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Selenium Dioxide Oxidations of Dialkyl-3*H*-Azepines: The First Synthesis of 2-Azatropone from Oxidation of 2,5-Di-*tert*-butyl-3*H*-azepine

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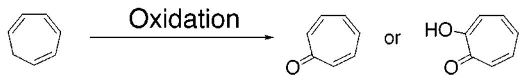
Oxidation reactions of 2,5- and 3,6-di-*tert*-butyl-3*H*-azepines (**1** and **2**) with selenium dioxide (SeO_2) were performed. The oxidation of **1** with SeO_2 gave 3-*tert*-butyl-7,7-dimethyl-4-oxo-octa-2,5-dienal **3** in 36% yield, 4-*tert*-butyl-5-(3,3-dimethyl-2-oxo-butylidene)-1,5-dihydro-pyrrol-2-one **4** in 13% yield, 2,6-di-*tert*-butyl-2-pyridinecarbaldehyde **5** in 12% yield, and 4,7-di-*tert*-butyl-2*H*-azepin-2-one (2-azatropone) **6** in 6% yield, respectively. Oxidation of **2** with SeO_2 gave 2,2-dimethyl-1-[2-(5-*tert*-butyl)-pyridyl]propanol **7** in 55% yield, and 3,6-di-*tert*-butyl-2*H*-azepine **8** in 5% yield, respectively. We found that selenium dioxide oxidation of **1** affords 4-oxo-octa-2,5-dienal **3** by a new ring cleavage reaction of **1**, and we described the first synthesis of 2-azatropone **6** from this oxidation of **1**. In the case of **2**, pyridylpropanol **7** was obtained as the major product. We now report in detail result of these oxidation reactions, which have led to the synthesis of a novel azatropone derivative.

1. Introduction

The contrasting chemical behaviors of 3*H*-azepines and isoelectronic 1,3,5-cycloheptatrienes are of interest. Although unsubstituted 3*H*-azepine is known as a labile compound that is difficult to handle,[1] we earlier developed a convenient procedure to allow the preparation of stable 2,5- and 3,6-di-*tert*-butyl-3*H*-azepines (**1** and **2**).[2] In the process of studying the reactivity of these molecules we found a new ring contraction reaction of **1** and **2** leading to pyridine derivatives.[3]

Several studies indicate that oxidation of 1,3,5-cycloheptatriene affords tropone or tropolone (eq 1).[4] Radlick has also reported the synthesis of tropone by oxidation of 1,3,5-cycloheptatriene with selenium dioxide (SeO_2).[5] This reaction, though not high in yield, afforded a simple one-step preparation of tropone from 1,3,5-cycloheptatriene. However, in the case of azepines, the only oxidation studies are by Sato et al. who reported that 2-ethoxy-3*H*-azepin-3-ones are produced rapidly by the oxidation of 7-ethoxy-6-hydroxy-4*H*-azepines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene.[6] According to our knowledge, there is no experimental data on the intrinsic reactivity of the azepine ring, and so in order to investigate similarities and differences in the chemical behavior of 3*H*-azepines and isoelectronic 1,3,5-cycloheptatrienes, oxidations of **1** and **2** with SeO_2 were examined. We found that selenium dioxide oxidation of **1** affords 4-oxo-octa-2,5-dienal **3** by a new ring cleavage reaction of **1**, and we reported the first synthesis of 2-azatropone **6** from this oxidation of **1**. In the case of **2**, pyridylpropanol **7** was obtained as the major product. We now report in detail result of these oxidation reactions, which have led to the synthesis of a novel azatropone derivative.



