Neighboring Group Participation of the N-Oxide Group in the Reaction of Methyl 1-Oxido-2-pyridyl Ketone Oxime with Tosyl Chloride

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The reactions of methyl 1-oxido-2-pyridyl ketone oximes, E- (I₆) and Z-forms (I₂), with tosyl chloride in the presence of NaOH were investigated to compare the reactivity of the N-oxide with that of the oxime group in the same molecule. In the reaction of I₆, neighboring group participation of the N-oxide group apparently occurred, and 3-methyl-2-tosoyloxy-2H-[1,2,5]-oxadiazolo[2,3-a]pyridine(III) was obtained. The mechanism of the formation of III is discussed. The hydrogenation of III with H₂/Pd-C afforded two 1,2,5-oxadiazole derivatives (IV and V); the hydrogenation conditions were examined in detail.

Keywords — methyl 1-oxido-2-pyridyl ketone oxime; Schotten–Baumann reaction; tosylation; neighboring group participation; 1,2,5-oxadiazole; hydrogenolysis; NMR

It is well known that both the N-oxide group and the oxime group readily react with acylating agents to give various types of products depending upon the reaction conditions. A previous report from our group showed that the reaction of 2-ethylpyridine 1-oxide with amyl nitrite and potassium amide in liquid ammonia gave E- (I₆) and Z-oximes (I₂) of methyl 1-oxido-2-pyridyl ketone.¹¹ In the present work, in order to compare the reactivity of the N-oxide with that of the oxime group in I₆ and I₂ toward acylating agents, we investigated the reaction of I with tosyl chloride in the presence of NaOH and found that neighboring group participation of the N-oxide group occurred in the reaction of I₆. There are few reports on neighboring group participation of the N-oxide group² or the nitrogen atom of the heterocyclic nucleus³ (Chart 1).

![Chart 1](image-url)

Compound I₂ reacted easily with tosyl chloride in the presence of NaOH to give only the tosylate (II) of the oxime group of I₂ in good yield, and no tosylation of the N-oxide was noticed. On the other hand, in the reaction of I₆ with tosyl chloride under the same conditions, neighboring group participation of the N-oxide group was observed. Addition of tosyl chloride in tetrahydrofuran (THF) to an alkaline solution of I₆ under ice-cooling followed by stirring of the mixture at room temperature for 2 h gave a colorless crystalline
substance, C_{14}H_{14}N_2O_4S (III), in 67% yield. Compound III is thermodynamically very stable and insensitive to acids. In the ultraviolet (UV) spectrum of III the absorption maximum appeared at 283 nm, and in the infrared (IR) spectrum no absorption bands of N-oxide, secondary amino group or carbonyl group could be seen.

The mass spectrum (MS) of III is shown in Fig. 1. The main fragment ions of III are as follows: m/z 306 (M^+), 155, 135 and 91. The symbol ‘*’ in Fig. 1 represents metastable ions detected by the linked scan method. The m/z 155 ion is formed by the loss of C_4H_5N_2O_2 from the molecular ion, and undergoes subsequent loss of SO_2 to give the tropylium ion (m/z 91). The peak at m/z 135 is formed by loss of the tosyloxy group from the molecular ion.

In the \(^1\text{H} NMR\) spectrum of III (Fig. 2-A), A_2B_2 type proton signals due to the \(p\)-substituted benzene ring (δ 7.31 and 7.78) and signals between δ 5.9 and 7.2 due to the adjacent protons of the 1,2-dihydropyridine ring are observed. The signals due to the protons of two methyl groups (δ 2.33 and 2.44) are also observed, but these are not shown in Fig. 2-A. Assignment of the protons \(H_a\), \(H_b\), \(H_c\), and \(H_d\) on the 1,2-dihydropyridine ring (shown in Fig. 2-A) was made by comparison with the spectra of similar compounds, and by the spin decoupling method. The spectrum in Fig. 2-B was obtained by irradiation at the frequency indicated by the arrow. The signals at δ 5.97 and 6.45 were assigned to the protons \(H_a\) and \(H_b\), respectively, by the method of double resonance. In general, when the ratio of the chemical shift difference and the spin coupling constant (Δν/\(J\)) is smaller than about 6, the spectrum exhibits complicated splitting patterns, i.e. the chemical shift difference no longer corresponds to the distance between the midpoints of the signals, and moreover, the \(J\)-value is no longer constant. The spectrum of III is still rather complicated at 100 MHz. Therefore, the signals of \(H_c\) and \(H_d\) could not be separately assigned. The \(^13\text{C}\) nuclear magnetic resonance (NMR) spectrum of III shows the signals arising from carbon atoms of two methyl groups and four quaternary carbon atoms.

