A novel Lewis acid-promoted enyne cycloisomerization of triester-substituted alkenes†

Shoko Yamazaki,*[a] Kuriko Yamada,[a] Tetsuya Otsubo,[a] Masayo Haruna,[a] Emiko Kutsuwa[a] and Hatsue Tamura[b]

[a] *Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan. E-mail: yamazaks@nara-edu.ac.jp*

[b] *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 1-16 Machikaneyama, Toyonaka, Osaka 560-0043, Japan*

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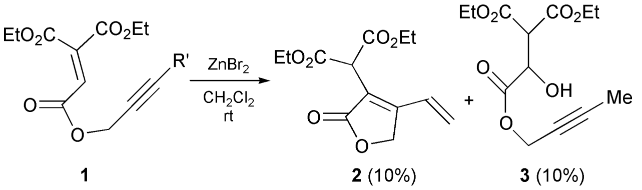
A novel cycloisomerization reaction of enynes 4 in the presence of $ZnBr_2$ and THF (1 eq.) in CH_2Cl_2 at −40 °C gave *exo*-methylenic 1,3-dienes 5 in moderate to good yield.

Lewis acid-promoted reactions are an important part of modern synthetic chemistry.[1] Recently, prototropic cycloisomerization reactions of enynes and dienes have been recognized as atom-economic tools to construct rings, and transition metal-catalyzed cycloisomerizations in particular have received much attention.[2] However, only a few examples of Lewis acid-promoted cycloisomerizations (intramolecular ene reactions) have been reported so far.[3,4a,b]

The design of a Lewis acid-promoted enyne cyclization requires that a highly electrophilic alkene (or alkyne) has coordination sites for a Lewis acid and that the other component (alkyne or alkene) works as a nucleophile. Alkenes with three ester groups are considered to be highly electrophilic and very reactive towards nucleophilic olefins,[5] and they may react intramolecularly with alkynes which are relatively unreactive nucleophiles.[6]‡ We thus examined Lewis acid-promoted intramolecular cyclization of the designed triester-substituted alkene **1**. Reaction of **1** in the presence of $ZnBr_2$ at rt gave cyclized product **2** and H_2O-adduct **3** in 45% and 10% yields, respectively (eqn. (1)).

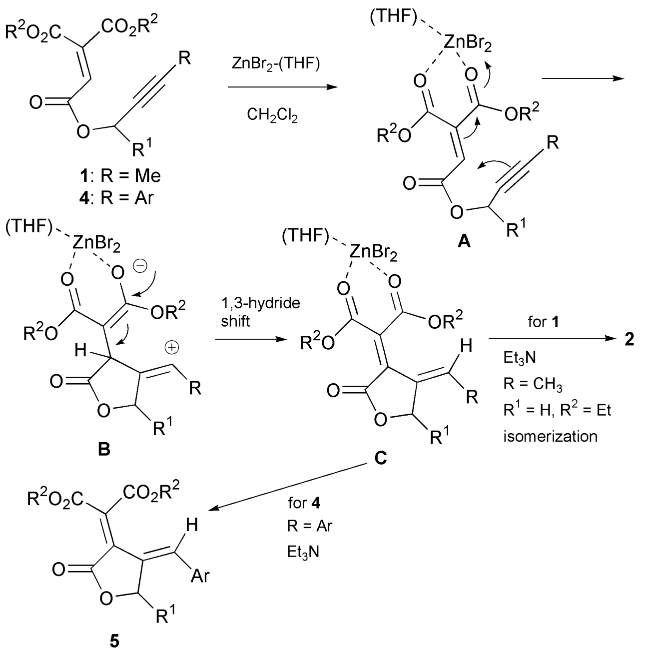


(1)

The formation of **2** can be explained as shown in Scheme 1.§ Nucleophilic attack of the alkyne moiety to the electrophilic olefin complexed with $ZnBr_2$ in **A** gives intermediate **B**.¶ A 1,3-hydride shift then leads to complex **C**, which isomerizes and then forms diene **2** with Et_3N. The formation of hydrated product **3** is presumed to result from attack by trace amounts of water on complex **A**.