2. Results and Discussion

The oxidation of **1** with SeO_2 in dioxane/H_2O at 65 °C for 7 h provided 4-oxo-octa-2,5-dienal **3** in 36% yield, 1,5-dihydro-pyrrol-2-one **4** in 13% yield, pyridinecarbaldehyde **5** in 12% yield, and 2*H*-azepin-2-one (2-azatropone) **6** in 6% yield, respectively (Scheme 1). The structure of **3** was characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis. In the ^1H NMR spectrum ($CDCl_3$) of the product **3** the resonance of the aldehyde proton ($\delta = 9.67$) was observed, and the values of the coupling constant for the doublet ($J = 7.5$ Hz) with the proton adjacent to the aldehyde proton were observed. In addition, compound **3** showed signals at $\delta = 7.43$ (C-5) (d,

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(1) Vogel, E.; Altenbach, H.-J.; Drossard, J.-M.; Schmickler, H.; Stegelmeier, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1016.

(2) (a) Satake, K.; Okuda. R.; Hashimoto. M.; Fujiwara, Y.; Watadani, I.; Okamoto, H.; Kimura, M.; Morosawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1154. (b) Satake, K.; Okuda. R.; Hashimoto. M.; Fujiwara, Y.; Okamoto, H.; Kimura, M.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1753.

(3) Satake, K.; Takaoka. K.; Hashimoto. M.; Okamoto, H.; Kimura, M.; Morosawa, S. *Chem. Lett.* **1996**, 1129.

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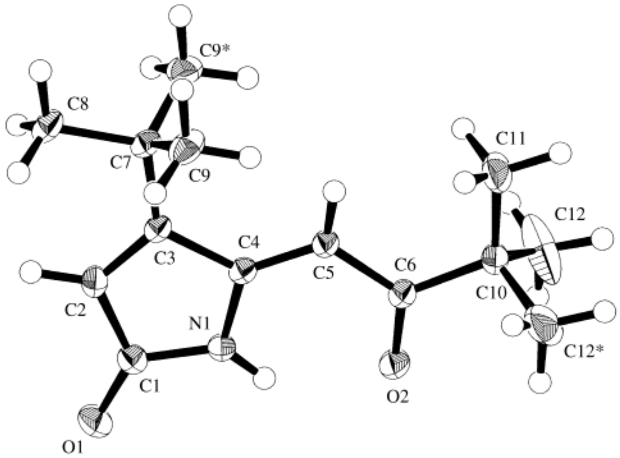
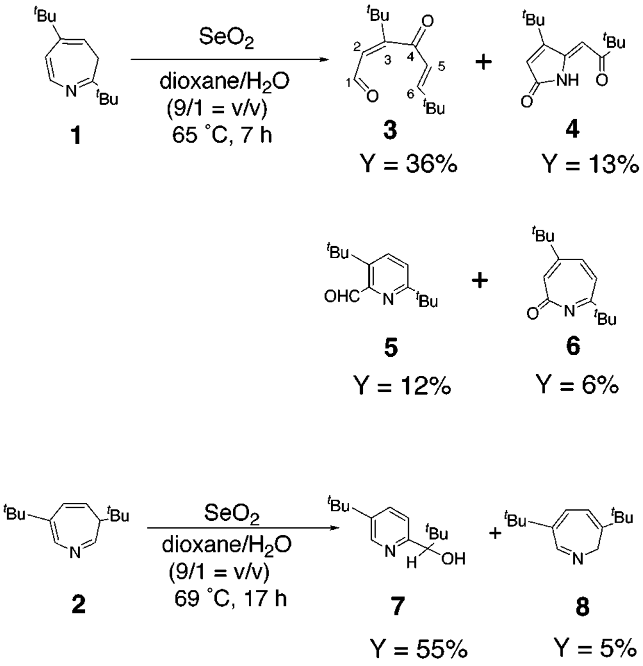


Figure 1. X-ray crystallographic structure and conformation of **4**.

