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SYNTHESIS OF TRISUBSTITUTED 4-OXEPANONES BY THE LEWIS ACID-PROMOTED THREE-COMPONENT RING-EXPANSION REACTION OF CYCLOPROPAPYRANONES, SILYL ENOLATES AND GLYOXYLATES

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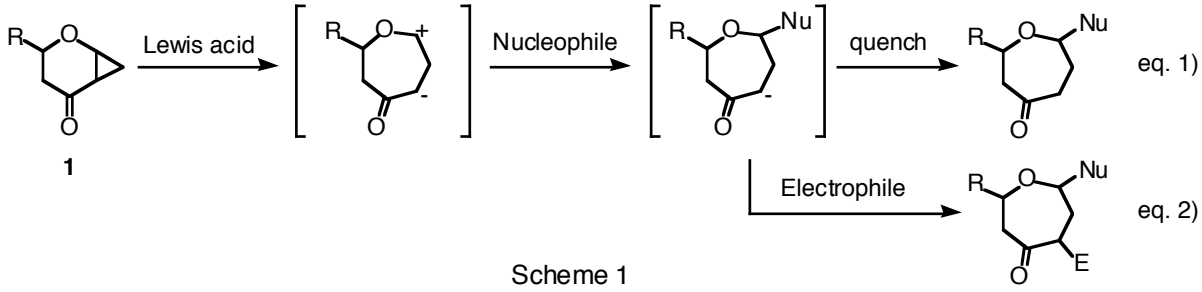
Abstract – In the presence of $SnCl_4$, cyclopropapyranones easily reacted with silyl enolates and ethyl glyoxylate to give the trisubstituted 4-oxepanones in good yields.

The seven-membered oxacycles are an important class of oxygenated heterocyclic compounds that have attracted the attention of organic chemists and biochemists due to their biological activities and occurrence in natural products.[1] Various methods for the construction of the seven-membered oxacycles have been reported.[2]

We recently reported the synthesis of 2,7-disubstituted 4-oxepanones by the Lewis acid-promoted ring-opening addition reactions of cyclopropapyranones (**1**) with silyl enolates as nucleophiles (eq. 1, Scheme 1).[3] From these reactions, the *trans*-isomers were mainly obtained.

We expected that the treatment of a cyclopropapyranone derivative with a Lewis acid readily generates a cyclic 1,3-zwitterion,[4] which can react with both silyl enolates and appropriate electrophiles to produce the trisubstituted 4-oxepanones (eq. 2). A cyclopropane with donor and acceptor substituents at the vicinal position on the cyclopropane ring is an equivalent of a ring-opened 1,3-zwitterion. Therefore, cyclopropapyranone (**1**) is recognized as a good reactant for electrophiles and nucleophiles.[5] We now report the synthesis of trisubstituted 4-oxepanones by the Lewis acid-promoted three-component ring-expansion reaction of cyclopropapyranones as the synthetic equivalents of cyclic 1,3-zwitterions.



Scheme 1

In our previous study, we have found that when the ring-opening addition reaction of the cyclopropapyranone (**1a**) with ketene silyl acetal (**2a**) was carried out, the use of $SnCl_4$ (0.3 eq.) as a Lewis acid gave the best result and the corresponding oxepanone (**5a**) was obtained in 71% yield with

moderate *trans*-selectivity.[3] The reaction of **1a**, **2a** with ethyl glyoxylate (**3a**)[6] was chosen as the model, and several reaction conditions were examined. Cyclopropapyranone (**1a**) and ketene silyl acetal (**2a**) in CH_2Cl_2 were reacted with $SnCl_4$ (0.3 eq.) at –78 °C for 10 min, and the resulting mixture was treated with ethyl glyoxylate (**3a**) to give the desired oxepanone (**4**) in 22% yield. However, the adduct (**5a**) was mainly obtained because the aldol type reaction as the second step did not completely occur using a catalytic amount of $SnCl_4$ (Table 1, Entry 1). In contrast, it was found that the use of a stoichiometric amount of $SnCl_4$ for the addition of **3a** resulted in an improvement of the chemical yield of the desired oxepanone from 22% to 48% (Entry 2). We also found that the addition of powdered molecular sieves 4A[7] (MA 4A) to the reaction mixture was effective for obtaining the desired product in good yield (77% yield) although the role of MS 4A is not clear (Entry 3).[8] In this reaction, the order of the addition of the reagents dramatically influenced the yield. Namely, the addition of **2a** to the reaction mixture of **1a** and **3a** led to the formation of a complex mixture not containing the desired product.

