FACILE IN SITU PREPARATION OF o-AZAXYLYLENE FROM N,O-DIETHOXYCARBONYL-o-AMINOBENZYL ALCOHOL

Kota Nishiyama, Hajime Kubo,* Tomohide Sato, Kimio Higashiyama, and Shigeru Ohmiya

Department of Synthetic Organic Chemistry, Institute of Medicinal Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa 142-8501, Japan

Abstract ----- o-Azaxylenes were generated only by gentle refluxing of N,O-diethoxycarbonyl-o-aminobenzyl alcohols in o-dichlorobenzene and then underwent the Diels-Alder reaction with dienophiles to give 1,2,3,4-tetrahydroquinolines.

INTRODUCTION

o-Azaxylenes are expected to exhibit excellent reactivities similar to o-xylylenes but they have been only slightly utilized in organic syntheses because of the requirement of extraordinary reaction conditions for the generation, e.g., flash vacuum thermolysis of o-aminobenzyl alcohols,1 and photolysis of o-aminophenyl diazomethane at 10 K under an argon atmosphere.2 Recently, milder reaction conditions for the generation of o-azaxylylene have been reported, for example, the pyrolysis of benzoisothiazoline dioxide at 215 °C,3 the 1,4-elimination of o-[N-alkyl-N-(trimethylsilyl)]amino]benzyltrimethylammonium halide at 50 °C4 and dehydration of o-alkylaminobenzyl alcohol with a Lewis acid.5 In this paper, we wish to report a facile method for the generation of o-azaxylylenes from N,O-diethoxycarbonyl-o-aminobenzyl alcohols and their application in the preparation of 1,2,3,4-tetrahydroquinoline derivatives.

RESULT AND DISCUSSION

o-Aminobenzyl alcohols have been used as a precursor in the preparation of o-azaxylylenes.1,5 For the purpose of the efficient formation of o-azaxylylene, o-aminobenzyl alcohols were converted to N,O-diethoxycarbonyl-o-aminobenzyl alcohols based on the enhancement in acidity of the hydrogen atom.
on the amide group. Refluxing in o-dichlorobenzene, \(N,O\)-diethoxycarbonyl-o-aminobenzyl alcohol (1a) produced 4\(H\)-3,1-benzoxadine (2) (58%). The 4\(\pi\) cycloaddition products of o-azaxylylenes, such as benzazetidines (3), were not observed. It was postulated that the o-azaxylylene (4) was formed by elimination of CO\(_2\) and ethanol from 1a, which causes the 6\(\pi\) electrocyclic reaction to give benzoxazine (2).\(^6\)

\[
\begin{align*}
\text{1a} & \quad \xrightarrow{\text{reaction}} \quad \text{4} \\
& \quad \xrightarrow{\text{reaction}} \quad \text{2}
\end{align*}
\]

Scheme

To confirm this hypothesis, the intermolecular cycloaddition reactions were attempted in the presence of dienophiles. \(N,O\)-Diethoxycarbonyl-o-aminobenzyl alcohols (1a-d) were heated with \(N\)-phenylmaleimide (5 eq.) as a dienophile at 180°C in o-dichlorobenzene under a nitrogen atmosphere for 8 h. The products (5a-d) were isolated by column chromatography. The yields and the structures of the products (5a-d) are shown in Table, entries 1-4. The yields of the products (5a-d) increased with the electron-donating potency of the substituent. This result agreed with the effects of a substituent on the dienes in a normal Diels-Alder reaction.\(^7\) The relative stereochemistries of 5a-d were determined by comparison with the \(^1\)H-NMR data of 5a-d and the reported \(^1\)H-NMR data of cis-1-benzyl-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid \(N\)-phenylimide.\(^8\) In the \(^1\)H-NMR spectrum of 5a, the H-2 proton was assigned to the signal at \(\delta\) 5.89 with a large coupling constant (\(J=9.1\) Hz).\(^9\) This indicated that the H-2 and H-3 protons were situated in cis configuration. Similar spectral features were found in the \(^1\)H-NMR spectra of the compounds (5b-5d), indicating that they have the same relative stereochemistry. Therefore, it was apparent that o-azaxylylenes would be generated in situ as intermediates by release of CO\(_2\) and ethanol from the \(N,O\)-diethoxycarbonyl-o-aminobenzyl alcohols and then reacted with \(N\)-
phenylmaleimide as dienes to give the cyclic adducts.

