

## A Facile Synthesis of 5,6-Dihydro-4H-1,3-Oxazine Derivatives

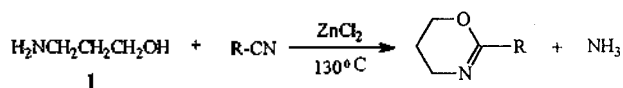
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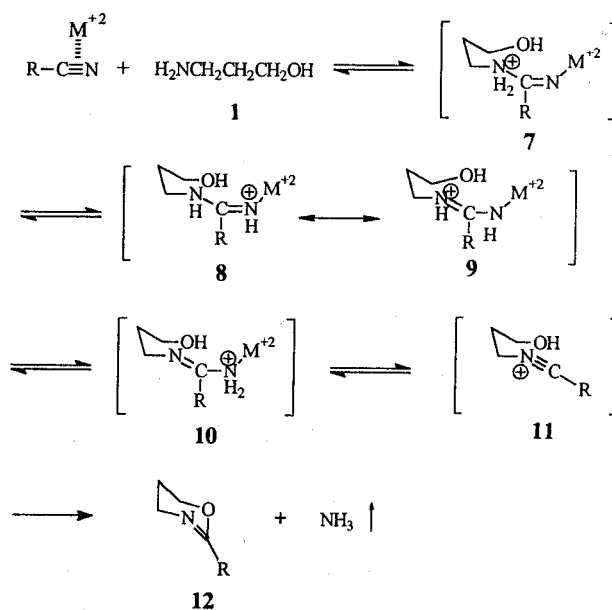
5,6-Dihydro-4H-1,3-oxazine **1** is a six-membered heterocyclic compound containing the imino ether ( $\text{-O-C=N-}$ ) structural unit. MM<sup>+</sup> calculation using the program HYPERCHEM shows that it is planar with a half-chair conformation (Figure 1). 1,3-Oxazines have been reported to be stable to both the strong basic reagents (RLi, RMgX, LAH, etc) and the strong oxidants (CrO<sub>3</sub>, KMnO<sub>4</sub>, etc).<sup>1</sup> They have been used elegantly as important intermediates for the synthesis of unusual aldehydes, such as *trans*  $\beta$ -inoylideneacetaldehyde.<sup>2</sup> A. I. Meyer<sup>3,4</sup> reported that 4,4,6-trimethyl-4H-1,3-oxazine reacted with alkyl halides to afford the 2-alkyloxazines which were hydrolyzed to give rise to a variety of aldehydes,  $\alpha,\beta$ -unsaturated acids or esters depending on work-up procedures. Recently, Saegusa<sup>5</sup> reported the ring opening polymerization of 1,3-oxazines utilizing various Lewis acids as catalyst to produce poly (N-acyltrimethylenimine). Hydrolysis of these polymers provided linear poly(trimethylenimines) which were suitable backbone skeletons for stimuli-sensitive polymers.<sup>6</sup> The stimuli-sensitive polymers change their conformations depending on temperature, pressure, or pH and are actively investigated as potential drug carriers in drug delivery system. After pioneering work by Saegusa, there have been numerous attempts utilizing the ring opening reactions of oxazines to synthesize the proper polymer skeletons with the necessary physical properties of a drug carrier. But difficulties involved in obtaining diverse oxazine derivatives as starting materials and the sensitive reaction conditions for the ring opening polymerization reaction have prevented from exploring their chemistry in detail.

Our ongoing efforts to develop new methodologies<sup>7</sup> for the synthesis of useful monomers for stimuli-sensitive polymers have prompted us to study facile synthetic routes to these important compounds.<sup>11</sup> 5,6-Dihydro-4H-1,3-oxazines have been previously prepared by a modification of Wenker's me-



**Table 1.** The Reaction of 3-Amino-1-propanol and Nitrile in the presence of ZnCl<sub>2</sub>

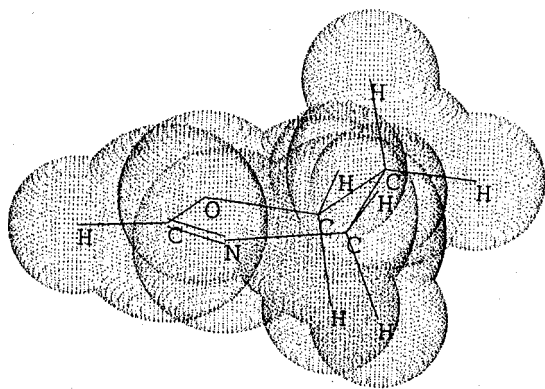
Nitriles	mol Cat./mol Nitrile (Eq.)	Time (hrs.)	Yield (%)
2. Acetonitrile	0.05	24	56.1
3. Propionitrile	0.05	24	68.9
4. Butyronitrile	0.01	48	76.3
5. Valeronitrile	0.01	48	89.9
6. Phenylacetonitrile	0.05	15	57.5



**Scheme 1.** The Proposed Mechanism of 3-Amino-1-Propanol and Nitrile Compounds.

thod<sup>8</sup>: the cyclization of N-acylaminoalcohol or by a thermal reaction between an aminoalcohol and a carboxylic acid at 250 °C.<sup>9</sup> Recently, the synthesis of oxazines from isonitrile with aminoalcohols in the presence of silver cyanide<sup>10</sup> was reported. However, all of these reactions required harsh conditions (high temperature, high pressure, or reactive reagents) and did not provide a general method for the preparation of various oxazines with different substitution groups. We report herein a new general synthetic method to the oxazines utilizing nitriles and aminoalcohols in the presence of a mild Lewis acid as a catalyst. The results are summarized in Table 1.<sup>11</sup>