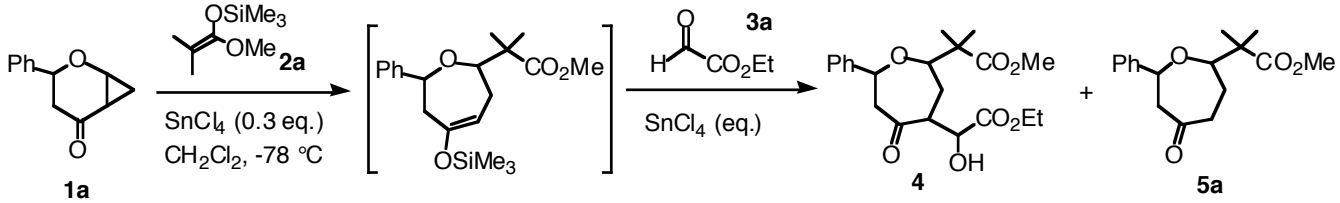
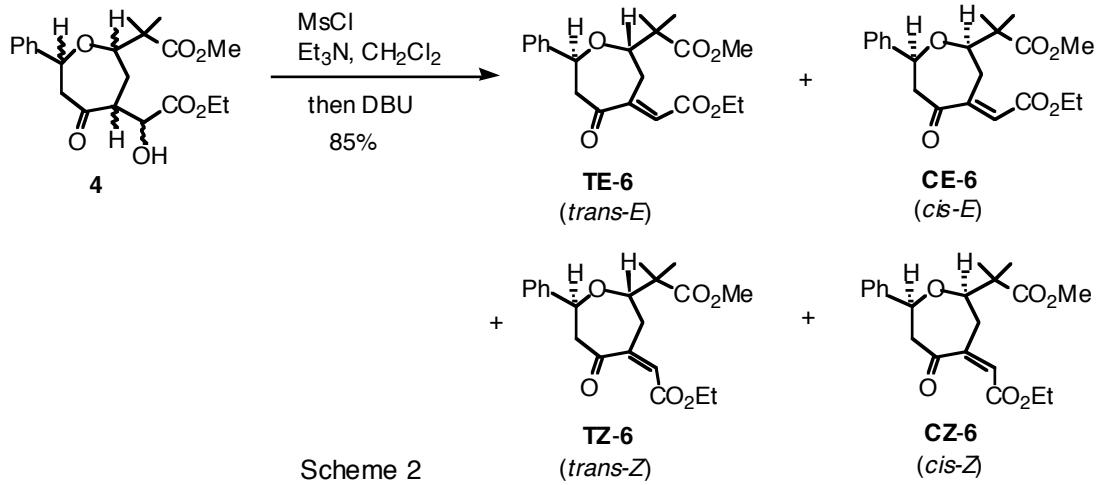


Table 1. Three-component reaction of **1a**, **2a** and ethyl glyoxylate (**3a**)

Entry	$SnCl_4$ (eq.)	MS 4A	Yield **4**/%	Yield **5a**/%
1	0	-	22	53
2	1.0	-	48	21
3	1.0	+	77	0

The obtained product (**4**) could be converted into four stereoisomeric oxepanones (**6**) by the mesylation of the hydroxy group of **4** followed by an elimination reaction (Scheme 2). The ratio of the stereoisomers (TE : CE : TZ : CZ) was determined as 71:19:8:2 by ^{1}H-NMR, and the stereochemical assignment of the isomers was established by the analysis of their NOE experiments (Figure 1). It was noted that in the ^{1}H-NMR spectrum the olefinic proton signal of the *Z*-isomers (TZ- and CZ-**6**) appeared at high field compared with that of the *E*-isomers (TE- and CE-**6**).