![Diagram](image)

In order to extend the application of this method, 4-substituted styrenes as dienophiles were employed in the intermolecular cycloaddition reaction. *N,O*-diethoxycarbonyl-**o**-aminobenzyl alcohol (1a) was heated with 4-substituted styrenes to give a single isomer of the 2-aryl-1,2,3,4-tetrahydroquinolines (6a-c). In the H-NMR spectra of 6a, 6b, and 6c, the H-2 proton was assigned to the signals at 5.40(t), 5.42(t), and 5.50(t), respectively. This indicated that the aryl group was situated at the 2 position of the tetrahydroquinoline and these reactions proceeded with regioselectivity. The same reaction of 1a was performed with 3,4-dihydro-2H-pyran (8 eq.) in a sealed tube to give a 10% yield of *cis*-10-ethoxycarbonyl-3,4,4a,5,10,10a-hexahydro-2H-pyr[a][6,5-b]quinoline (7).

<table>
<thead>
<tr>
<th>Table</th>
<th>Reaction of <em>N,O</em>-diethoxycarbonyl-<strong>o</strong>-aminobenzyl alcohols with dienophiles</th>
</tr>
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<tbody>
<tr>
<td>entry</td>
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<tr>
<td>1</td>
<td>1a</td>
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<tr>
<td>2</td>
<td>1b</td>
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<td>7</td>
<td>1a</td>
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<td>8</td>
<td>1a</td>
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As a result, the present study showed that unstable **o**-azaxylylenes were generated from *N,O*-diethoxycarbonyl-**o**-aminobenzyl alcohols at low temperature and atmospheric pressure. Since the
intermolecular cycloaddition reaction proceeds with high stereo- and regio-selectivities and the N-ethoxycarbonyl group of the products is easily deprotected, this method is facile for the preparation of 1,2,3,4-tetrahydroquinolines and related compounds.

REFERENCES AND NOTE

6. 2-Ethoxy-4H-3,1-benzoxazine (2)
Colorless viscous oil. 1H-NMR (CDCl3) δ : 1.36 (3H, t, J=7.2 Hz, CH2CH3), 4.38 (2H, t, J=7.2 Hz, CH2CH3), 5.33 (2H, s, Ar-CH2), 6.97 (1H, d, J=7.9 Hz, H-8), 7.05 (1H, t, J=7.9 Hz, H-7), 7.05 (1H, d, J=7.9 Hz, H-5), 7.24 (1H, t, J=7.9 Hz, H-6). MS m/z : CI, 178 (M' +1), 150 (M' +1 -28); EI, 177 (M'), 149 (M'-28).
9. cis-1-Ethoxycarbonyl-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid N-phenylimide (5a)
Colorless crystal, mp 138-139 °C (n-hexane/CH2Cl2). 1H-NMR (CDCl3) δ : 1.19-1.48 (3H, br, CH2CH3), 2.98 (1H, dd, J=7.4, 14.5 Hz, Ar-CH2), 3.21 (1H, d, J=14.5 Hz, Ar-CH2), 3.82 (1H, ddd, J=1.7, 7.4, 9.1 Hz, Ar-CH2CH2), 4.16-4.46 (2H, br, CH2CH3), 5.89 (1H, m, N-CH), 6.83-7.38 (9H, m, Aromatic-H). MS m/z: EI 350 (M'), 278 (M'-72). Anal. Calcd for C29H18N2O4: C, 68.56; H, 5.18 N 8.00. Found C, 68.42; H, 5.24; N, 8.06.

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