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Synthesis of multifunctional 4-hydroxymethyl 2-oxazolidinones from glycidyl carbamate derivatives catalyzed by bicyclic guanidine

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ABSTRACT

4-Hydroxymethyl 2-oxazolidinones have been successfully synthesized under mild conditions by the intramolecular cyclization of glycidyl carbamate derivatives with a bicyclic guanidine as the efficient catalyst. This reaction system, which is also applicable to the multifunctional compounds, can provide bi- and tri-functional alcohols having oxazolidinone moieties.

Oxazolidinone derivatives are well known as important compounds in the medical and biochemical fields, because the oxazolidinone moieties and/or derivatives are the cores and intermediates for the biologically active compounds [1–4]. As one of the synthetic methods of oxazolidinone derivatives, the coupling reactions of epoxides and isocyanates have been advanced by the development of various catalysts such as organometallic compounds and organocatalysts [5–15]. In the reaction system, the isomers of 4- and 5-substituted 2-oxazolidinones are able to be prepared by the formation of a five-membered heterocycle from epoxide and isocyanate, whereas 5-substituted 2-oxazolidinones are provided from many epoxide compounds [9–13]. Among them, previous reports have demonstrated that 4-substituted 2-oxazolidinones are selectively prepared from glycidol and isocyanates [12–15]. That is because isocyanates first react with hydroxy group of glycidol to yield glycidyl carbamates and then 4-hydroxymethyl 2-oxazolidinones are prepared by the intramolecular cyclization between carbamate group and epoxide ring, although 5-substituted 2-oxazolidones are formed by the [3 + 2] addition of isocyanates and epoxides in most cases [12–14]. Thus, we expected that multifunctional 4-hydroxymethyl 2-oxazolidinones, which are applicable to alcohol monomers for a new type of polyurethanes and polyesters, can be synthesized by the coupling reaction of multifunctional isocyanates and glycidol. However, we concerned that the one-pot reaction of multifunctional isocyanates and glycidol gave rise to the byproducts and side reaction such as mono-functionalized compounds [16], self-curing of epoxide moiety [17–22], and direct addition reaction of epoxide to isocyanate group [23,24]. In addition, the intramolecular cyclization of glycidyl carbamates require a large amount and/or strong base [25–27], although self-curing of glycidol and multifunctional glycidyl carbamates is promoted in the presence of bases at high temperature [17–22]. Accordingly, we have attempted the intramolecular cyclization of glycidyl carbamate derivatives, which are synthesized from various isocyanates and glycidol as the starting materials, with a strong base at room temperature to yield multifunctional 4-hydroxymethyl 2-oxazolidinones.

At first, we studied catalytic efficiency of four types of amines, *i.e.* 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and DBU-hydroiodide (DBU-HI) [28], for the intramolecular cyclization from *N*-phenyl glycidyl carbamate (**1a**) to 4-(Hydroxymethyl)-3-phenyl-2-oxazolidinone (**2a**). To confirm the catalytic efficiency of those amines, the time conversion of **1a** was monitored in acetone d_6 solvent at 25 °C in the presence of each amine by using ^{1}H nuclear magnetic resonance (NMR). Fig. 1**a** shows the conversion from **1a** to **2a** in the presence of amines within 24 h. **1a** was completely consumed with TBD for 6 h, and converted to **2a** in 100% yield. On the other hand, the reaction of **1a** with MTBD and DBU exhibited moderate yield (72% and 52%, respectively) and the catalytic effect of DBU-HI was scarcely observed even after 24 h. In order to speculate the catalytic cycle of TBD, ^{1}H NMR of stoichiometric mixture of **1a** and TBD was mea-

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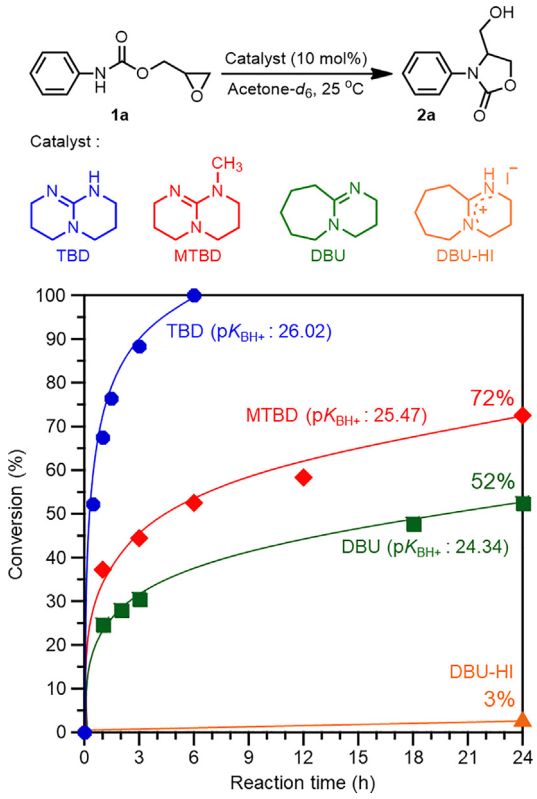


Fig. 1. Time conversion for the intramolecular cyclization from **1a** to **2a** with four types of bicyclic guanidine and amidine derivatives.

