Syntheses of 3,4-Disubstituted 2-Tosylpyrroles and 5-Tosyl-1,5-dihydro-2*H*-pyrrol-2-ones Starting from Ethyl 3,4-Disubstituted 2-Pyrrolecarboxylates

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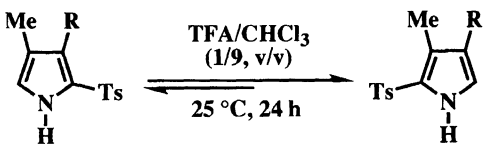
The syntheses of 3,4-disubstituted 2-tosylpyrroles and 5-tosyl-1,5-dihydro-2*H*-pyrrol-2-ones were accomplished via 3,4-disubstituted 2-iodo-5-tosylpyrroles starting from ethyl 3,4-disubstituted 2-pyrrolecarboxylates.

In our previous works,[1,2] 3,4-disubstituted 2-*p*-tolylsulfonyl (=tosyl, Ts) pyrroles, which were easily prepared by the reaction of *p*-tolylsulfonylmethyl isocyanide (TsMIC) and substituted nitro olefins or *β*-acetoxy nitro alkanes in the presence of a base,[3] proved to be very useful starting materials for the preparation of 3,4-disubstituted 5-tosyl-1,5-dihydro-2*H*-pyrrol-2-ones (**8**, pyrrolinones), which are regarded as being synthetic equivalents of the D-ring of a tetrapyrrole bile pigment like phytochromobilin and phycocyanobilin.[4] During the course of our continuous studies on pyrrole chemistry, we recently found that the tosyl group of 3,4-disubstituted 2-tosylpyrroles readily rearranges from the 2- to 5-position of the pyrrole ring in trifluoroacetic acid/chloroform (1/9, v/v), and that the ratio of the regioisomers at equilibrium was definitely influenced by the bulkiness of the substituent at the 3-position of the starting 2-tosylpyrroles (Scheme 1).[5] Eventually, this rearrangement provided a very convenient method for preparing both regioisomers of 3,4-disubstituted 2-tosylpyrroles. For instance, 3-*t*-butyl-4-methyl-2-tosylpyrrole (**1e**) was completely transformed to the regioisomer, 4-*t*-butyl-3-methyl-2-tosylpyrrole (**2e**), in excellent yield after 24 h at 25 °C. However, in other cases (**1a—d, f**), the rearrangement was not complete, and gave an equilibrium mixture of the regioisomers in a ratio of around 30/70 (**1/2**).

Herein we wish to report on the regioselective preparative method for 3,4-disubstituted 2-tosylpyrroles (**2**) via ethyl 3,4-disubstituted 5-tosyl-2-pyrrolecarboxylates (**5**) starting from ethyl 3,4-disubstituted 2-pyrrolecarboxylates (**3**).[6]



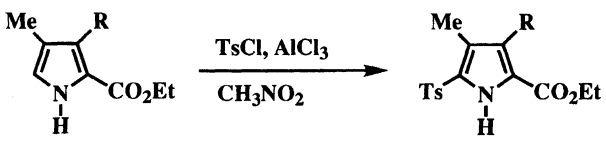
1a~f (0.10 M) **2a~f**

1a: R=*p*-$CH_3C_6H_4$ **1d:** R=$Ph(CH_2)_2$
1b: R=Et **1e:** R=^{t}Bu
1c: R=*p*-$CH_3OC_6H_4$ **1f:** R=^{i}Pr

Scheme 1.

First, the direct tosylation of **3** was examined in order to prepare ethyl 5-tosyl-2-pyrrolecarboxylates (**5**) by the Friedel–Crafts type reaction.[7] Namely, ethyl 4-methyl-3-(*p*-tolyl)-2-pyrrolecarboxylate (**3a**) was treated with 3 molar amounts of tosyl chloride in the presence of 3 molar amounts of $AlCl_3$ in nitromethane at room temperature overnight to afford the desired product (**5a**) in 58% yield, accompanied by a small amount of ethyl 4-methyl-3-(4-methyl-3-tosylphenyl)-2-pyrrolecarboxylate as a by-product. Similarly, compound **5b** was obtained in 71% yield. On the other hand, in cases of the starting pyrroles **3c,d**, the desired products (**5c,d**) were not obtained at all, but tosylation took place mainly on the aromatic ring of the substituent at the 3-position of compounds **3c,d** (Scheme 2).

Recently, Ogawa et al. reported that the reaction of the vinyl bromide derivative with potassium diphenyl phosphite in the presence of CuI in hexamethylphosphoric triamide (HMPA) gave the corresponding vinylphosphonate derivative in good yield.[8] This finding prompted us to develop an alternative method for preparing compound **5** through ethyl 3,4-disubstituted 5-halo-2-pyrrolecarboxylate **4**. Then, **3a** was transformed to ethyl 5-bromo-4-methyl-3-(*p*-tolyl)-2-pyrrolecarboxylate (**4a′**) with trimethyl(phenyl)ammonium tribromide in CH_2Cl_2 at 0 °C for 30 min in 91% yield.[2] Next, a substitution reaction of the brominated product **4a′** with an-



3a~d **5a~d**

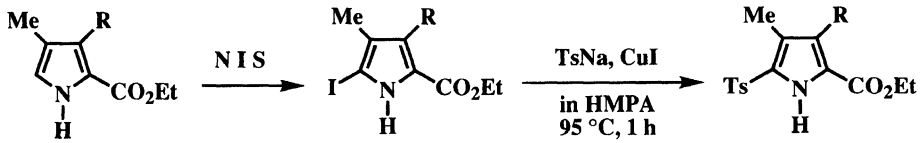
3a: R=*p*-$CH_3C_6H_4$ **5a:** 58%
3b: R=Et **5b:** 71%
3c: R=*p*-$CH_3OC_6H_4$ **5c:** —
3d: R=$C_6H_5(CH_2)_2$ **5d:** —

