$_3$), 7.41 (1H, d, $J = 8$ Hz, H-5), 8.34 (1H, dd, $J = 8$, 1 Hz, H-6 or H-4), 8.47 (1H, d, $J = 8$ Hz, H-4 or H-6), 10.60 (1H, br s, H-1). Anal. Calcd for C$_{12}$H$_{10}$N$_2$O$_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.86; H, 3.67; N, 10.13.

Dimethyl 1-Benzyl-4-nitroindole-2,3-dicarboxylate (2b); mp 114 °C (EtOH). IR (CHCl$_3$) cm$^{-1}$: 1724, 1532. 
$^1$H-NMR (CDCl$_3$): $\delta$: 3.91, 4.00 (6H, s, 2xCO$_2$CH$_3$), 5.85 (2H, s, CH$_2$), 7.00-7.08 (2H, m, arom), 7.23-7.32 (3H, m, arom), 7.42 (1H, t, $J = 8$ Hz, H-6), 7.69 (1H, d, $J = 8$ Hz, H-7 or 5), 8.11 (1H, d, $J = 8$ Hz, H-5).
Hz, H-5 or 7). Anal. Calcd for C_{19}H_{16}N_{2}O_{6}: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.89; H, 4.43; N, 7.61.

Dimethyl 1-Benzyl-5-nitroindole-2,3-dicarboxylate (3b); mp 147 °C (AcOEt). IR (CHCl$_3$) cm$^{-1}$: 1714, 1524. 1H-NMR (CDCl$_3$): 3.94, 3.99 (6H, s, 2xCO$_2$CH$_3$), 5.48 (2H, s, CH$_2$), 7.07-7.13 (2H, m, arom), 7.28-7.33 (3H, m, arom), 7.38 (1H, d, $J$ = 9 Hz, H-7), 8.18 (1H, dd, $J$ = 9, 2 Hz, H-6), 9.07 (1H, d, $J$ = 2 Hz, H-4). Anal. Calcd for C$_{19}$H$_{16}$N$_2$O$_6$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.91; H, 4.39; N, 7.60.

Dimethyl 1-Benzyl-6-nitroindole-2,3-dicarboxylate (4b); mp 167 °C (AcOEt). IR (CHCl$_3$) cm$^{-1}$: 1713, 1522. 1H-NMR (CDCl$_3$): 3.94, 3.96 (6H, s, 2xCO$_2$CH$_3$), 5.50 (2H, s, CH$_2$), 7.10-7.16 (2H, m, arom), 7.28-7.34 (3H, m, arom), 8.16 (1H, dd, $J$ = 9, 2 Hz, H-5), 8.27 (1H, d, $J$ = 9 Hz, H-4), 8.29 (1H, d, $J$ = 2 Hz, H-7). Anal. Calcd for C$_{19}$H$_{16}$N$_2$O$_6$: C, 61.95; H, 4.38; N, 7.61. Found: C, 62.10; H, 4.39; N, 7.63.

Dimethyl 5-Bromo-4-nitroindole-2,3-dicarboxylate (7a); mp 230-232 °C (MeOH). IR (CHCl$_3$) cm$^{-1}$: 1719, 1543. 1H-NMR (CDCl$_3$): 3.91, 3.99 (6H, s, 2xCO$_2$CH$_3$), 7.48 (1H, d, $J$ = 9 Hz, H-6 or H-7), 7.61 (1H, d, $J$ = 9 Hz, H-7 or H-6), 9.48 (1H, br s, H-1). Anal. Calcd for C$_{12}$H$_9$N$_2$O$_6$Br: C, 40.36; H, 2.54; N, 7.85. Found: C, 40.26; H, 2.59; N, 7.90.

Dimethyl 5-Bromo-6-nitroindole-2,3-dicarboxylate (8a); mp 224-226 °C (MeOH). IR (CHCl$_3$) cm$^{-1}$: 1716. 1H-NMR (CDCl$_3$): 4.01, 4.04 (6H, s, 2xCO$_2$CH$_3$), 8.04 (1H, s, H-4 or H-7), 8.47 (1H, s, H-7 or H-4). Anal. Calcd for C$_{12}$H$_9$N$_2$O$_6$Br: C, 40.36; H, 2.54; N, 7.85. Found: C, 40.37; H, 2.55; N, 7.87.

