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LEWIS ACID-MEDIATED RING EXPANSION REACTION OF BENZO[*b*]CYCLOPROPA[*e*]PYRAN-7-OL ACETATES: FACILE SYNTHESIS OF 2-ALKYL SUBSTITUTED 2,3-DIHYDRO-1-BENZOXEPINS

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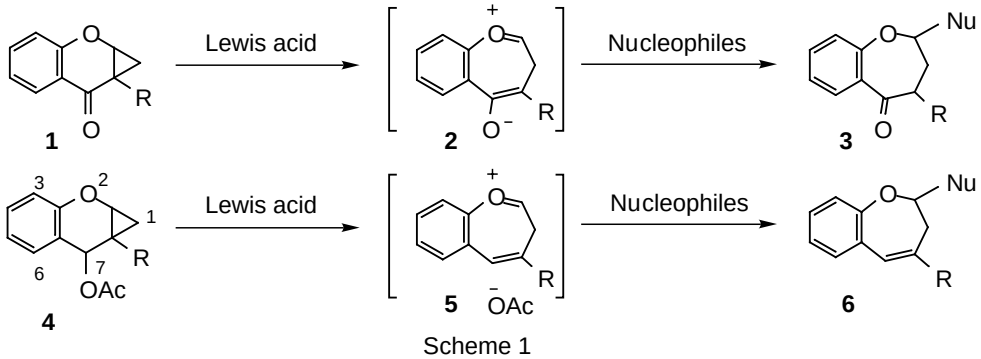
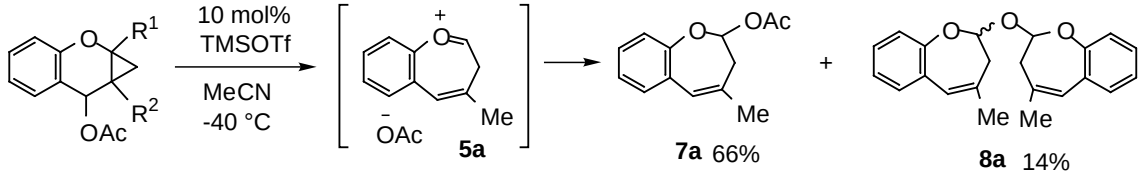
Abstract - In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), benzo[*b*]cyclopropa[*e*]pyran-7-ol acetates easily reacted with silyl enol ethers to give 2-alkyl substituted 2,3-dihydro-1-benzoxepin derivatives in good yields.

Cyclopropanes having an electron-withdrawing or donating group are susceptible to ring opening reactions.[1] We have recently reported that benzocyclopropapyranone (**1**) was transformed into a ring-opened 1,3-zwitterion (**2**) in the presence of a Lewis acid, and that **2** reacted with silyl enol ethers to give the ring expanding product (**3**).[2] During the course of our study to find further applications of benzocyclopropapyrans, we examined the reaction of 7-acetoxybenzo[*b*]cyclopropa[*e*]pyran (**4**) with nucleophiles. We expected that **4** was transformed into a cyclic oxonium ion intermediate *via* removal of the acetoxy group by the action of a Lewis acid, and that the intermediate may react with nucleophiles to provide several 2-alkyl substituted 2,3-dihydro-1-benzoxepins (**6**) as the ring-expanded products (Scheme 1).[3] Although there are many examples of the synthesis of 2,3-dihydro-1-benzoxepins,[4] only a few examples are reported for the construction of those having an alkyl group at the 2-position on the ring, and no systematic study has been reported.[5] We now report the synthesis of 2-alkyl substituted 2,3-dihydro-1-benzoxepins by the Lewis acid-promoted reaction of 7-acetoxybenzo[*b*]cyclopropa[*e*]pyran derivatives (**4**) with silyl enol ethers *via* a cyclic oxonium ion.[6] As the reactions of **4**, only a few solvolytic ring opening reactions have been reported.[7] To our knowledge, there has been no publication concerning the carbon-carbon bond forming reactions of **4** under the Lewis acid-promoted conditions.