Scheme 1



$^3J_{\text{trans}} = 15.5$ Hz, 1H) and $\delta = 6.61$ (C-6) (d, $^3J_{\text{trans}} = 15.5$ Hz, 1H). In the IR spectrum the carbonyl absorption of the product **3** characteristically occurs at low wavenumbers, as also in benzylideneacetone (1674−1699 cm^{-1}) and α,β-unsaturated aldehydes (1685−1710 cm^{-1}).[7] The product **3** similarly shows two signals of 1682 and 1670 cm^{-1} for the carbonyl absorption. X-ray analysis of compound **4** and **6** were undertaken in order to confirm that their molecular structures were as shown in Figures 1 and 2. In addition, the structure of **6** was characterized by ^{1}H NMR, ^{13}C NMR, IR, and high-resolution MS. It is noteworthy that 2-azatropone **6** was obtained from oxidation of the 3*H*-azepine **1**. We have also confirmed the formation of 2-azatropone **6** from a reaction of 3*H*-azepine **1** with *N*-bromosuccinimide (NBS).[8]

Oxidation of **2** with SeO$_2$ in dioxane/H$_2$O at 69 °C for 17 h gives pyridylpropanol **7** in 55% yield and 3,6-di-*tert*-butyl-2*H*-azepine **8**^{2b} in 5% yield, respectively (Scheme 1). Compound of **7** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and elemental analysis. Presence of the pyridine ring in **7** was indicated in ^{1}H NMR by low field signals at $\delta = 8.59$ (dd, $J = 2.4$ and 0.9 Hz, 1H), $\delta = 7.62$ (dd, $J = 8.4$ and 2.4 Hz, 1H), and $\delta = 7.11$ (dd, $J = 8.4$ and 0.9 Hz, 1H), respectively. The IR spectrum of compound **7** showed a hydroxyl absorption at 3186 cm^{-1}.

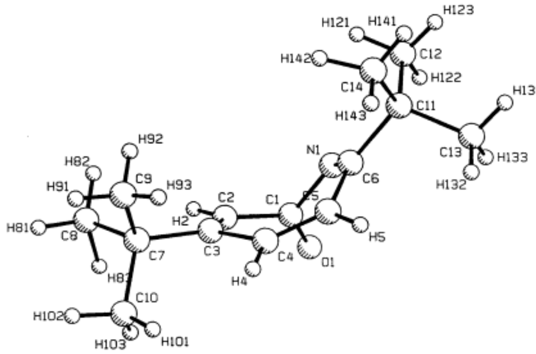


Figure 2. X-ray crystallographic structure and conformation of **6**.

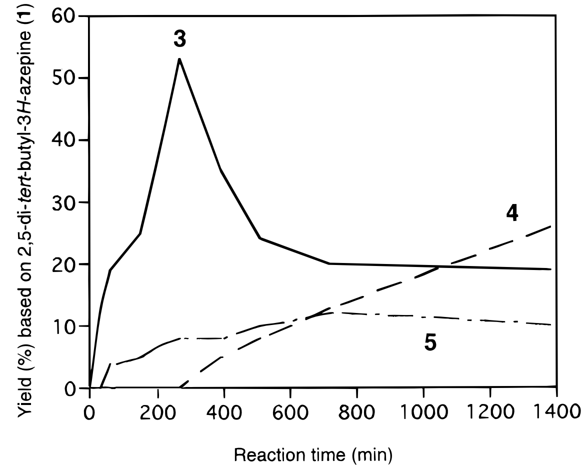


Figure 3. Time-dependence curves for the reaction of **1** with SeO$_2$ in dioxane/H$_2$O at 70 °C. The figures on the curves refer to the respective compounds given in Scheme 1.

Figure 3 shows time-dependence curves for the oxidation of **1** with SeO$_2$. At an early stage of the reaction, **3** is produced as the major product. After 1400 min (about 24 h), **4** is obtained as the major product, and the yield of **3** decreases. This indicates that **4** is produced through the formation of **3**. On the other hand, the yield of **5** is unchanged with time. Compound **6** was not observed in any appreciable yield. The formation of **4** can be explained in term of the product **3** reacted with NH$_3$ produced in solution during reaction. This is supported by the observation that reaction of **3** with NH$_3$ solution in dioxane/H$_2$O at 70 °C for 48 h provides **4** as the major product. During SeO$_2$ oxidation, the NH$_3$ solution may be formed by release of NH$_3$ gas from the intermediate **10** as shown in Scheme 2, which gives a plausible mechanism for formation of the product **3**. Selenium dioxide exists as selenous acid in a solvent containing water, and it is considered that formation of the intermediate diol **9** can be explained in term of electrophilic attack of selenous acid on the 3*H*-azepine ring of **1**. As a general rule, addition of selenous acid to double bonds