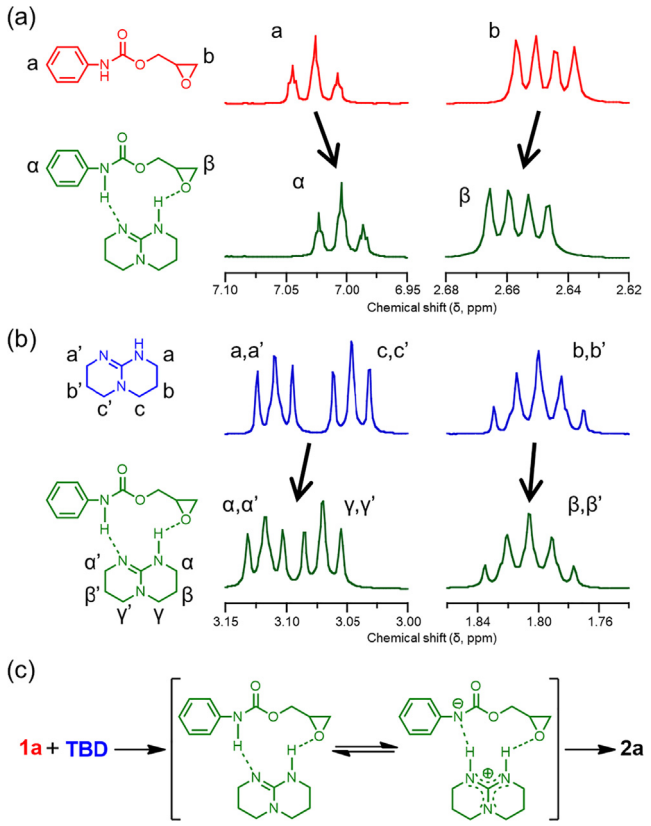
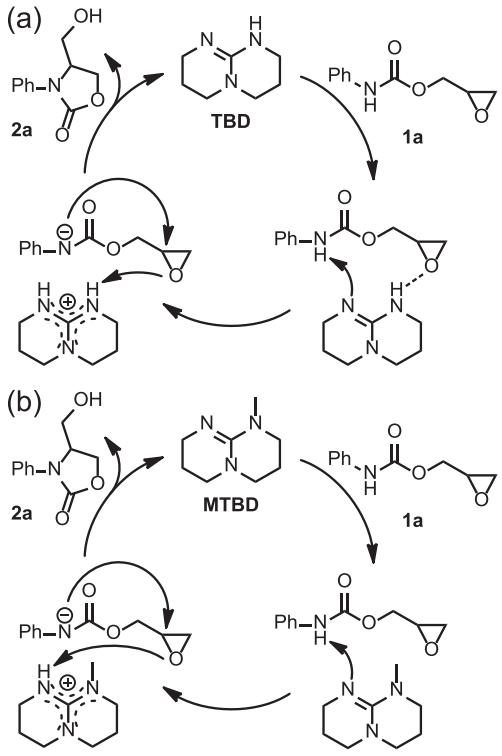


Fig. 2. ^{1}H NMR spectra of stoichiometric mixture of **1a** and TBD. (a) Chemical shift of the protons assigned to phenyl group and epoxy ring. (b) Chemical shift of the protons assigned to TBD. (c) Proposed structure of the intermediate prepared with **1a** and TBD.

sured in acetone d_6 solvent. As shown in Fig. 2**a**, the proton signals assigned to phenyl group shifted to higher magnetic field, whereas that of epoxy ring shifted to lower magnetic field. Fig. 2**b** also showed that the proton signals due to TBD shifted to lower magnetic field. Especially, α proton of phenyl group and γ proton of TBD in the **1a**-TBD intermediate shifted significantly compared to the others.

