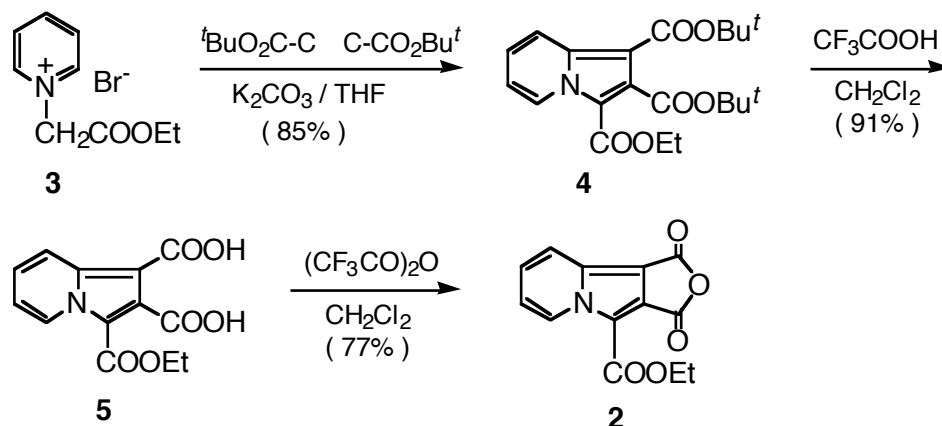


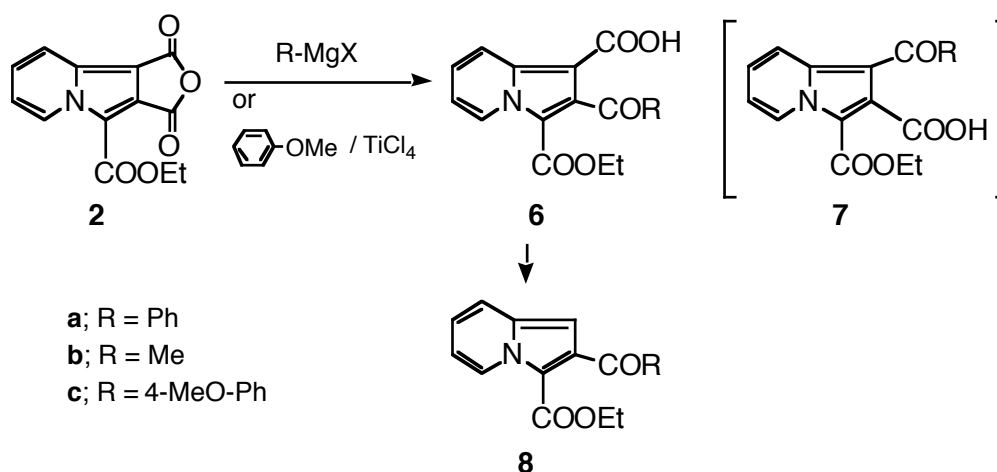
trifluoroacetic acid to afford the corresponding indolizine-1,2-dicarboxylic acid (**5**)(91%), which was treated with trifluoroacetic anhydride in refluxing dichloromethane to provide the anhydride (**2**)(77%).

Scheme 1



Reaction of the anhydride (**2**) with phenylmagnesium bromide in tetrahydrofuran at -78°C gave 2-benzoyl-3-ethoxycarbonylindolizine-1-carboxylic acid (**6a**) in 92% yield, but 1-benzoyl-3-ethoxycarbonylindolizine-2-carboxylic acid (**7a**) was not isolated. In a similar manner, treatment of **2** with methylmagnesium bromide afforded 2-acetyl-3-ethoxycarbonylindolizine-1-carboxylic acid (**6b**) in 96% yield. **2** also reacted with anisole in the presence of titanium(IV) chloride to give 2-(4-methoxybenzoyl)-3-ethoxycarbonylindolizine-1-carboxylic acid (**6c**) in 95% yield. Decarboxylation of 2-benzoylindolizine-1-carboxylic acid (**6a**) was performed by treatment of hot quinoline in the presence of copper chromite to provide ethyl 2-benzoylindolizine-3-carboxylate (**8a**) in 78% yield. **6b,c** were also converted to ethyl 2-acetylindolizine-3-carboxylate (**8b**) and ethyl 2-(4-methoxybenzoyl)indolizine-1-carboxylate (**8c**) in 59%