If the isomerization step in **C** is prevented, *exo*-methylenic 1,3-dienes should be the primary products in this process. The enyne **4**, which is prevented from undergoing isomerization due to the lack of a proton, was designed and Lewis acid mediated reactions examined. After several conditions were examined (see below), reaction of **4** in the presence of $ZnBr_2$ (1.2 eq.) and THF (1 eq.) in CH_2Cl_2 at −40 °C for 17–19 h gave *exo*-methylenic 1,3-dienes **5** in 29–67% yields (eqn. (2), Table 1).‖ The γ-lactone structure of **5** was suggested by the presence of a characteristic C=O absorption (1771–1779 cm^{-1}). ^1H, ^{13}C, $^1H/^{13}C$-HSQC, HMBC and NOESY spectra were in agreement with the lactone structure drawn in eqn. (2). The crystal structure of **5a** was elucidated by X-ray diffraction analysis (Fig. 1).** The diene is slightly twisted from the plane in order to reduce steric repulsion between the ester and HPhC= groups; the torsion angle of the diene moiety (∠C5-C3-C2-C12) is 21.9°. This *cisoid* diene may be effective as an acceptor in the inverse electron demand Diels–Alder reaction (see below).

$$\mathbf{4} \xrightarrow[CH_2Cl_2, -40\ °C, 17–19\ h]{ZnBr_2–THF} \mathbf{5} \qquad (2)$$



Scheme 1

Table 1 Cycloisomerization of **4** to **5**

Substrate[a]	R¹	R²	Ar	Product (yield)
4a	H	Et	Ph	**5a** (67%)
4b	H	Et	*p*-Tol	**5b** (58%)
4c	H	Et	*p*-MeO-C_6H_4	**5c** (41%)
4d	Me	Et	Ph	**5d** (53%)
4e	*n*-Propyl	Et	Ph	**5e** (46%) (**4e** recovered 36%)
4f	H	Me	Ph	**5f** (29%)
4g	H	^iPr	Ph	**5g** (50%)[b]

[a] All reactions were carried out using 0.30–0.58 mmol of **4**, 1.2 eq. of $ZnBr_2$, and 1.0 eq. of THF at 0.41 M for **4** in CH_2Cl_2 at −40 °C for 17–19 h, unless otherwise noted. [b] THF was not added. Addition of THF gave **5g** in 40% yield along with recovered **4g** (24%).

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† Electronic supplementary information (ESI) available: experimental procedures and spectral data for described compounds and crystallographic data for **5a**. See http://www.rsc.org/suppdata/cc/b0/b008103p/

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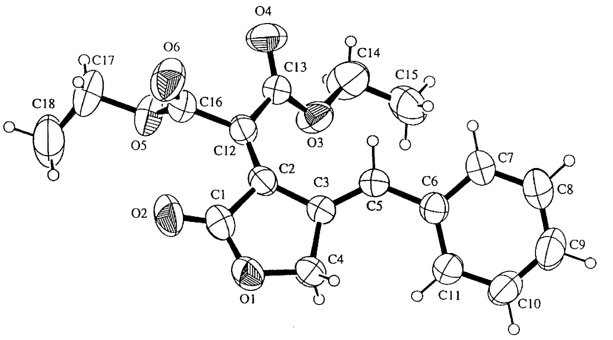


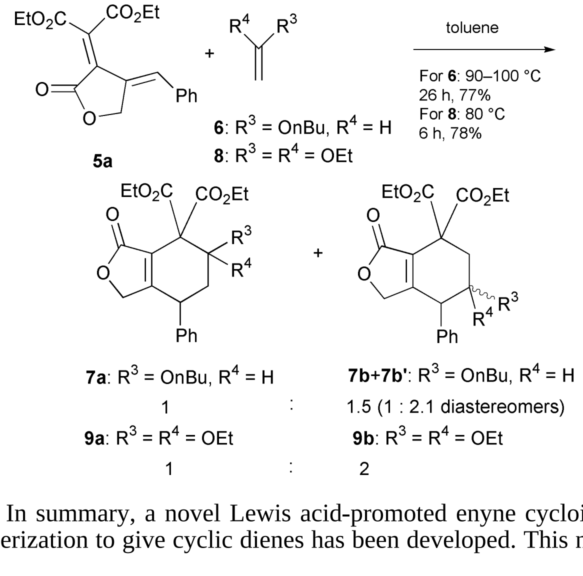
Fig. 1 ORTEP drawing of **5a** (50% probability ellipsoids). Selected bond lengths (Å) and torsion angle (°): C1–C2 = 1.499(3); C2–C3 = 1.460(2); C3–C4 = 1.501(2); C1–O1 = 1.344(2); O1–C4 = 1.444(2); C2–C12 = 1.345(2); C3–C5 = 1.344(2); ∠C5–C3-C2–C12 = 21.9(3). More detailed structure data are given in the supplementary data.