The hydrogenation of III over Pd-C in THF at atmospheric pressure was carried out in
Fig. 1. Mass Spectrum of III

Fig. 2. NMR Spectra of III in CDCl₃ at 100 MHz
order to elucidate chemically the structure of III. Less than 3 mol of hydrogen was absorbed, and compounds IV (C₁₄H₁₄N₂O₂S) and V (C₇H₁₂N₂O) were obtained. The former is insoluble and the latter is soluble in petroleum ether. The structure of IV was determined from the spectral data, \textit{i.e.}, IR, UV, mass, $^1$H and $^{13}$C NMR spectra. The IR spectrum of V was identical with that of an authentic sample prepared by a method similar to that of Behr and Brent,\textsuperscript{4} and the structure of V is also supported by the other spectral data.

![Chart 3](image)

The reduction conditions were investigated in detail in order to confirm whether compound V is formed \textit{via} IV or directly from III. The experimental results are listed in Table I. On hydrogenation of III over Pd-C under neutral (A) or acidic (B) conditions at atmospheric pressure, no significant differences were observed in the ratio of IV to V, as shown in Table I. On the other hand, when IV was treated under the same conditions A and B, most of the starting material was recovered, together with a trace of V. Under more drastic reduction conditions, C (PtO₂ in acetic acid), compound V was obtained from IV in 89\% yield. On the basis of the present results, it is concluded that V is formed not from IV, but directly from III under conditions A and B.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conditions</th>
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<tbody>
<tr>
<td></td>
<td>(A) Pd-C (neutral)</td>
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<tr>
<td></td>
<td>Product</td>
</tr>
<tr>
<td>III</td>
<td>IV</td>
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<tr>
<td></td>
<td>V</td>
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<tr>
<td>IV</td>
<td>Recovery V</td>
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<td>Trace\textsuperscript{a}</td>
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\textsuperscript{a} Detected by thin layer chromatography.

From the chemical and spectral data described above, all the reactions reported in this paper are considered to proceed according to the scheme in Chart 4. First, tosylation of the hydroxyl group of Iₖ by tosyl chloride occurs, and subsequently the oxygen atom of the N-oxide group attacks the nitrogen atom of the oxime group to give III. Clearly, neighboring group participation of the N-oxide group is involved in this reaction. The formation of V on hydrogenation over Pd-C is illustrated by path A in Chart 4.

Based on the results described above, it is concluded that the oxime group reacts with tosyl chloride more easily than the N-oxide group in the reaction of I with tosyl chloride.
Experimental

Melting points were determined on a micro melting point apparatus (Yanaco) and are uncorrected. Spectral data were recorded on the following spectrometers: UV spectra, Hitachi 556; IR spectra, Hitachi 295; ¹H NMR spectra, JNM C-60-H (60 MHz), Hitachi R-22 (90 MHz) and JEOL FX-100 (100 MHz); ¹³C NMR spectra, JEOL FX-100 (25.1 MHz); mass spectra, JEOL JMS-DX300.