In addition, –NH peak of **1a**, which was observed at 8.74 ppm, completely disappeared in NMR spectra of the mixture containing TBD (Figs. S1 and S2). These NMR spectra suggested that specific intermolecular interaction between **1a** and TBD such as a hydrogen bond followed by a proton transfer from **1a** to TBD as shown in Fig. 2**c**. In recent years, a large number of reports has demonstrated that TBD is significantly efficient catalyst for not only base-mediated organic reactions [29–32] but also polymer synthesis such as ring-opening polymerization of cyclic monomers [33,34] and polyhydroxyurethanes by a non-isocyanate method [35–37]. Among them, some reports have revealed a bifunctional catalytic system as the strong basicity of the cyclic guanidine moiety and the activator based on a hydrogen bond of the active proton [38,39]. Accordingly, the assumed catalytic system for intramolecular cyclization of **1a** with TBD was shown in Scheme 1**a**. In the first step, an acidic proton on the carbamate moiety of **1a** is transferred to TBD, and simultaneously an epoxide moiety of **1a** is also activated due to a hydrogen bond with an active proton of TBD. Next, the activated epoxide undergoes nucleophilic attack from the activated nitrogen atom on the carbamate to form 2-oxazolidinone structure, and simultaneously one of two active protons of TBD is also transferred to the oxygen atom on epoxy moiety to form a hydroxy methyl group on the 4-position of oxazolidinone structure. The intramolecular cyclization of **1a** with MTBD and DBU also proceeds according to the similar reaction mechanism as shown in Scheme 1**b**, because ^{1}H NMR spectra of the mixtures

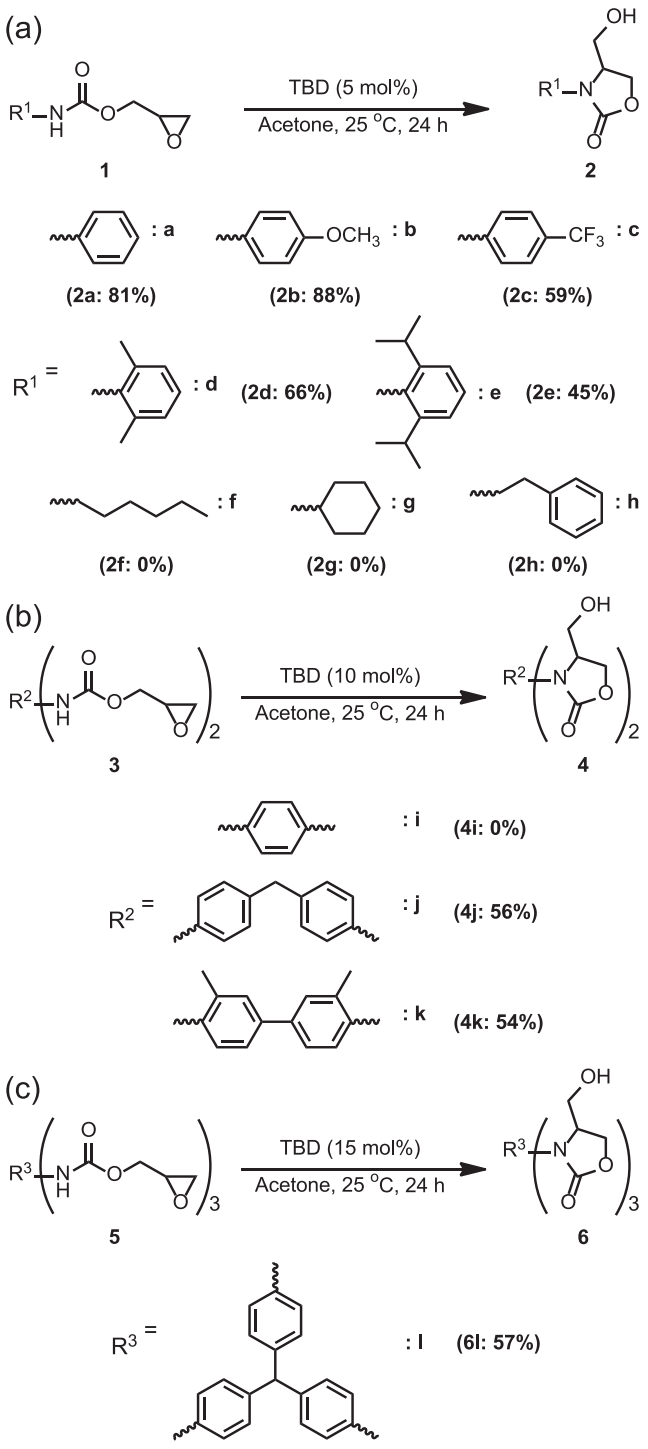


Scheme 1. Speculated mechanism of the intramolecular cyclization from **1a** to **2a** catalyzed with (a) TBD and (b) MTBD.