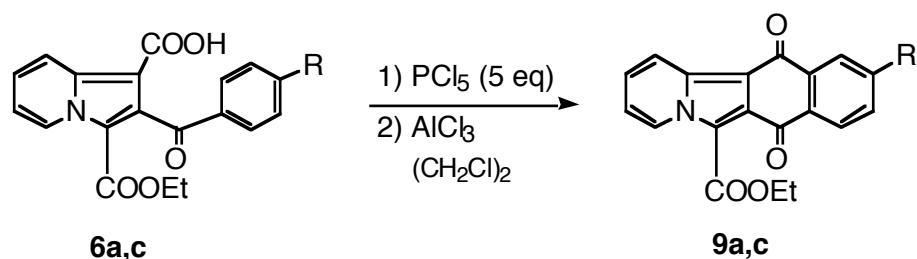
Scheme 2



and 35% yields, respectively, but treatment of **6c** with 20% perchloric acid in hot acetic acid gave **8c** in 82% yield.

Treatment of the carboxylic acid (**6a**) with phosphorus pentachloride, followed by aluminum(III) chloride afforded the corresponding quinone (**9a**) in 85% yield. In a similar manner, the carboxylic acid (**6c**) was also converted to the quinone (**9c**) in 37% yield.

Scheme 3



a; R = H
c; R = OMe

R	Condition	Yield(%)
a	50°C 4 h	85
c	reflux 6 h	37

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. Phenylmagnesium bromide (1.0 M solution in THF) and methylmagnesium bromide (1.4 M solution in toluene and tetrahydrofuran) were purchased from Aldrich.

Di-*tert*-butyl 3-Ethoxycarbonylindolizine-1,2-dicarboxylate (**4**)

To a suspension of *N*-ethoxycarbonylmethylpyridinium bromide (**3**) (19.68 g, 80 mmol) in THF (800 mL) were added K₂CO₃ (15.56 g, 120 mmol) and di-*tert*-butyl acetylenedicarboxylate (18.08 g, 80 mmol) and the mixture was stirred at rt for 4 days. The insoluble material was filtered off and the filtrate was concentrated to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give di-*tert*-butyl 3-ethoxycarbonylindolizine-1,2-dicarboxylate (**4**) (26.57 g, 85%) as a white solid: mp 136-137°C (MeOH). IR (CHCl₃) ν: 1734, 1693 cm⁻¹; ¹H-NMR (CDCl₃) δ: 1.39 (3H, t, *J* = 7 Hz, CH₂CH₃), 1.63 (9H, s, C(CH₃)₃), 1.66 (9H, s, C(CH₃)₃), 4.43 (3H, q, *J* = 7 Hz, CH₂CH₃), 6.96 (1H, dt, *J* = 7, 1 Hz, H-6), 7.29 (1H, ddd, *J* = 9, 7, 1 Hz, H-7), 8.19 (1H, dt, *J* = 9, 1 Hz, H-8), 9.54 (1H,

dt, $J = 7$, 1 Hz, H-5). *Anal.* Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.43; H, 6.88; N, 3.32.