**Reaction of Iₚ with Tosyl Chloride**—Tosyl chloride (1.90g) in dioxane (10 ml) was added dropwise to a mixture of Iₚ (1.0 g) and aqueous NaOH solution (NaOH 1.08g and H₂O 5 ml) with shaking under ice-cooling. A crystalline substance separated out within a few min. The resulting mixture was further shaken for 2h at room temperature. The crystalline substance was filtered off, and recrystallized from benzene to give colorless needles (II), mp 186 °C (dec.), 1.78 g (99.9% yield). Anal. Calcd for C₁₄H₁₂N₂O₅S: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.18; H, 4.72; N, 9.07. UV λmax [nm (log ε): 269.5 (4.09), λmax [nm: 283.5. IR νmax cm⁻¹: 1634 (C = N), 1366 (SO₂), 1238 (N = O), 1185, 1172 (SO₂). ¹H NMR δ(⁴DCHL) (60 MHz): 2.32 (3H, s, CH₃), 2.43 (3H, s, tolyl-CH₃), 7.17—7.50 (5H, m, arom-H), 7.85 (2H, d, J = 8 Hz, arom-H), 8.22 (1H, m, arom-H).

**Reaction of Iₚ with Tosyl Chloride**—Tosyl chloride (1.90g) in THF (10 ml) was added dropwise to a solution of Iₚ (1.0g) in aqueous NaOH solution (NaOH 1.08g and H₂O 5 ml) with shaking under ice-cooling. The resulting solution was further shaken for 2h at room temperature. The solution was concentrated in vacuo to a half of its original volume. The precipitated crystals were filtered off and recrystallized from acetone–petr. ether to give colorless prisms (III), mp 96 °C (67% yield). Anal. Calcd for C₁₄H₁₂N₂O₅S: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.75; H, 4.58; N, 9.07. UV λmax [nm (log ε): 283 (4.05). IR νmax cm⁻¹: 1393, 1196, 1182 (SO₂), νC = O: 1710 cm⁻¹. ¹H NMR δ(⁴DCHL) (90 MHz): 2.33 (3H, s, 3-CH₃), 2.44 (3H, s, 4-CH₃), 5.97 (1H, d, J = 11 Hz, 4-H), 6.3—6.7 (1H, m, 5-H), 7.0—7.1 (2H, m, 6, 7-H), 7.36, 7.80 (4H, ABq, J = 8 Hz, arom-H). Decoupling δ(⁴DCHL) (100 MHz): 7.08 (6, 7-H) → 6.55 (m → d, J = 11 Hz, 5-H). ¹³C NMR δ(⁴DCHL) (25.1 MHz): 150.4 (s, C-3), 145.8 (s, C-3a and C-4'), 132.2 (s, C-1'), 21.7 (s, 4-CH₃), 8.0 (s, 5-CH₃). MS Calcd for C₁₄H₁₂N₂O₅S: M, 306.067. Found m/z: M⁺, 306.067.