With **4a**,**b**, the yield of **5** decreased when THF was omitted from the reaction (for **5a** to 11–36%, for **5b** to 11–25%).†† The effect of THF is presumed to be that coordination of THF to Zn adjusts the strength of the Lewis acid and prevents side reactions.‡‡ For **4g**, the reaction without THF gave a slightly better yield (see Table 1).

Use of ZnI_2–THF instead of $ZnBr_2$–THF gave **5a** in 62% yield. Use of $SnCl_4$ (−78 °C) or $ZnCl_2$–THF (−40 °C) gave **5a** in lower yield (24–-39% including inseparable complex mixtures). The reaction of **4a** with $ZnBr_2$–THF was also performed at a higher temperature (0 °C to rt), however, the yield of **5a** decreased (32%), probably because of the instability of the diene product. The reaction of **4a** using 0.3 eq. of $ZnBr_2$–THF afforded 19% of **5a** along with recovered **4a** (62%), therefore the reaction requires a stoichiometric amount of Lewis acid.§§

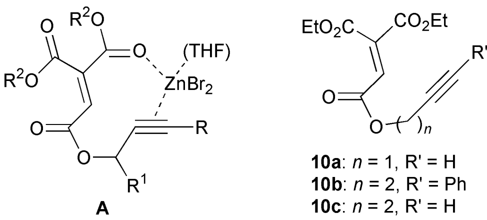
Thermal reactions of **4a** and **1** (CH_3CN, 80 °C, 24 h or toluene, 110 °C, 24 h) without Lewis acid only afforded complex mixtures along with recovered starting materials (38–87%). A RuClH(CO)$(PPh_3)_3$-catalyzed reaction (toluene, 110 °C, 7 h) of **4a** was examined but did not proceed.[8]

Only a few examples of synthesis of heterocycles by cycloisomerization using transition metal catalysts have been reported.[9] Therefore, the present method should provide an efficient alternative to transition metal-catalyzed cycloisomerizations. Also, the product cyclic dienes are electron-deficient and suitable for cycloadditions such as inverse electron demand Diels–Alder reaction[10] and transition metal-catalyzed [4 + 3] cycloadditions.[11] The inverse electron demand Diels–Alder reactions of **5a** with the electron rich dienophiles **6** and **8** were thus examined (eqn. (3)). C–C bond formation proceeds readily, however, the observed regio- and stereoselectivity was low.¶¶



(3)

In summary, a novel Lewis acid-promoted enyne cycloisomerization to give cyclic dienes has been developed. This new reaction provides a highly efficient means to prepare electron-deficient cyclic dienes. The application of this methodology towards the construction of carbocycles and diverse heterocycles is under investigation.



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Notes and references

‡ Thermal ene reactions[6a,b] and $FeCl_3$-promoted chlorinated cyclizations[6c] of allylic and propargylic esters of ethylenetricarboxylic acid have been reported.

§ The alternative mechanism is that **1** undergoes an ene reaction initially to give a cyclic allene that rearranges to **2**.

¶ The coordination of a Lewis acid to a C≡C bond was reported recently.[12] The intermediate **A** (Scheme 1) can be drawn as shown above.

‖ Cyclizations were also examined using **10a**–**c** as substrates. Using similar conditions, only starting material was recovered.

** *Crystal data*: $C_{18}H_{18}O_6$, M = 330.34, monoclinic, a = 8.1206(3), b = 10.5914(3), c = 19.7984(7) Å, β = 100.513(1)°, V = 1674.2(1) Å^3, T = 296 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) = 0.099 mm^{-1}, number of reflections measured = 4062, number of independent reflections = 3845 (R_{int} = 0.025), R, R_w = 0.047, 0.052 for 2473 observed reflections ($I > 2\sigma(I)$). CCDC 182/1839. See http://www.rsc.org/suppdata/cc/b0/b008103p/ for crystallographic files in .cif format.

†† The reaction of **4a** in THF as a solvent did not proceed.

‡‡ Use of propylene oxide instead of THF in the reaction of **4a** gave **5a** in lower yield (28%), along with recovered **4a** (21%). The combination of Lewis acid and Lewis base is used in some Lewis acid-mediated reactions.[7]

§§ Formation of cyclic dienes is in marked contrast with the $FeCl_3$-promoted reaction of dimethyl ester analog of **1** and **4d** giving chlorinated cyclization products.[6c] Investigation of the difference in Lewis acids is underway.

¶¶ The stereochemistries of **7a**, **7b** and **7b′** were tentatively assigned as shown in the supplementary information by the observed NOE's.

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