Scheme 2

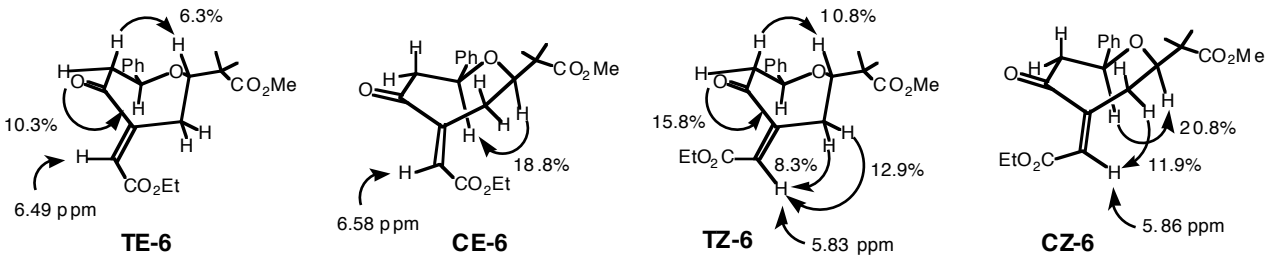


Figure 1

Several examples of the three-component ring-expansion reaction of **1a** were examined and these results are summarized in Table 2 (Entries 1-4). For the reaction of **1a**, **2a**, and methyl glyoxylate (**3b**),[6] a similar tendency was observed (Entry 2). As the nucleophiles, silyl enol ethers (**2b**, **2c**) also reacted with **1a** under similar conditions to give the corresponding oxepanones (**8**,[9] **9**), even though a slight decrease in yield was observed compared to that of the reactions of the ketene silyl acetal (**2a**) (Entries 3, 4).

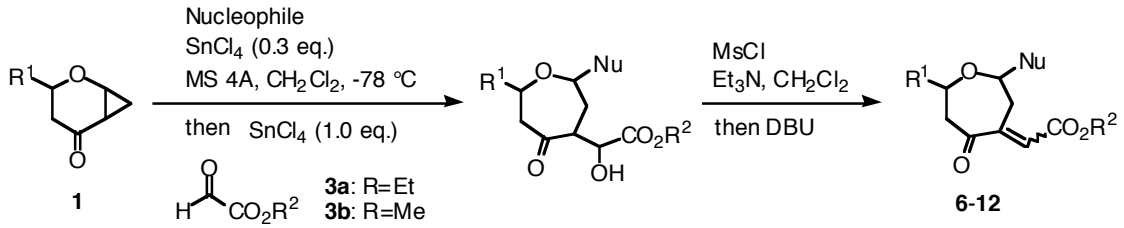
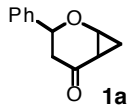
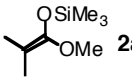
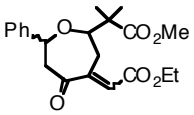
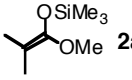
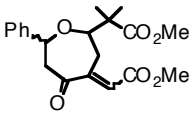
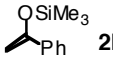
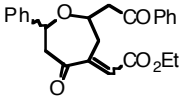
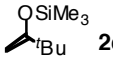
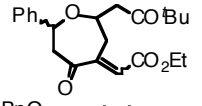
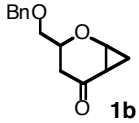
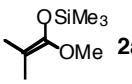
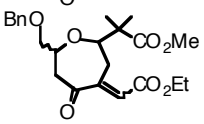
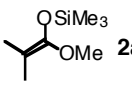
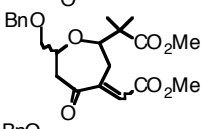
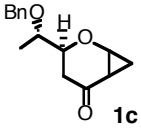
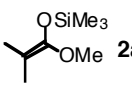
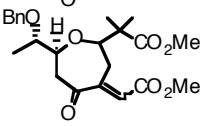