Scheme 2.

hydrous sodium *p*-toluenesulfinate (TsNa) in the presence of copper salt was attemped under various reaction conditions. When copper(I) or copper(II) chloride was used as the copper salt, the yields were very poor. Then, copper(I) iodide was employed instead of copper chlorides. Eventually, we found that the treatment of **4a′** with 3.4 molar amounts of TsNa and CuI in HMPA at 155 °C for 1 h afforded the corresponding 5-tosyl-2-pyrrolecarboxylate **5a** in 88% yield. Though the substitution reaction of the bromide with *p*-toluenesulfinate was accomplished in a satisfactory yield, the reproducibility of this method was poor. Therefore, a substitution reaction of 5-iodo-2-pyrrolecarboxylate (**4a**), which was readily obtained from **3a** utilizing *N*-iodosuccinimide (NIS),[9] was examined similarly. Consequently, the substitution reaction underwent very smoothly under milder reaction conditions (95 °C for 1 h) compared with that of the brominated compound **4a′** to afford **5a** in 91% yield. Compounds **3b**—**f** were similarly converted to the corresponding 5-tosyl-2-pyrrolecarboxylic acid esters (**5b**—**f**) via 5-iodo-2-pyrrolecarboxylates **4b**—**f** in high yields, as shown in Scheme 3.

Next, in order to replace the ethoxycarbonyl group of **5** with hydrogen, 5-tosyl-2-pyrrolecarboxylates **5a**—**f** were hydrolyzed with 10 molar amounts of 1 M NaOH in refluxing ethanol (1 M=1 mol dm^{-3}), followed by iodination of the resulting 5-tosyl-2-pyrrolecarboxylic acids **6a**—**f** with an equimolar amount of iodine, 2.5 molar amounts of potassium iodide, and 3 molar amounts of sodium hydrogencarbonate in aqueous methanol to afford the corresponding 3,4-disubstituted 2-iodo-5-tosylpyrroles **7a**—**f** in excellent yields. The hydrogenolysis of the 2-iodopyrroles **7a**—**f** was carried out over 5% Pd–charcoal under a hydrogen atmosphere in the presence of 1. 1 molar amounts of sodium acetate to give the desired 3,4-disubstituted 5-tosyl-pyrroles **2a**—**f** in quantitative yields, as illustrated in Scheme 4.

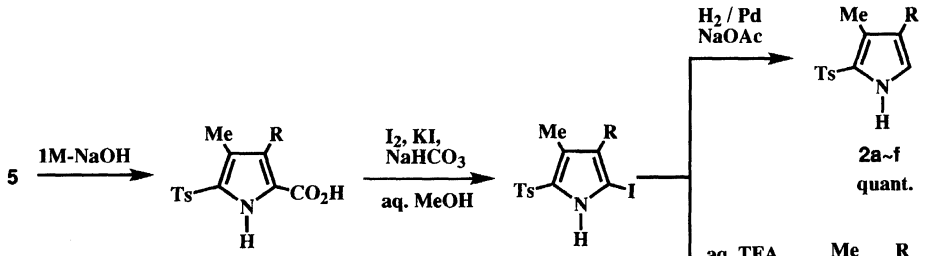
In a previous paper,[1] we reported that 3,4-disubstituted 2-bromo-5-tosylpyrroles were regioselectively hydrolyzed in aqueous trifluoroacetic acid (TFA) to afford the corresponding 3,4-disubstituted 1,5-dihydro-2*H*-pyrrol-2-ones, which reacted with a variety of aldehydes by a new Wittig-type reaction to yield 5-exomethylene compounds in high yields. Then, the hydrolysis of 2-iodo-5-tosylpyrrole **7a** was attempted under the same reaction conditions as those reported previously. However, the yield of the expected pyrrolinone derivative **8a** was disappointedly very poor (24% yield) due to formation of 3-methyl-4-(*p*-tolyl)-2-tosylpyrrole, reduced by the hydrogen iodide formed during the progress of the reaction. The improvement in the yield was examined under various reaction conditions in the presence of a silver salt, such as silver nitrate, silver carbonate, and silver acetate, to scavenge the hydrogen iodide. Silver acetate was



3a~f **4a~f** **5a~f**

3a: R=*p*-$CH_3C_6H_4$	**4a**: quant	**5a**: 91%
3b: R=Et	**4b**: 99%	**5b**: 84%
3c: R=*p*-$CH_3OC_6H_4$	**4c**: 99%	**5c**: 85%
3d: R=$C_6H_5(CH_2)_2$	**4d**: 94%	**5d**: 99%
3e: R=^{t}Bu	**4e**: 96%	**5e**: 78%
3f: R=^{i}Pr	**4f**: 97%	**5f**: 83%

Scheme 3.



6a~f **7a~f** **8a~f**

6a: R=*p*-$CH_3C_6H_4$	**7a**: 99%	**8a**: 68% **8d**: 63%
6b: R=Et	**7b**: 95%	**8b**: 69% **8e**: 46%
6c: R=*p*-$CH_3OC_6H_4$	**7c**: 92%	**8c**: 64% **8f**: 70%
6d: R=$C_6H_5(CH_2)_2$	**7d**: 98%	
6e: R=^{t}Bu	**7e**: 88%	
6f: R=^{i}Pr	**7f**: 95%	

Scheme 4.

found to be the most effective among them; the yield was improved up to 68% by using an equimolar amount of silver acetate in TFA/H_2O (5/1, v/v) at room temperature for 5 h. Similarly, other 2-iodopyrrole derivatives **7b—f** could be converted into the corresponding 5-tosyl-1,5-dihydro-2*H*-pyrrol-2-ones(**8b—f**) in moderate yields, except for **8e**, as shown in Scheme 4.