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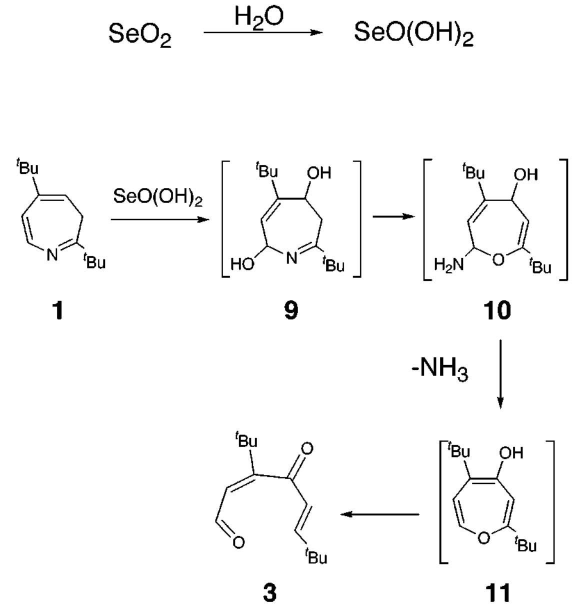
(8) Satake, K.; Tawada, Y.; Takaoka, K.; Kimura, M. **1997**, unpublished results.

Scheme 2

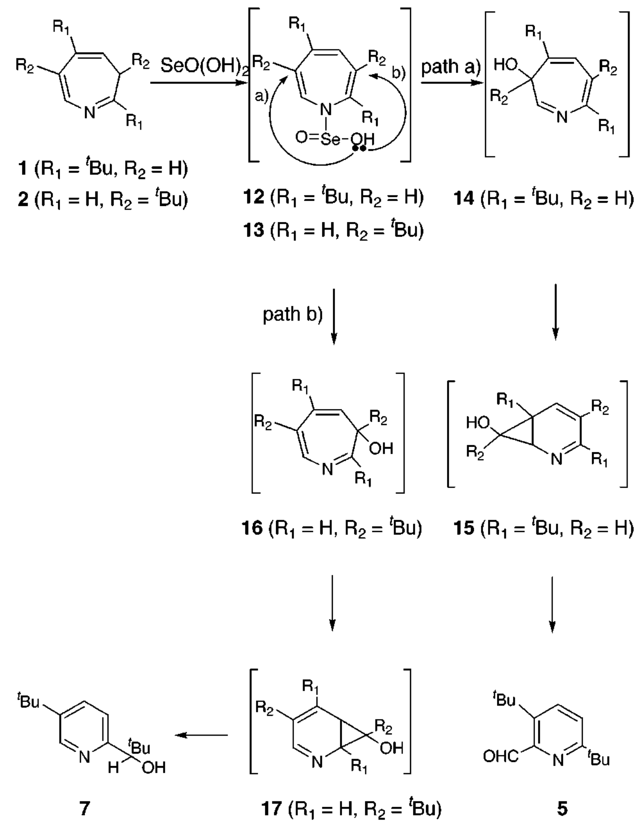


gives an intermediate diol.[9] In the case of **1**, electrophilic attack of selenous acid toward 4,6-diene of 3*H*-azepine ring in **1** gave the intermediate diol **9** in the conjugation to the double bond. We assume that the intermediate diol **9** is converted to final product **3** via the oxepine structure **11**, followed by elimination of NH$_3$. To the best of our knowledge, this is the first example of this type of ring cleavage reaction in 3*H*-azepines.