Scheme 1

7-Acetoxybenzo[*b*]cyclopropa[*e*]pyran (**4**) was synthesized by the $NaBH_4$ reduction of the corresponding benzocyclopropapyranone derivatives,[7,8] prepared from chromones and dimethyloxosulfonium methylide, followed by the treatment of the resulting alcoholes with Ac_2O/Et_3N in the presence of a catalytic amount of DMAP. First, the reactivity of 7-acetoxy-1,1a,7,7a-tetrahydro-7a-methylbenzo[*b*]-cyclopropa[*e*]pyran (**4a**) by the action of a Lewis acid was examined. A solution of a catalytic amount of TMSOTf in MeCN was added to a solution of **4a** in MeCN at -40 °C to give the 2-acetoxy-2,3-dihydro-4-methyl-1-benzoxepin (**7a**) and the dimeric compound (**8a**) in 66% and 14% yields, respectively (Scheme 2). A similar tendency was observed with $TiCl_4$ as the Lewis acid. It was found that **4a** is very unstable under acidic conditions and was converted into **7a** even when **4a** was processed by silica gel column chromatography. From this result, we considered that **4a** is the equivalent of a cyclic oxonium ion (**5a**) under the Lewis acid-promoted conditions.



4a: R^1=H, R^2=Me, **4b**: R^1=H, R^2=Ph
4c: R^1=Ph, R^2=H, **4d**: R^1=Me, R^2=Me

Scheme 2

We next examined the carbon-carbon bond-forming reactions of the cyclopropane (**4**) with silyl enol ethers as the nucleophile. The reaction of **4a** with silyl enol ether (**9**) was chosen as the model. When the reaction was performed in the presence of $TiCl_4$ in CH_2Cl_2 at -40 °C, however, **7a** was obtained as the major product and the desired adduct was obtained in low yield (Table 1, Entry 1). In order to improve of the yield of **6b**, we examined the various reaction conditions such as the addition order of the reagents, solvent, and Lewis acid. As a Lewis acid, TMSOTf worked nicely as compared to a typical Lewis acid such as $TiCl_4$ or $SnCl_4$ (Entries 4 and 5). The use of MeCN as a polar solvent increased the

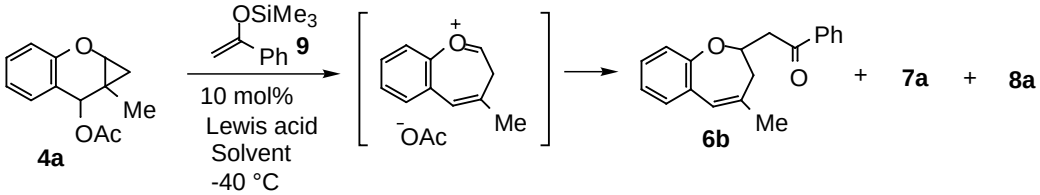


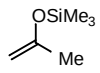
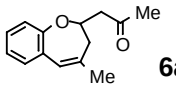
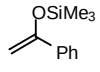
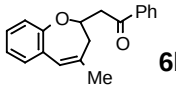
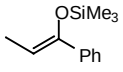
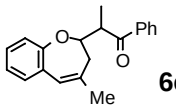
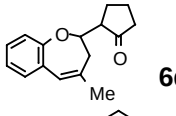
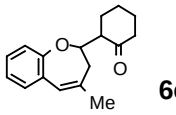
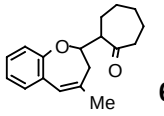
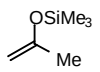
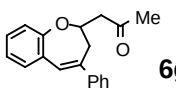
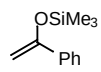
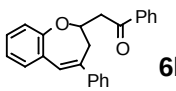
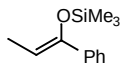
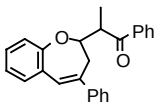
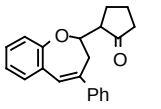
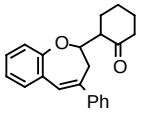
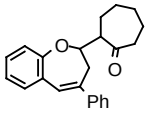
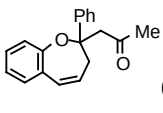
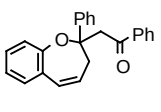
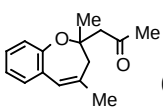
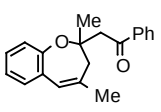
Table 1. Effects of Lewis Acid and Solvent