As mentioned above, the present method provides a new convenient method for the regioselective preparation of 3,4-disubstituted 2-tosylpyrroles **2** as regioisomers of compound **1** and the corresponding 5-tosyl-1,5-dihydro-2*H*-pyrrol-2-ones starting from ethyl 3,4-disubstituted 2-pyrrolecarboxylates **3**.

Experimental

All of the melting points were determined with a micro melting apparatus (Yanagimoto Seisakusho) and were uncorrected. The ^{1}H NMR, IR, and MS spectra were recorded on a JEOL JNMGX 400 (400 MHz) FT-NMR spectrometer, a JASCO IRA-1 diffraction grating or a JASCO FT/IR-230 infrared spectrometer, and a JEOL SX-102A mass spectrometer, respectively. The chemical shifts of NMR are reported in the δ-scale relative to TMS as an internal standard. All of the solvents were distilled and stored over a drying agent. Thin-layer chromatography (TLC) and flash-column chromatography were performed using Merck's silica gel 60 PF_{254} (Art. 7749) and Wakogel C300, respectively.

Preparation of Ethyl 3,4-Disubstituted 2-Pyrrolecarboxylates (3a—f): Compounds **3a—f** were prepared from ethyl isocyanoacetate, and substituted nitro olefins or β-acetoxy nitro alkanes according to the reported methods.[3,6]

The physical and spectra data of **3a—f** are shown in the following.

Ethyl 4-Methyl-3-(*p*-tolyl)-2-pyrrolecarboxylate (3a): Mp 100.0—101.0 °C (from hexane); IR (KBr) 3302, 2979, 2864, 1658, 1528, 1410, 1285, 1242, 1158, 1022, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.16 (t, 3H, J = 7.15 Hz), 2.00 (s, 3H), 2.38 (s, 3H), 4.17 (q, 2H, J = 7.15 Hz), 6.76 (d, 1H, J = 2.75 Hz), 7.17 (d, 2H, J = 8.25 Hz), 7.23 (d, 2H, J = 8.25 Hz), 8.99 (br, 1H). Found: C, 74.12; H, 7.03; N, 5.68%. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%.

Ethyl 3-Ethyl-4-methyl-2-pyrrolecarboxylate (3b): Mp 73.0—73.5 °C (from EtOH–H_2O) [lit, mp 75 °C (from EtOH–H_2O)].[10]

Ethyl 3-(*p*-Methoxyphenyl)-4-methyl-2-pyrrolecarboxylate (3c): Mp 106.0—107.0 °C (from EtOH); IR (KBr) 3303, 2936, 2834, 1662, 1527, 1412, 1289, 1245, 1190, 871 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.17 (t, 3H, J = 7.15 Hz), 2.00 (d, 3H, J = 0.73 Hz), 3.84 (s, 3H), 4.17 (q, 2H, J = 7.15 Hz), 6.76 (dd, 1H, J = 0.73, 2.75 Hz), 6.92 (d, 2H, J = 8.80 Hz), 7.27 (d, 2H, J = 8.80 Hz), 8.95 (br, 1H). Found: C, 69.55; H, 6.67; N, 5.40%. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40%.

Ethyl 4-Methyl-3-phenethyl-2-pyrrolecarboxylate (3d): Mp 72.5—73.5 °C (from hexane); IR (KBr) 3300, 3020, 2960, 2850, 1650, 1450, 1400, 1340, 1270, 1130, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.37 (t, 3H, J = 7.02 Hz), 1.92 (s, 3H), 2.80 (m, 2H), 3.01 (m, 2H), 4.32 (q, 2H, J = 7.02 Hz), 6.65 (d, 1H, J = 2.44 Hz), 7.16—7.28 (m, 5H), 8.72 (br, 1H). Found: C, 74.68; H, 7.44; N, 5.44%. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.46; N, 5.42%.

Ethyl 3-*t*-Butyl-4-methyl-2-pyrrolecarboxylate (3e): An oil; MS *m/z* 209 (M^+; 12.28%), 194 (8.88), 152 (100.00), 137 (9.73), 58 (35.42), 29 (14.47); IR (neat) 3371, 2957, 1712, 1371, 1351, 1262, 1137, 959, 778, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.35 (t, 3H, J = 7.02 Hz), 1.48 (s, 9H), 2.22 (s, 3H), 4.29 (q, 2H, J = 7.02 Hz), 6.55 (d, 1H, J = 3.05 Hz), 9.34 (br, 1H).

Ethyl 4-Methyl-3-isopropyl-2-pyrrolecarboxylate (3f): Mp 53.0—54.0 °C (from EtOH–H_2O); IR (KBr) 3322, 2958, 1677, 1411, 1275, 1179, 1120, 800, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.29 (d, 6H, J = 7.01 Hz), 1.35 (t, 3H, J = 7.02 Hz), 2.12 (s, 3H), 3.69 (sep, 1H, J = 7.01 Hz), 4.30 (q, 2H, J = 7.02 Hz), 6.60 (d, 1H, J = 3.05 Hz), 8.68 (br, 1H). Found: C, 67.38; H, 9.11; N, 7.03%. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17%.