The formation of **5** or **7** can be explained in term of electrophilic attack of selenous acid on the C═N double bond in 3*H*-azepine **1** or **2** and then nucleophilic attack of carbonyl group of selenous acid on the 3-position of methylene proton in **1** or **2** (Scheme 3). We assume that after this attack on **1** or **2** the intermediate **12** or **13** is formed having a N−Se bond, leading then to intermediate **14** or **16** via a [2,3] sigmatropic shift. This seems reasonable in view of the mechanism for oxidation of olefins by SeO$_2$.[10] It is considered that the intermediate **14** was formed via path a from **12** because of steric hindrance at the 2-position due to the *tert*-butyl group in the intermediate **12**. Second, the intermediate **14** or **16** is converted to the 2-azanorcardiene intermediate **15** or **17** and then to final product **5** or **7**. We have earlier reported the isolation of 4,7-di-*tert*-butyl-3-methoxy-2-azanorcardiene from reaction of 3*H*-azepine **2** with bromine and absolute MeOH.[11] We have found that the seven-membered azatriene system of 3*H*-azepines ring is electron-poor triene compared to the corresponding cycloheptatriene system.

In the literature, attack of SeO$_2$ on methylene protons of 1,3,5-cycloheptatriene has been reported.[5] If this assumption is correct, then we can conclude the following. These reactions of 3*H*-azepine **1** or **2** with SeO$_2$ are similar to those of 1,3,5-cycloheptatriene, but the formation of pyridine structures **5** or **7** is entirely different from the case of 1,3,5-cycloheptatriene. In addition, we found that the formation of **5** was in low yield from reaction of **1** with SeO$_2$, whereas **7** was the major product from reaction of **2**.

Scheme 3



In the case of formation of **8**, we have previously reported that a 1,5-hydrogen shift in 3,6-di-*tert*-butyl-3*H*-azepine **2** was observed between **2**, 2*H*-azepine **8**, and 3,6-di-*tert*-butyl-4*H*-azepine.[2b] We have also confirmed the efficient isomerization reaction of **2** giving 2*H*-azepine **8** at a moderate temperature (65 °C).[12] Therefore, the formation of **8** can be explained from a 1,5-hydrogen shift in 3,6-di-*tert*-butyl-3*H*-azepine **2** under these conditions.

3. Conclusions

In conclusion, we have shown that the oxidation of 2,5-di-*tert*-butyl-3*H*-azepine **1** with SeO$_2$ produces a new 3*H*-azepine ring cleavage reaction. On the other hand, the selenium dioxide oxidation of 3,6-di-*tert*-butyl-3*H*-azepine **2** is similar to the reaction of 1,3,5-cycloheptatriene, although the formation in the product mix of pyridine derivative **7** via the 2-azanorcardiene intermediate **17** is entirely different to oxidation of the carbocyclic 1,3,5-cycloheptatriene. Therefore, we have shown that the reactivity of 3*H*-azepine **1** or **2** with SeO$_2$ changes appreciably with position of the *tert*-butyl groups for **1** or **2**. Finally, we have described the first synthesis of a 2-azatropone from oxidation of the seven-membered azatriene system with SeO$_2$.

4. Experimental Section

General Procedure. Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 500 and 300 MHz, and the

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^{13}C NMR spectra were recorded at 67 and 50 MHz, respectively in CDCl$_3$ solution. TLC was performed with Merck silica gel 60 F $_{254}$ (0.2 mm) precoated plates. Silica gel Woelm 32−63 for preparative MPLC were used. IR spectra were recorded on a JASCO FT-IR 5000 spectrophotometer. Electronic Spectra were measured in ethyl alcohol. Mass spectrometry was performed on a JEOL JMS-DX300 mass spectrometer coupled to JMA-3100 data analysis system. High-resolution mass spectral data were obtained on a Hewlett-Packard 5890 SERIES II mass spectrometer. Elemental analyses were performed by the Microanalytical Laboratory at the Department of Chemistry, Faculty of Science, Kyushu University.

Oxidation of 2,5-Di-*tert*-butyl-3*H*-azepine 1 with selenium dioxide.

