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*-Azaxylylenes 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.

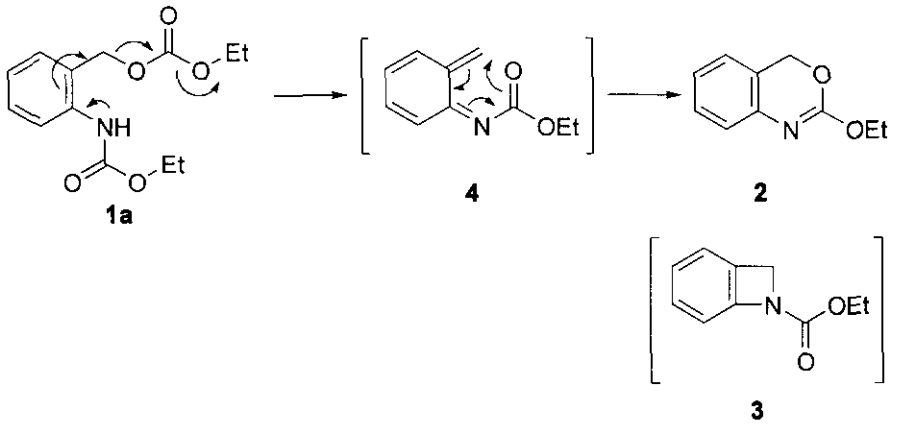
INTRODUCTION

o-Azaxylylenes 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*-aminophenyldiazomethane 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 °C[4] 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*-diethoxylcarbonyl-*o*-aminobenzyl alcohols based on the enhancement in acidity of the hydrogen atom

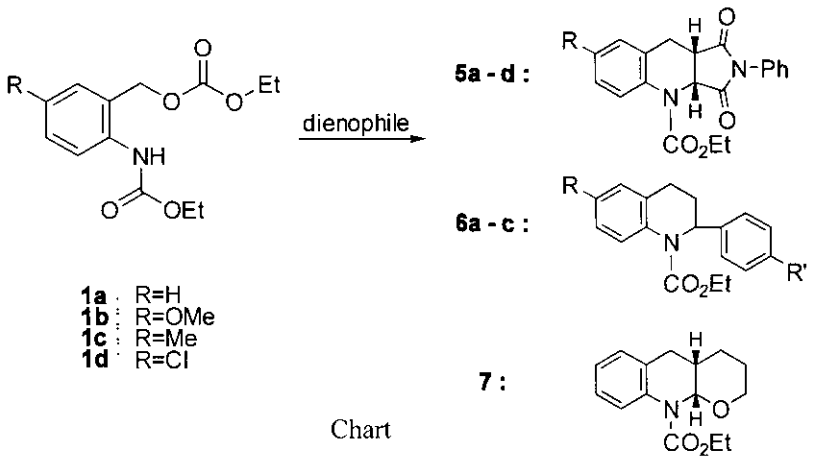
on the amide group. Refluxing in *o*-dichlorobenzene, *N,O*-diethoxycarbonyl-*o*-aminobenzyl alcohol(**1a**) produced 4*H*-3,1-benzoxadine(**2**)(58%). The 4π cycloaddition products of *o*-azaxylylenes, such as benzazetidines(**3**), were not observed. It was postulated that the *o*-azaxylylene(**4**) was formed by elimination of CO_2 and ethanol from **1a**, which causes the 6π electrocyclic reaction to give benzoxazine(**2**).[6]



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*-phenyl-maleimide(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 δ 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.



Chart

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 ^{1}H-NMR spectra of **6a**, **6b**, and **6c**, the H-2 proton was assigned to the signals at δ 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 regioselectivety. The same reaction of **1a** was performed with 3,4-dihydro-2*H*-pyran (8 eq.) in a sealed tube to give a 10% yield of *cis*-10-ethoxycarbonyl-3,4,4a,5,10,10a-hexahydro-2*H*-pyra[6,5-*b*]quinoline(**7**).

Table Reaction of *N,O*-diethoxycarbonyl-*o*-aminobenzyl alcohols with dienophiles

entry	starting material	dienophile	product	yield (%)
1	**1a**	*N*-phenylmaleimide	**5a**	52
2	**1b**	*N*-phenylmaleimide	**5b**	85
3	**1c**	*N*-phenylmaleimide	**5c**	63
4	**1d**	*N*-phenylmaleimide	**5d**	40
5	**1a**	4-*N,N*-dimethylaminostyrene	**6a**	70
6	**1a**	4-methoxystyrene	**6b**	51
7	**1a**	4-nitrostyrene	**6c**	31
8	**1a**	3,4-dihydro-2*H*-pyran	**7**	10

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-selectiveties 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

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6. **2-Ethoxy-4*H*-3,1-benzoxazine (2)**

Colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ : 1.36 (3H, t, *J*=7.2 Hz, $CH_2C\underline{H}_3$), 4.38 (2H, t, *J*=7.2 Hz, $C\underline{H}_2CH_3$), 5.33 (2H, s, Ar-CH_2), 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).

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9. ***cis*-1-Ethoxycarbonyl-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid *N*-phenylimide (5a)**

Colorless crystal, mp 138-139 °C (*n*-hexane/CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ : 1.19-1.48 (3H, br, $CH_2C\underline{H}_3$), 2.98 (1H, dd, *J*=7.4, 14.5 Hz, Ar-CH_2), 3.21 (1H, d, *J*=14.5 Hz, Ar-CH_2), 3.82 (1 H, ddd, *J*=1.7, 7.4, 9.1 Hz, Ar-$CH_2C\underline{H}$), 4.16-4.46 (2H, br, $C\underline{H}_2CH_3$), 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 $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18 N 8.00. Found C, 68,42; H,5.24; N, 8.06.

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