A General Procedure for the Preparation of Ethyl 3,4-Disubstituted 5-Iodo-2-pyrrolecarboxylates (4a—f): A solution of **3a** (486 mg, 2.0 mmol) and NIS (676 mg, 3.0 mmol) in 10 ml of CH_2Cl_2 was stirred for 3 h. After removal of the solvent, the residue was dissolved in ether. The ethereal solution was successively washed with aq $NaHSO_3$, aq $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to afford **4a** as a single product (771 mg), which was recrystallized from AcOEt–hexane. The other 5-iodo-2-pyrrolecarboxylates **4b—f** were also prepared in a similar way.

The physical and spectra data of **4a—f** are shown in the following.

Ethyl 5-Iodo-4-methyl-3-(*p*-tolyl)-2-pyrrolecarboxylate (4a): Mp 160.0 °C (from AcOEt–hexane); IR (KBr) 3251, 1673, 1410, 1258, 1233, 1182, 1028, 822, 772, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.16 (t, 3H, J = 7.02 Hz), 1.94 (s, 3H), 2.39 (s, 3H), 4.17 (q, 2H, J = 7.02 Hz), 7.18 (s, 4H), 9.01 (s, 1H). Found: C, 48.72; H, 4.35; N, 3.77%. Calcd for $C_{15}H_{16}NO_2I$: C, 48.80; H, 4.37; N, 3.79%.

Ethyl 3-Ethyl-5-iodo-4-methyl-2-pyrrolecarboxylate (4b): Mp 117.0—118.0 °C (from EtOH); IR (KBr) 3269, 1674, 1414, 1385, 1242, 1215, 1146, 1021, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.10 (t, 3H, J = 7.63 Hz), 1.36 (t, 3H, J = 7.02 Hz), 1.98 (s, 3H), 2.77 (q, 2H, J = 7.63 Hz), 4.31 (q, 2H, J = 7.02 Hz), 8.74 (s, 1H). Found: C, 39.13; H, 4.72; N, 4.49%. Calcd for $C_{10}H_{14}NO_2I$: C, 39.11; H, 4.59; N, 4.56%.

Ethyl 5-Iodo-3-(*p*-methoxyphenyl)-4-methyl-2-pyrrolecarboxylate (4c): Mp 150.0—151.0 °C (from AcOEt–hexane); IR (KBr) 3273, 1657, 1410, 1230, 1180, 1023, 830, 774, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.17 (t, 3H, J = 7.02 Hz), 1.94 (s, 3H), 3.84 (s, 3H), 4.17 (q, 2H, J = 7.02 Hz), 6.92 (d, 2H, J = 8.85 Hz), 7.22 (d, 2H, J = 8.85 Hz), 8.96 (s, 1H). Found: C, 46.92; H, 4.19; N, 3.74%. Calcd for $C_{15}H_{16}NO_3I$: C, 46.77; H, 4.19; N, 3.64%.

Ethyl 5-Iodo-4-methyl-3-phenethyl-2-pyrrolecarboxylate (4d): Mp 144.0—144.5 °C (from AcOEt–hexane); IR (KBr) 3268, 1671, 1412, 1384, 1236, 1140, 1025, 772, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.37 (t, 3H, J = 7.02 Hz), 1.88 (s, 3H), 2.75—2.79 (m, 2H), 3.01—3.05 (m, 2H), 4.32 (q, 2H, J = 7.02 Hz), 7.17—7.29 (m, 3H), 7.27 (t, 2H, J = 7.32 Hz), 8.80 (s, 1H). Found: C, 50.31; H, 4.69; N, 3.60%. Calcd for $C_{16}H_{18}NO_2I$: C, 50.15; H, 4.73; N, 3.65%.

Ethyl 3-*t*-Butyl-5-iodo-4-methyl-2-pyrrolecarboxylate (4e): Mp 125.5—126.0 °C (from EtOH); IR (KBr) 3233, 1675, 1440, 1346, 1293, 1242, 1172, 1086, 1023, 777, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.36 (t, 3H, J = 7.02 Hz), 1.46 (s, 9H), 2.21 (s, 3H), 4.30 (q, 2H, J = 7.02 Hz), 8.95 (s, 1H). Found: C, 42.77; H, 5.58; N, 4.11%. Calcd for $C_{12}H_{18}NO_2I$: C, 43.00; H, 5.41; N, 4.18%.

Ethyl 5-Iodo-3-isopropyl-4-methyl-2-pyrrolecarboxylate (4f): Mp 83.0—85.0 °C (from benzene–hexane); IR (KBr) 3205, 1691, 1249, 1173, 1060, 1024, 777, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.26 (d, 6H, J = 7.33 Hz), 1.36 (t, 3H, J = 7.02 Hz), 2.07 (s, 3H), 3.69 (sep, 1H, J = 7.33 Hz), 4.30 (q, 2H, J = 7.02 Hz), 8.73 (s, 1H). Found: C, 41.07; H, 5.11; N, 4.41%. Calcd for $C_{11}H_{16}NO_2I$: C, 41.14; H, 5.02; N, 4.36%.

Preparation of Ethyl 3,4-Disubstituted 5-Tosyl-2-pyrrolecarboxylates (5): Method A (by Direct Tosylation of 3a and 3b): To a solution of $AlCl_3$ (195 mg, 1.46 mmol) in 4 ml of dry nitromethane was added a solution of *p*-toluenesulfonyl chloride (278 mg, 1.46 mmol) in 3 ml of dry nitromethane under N_2 at room temperature. Then, a solution of **3a** (118 mg, 0.485 mmol) in 3 ml of dry nitromethane was added, and the reaction mixture was allowed to stand overnight with stirring. The reaction was stopped by adding a saturated aq NH_4Cl solution. The mixture was extracted with ether a couple of times, and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was subjected to preparative TLC (SiO_2, hexane : AcOEt=3 : 1, v/v) to afford **5a** in 58% yield (112 mg). In a similar manner, **5b** was prepared from **3b** (290 mg, 1.6 mmol), TsCl (915 mg, 4.80 mmol), and $AlCl_3$ (647 mg, 4.85 mmol) in 71% yield (379 mg).