Entry	Lewis acid	Solvent	Products (%)[a] 6b	7a	8a
1	$TiCl_4$	CH_2Cl_2	2	30	6
2	$SnCl_4$	CH_2Cl_2	15	58	0
3	$SnCl_4$	MeCN	60	27	0
4	TMSOTf	CH_2Cl_2	66	trace	7
5	TMSOTf	MeCN	99 (66)[b]	0 (31)[b]	0

[a] Isolated yield. [b] To a solution of **4a** and **9** in MeCN was added a solution of TMSOTf in MeCN.

yield of the desired adduct compared with the use of CH_2Cl_2 (Entries 4 and 5). It was also found that the order of the addition of the reagents dramatically influenced the yield. While the desired adduct (**6b**) was produced in quantitative yield by the slow addition of a dilute solution of **4a** in MeCN to a mixture of **9** and TMSOTf in MeCN, the decrease in the yield of **6b** from 99% to 66% was observed and **7a** was obtained in 31% yield when TMSOTf was added to a solution of **4a** and **9** in MeCN (Entry 5).[9] Several examples of the TMSOTf-catalyzed ring expansion reactions were examined and the results are summarized in Table 2. As expected, the reaction of **4a** with several silyl enol ethers smoothly proceeded to give the corresponding benzoxepins in high yields (Entries 1~6). As for the cyclopropanes, **4b** as well as **4a** effectively reacted with silyl enol ethers to give the benzoxepins in good yields (Entries 7~12). Under the same reaction conditions, the cyclopropane (**4c**) having a phenyl group at the 1a-position also gave the 2,2-disubstituted benzoxepins (**6m** and **6n**) in moderate yields (Entries 13 and 14). Furthermore, the dialkyl substituted cyclopropane (**4d**) reacted with silyl enol ethers to give the 2,2,4-trialkyl-2,3-dihydro-1-benzoxepins in good yields (Entries 15 and 16).

Table 2. Reaction of 7-Acetoxy-1,1a,7,7a-tetrahydrobenzo[*b*]cyclopropa[*e*]pyrans (**4**) with Silyl Enol Ethers[a]

Entry	4	Silyl enol ether	Product	Yield (%)[b]
1	**4a**		 **6a**	81
2	**4a**		 **6b**	99
3	**4a**		 **6c**	81[c]
4	**4a**		 **6d**	91[c]
5	**4a**		 **6e**	89[c]
6	**4a**		 **6f**	80[c]
7	**4b**		 **6g**	68
8	**4b**		 **6h**	85
9	**4b**		 **6i**	97[c]
10	**4b**		 **6j**	82[c]
11	**4b**		 **6k**	83[c]
12	**4b**		 **6l**	85[c]
13	**4c**		 **6m**	70
14	**4c**		 **6n**	36
15	**4d**		 **6o**	52
16	**4d**		 **6p**	70

[a] All reactions were carried out in dry MeCN at -40 °C in the presence of 10 mol% of TMSOTf. [b] Isolated yield. [c] Two diastereomers were formed in the ratio of 1 : 1.

In summary, we have demonstrated that the TMSOTf-catalyzed ring opening addition reactions of **4** with silyl enol ethers smoothly proceeded to afford the corresponding 2,3-dihydro-1-benzoxepins in good yields. We are now investigating the Lewis acid-mediated ring expansion reactions of **4** with various nucleophiles, and the results will be reported in due course.

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9. General procedure for the reaction of **4** with silyl enol ethers: This is exemplified by the reaction of **4a** with silyl enol ether (**9**) using TMSOTf as a Lewis acid. To a stirred solution of silyl enol ether (**9**) (192 mg, 1 mmol) and TMSOTf (11 mg, 0.05 mmol) in MeCN (4 mL) was dropwise added a solution of **4a** (109 mg, 0.5 mmol) in MeCN (1 mL) over a 30 min period at -40 °C under an argon atmosphere. After being stirred for 30 min, the reaction was quenched at the same temperature by adding saturated aqueous $NaHCO_3$ (2 mL). The mixture was vigorously stirred for 10 min and allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (20 mL x 3), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-AcOEt = 10 : 1) to give the benzoxepin (**6b**) (138 mg, 99%).