3-Ethoxycarbonylindolizine-1,2-dicarboxylic Acid (5)

Trifluoroacetic acid (46.2 mL, 600 mmol) was added to a solution of di-*tert*-butyl 3-ethoxycarbonylindolizine-1,2-dicarboxylate (4) (23.34 g, 60 mmol) in CH_2Cl_2 (240 mL) and the mixture was stirred at rt overnight. The precipitates were collected by filtration and the precipitates were washed with *n*-hexane to afford 3-ethoxycarbonylindolizine-1,2-dicarboxylic acid (5) (15.14 g, 91%) as a white solid: mp 221-222°C (from MeOH). IR (Nujol) ν : 1712, 1662 cm^{-1} ; 1H -NMR (DMSO- d_6) δ : 1.31 (3H, t, $J = 7$ Hz, CH_2CH_3), 4.32 (3H, q, $J = 7$ Hz, CH_2CH_3), 7.22 (1H, dt, $J = 7$, 1 Hz, H-6), 7.50 (1H, ddd, $J = 9$, 7, 1 Hz, H-7), 8.29 (1H, dt, $J = 9$, 1 Hz, H-8), 9.42 (1H, dt, $J = 7$, 1 Hz, H-5). MS m/z : 277. HRMS m/z (M^+) calcd for $C_{13}H_{11}NO_6$: 277.0586. Found: 277.0576.

3-Ethoxycarbonylindolizine-1,2-dicarboxylic Anhydride (2)

A suspension of 3-ethoxycarbonylindolizine-1,2-dicarboxylic acid (5) (11.08 g, 40 mmol) and trifluoroacetic anhydride (18.0 mL, 120 mmol) in CH_2Cl_2 (120 mL) was refluxed for 2 h. The reaction mixture was evaporated off to provide a solid. The solid was suspended in *n*-hexane : ether (1 : 1) and the insoluble solid was collected by filtration to give 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (2) (7.94 g, 77%): mp 173°C (from AcOEt). IR ($CHCl_3$) ν : 1836, 1775, 1705 cm^{-1} ; 1H -NMR ($CDCl_3$) δ : 1.50 (3H, t, $J = 7$ Hz, CH_2CH_3), 4.50 (3H, q, $J = 7$ Hz, CH_2CH_3), 7.26 (1H, dt, $J = 7$, 1 Hz, H-6), 7.57 (1H, ddd, $J = 9$, 7, 1 Hz, H-7), 7.98 (1H, dt, $J = 9$, 1 Hz, H-8), 9.70 (1H, dt, $J = 7$, 1 Hz, H-5). HRMS m/z (M^+) calcd for $C_{13}H_9NO_5$: 259.0481. Found: 259.0464. *Anal.* Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 60.30; H, 3.50; N, 5.41.

2-Benzoyl-3-ethoxycarbonylindolizine-1-carboxylic Acid (6a)

To a suspension of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (2) (2.10 g, 8 mmol) in THF (40 mL) was added phenylmagnesium bromide (16 mL of a 1.0 M THF solution, 16 mmol) at 0°C under argon and the mixture was stirred for 1 h. The solution was acidified with 10% hydrochloric acid and the mixture was extracted with CH_2Cl_2 . The combined extracts were washed with water and dried over Na_2SO_4 . The solvent was evaporated off to afford a residue, which was purified by column chromatography ($CHCl_3$: MeOH = 50 : 1) to give 2-benzoyl-3-ethoxycarbonylindolizine-1-carboxylic acid (6a) (2.50 g, 92%): mp 250-252 ° C (THF-*n*-hexane). IR (Nujol) ν : 1688, 1657 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 0.85 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$), 4.08 (2H, q, $J = 7$ Hz, $COOCH_2CH_3$), 7.38-7.47 (3H, m, H-3' and H-5'), 7.10 (1H, dt, $J = 7$, 1 Hz, H-6), 7.56 (1H, tt, $J = 7$, 2, 1 Hz, H-4'), 7.86 (2H, dt, $J = 7$, 1 Hz, H-2' and H-6'), 8.41 (1H, dt, $J = 9$, 1 Hz, H-8), 9.61 (1H, dt, $J = 7$, 1 Hz, H-5). *Anal.* Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.59; H, 4.53; N, 4.11.