Method B (Starting from the Compounds 4): A mixed suspension of **4a** (37 mg, 0.1 mmol), anhydrous TsNa (60 mg, 0.34 mmol), and CuI (65 mg, 0.34 mmol) in 1 ml of HMPA was warmed to 95 °C under N_2 to give a clear solution. After stirring for 1 h, it was diluted with a large amount of water. The mixture was extracted with ether several times and the combined extracts were successively washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to preparative TLC (SiO_2, hexane : AcOEt = 3 : 1, v/v) to give **5a** in 91% yield. Similarly, 5-tosyl-2-pyrrolecarboxylates **5b—f** were prepared.

The physical and spectral data of **5a—f** are shown in the following.

Ethyl 4-Methyl-3-(*p*-tolyl)-5-tosyl-2-pyrrolecarboxylate (5a): Mp 141.0—142.0 °C (from EtOH); IR (KBr) 3240, 1670, 1590, 1320, 1260, 1220, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.18 (t, 3H, J = 7.02 Hz), 2.06 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 4.19 (q, 2H, J = 7.02 Hz), 7.09 (d, 2H, J = 8.24 Hz), 7.15 (d, 2H, J = 8.24 Hz), 7.34 (d, 2H, J = 8.24 Hz), 7.84 (d, 2H, J = 8.24 Hz), 9.60 (br, 1H). Found: C, 61.17; H, 6.34; N, 4.18%. Calcd for $C_{22}H_{23}NO_4S$: C, 60.87; H, 6.31; N, 4.18%.

Ethyl 3-Ethyl-4-methyl-5-tosyl-2-pyrrolecarboxylate (5b): Mp 136.0—137.0 °C (from EtOH–hexane); IR (KBr) 3289, 1685, 1325, 1239, 1146, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.06 (t, 3H, J = 7.63 Hz), 1.38 (t, 3H, J = 7.02 Hz), 2.14 (s, 3H), 2.41 (s, 3H), 2.67 (q, 2H, J = 7.63 Hz), 4.37 (q, 2H, J = 7.02 Hz), 7.31 (d, 2H, J = 8.24 Hz), 7.79 (d, 2H, J = 8.24 Hz), 9.39 (br, 1H). Found: C, 66.69; H, 5.84; N, 3.53%. Calcd for $C_{17}H_{21}NO_4S$: C, 66.48; H, 5.83; N, 3.52%.

Ethyl 3-(*p*-Methoxyphenyl)-4-methyl-5-tosyl-2-pyrrolecarboxylate (5c): Mp 133.0—133.5 °C (from AcOEt–hexane); IR (KBr) 3181, 1677, 1321, 1268, 1248, 1221, 1150, 1099, 717 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.19 (t, 3H, J = 7.02 Hz), 2.06 (s, 3H), 2.43 (s, 3H), 3.82 (s, 3H), 4.20 (q, 2H, J = 7.02 Hz), 6.89 (d, 2H, J = 8.85 Hz), 7.13 (d, 2H, J = 8.85 Hz), 7.34 (d, 2H, J = 8.24 Hz), 7.85 (d, 2H, J = 8.24 Hz), 9.61 (s, 1H). Found: C, 64.10; H, 5.67; N, 3.30%. Calcd for $C_{22}H_{23}NO_5S$: C, 63.91; H, 5.61; N, 3.39%.

Ethyl 4-Methyl-3-phenethyl-5-tosyl-2-pyrrolecarboxylate (5d): Mp 140.0—141.0 °C (from AcOEt–hexane); IR (KBr) 3187, 1678, 1326, 1248, 1149, 1094, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.39 (t, 3H, J = 7.02 Hz), 1.93 (s, 3H), 2.43 (s, 3H), 2.70—2.74 (m, 2H), 2.91—2.95 (m, 2H), 4.35 (q, 2H, J = 7.02 Hz), 7.06 (d, 2H, J = 7.94 Hz), 7.11—7.19 (m, 3H), 7.32 (d, 2H, J = 7.94 Hz), 7.77 (d, 2H, J = 8.24 Hz), 9.47 (s, 1H). Found: C, 67.29; H, 6.20; N, 6.20%. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 6.12%.

Ethyl 3-*t*-Butyl-4-methyl-5-tosyl-2-pyrrolecarboxylate (5e): Mp 155.0—157.0 °C (from AcOEt); IR (KBr) 3290, 1674, 1315, 1225, 1153, 817, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.40 (t, 3H, J = 7.02 Hz), 1.41 (s, 9H), 2.31 (s, 3H), 2.43 (s, 3H), 4.35 (q, 2H, J = 7.02 Hz), 7.32 (d, 2H, J = 8.24 Hz), 7.79 (d, 2H, J = 8.24 Hz), 9.66 (s, 1H). Found: C, 62.60; H, 7.09; N, 3.77%. Calcd for $C_{19}H_{25}NO_4S$: C, 62.79; H, 6.93; N, 3.85%.

Ethyl 3-Isopropyl-4-methyl-5-tosyl-2-pyrrolecarboxylate (5f): Mp 122.0—123.0 °C (from AcOEt–hexane); IR (KBr) 3349, 1677, 1320, 1256, 1206, 1153, 1109, 828, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.23 (d, 6H, J = 7.02 Hz), 1.38 (t, 3H, J = 7.02 Hz), 2.22 (s, 3H), 2.42 (s, 3H), 3.57 (sep, 1H, J = 7.02 Hz), 4.35 (q, 2H, J = 7.02 Hz), 7.32 (d, 2H, J = 8.24 Hz), 7.80 (d, 2H, J = 8.24 Hz), 9.44 (s, 1H). Found: C, 61.66; H, 6.77; N, 3.98%. Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01%.