A solution of **1** (113 mg, 0.55 mmol) and selenium dioxide (85 mg, 0.77 mmol) in 1,4-dioxane and water (9/1, 10 mL) was stirred at 65 °C for 7 h, until TLC (30% EtOAc/hexane) showed complete disappearance of **1**. The solution was allowed to cool to room temperature and the solvent was evaporated. The oily residue was dissolved in K$_2$CO$_3$ aq and extracted with ether. The organic layer was dried over MgSO$_4$ and evaporated to dryness. The residue was filtered through silica gel column chromatography (5% to 20% EtOAc/hexane) and afforded 44 mg (36%) of 3-*tert*-butyl-7,7-dimethyl-4-oxo-octa-2,5-dienal **3** and 16 mg (13%) of 4-*tert*-butyl-5-(3,3-dimethyl-2-oxo-butylidene)-1,5-dihydro-pyrrol-2-one **4** and 14 mg (12%) of 2,5-di-*tert*-butyl-3-pyridinecarbaldehyde **5** and 7 mg (6%) of 4,7-di-*tert*-butyl-2*H*-azepin-2-one **6**.

3-*tert*-Butyl-7,7-dimethyl-4-oxo-octa-2,5-dienal (3): Red oil; ^{1}H NMR (300 MHz, CDCl$_3$) $\delta = 9.67$ (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 15.5$ Hz, 1H), 6.61 (d, $J = 15.5$ Hz, 1H), 6.14 (d, $J = 7.5$ Hz, 1H), 1.18 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (67 MHz, CDCl$_3$) $\delta = 202.8$ (s), 192.9 (d), 170.3 (s), 137.9 (d), 131.1 (d), 127.4 (d), 43.1 (s), 37.2 (s), 28.9 (q), 25.9 (q); IR (neat) 2972, 1682, 1670 cm^{-1}; MS (FAB) m/z 223 (M$^+$; 62%), 167 (23), 154 (48), 57 (100); UV λmax (EtOH) 213 (3.98), 261 (4.01) nm. Anal. Calcd for C$_{14}$H$_{22}$O$_2$: C, 75.63; H, 9.97. Found: C, 75.80; H, 10.20.

Crystal Data for (4): C$_{14}$H$_{21}$NO$_2$, orthorhombic, space group *Pnma*, $a = 19.3803(7)$ Å, $b = 6.8744(2)$ Å $c = 10.0180(3)$ Å, $V = 1334.7(2)$ Å^3, $Z = 4$, $D_c = 1.171$ g/cm^3, $F(000) = 512$, $T = 127$ K, $R = 0.044$, $R_w = 0.066$. Intensity data were collected on Rigaku RAXIS diffractometer with graphite monochromated Cu−Kα radiation ($\lambda = 1.54178$ Å). The structure was solved by direct methods with SIR92[13] and refined by the full matrix least-squares method. All of the nonhydrogen atoms were refined anisotropically. The final cycle of the least-squares refinement was based on 1048 observed reflection [$I > 3\sigma(I)$] and 98 variable parameters for **4**.

2,6-Di-*tert*-butyl-2-pyridinecarbaldehyde (5): Yellow oil; ^{1}H NMR (500 MHz, CDCl$_3$) $\delta = 11.2$ (s, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 1.43 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) $\delta = 196.0$ (d), 165.9 (s), 150.6 (s), 144.0 (s), 135.5 (d), 121.7 (d), 37.0 (s), 34.7 (s), 30.6 (q), 30.0 (q); IR (neat) 1702 cm^{-1}; MS (EI$^+$) m/z 219 (M$^+$; 15%), 204 (6), 162 (35), 57 (100); UV $\lambda_{\max}$ (EtOH) 230 sh (log ϵ 4.15), 270 (3.60) nm; HRMS (FAB) Calcd for C$_{14}$H$_{22}$NO 220.1701, Found 220.1709.