2-Acetyl-3-ethoxycarbonylindolizine-1-carboxylic Acid (6b)

To a suspension of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (2) (259 mg, 1 mmol) in THF (40 mL) was added methylmagnesium bromide (1.08 mL of a 1.0 M THF solution, 1.08 mmol) at -78°C under argon and the mixture was stirred for 30 min, then allowed to reach rt. The reaction mixture was acidified with 10% hydrochloric acid and the mixture was extracted with CH_2Cl_2 . The combined extracts were washed with water and dried over Na_2SO_4 . The solvent was evaporated off to afford a residue,

which was purified by column chromatography (CHCl₃ : MeOH = 5 : 1) to give 2-acetyl-3-ethoxycarbonylindolizine-1-carboxylic acid (**6b**) (264 mg, 96%) as a yellow solid: mp 239-241 ° C (MeOH). IR (Nujol) ν : 1710, 1658 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.39 (3H, t, J = 7 Hz, COOCH₂CH₃), 2.68 (1H, s, COCH₃), 4.38 (2H, q, J = 7 Hz, COOCH₂CH₃), 7.08 (1H, dt, J = 7, 1 Hz, H-6), 7.43 (1H, ddd, J = 9, 7, 1 Hz, H-7), 8.40 (1H, dt, J = 7, 1 Hz, H-8), 9.57 (1H, dt, J = 7, 1 Hz, H-5). HRMS m/z (M⁺) calcd for C₁₄H₁₃NO₅: 275.0754. Found: 275.0775. *Anal.* Calcd for C₁₄H₁₃NO₅: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.02; H, 4.78; N, 5.10.

3-Ethoxycarbonyl-2-(4-methoxybenzoyl)indolizine-1-carboxylic Acid (**6c**)

To a suspension of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (**2**) (1.04 g, 4 mmol) and anisole (434 μ L, 4 mmol) in CH₂Cl₂ (16 mL) was added titanium(IV) tetrachloride (8 mL of a 1.0 M CH₂Cl₂ solution, 8 mmol) at 0°C and the mixture was stirred for 2 h. Water was added to the reaction mixture and the mixture was extracted with CH₂Cl₂. The combined extracts were washed with water and dried over Na₂SO₄. The solvent was evaporated off to provide a residue, which was purified by column chromatography (CHCl₃ : MeOH = 10 : 1) to give 3-ethoxycarbonyl-2-(4-methoxybenzoyl)indolizine-1-carboxylic acid (**6c**) (1.40 g, 95%) as a white solid: mp 207-208 ° C (acetone-*n*-hexane). IR (Nujol) ν : 1698, 1659, 1600 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.90 (3H, t, J = 7 Hz, COOCH₂CH₃), 3.87 (1H, s, OMe), 4.09 (2H, q, J = 7 Hz, COOCH₂CH₃), 6.90 (2H, d, J = 9 Hz, H-3' and H-5'), 7.09 (1H, dt, J = 7, 1 Hz, H-6), 7.81 (2H, d, J = 9 Hz, H-2' and H-6'), 7.42 (1H, ddd, J = 9, 7, 1 Hz, H-7), 8.41 (1H, dt, J = 7, 1 Hz, H-8), 9.60 (1H, dt, J = 7, 1 Hz, H-5). HRMS m/z (M⁺) calcd for C₂₀H₁₇NO₆: 367.1056. Found: 367.1072. *Anal.* Calcd for C₂₀H₁₇NO₆: C, 65.39; H, 3.81; N, 4.66. Found: C, 65.21; H, 3.80; N, 4.67.

Ethyl 2-Benzoylindolizine-3-carboxylate (**8a**)