Preparation of 3,4-Disubstituted 2-Iodo-5-tosylpyrroles (7a—f): To a solution of compound **5b** (335 mg, 1.0 mmol) in 5 ml of EtOH was added 10 ml of 1 M aq NaOH. The mixture was refluxed for 6 h and then diluted with water. After washing with ether, the alkaline solution was acidified with 1 M aq HCl. The liberated precipitate of free acid was collected, washed with a small amount of cold water, and dried (**6b**, 297 mg, 97% yield). It was recrystallized for analysis from $CHCl_3$–hexane; mp 222.0—223.0 °C (90% yield); IR (KBr) 3419, 2926, 1670, 1482, 1322, 1256, 1164, 1145, 1090, 809, 709 cm^{-1}. Found: C, 58.49; H, 5.54; N, 4.52%. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56%.

The acids **6a** and **6c—f** thus obtained in good yields were used in the subsequent reaction without further purification.

To a solution of the foregoing **6b** (61 mg, 0.2 mmol) in 1.5 ml of MeOH was added a solution of $NaHCO_3$ (51 mg, 0.6 mmol) in 0.5 ml of water. To the solution was dropwise added a solution of I_2 (51 mg, 0.2 mmol) and KI (83 mg, 0.5 mmol) in MeOH/H_2O (1 ml/0.2 ml) at 60 °C. The mixture was stirred for 1 h at the temperature and then the MeOH was removed under reduced pressure. The residue was partitioned between AcOEt and water, and the aqueous layer was extracted with AcOEt. The combined AcOEt solution was successively washed with aq $NaHSO_3$, aq $NaHCO_3$, and brine, and dried over $MgSO_4$. Removal of the solvent afforded the desired compound **7b** as a single product in quantitative yield. In a similar manner, **7a** and **7c—f** were prepared.

The physical and spectral data of **7a—f** are shown in the following.

2-Iodo-4-methyl-3-(*p*-tolyl)-5-tosylpyrrole (7a): Mp 172.0—173.0 °C (from EtOH); MS *m/z* 451 (M^+; 100.00%), 325 (17.04), 244 (10.95), 168 (51.15), 141 (26.02), 115 (25.44), 91 (24.67), 65 (13.62); IR (KBr) 3321, 1310, 1143, 1099, 823, 811, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.15 (S, 3H), 2.38 (s, 3H), 2.43 (s, 3H), 7.17 (d, 2H, J = 8.24 Hz), 7.24 (d, 2H, J = 8.24 Hz), 7.33 (d, 2H, J = 8.24 Hz), 7.82 (d, 2H, J = 8.24 Hz), 8.96 (s, 1H). Found: C, 50.94; H, 4.12; N, 3.01%. Calcd for $C_{19}H_{18}NO_2SI$: C, 50.56; H, 4.02; N, 3.10%.

3-Ethyl-2-iodo-4-methyl-5-tosylpyrrole (7b): Mp 166.0—167.0 °C (from EtOH–H_2O); IR (KBr) 3296, 1597, 1304, 1163, 1140, 1094, 807, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.00 (t, 3H, J = 7.63 Hz), 2.19 (s, 3H), 2.32 (q, 2H, J = 7.63 Hz), 2.41 (s, 3H), 7.30 (d, 2H, J = 8.24 Hz), 7.77 (d, 2H, J = 8.24 Hz), 8.79 (s 1H). Found: C, 43.36; H, 4.18; N, 3.56%. Calcd for $C_{14}H_{16}NO_2SI$: C, 43.20; H, 4.14; N, 3.60%.

2-Iodo-4-methyl-3-(*p*-methoxyphenyl)-5-tosylpyrrole (7c): Mp 196.0—197.0 °C (from EtOH); IR (KBr) 3273, 1657, 1410, 1230, 1179, 1023, 829, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.15 (s, 3H), 2.43 (s, 3H), 3.83 (s, 3H), 6.92 (d, 2H, J = 8.85 Hz), 7.13 (d, 2H, J = 8.85 Hz), 7.33 (d, 2H, J = 8.24 Hz), 7.82 (d, 2H, J = 8.24 Hz), 8.93 (s, 1H). Found: C, 49.13; H, 3.96; N, 2.87%. Calcd for

$C_{19}H_{18}NO_3SI$: C, 48.83; H, 3.88; N, 3.00%.

2-Iodo-4-methyl-3-phenethyl-5-tosylpyrrole (7d): Mp 167.0—168.0 °C (from EtOH); IR (KBr) 3271, 1594, 1303, 1212, 1150, 1092, 821, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.01 (s, 3H), 2.42 (s, 3H), 2.55—2.60 (m, 2H), 2.64—2.67 (m, 2H), 7.05 (d, 2H, J = 9.46 Hz), 7.15—7.19 (m, 3H), 7.30 (d, 2H, J = 8.24 Hz), 7.74 (d, 2H, J = 8.24 Hz), 8.82 (s, 1H). Found: C, 51.83; H, 4.40; N, 2.98%. Calcd for $C_{20}H_{20}NO_2SI$: C, 51.62; H, 4.30; N, 3.01%.