4,7-Di-*tert*-butyl-2*H*-azepin-2-one (6): Colorless needles; mp 80.5−81.5 °C; ^{1}H NMR (300 MHz, CDCl$_3$) $\delta = 7.14$ (dd, $J = 12.3$ and 2.4 Hz, 1H), 6.98 (d, $J = 12.3$ Hz, 1H), 6.40 (d, $J = 2.4$ Hz, 1H), 1.25 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (50 MHz, CDCl$_3$) $\delta = 176.8$ (s), 172.2 (s), 152.9 (s), 137.8 (d), 128.1 (d), 124.6 (d), 38.9 (s), 35.6 (s), 29.4 (q), 28.2 (q); IR (neat) 2968, 1682 cm^{-1}; MS (GC) m/z 219 (M$^+$; 14%), 204 (18), 176 (100), 149 (92), 57 (96); UV $\lambda_{\max}$ (EtOH) 248 sh (log ϵ 3.60) nm; HRMS (FAB) Calcd for C$_{14}$H$_{21}$NO 220.1701, Found 220.1679.

Crystal Data for (6):[14] C$_{14}$H$_{21}$NO, monoclinic, space group $P2_1/c$, $a = 9.055(8)$ Å, $b = 23.19(1)$ Å, $c = 13.374(4)$ Å, $\beta = 98.69(5)^{\circ}$, $V = 2776(5)$ Å^3, $Z = 8$, $D_c = 1.049$ g/cm^3, $F(000) = 960$, $T = 298$ K, $R = 0.064$, $R_w = 0.032$. Rigaku AFC5R diffractometer with graphite monochromated Mo−Kα radiation ($\lambda = 0.71069$ Å). The structure of **6** was solved by direct methods with MITHRIL[15] and refined by the full matrix least-squares method. All of the nonhydrogen atoms were refined anisotropically. The final cycle of the least-squares refinement was based on 1967 observed reflection [$I > 2\sigma(I)$] and 350 variable parameters for **6**.

Oxidation of 3,6-Di-*tert*-butyl-3*H*-azepine 2 with Selenium Dioxide. A solution of **2** (125 mg, 0.61 mmol) and selenium dioxide (152 mg, 1.37 mmol) in 1,4-dioxane and water (9/1, 10 mL) was stirred at 69 °C for 17 h, until TLC (30% EtOAc/hexane) showed complete disappearance of **2**. The solution was allowed to cool to room temperature. After evaporationof the solvent, the residue was extracted with ether. The organic layer was dried over MgSO$_4$ and evaporated to dryness. The residue was filtered through silica gel column chromatography (5% to 20% EtOAc/hexane) and afforded 74 mg (55%) of 2,2-dimethyl-1-[2-(5-*tert*-butyl)-pyridyl]propanol **7** and 6 mg (5%) of 3,6-di-*tert*-butyl-2*H*-azepine **8**.[2b]

2,2-Dimethyl-1-[2-(5-*tert*-butyl)-pyridyl]propanol (7): Colorless prisms; mp 111−112.5 °C; ^{1}H NMR (300 MHz, CDCl$_3$) $\delta = 8.59$ (dd, $J = 2.4$ and 0.9 Hz, 1H), 7.62 (dd, $J = 8.4$ and 2.4 Hz, 1H), 7.11 (dd, $J = 8.4$ and 0.9 Hz, 1H), 4.33 (br s, 2H), 1.35 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (50 MHz, CDCl$_3$) $\delta = 156.8$ (s), 145.2 (d), 144.6 (s), 132.6 (d), 122.1 (d), 80.0 (d), 36.3 (s), 33.5 (s), 31.0 (q), 25.1 (q); IR (KBr) 3186, 2872 cm^{-1}; MS (GC) m/z 203 (M − 18; 7%) 135 (100); UV $\lambda_{\max}$ (EtOH) 213 (log ϵ 3.94), 266 (3.60) nm. Anal. Calcd for C$_{14}$H$_{23}$NO: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.96; H, 10.44; N, 6.40.

Acknowledgment. We thank Prof. Y. Naruta, Mr. T. Chishiro, and Dr. Y. Tachi, Institute for Fundamental Research of Organic Chemistry, Kyushu University, for the X-ray crystal structure determination of compound **4**.

Supporting Information Available: Tables of data derived from the X-ray crystallographic analyses of compounds **4** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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