A mixture of 2-benzoyl-3-ethoxycarbonylindolizine-1-carboxylic acid (**6a**) (866 mg, 2.6 mmol) and copper chromite (104 mg) in quinoline (9 mL) was heated to reflux for 30 min and the insoluble material was removed by filtration through Celite. Water was added to the reaction mixture and the mixture was extracted with ether. The combined extracts were washed with water, then with 5% hydrochloric acid and water. The solution was dried over Na₂SO₄ and evaporated off to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to yield 2-benzoyl-3-ethoxycarbonylindolizine (**8a**) (590 mg, 78%) as a yellow solid: mp 101-103°C (*n*-hexane). IR (Nujol) ν : 1681, 1665, 1649 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.82 (3H, t, J = 7 Hz, COOCH₂CH₃), 4.01 (2H, q, J = 7 Hz, COOCH₂CH₃), 7.43 (6H, m, aromatic protons), 6.65 (1H, s, H-1), 6.91 (1H, dt, J = 7, 1 Hz, H-6), 7.11 (1H, ddd, J = 9, 7, 1 Hz, H-7), 9.47 (1H, dt, J = 7, 1 Hz, H-5). HRMS m/z (M⁺) calcd for C₁₈H₁₅NO₃: 293.1052. Found: 293.1027. *Anal.* Calcd for C₁₈H₁₅NO₃: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.76; H, 5.14; N, 4.75.

Ethyl 2-Acetylindolizine-3-carboxylate (**8b**)

Using a procedure similar to that described for the preparation of **8a**, **8b** (59%) was obtained from **6b**, mp 85-87 °C (*n*-hexane) as a pale yellow solid. IR (Nujol) ν : 1687 cm⁻¹; ¹H-NMR (CDCl₃) δ : 1.38 (3H, t, J = 7 Hz, COOCH₂CH₃), 2.61 (1H, s, COCH₃), 4.39 (2H, q, J = 7 Hz, COOCH₂CH₃), 6.88 (1H, dt, J = 7, 1 Hz, H-6), 7.07 (1H, ddd, J = 9, 7, 1 Hz, H-7), 7.51 (1H, dt, J = 7, 1 Hz, H-8), 9.39 (1H, dt, J = 7, 1

Hz, H-5). HRMS m/z (M^+) calcd for $C_{13}H_{13}NO_3$: 231.0845. Found: 231.0889. *Anal.* Calcd for $C_{13}H_{13}NO_3$ C, 73.71; H, 5.15; N, 4.78. Found: C, 73.76; H, 5.14; N, 4.75.

Ethyl 2-(4-Methoxybenzoyl)indolizine-3-carboxylate (8c)

1. In the Presence of Copper Chromite

Using a procedure similar to that described for the preparation of **8a**, **8c** (35%) was obtained from **6c**.

2. In Perchloric Acid

A suspension of **6c** (220 mg, 0.6 mmol) in 20% perchloric acid (4 mL) and acetic acid (2 mL) was refluxed for 25 min. The reaction mixture was diluted with water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4 , and evaporated off to give a residue, which was purified by column chromatography ($CHCl_3$) to afford ethyl 2-(4-methoxybenzoyl)indolizine-3-carboxylate (**8c**) (156 mg, 82%) as an oil. IR (Nujol) ν : 1681, 1656, 1599 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 0.88 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$), 3.87 (1H, s, OMe), 4.05 (2H, q, $J = 7$ Hz, $COOCH_2CH_3$), 6.90 (2H, d, $J = 9$ Hz, H-3' and H-5'), 6.89 (1H, dt, $J = 7, 1$ Hz, H-6), 7.84 (2H, d, $J = 9$ Hz, H-2' and H-6'), 7.11 (1H, ddd, $J = 9, 7, 1$ Hz, H-7), 7.54 (1H, dt, $J = 7, 1$ Hz, H-8), 9.47 (1H, dd, $J = 7, 1$ Hz, H-5). HRMS m/z (M^+) calcd for $C_{19}H_{17}NO_4$: 323.1158. Found: 323.1194.