3-*t*-Butyl-2-iodo-4-methyl-5-tosylpyrrole (7e): Mp 167.0—169.0 °C (from EtOH); MS *m/z* 417 (M^+; 100.00%), 403 (92.97), 276 (51.74), 139 (13.98), 120 (23.83), 91 (37.14), 65 (15.95); IR (KBr) 3295, 2966, 1596, 1313, 1145, 1105, 812, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.38 (s, 9H), 2.33 (s, 3H), 2.42 (s, 3H), 7.30 (d, 2H, J = 8.24 Hz), 7.76 (d, 2H, J = 8.24 Hz), 8.81 (s, 1H). Found: C, 46.43; H, 5.03; N, 3.34%. Calcd for $C_{16}H_{20}NO_2SI$: C, 46.05; H, 4.83; N, 3.36%.

2-Iodo-3-isopropyl-4-methyl-5-tosylpyrrole (7f): Mp 174 °C (from EtOH–H_2O); IR (KBr) 3266, 1596, 1312, 1143, 1092, 811, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.20 (d, 6H, J = 7.01 Hz), 2.23 (s, 3H), 2.42 (s, 3H), 2.84 (sep, 1H, J = 7.01 Hz), 7.30 (d, 2H, J = 7.94 Hz), 7.76 (d, 2H, J = 7.94 Hz), 8.75 (s, 1H). Found: C, 44.82; H, 4.61; N, 3.47%. Calcd for $C_{15}H_{18}NO_2SI$: C, 44.67; H, 4.50; N, 3.47%.

Preparation of 3,4-Disubstituted 2-Tosylpyrroles (2a—f): A solution of **7a** (45 mg, 0.1 mmol) in 2 ml of MeOH was stirred over 5%-Pd/C (11 mg, 5 mol%) under a hydrogen atmosphere in the presence of NaOAc (9 mg, 0.11 mmol) at room temperature. After stirring for 1 h, insoluble substances were filtered off and washed with MeOH. The filtrate was concentrated in vacuo to give a residue, which was taken up into AcOEt. The AcOEt solution was successively washed with aq $NaHSO_3$, aq $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Removal of the solvent gave the desired product **2a** (32 mg, quant.), which was recrystallized for an analysis from *i*-PrOH. Similarly, **2b—f** are prepared.

The physical and spectral data of **2a—f** are shown in the following.

3-Methyl-4-(*p*-tolyl)-2-tosylpyrrole (2a): Mp 168.0—168.5 °C (from *i*-PrOH); IR (KBr) 3297, 3126, 3048, 3022, 2920, 1597, 1559, 1485, 1382, 1335, 1313, 1304, 1229, 1189, 1143, 1086, 1056, 1016, 818, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.29 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 6.96 (d, 1H, J = 3.41 Hz), 7.15 (d, 2H, J = 8.30 Hz), 7.18 (d, 2H, J = 8.30 Hz), 7.29 (d, 2H, J = 8.30 Hz), 7.82 (d, 2H, J = 8.30 Hz), 9.50 (br, 1H). Found: C, 70.21; H, 6.05; N, 4.28%. Calcd for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30%.

4-Ethyl-3-methyl-2-tosylpyrrole (2b): Mp 117.0—118.0 °C (from *i*-PrOH); IR (KBr) 3308, 2973, 2959, 2927, 2897, 1596, 1495, 1450, 1366, 1293, 1215, 1182, 1146, 1088, 1056, 810, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.12 (t, 3H, J = 7.33 Hz), 2.15 (s, 3H), 2.35 (q, 2H, J = 7.33 Hz), 2.39 (s, 3H), 6.69 (d, 1H, J = 2.93 Hz), 7.27 (d, 2H, J = 8.30 Hz), 7.77 (d, 2H, J = 8.30 Hz), 9.02 (br, 1H). Found: C, 63.69; H, 6.61; N, 5.29%. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32%.

4-(*p*-Methoxyphenyl)-3-methyl-2-tosylpyrrole (2c): Mp 147.0—149.0 °C (from *i*-PrOH); IR (KBr) 3327, 3038, 3004, 2936, 2838, 1614, 1596, 1558, 1518, 1486, 1457, 1442, 1302, 1287, 1249, 1185, 1142, 1087, 1054, 1034, 830, 812 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.27 (s, 3H), 2.40 (s, 3H), 3.81 (s, 3H), 6.89 (d, 2H, J = 8.79 Hz), 6.93 (d, 1H, J = 2.93 Hz), 7.20 (d, 2H, J = 8.79 Hz), 7.29 (d, 2H, J = 8.30 Hz), 7.82 (d, 2H, J = 8.30 Hz), 9.53 (br, 1H). Found: C, 66.98; H, 5.66; N, 4.07%. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10%.

3-Methyl-4-phenethyl-2-tosylpyrrole (2d): Mp 131.5—132.5 °C (from *i*-PrOH); IR (KBr) 3303, 3126, 3056, 3026, 2917, 2858, 1654, 1597, 1559, 1496, 1453, 1374, 1311, 1301, 1222, 1194, 1145, 1082, 1016, 813 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.09 (s, 3H), 2.40 (s, 3H), 2.64 (t, 2H, J = 8.30 Hz), 2.77 (t, 2H, J = 8.30 Hz), 6.63 (d, 1H, J = 2.93 Hz), 7.08—7.26 (m, 5H), 7.28 (d, 2H, J = 8.30 Hz), 7.75 (d, 2H, J = 8.30 Hz), 8.89 (br, 1H). Found: C, 70.77; H, 6.25; N, 3.93%. Calcd for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13%.

4-*t*-Butyl-3-methyl-2-tosylpyrrole (2e): Mp 135.0—136.0 °C (from *i*-PrOH); IR (KBr) 3316, 2965, 2900, 2867, 1597, 1547, 1493, 1458, 1385, 1361, 1345, 1311, 1242, 1226, 1184, 1168, 1138, 1095, 1078, 1048, 1019, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.23 (s, 9H), 2.32 (s, 3H), 2.40 (s, 3H), 6.69 (d, 1H, J = 2.93 Hz), 7.28 (d, 2H, J = 8.30 Hz), 7.76 (d, 2H, J = 8.30 Hz), 8.98 (br, 1H). Found: C, 65.71; H, 7.45; N, 4.75%. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81%.