Preparation of Dimethyl 5-Aminoindole-2,3-dicarboxylate (9), Dimethyl 4-Aminoindole-2,3-dicarboxylate (10), and Dimethyl 5-Bromo-4-aminoindole-2,3-dicarboxylate (11) by Reduction of Dimethyl Nitroindole-2,3-dicarboxylate (3a and 7a): General Procedure

a) Using Ammonium Formate in the Presence of 10% Pd/C
A mixture of dimethyl 5-bromo-4-nitroindole-2,3-dicarboxylate (3a) (56 mg, 0.2 mmol), ammonium formate (76 mg, 1.2 mmol), and 10% Pd/C (6 mg) in MeOH (2 mL) was refluxed for 2 h. The catalyst was removed by filtration through Cerite, and the filtrate was evaporated. The residue was purified by preparative thin-layer chromatography (n-hexane : AcOEt = 1 : 1) to give dimethyl 5-aminoindole-2,3-dicarboxylate (9) (44 mg, 88%) as a yellow solid. These reaction conditions and results are shown in Table 3.

b) Using Sodium Borohydride or Tetrabutylammonium Borohydride
A suspension of dimethyl 5-bromo-4-nitroindole-2,3-dicarboxylate (7a) (36 mg, 0.1 mmol), tin (II) chloride (SnCl$_2$·2H$_2$O), sodium borohydride or tetrabutylammonium borohydride in MeOH or THF (1 mL) was stirred or refluxed. Water was added to the reaction mixture, and the mixture was extracted with CHCl$_3$. The extracts were washed with water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford a residue, which was purified by chromatography on silica gel (n-hexane : AcOEt = 1 : 1) to afford dimethyl 4-amin indo-2,3-dicarboxylate (10) and dimethyl 5-bromo-4-aminoindole-2,3-dicarboxylate (11). These reaction conditions and results are shown in Table 3.

Dimethyl 5-Aminoindole-2,3-dicarboxylate (9); mp 74-77 °C (n-hexane-CH$_2$Cl$_2$). IR (CHCl$_3$) cm$^{-1}$:
3403, 3318, 1716, 1683. $^1$H-NMR (CDCl$_3$) $\delta$: 3.69 (2H, br s, NH$_2$), 3.97 (6H, s, 2xCO$_2$CH$_3$), 6.83 (1H, dd, $J = 8$, 1.5 Hz, H-6), 7.23 (1H, d, $J = 8$ Hz, H-7), 7.33 (1H, d, $J = 1.5$ Hz, H-6), 9.08 (1H, br s, H-1).

HRMS (FAB) $m/z$: Calcd for C$_{12}$H$_{11}$O$_4$N$_2$Br: 325.9902. Found: 325.9883.

**Dimethyl 4-Aminoindole-2,3-dicarboxylate (10):** mp 128-130 °C (n-hexane-ether). IR (CHCl$_3$) cm$^{-1}$: 3449, 3360, 1730, 1698. $^1$H-NMR (CDCl$_3$) $\delta$: 3.95, 3.96 (6H, s, 2xCO$_2$CH$_3$), 5.49 (2H, br s, NH$_2$), 6.66 (1H, d, $J = 9$ Hz, H-6 or H-7), 7.37 (1H, d, $J = 9$ Hz, H-7 or H-6), 8.97 (1H, br s, H-1). **Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.96; H, 4.85; N, 11.17.**

**Dimethyl 4-Amino-5-bromoindole-2,3-dicarboxylate (11):** mp 172-173 °C (MeOH). IR (KCl) cm$^{-1}$: 3445, 3303, 1698. $^1$H-NMR (CDCl$_3$) $\delta$: 3.95, 3.96 (6H, s, 2xCO$_2$CH$_3$), 5.49 (2H, br s, NH$_2$), 6.66 (1H, d, $J = 9$ Hz, H-6 or H-7), 7.37 (1H, d, $J = 9$ Hz, H-7 or H-6), 8.97 (1H, br s, H-1). **Anal. Calcd for C$_{12}$H$_{11}$N$_2$O$_4$Br: C, 43.94; H, 3.34; N, 8.46. Found: C, 44.06; H, 3.39; N, 8.57.**

**ACKNOWLEDGEMENT**
This work was supported by “High-Tech Research Center Project” for Private Universities: matching fund subsidy from MEXT (2007) and Kinki University.

**REFERENCES**