containing MTBD and DBU showed complete disappearance of –NH peak of **1a** as well as that of TBD (Fig. S2). Nevertheless, the catalytic efficiency of MTBD and DBU is insufficient compared to that of TBD. The reason could be explained that MTBD and DBU without containing active protons are not able to sufficiently activate an epoxy moiety of **1a**, and also are not able to smoothly give rise to the proton transfer from carbamate to epoxy moieties. These results indicate that superior efficiency of TBD catalyst is due to specific intermolecular interaction between **1a** and TBD based on a hydrogen bond. Therefore, the intramolecular cyclization of **1a** with TBD immediately proceeds together with a proton transfer from carbamate moiety to epoxy ring *via* guanidinium cation of TBD. Moreover, a basicity of the catalysts might also depend on the catalytic efficiency, because the reaction rate of the intramolecular cyclization of **1a** increased with increasing pK_{BH+} values (Fig. 1) [40,41]. On the other hand, an inactivity of DBU-HI is because of fairly weak interaction between **1a** and DBU-HI. In fact, the broaden peak due to –NH proton of **1a** was observed at 8.80 ppm in ^{1}H NMR spectrum of the mixture containing DBU-HI, although ^{1}H NMR spectra of the mixtures containing the other catalysts never showed the peak of –NH proton in the same range (Fig. S2). This result indicates that the intramolecular cyclization scarcely proceeds together with a proton transfer from **1a** to DBU-HI at least under room temperature.

Next, the substituent effects such as electronic and steric effects for the intramolecular cyclization of glycidyl carbamates having various functional groups were examined with TBD according to Scheme 2a. The intramolecular cyclization of **1b** having a methoxy group as an electron donating group proceeded in a high yield, whereas **1c** having a trifluoromethyl group as an electron withdrawing group exhibited a lower yield than the reaction from **1a** and **1b**. As mentioned above, the intramolecular cyclization of phenyl glycidyl carbamate proceeds due to the nucleophilic attack of the electron-rich nitrogen atom on the carbamate moiety to the epoxide moiety. Therefore, the phenyl glycidyl carbamates having electron donating groups exhibits a high yield in this reaction system. Moreover, the phenyl glycidyl carbamates having bulky groups such as *ortho*-dimethyl (**1d**) and diisopropyl (**1e**) groups afforded the target compounds in moderate yields, because the nucleophilic attack of the nitrogen atom on the carbamate moiety to the epoxide moiety is restricted owing to the steric hindrance of bulky groups. The reaction of glycidyl carbamates having aliphatic groups such as *n*-hexyl (**1f**), cyclohexyl (**1 g**), and benzyl (**1 h**) groups were also performed under the same conditions, however, all of the glycidyl carbamates were never converted to 2-oxazolidinone derivatives. This is because the acidity of the N—H proton on aliphatic glycidyl carbamates is fairly lower than that of aromatic glycidyl carbamates owing to the electron donating effect from the aliphatic functional groups [12–13]. On the basis of these results, the synthesis of bifunctional 2-oxazolidinone derivatives was attempted with TBD from aromatic bifunctional glycidyl carbamates (**3**) according to Scheme 2b.

As well as the reaction system of monofunctional phenyl glycidyl carbamates, bifunctional glycidyl carbamates having the aromatic groups such as methylene bisphenyl (**3j**) and dimethylbiphenyl (**3 k**) groups afforded successfully the bifunctional 4-hydroxymethyl 2-oxazolidinones (**4**) in moderate yields. On the other hand, the bifunctional glycidyl carbamate having the *para*-phenylene group (**3i**) was never converted to the target compound, because the lone pairs on the nitrogen atoms of both carbamate moieties were delocalized owing to the conjugate effect between phenylene and carbamate units. Furthermore, the reaction of the trifunctional glycidyl carbamate having triphenylmethane group (**5 l**) was also performed under standard conditions according to Scheme 2c, and the trifunctional 4-hydroxymethyl 2-oxazolidinones (**6 l**) was successfully synthesized in 57% yield.



Scheme 2. Synthesis of 4-hydroxymethyl 2-oxazolidinone derivatives with TBD in acetone at 25 °C for 24 h from, (a) glycidyl carbamates having various functional groups, (b) bifunctional glycidyl carbamates having aromatic groups, and (c) trifunctional glycidyl carbamate.

In summary, we achieved a synthesis of 4-hydroxymethyl 2-oxazolidinones having various functional groups by the intramolecular cyclization of glycidyl carbamates with a catalytic amount of amine at room temperature. Among the amine catalysts, TBD was significantly effective catalyst for the intramolecular cyclization of glycidyl carbamates because the carbamate and

epoxide moieties of glycidyl carbamates were simultaneously activated by the bicyclic guanidine moiety of TBD. Furthermore, multifunctional 4-hydroxymethyl 2-oxazolidinone derivatives were also synthesized successfully from bi- and tri-functional glycidyl carbamates in this reaction system. Such multifunctional alcohols having an oxazolidinone structure are expected as a new type of monomers for functional polymer materials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153086.

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