4-Isopropyl-3-methyl-2-tosylpyrrole (2f): Mp 121.5—122.0 °C (from *i*-PrOH); IR (KBr) 3329, 3057, 2959, 2926, 2867, 2366, 1717, 1595, 1558, 1494, 1457, 1382, 1314, 1287, 1227, 1179, 1054, 922, 846, 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.13 (d, 6H, J = 6.84 Hz), 2.17 (s, 3H), 2.39 (s, 3H), 2.73 (sep, 1H, J = 6.84 Hz), 6.68 (d, 1H, J = 2.93 Hz), 7.27 (d, 2H, J = 8.30 Hz), 7.77 (d, 2H, J = 8.30 Hz), 9.05 (br, 1H). Found: C, 64.95; H, 6.93; N, 5.02%. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05%.

Hydrolysis of Compounds 7a—f into 3,4-Disubstituted 5-Tosyl-1,5-dihydro-2*H*-pyrrol-2-ones (8a—f): To a mixed solution of the 2-iodopyrrole compound **7a** (45 mg, 0.1 mmol) and AgOAc (17 mg, 0.1 mmol) in 2 ml of TFA was added 0.4 ml of water; the mixture was stirred in the dark for 5 h at room temperature. Then, the solvent was removed under reduced pressure to afford a residue, which was taken up into AcOEt. The AcOEt solution was washed with aq $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Removal of the solvent gave a crude product, which was purified with preparative TLC (SiO_2, hexane : AcOEt = 2 : 1, v/v) to afford **8a** in 67% yield. In the same way, other products **8b—f** were prepared.

The physical and spectral data of **8a—f** are shown in the following.

4-Methyl-3-(*p*-tolyl)-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8a): Mp 178.0—179.0 °C (from EtOH); IR (KBr) 2924, 1699, 1316, 1145, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.31 (s, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 5.13 (s, 1H), 6.40 (br, 1H), 6.95 (d, 2H, J = 8.24 Hz), 7.14 (d, 2H, J = 8.24 Hz), 7.31 (d, 2H, J = 8.24 Hz), 7.71 (d, 2H, J = 8.24 Hz). Found: C, 66.73; H, 5.63; N, 4.04%. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10%.

3-Ethyl-4-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8b): Mp 137.0—139.0 °C (from EtOH–H_2O); IR (KBr) 3199, 3064, 1692, 1320, 1132, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.61 (t, 3H, J = 7.63 Hz), 1.98 (dq, 1H, J = 7.63, 13.74 Hz), 2.04 (dq, 1H, J = 7.63, 13.74 Hz), 2.16 (s, 3H), 2.41 (s, 3H), 4.50 (s, 1H), 6.35 (br, 1H), 7.31 (d, 2H, J = 8.24 Hz), 7.66 (d, 2H, J = 8.24 Hz). Found: C, 60.06; H, 6.10; N, 4.94%. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01%.

3-(*p*-Methoxyphenyl)-4-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8c): Mp 167.0—169.0 °C (from EtOH); IR (KBr) 3198, 3066, 2925, 1688, 1515, 1319, 1297, 1257, 1147, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.32 (s, 3H), 2.39 (s, 3H), 3.80 (s, 3H), 5.13 (s, 1H), 6.44 (br, 1H), 6.86 (d, 2H, J = 8.85 Hz), 7.03 (d, 2H, J = 8.85 Hz), 7.31 (d, 2H, J = 8.54 Hz), 7.71 (d, 2H, J = 8.54 Hz). Found: C, 63.58; H, 5.41; N, 3.76%. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92%.

4-Methyl-3-phenethyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8d): Mp 177.0—178.0 °C (from EtOH); IR (KBr) 3195, 3083, 1706, 1302, 1130, 816, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.98 (s,

3H), 2.25—2.39 (m, 4H), 2.41 (s, 3H), 4.99 (s, 1H), 6.32 (br, 1H), 7.06 (d, 2H, J=8.24 Hz), 7.19—7.32 (m, 5H), 7.67 (d, 2H, J=8.24 Hz). Found: C, 67.54; H, 6.01; N, 3.95%. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94%.

3-*t*-Butyl-4-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8e): Mp 174.0—175.0 °C (from EtOH–H_2O); IR (KBr) 3189, 3078, 2966, 2926, 1715, 1677, 1310, 1292, 1146, 1086, 1069, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (s, 9H), 2.30 (s, 3H), 2.42 (s, 3H), 4.86 (s, 1H), 6.33 (br, 1H), 7.32 (d, 2H, J=8.24 Hz), 7.67 (d, 2H, J=8.24 Hz). Found: C, 62.55; H, 6.94; N, 4.43%. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56%.

4-Methyl-3-isopropyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (8f): Mp 148 °C (from EtOH–H_2O); IR (KBr) 3202, 3068, 2956, 1705, 1316, 1302, 1141, 1084, 826, 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.76 (d, 3H, J=7.02 Hz), 0.94 (d, 3H, J=7.01 Hz), 2.16 (s, 3H), 2.41 (s, 3H), 2.54 (qq, 1H, J=7.01, 7.02 Hz), 4.94 (s, 1H), 6.22 (br, 1H), 7.31 (d, 2H, J=8.24 Hz), 7.66 (d, 2H, J=8.24 Hz). Found: C, 61.17; H, 6.65; N, 4.76%. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.48%.

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