Typical reaction conditions are the following: 3-Amino-1-propanol **1** (0.133 mole, 10.0 g) was added dropwise to valeronitrile (0.133 mol, 1.00 eq, 13.9 mL, 11.1 g) in the presence of a catalytic amount of zinc chloride (1.33 mmole, 0.01 eq, 180 mg) at ambient temperature under argon atmosphere. The solution was gradually warmed to 130 °C over 48 h with stirring. Vigorous evolution of NH<sub>3</sub> gas was observed during the reaction and served as an indicator for monitoring the



**Figure 1.** Structure of 5,6-Dihydro-4H-1,3-oxazine.

progress of the reaction. Once the gas evolution ceased, the mixture was subjected to vacuum distillation to afford 16.9 g (89.9%) of 2-n-butyl-5,6-dihydro-4H-1,3-oxazine as a colorless oil: bp 62-64 °C(12 mmHg); TLC  $R_f$  0.69 (MeOH/CHCl<sub>3</sub>, 1/9); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 4.20 (t, 2H, -OCH<sub>2</sub>-), 3.21 (t, 2H, =NCH<sub>2</sub>-), 2.05 (t, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>-), 1.75 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.40 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>-), 0.85 (t, 3H, -CH<sub>3</sub>); IR (neat) 1670 (-C=N-), 1080 (-C-O-C-) cm<sup>-1</sup>; EI-MS  $m/z$  (relative intensity) 140 (1.40), 126 (11.25), 112 (24, 76), 99 (100.00), 84 (12.98), 71 (17.86), 57 (14.17), 41 (21.23).

Based upon our observations during the reaction, we proposed the following reaction mechanism (Scheme 1).

The nitrile was activated by the coordination of Lewis acid catalyst (ZnCl<sub>2</sub>, Zn(OAc)<sub>2</sub>, Cu(OAc)<sub>2</sub>) and attacked by 3-amino-1-propanol 1 to form the key intermediate 7. Following prototropic rearrangement and cyclization afford 5,6-dihydro-4H-1,3-oxazine 12 with the expulsion of ammonia irreversibly driving the reaction to completion. All of nitriles and aminoalcohols that we tried afforded moderate to good yields. The yield of the reaction was increased as the carbon of alkyl group in nitrile increased because of the stability of these products at the stage of distillation. Zinc chloride showed better catalytic reactivity than zinc acetate or copper acetate.

In conclusion, a facile synthetic route for various 1,3-oxazine derivatives has been developed. Application of these compounds to the ring opening polymerization is currently under investigation in our laboratory.

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11. All compounds were fully characterized by spectroscopic methods. All yields refer to be isolated compounds.

## The v-J Correlation in the photodissociation of *t*-butyl hydroperoxide at 266 nm

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A detailed study on photodissociation dynamics of polyatomic molecules requires precise measurements of certain experimental observables. Among these experimental observables, internal and translational energy distribution among fragments are scalar properties while angular distribution of the fragments, transition dipole moment, and rotational angular momenta are vector properties. In order to study the dynamics and mechanism of the process in detail, correlations between these vector properties are especially important. Experimentally, if the photofragments absorb or emit radiation of easily accessible spectral region, Doppler profiles of the spectra can provide such valuable information on the photodissociation process.<sup>1-3</sup>

When the photofragments are polyatomic molecules, the fragments have rotational angular momenta  $J$  which have definite relationship with the recoil velocities. Since this  $v$ - $J$  correlation is developed when the fragmentation occurs, the  $v$ - $J$  correlation may appear even when the angular distribution is isotropic. For example, let's consider  $J$  is predominantly aligned parallel to the recoil direction (out-of-plane dissociation). When the Q-branch transition is probed where transition dipole moment of the fragments  $\mu_e$  is parallel to  $J$  in the classical limit, the fragments moving in the direction of propagation of the probe light  $k_p$ , will absorb photons at the wings of the Doppler profiles. On the other hand, the fragments moving in the plane perpendicular to  $k_p$  will absorb at the center of the profiles. Since the absorption takes place when  $\mu_e$  is parallel to  $\epsilon_p(\perp k_p \parallel z)$ , the profile shows a maximum at the center. Contrary to the Q-branch transitions, when the P and R-branch transitions are probed where  $\mu_e$  is perpendicular to  $J$ , the Doppler profiles show the minimum at the center. In this case, the observed Doppler profiles are given by

$$I(v) = (4\pi)^{-1} [1 + \beta_{\text{eff}} P_2(\cos \theta_{v,z}) P_2(\cos \theta_{e,z})]$$

where  $P_2$  is the second order Legendre Polynomials and  $\beta_{\text{eff}}$  includes all the vector correlations.  $\theta_{v,z}$  and  $\theta_{e,z}$  are angles between the propagation direction of the probe light and the recoil velocity, the electric vector of the dissociating light, respectively.

*t*-Butyl hydroperoxide is one of the good candidates to study detailed photodissociation dynamics using the Doppler spectroscopy because most of the available energy is known to be transformed into product translation at 248 nm.<sup>4</sup> The large translational energy of the fragments can provide the Doppler shift wide enough to be measured with conventional laser spectroscopic techniques such as laser induced fluorescence (LIF).

The LIF spectra of the fragment OH have been measured in a flow cell with a conventional pump-probe geometry. The