6-Ethoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone (9a)

A suspension of 2-benzoyl-3-ethoxycarbonylindolizine-1-carboxylic acid (**6a**) (51 mg, 0.15 mmol) and phosphorus pentachloride (156 mg, 0.75 mmol) in 1,2-dichloroethane (1 mL) was stirred at rt overnight. Aluminum(III) chloride (100 mg, 0.75 mmol) was added to the solution and the reaction mixture was stirred at 50°C for 2 h. The mixture was heated with another aluminum(III) chloride (40 mg, 0.3 mmol) at 50°C under stirring for additional 2 h. The mixture was diluted with water and extracted with CH_2Cl_2 . The combined extracts were washed with water, dried over Na_2SO_4 , and evaporated off to give a residue, which was purified by column chromatography (n -hexane : AcOEt = 5 : 1) to afford 6-ethoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone (**9a**) (41 mg, 85%) as a yellow solid: mp 168-169 °C (AcOEt). IR (Nujol) ν : 1693, 1674, 1644 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 1.54 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$), 4.58 (2H, q, $J = 7$ Hz, $COOCH_2CH_3$), 7.12 (1H, dt, $J = 7, 1$ Hz, H-3), 7.47 (1H, ddd, $J = 9, 7, 1$ Hz, H-2), 7.70-7.76 (2H, m, H-8 and H-11), 8.23-8.29 (2H, m, H-9 and H-10), 8.67 (1H, dt, $J = 7, 1$ Hz, H-1), 9.32 (1H, dt, $J = 7, 1$ Hz, H-4). HRMS m/z (M^+) calcd for $C_{19}H_{13}NO_4$: 319.0845. Found: 319.0842. *Anal.* Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.58; H, 4.20; N, 4.30.

6-Ethoxycarbonyl-10-methoxynaphtho[2,3-*a*]indolizine-7,12-quinone (9c)

A suspension of 3-ethoxycarbonyl-2-(4-methoxybenzoyl)indolizine-1-carboxylic Acid (**6c**) (282 mg, 0.77 mmol) and phosphorus pentachloride (320 mg, 1.54 mmol) in 1,2-dichloroethane (5 mL) was stirred at rt overnight. Aluminum(III) chloride (205 mg, 1.54 mmol) was added to the solution and the reaction mixture was refluxed for 6 h. The mixture was diluted with water and extracted with CH_2Cl_2 . The combined extracts were washed with water, dried over Na_2SO_4 , and evaporated off to give a residue, which was purified by column chromatography (n -hexane : AcOEt = 5 : 1) to afford 6-ethoxy-10-methoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone (**9c**) (99 mg, 37%) as a red solid: mp 165-168°C (AcOEt). IR (Nujol) ν : 1670, 1647 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 1.52 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$),

4.56 (2H, q, $J = 7$ Hz, COOCH₂CH₃), 3.97 (1H, s, OMe), 7.10 (1H, dt, $J = 7, 1$ Hz, H-3), 7.18 (1H, dd, $J = 9, 1$ Hz, H-9), 7.45 (1H, ddd, $J = 9, 7, 1$ Hz, H-2), 7.70 (1H, d, $J = 1$ Hz, H-11), 8.20 (1H, d, $J = 9$ Hz, H-8), 8.63 (1H, dt, $J = 9, 1$ Hz, H-1), 9.28 (1H, dt, $J = 7, 1$ Hz, H-4). HRMS m/z (M^+) calcd for C₂₀H₁₅NO₅: 349.0950. Found: 349.0958. *Anal.* Calcd for C₂₀H₁₅NO₅: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.75; H, 4.32; N, 4.00.

REFERENCES

1. Y. Miki, H. Hachiken, and I. Yoshikawa, *Heterocycles*, 1997, **45**, 1143.
2. Y. Miki, H. Hachiken, Y. Sugimoto, and N. Yanase, *Heterocycles*, 1997, **45**, 1759.
3. Y. Miki and H. Hachiken, *Synlett*, 1993, 333.
4. Y. Miki, Y. Tada, N. Yanase, H. Hachiken, and K. Matsushita, *Tetrahedron Lett.*, 1996, **37**, 7753; Y. Miki, Y. Tada, and K. Matsushita, *Heterocycles*, 1998, **48**, 1593.
5. For reviews, see: T. Uchida and K. Matsumoto, *Synthesis*, 1976, 209; W. Flitsch, 'Comprehensive Heterocyclic Chemistry', ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Vol. 4, p. 442 (1984).