Table 2. Three-component reaction of cyclopropapyranones (**1**), silyl enolates (**2**) and glyoxylates (**3**)

Entry	Cyclopropane	Nucleophile	Glyoxylate	Product	Yield[a]/% (TE : CE : TZ : CZ)[b]
1	 **1a**	 **2a**	**3a**	 **6**	66 (71 : 19 : 8 : 2)
2	**1a**	 **2a**	**3b**	 **7**	57 (73 : 17 : 5 : 5)
3	**1a**	 **2b**	**3a**	 **8**	48 (78 : 13 : 8 : 1)
4	**1a**	 **2c**	**3a**	 **9**	26[c] (81 : 10 : 8 : 1)
5	 **1b**	 **2a**	**3a**	 **10**	57 (81 : 12 : 5 : 2)
6	**1b**	 **2a**	**3b**	 **11**	58 (80 : 10 : 9 : 1)
7	 **1c**	 **2a**	**3b**	 **12**	66 (80 : 15 : 5 : -[d])

[a] Total yield from **1**. [b] The ratio of the srereoisomers was determined by 500 MHz ^{1}H-NMR. [c] Disubstituted 4-oxepanone (**5**) was also obtained in 45%. [d] Not detected.

In order to extend the scope and synthetic utility of this methodology, the reactions of other cyclopropapyranones under similar conditions were examined. The reactions of **1b**,[3] **2a**, and alkyl glyoxylates (**3a**, **3b**) gave the corresponding oxepanones (**10**,[9] **11**) in good yields (Entries 5, 6). Under similar conditions, the chiral cyclopropapyranone (**1c**)[3] also reacted with **2a** and **3b** to give the corresponding chiral oxepanone (**12**) in 66% yield with moderate stereoselectivity (Entry 7). In all the reactions, the *trans-E*-isomer was mainly obtained.

In summary, we have demonstrated that the $SnCl_4$-promoted three-component ring-expansion reaction of cyclopropapyranones, silyl enolates, and glyoxylates smoothly proceeded to afford the corresponding trisubstituted 4-oxepanones in good yields with moderate stereoselectivity. Further applications of this reaction are now under investigation in our laboratory.

A typical experimental procedure is described for the reaction of cyclopropane (**1a**), ketene silyl acetal (**2a**), and ethyl glyoxylate (**3a**): To a mixture of **1a** (75 mg, 0.4 mmol), **2a** (104 mg, 0.6 mmol), and molecular sieves 4A (150 mg) in CH_2Cl_2 (3 mL) was added $SnCl_4$ (1.0 *M* sol. in CH_2Cl_2, 0.12 mL, 0.12 mmol) at –78 ˚C under an argon atmosphere. After the mixture was stirred for 10 min, **3a** (82 mg, 0.8 mmol) and $SnCl_4$ (1.0 *M* sol. in CH_2Cl_2, 0.4 mL, 0.4 mmol) were successively added. After being stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through a celite pad, and the filtrate was concentrated. The residue was dissolved in THF-1*N* HCl (2:1, 4 mL) and stirred for 10 min at 0 ˚C. The mixture was then extracted with ether. After the combined organic layers were dried and concentrated, the residue was chromatographed on silica gel to produce **4** (121 mg, 77%). To a solution of **4** (117 mg, 0.3 mmol), Et_3N (121 mg, 1.2 mmol), and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (4 mL) was added MsCl (69 mg, 0.6 mmol) in CH_2Cl_2 (0.5 mL) at 0 ˚C. After being stirred for 1 h at rt, DBU (91 mg, 0.6 mmol) was added to the mixture and refluxed for 2 h. After an extractive work up and purification by silica gel column chromatography, the corresponding oxepanone (**6**) was obtained in 85% yield (95 mg).

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7. MS 4A was used after drying at 150 ˚C for 6 h under reduced pressure.
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9. The stereochemical assignment of the compounds (TE-**8**, CE-**8**, and TZ-**10**) was also mainly established by analysis of their NOE experiments (see figure below).