**Hydrogenation of III over Pd-C (Neutral Conditions)**—A solution of III (0.5 g (0.0016 mol)) in THF (15 ml) was
shaken with Pd-C (prepared from 1.7% PdCl₂ soln. (3.5 ml) and active charcoal (0.25 g); acid-free) in an H₂ stream at atmospheric pressure. Reduction was complete when ca. 110 ml of H₂ had been absorbed. The catalyst was removed by filtration. The solvent was evaporated off \textit{in vacuo} and the residue was taken up in ether. The ether layer was washed with 10% NaOH aq. solution, then dried over Na₄SO₄, and the solvent was removed. The residue was divided into petr. ether-insoluble (IV) and -soluble (V) fractions. Compound IV was recrystallized from ether-petr. ether to give colorless prisms, mp 59—60°C, 0.11 g (22% yield). \textit{Anal.} Calcld for C₁₄H₁₄N₂O₅S: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.05; H, 5.83; N, 8.92. UV $\lambda_{\text{max}}$ nm (log e): 263.2 (2.72). IR $\nu_{\text{max}}$ cm⁻¹: 1355, 1193 (SO₂). \textsuperscript{1}H NMR $\delta_{\text{ppm}}$ (90 MHz): 1.64—1.94 (4H, m, 5- and 6-CH₂), 2.32 (3H, s, 3-CH₃), 2.44 (3H, s, 4’-CH₃), 2.52—2.80 (2H, m, 4-CH₂), 3.98—4.22 (2H, m, 7-CH₂), 7.32, 7.77 (4H, AB q, $J = 9$ Hz, arom-H). \textsuperscript{13}C NMR $\delta_{\text{ppm}}$ (25.1 MHz): 153.7 (s, C-3a), 150.4 (s, C-3), 144.9 (s, C-4’), 132.9 (s, C-2), 21.6 (s, 4’-CH₃), 8.1 (s, 3-CH₃). MS Calcld for C₁₄H₁₄N₂O₅S: M, 310.098. Found m/z: $M^+$, 310.098. Compound V was distilled under reduced pressure to give a colorless liquid, bp 100—103°C (28 mmHg), 0.12 g (52% yield). \textit{Anal.} Calcld for C₃H₇N₂O: C, 59.97; H, 8.63; N, 19.99. Found: C, 59.89; H, 8.66; N, 19.84. UV $\lambda_{\text{max}}$ nm (log e): 218 (4.02). \textsuperscript{1}H NMR $\delta_{\text{ppm}}$ (90 MHz): 0.82—1.10 (3H, m, CH₃-(CH₂)₃-), 1.20—1.94 (4H, m, CH₂-(CH₂)₃-CH₂-), 2.33 (3H, s, 4-CH₃), 2.55—2.82 (2H, m, CH₂-(CH₂)₃-CH₂-). \textsuperscript{13}C NMR $\delta_{\text{ppm}}$ (25.1 MHz): 154.6 (s, C-4), 150.6 (s, C-3), 13.6 (s, 3-CH₃), 8.0 (s, 4-CH₃). MS Calcld for C₃H₇N₂O: M, 140.094. Found m/z: $M^+$, 140.095.

Hydrogenation of III over Pd-C (Acidic Conditions)—A mixture of 1.7% PdCl₂ soln. (3.5 ml) and active charcoal (0.25 g) was shaken in an H₂ stream at atmospheric pressure. After the absorption of H₂ had stopped, a solution of III (0.5 g) in THF (15 ml) was added to the solution, and the resulting mixture was further shaken in an H₂ stream at atmospheric pressure. The reaction mixture was treated in a manner similar to that described above. Compound IV, 0.12 g (25% yield). Compound V, 0.12 g (55% yield).

Hydrogenation of IV over Pd-C (Neutral Conditions)—Compounds IV (0.08 g) was treated under the same conditions as described for the hydrogenation of III (neutral conditions). IV was recovered in 77% yield (0.06 g). A trace of V was detected by thin layer chromatography (TLC).

Hydrogenation of IV over Pd-C (Acidic Conditions)—Compounds IV (0.1 g) was treated under the same conditions as described for the hydrogenation of III (acidic conditions). IV was recovered in 90% yield (0.09 g). A trace of V was detected by TLC.

Hydrogenation of IV over PtO₂ in Acetic Acid—A solution of IV (0.5 g) in acetic acid (10 ml) was shaken with PtO₂ (0.1 g) in an H₂ stream at atmospheric pressure. Compound V was obtained in 89% yield (0.2 g).

Treatment of III with HCl—A solution of III in conc. HCl (or conc. HCl—dioxane or conc. HCl—MeOH) was refluxed for 7—10 min and was recovered in ca. 80% yield.

Synthesis of 3-Butyl-4-methylfurazan—A mixture of succinic anhydride 6.33 g (0.063 mol) and methyl butyl glyxime 10 g (0.063 mol) was placed into a three-necked flask equipped with a stirrer, a thermometer, and an outlet tube connected to an air-cooled condenser, arranged for distillation. The mixture was heated slowly on an oil bath with stirring, and the mixture liquefied at about 120°C. Distillation of the product began at about 160°C and continued until the temperature reached 200°C; this temperature was maintained for 10 min. The reaction mixture was then steam-distilled; the distillate was extracted with ether. The extracts were combined with the product obtained by direct distillation. The ether solution was dried over anhydrous MgSO₄, and the solvent was removed. The residue was distilled at 100—103°C (28 mmHg) as a colorless liquid. The yield was 4.0 g (45%).

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References and Notes