

Facile Synthesis of Lactones from Silyl  $\omega$ -Siloxycarboxylates  
Using *p*-Trifluoromethylbenzoic Anhydride and a Catalytic Amount of Active Lewis Acid

Teruaki MUKAIYAMA, Jun IZUMI, Mitsutomo MIYASHITA, and Isamu SHIINA

Department of Applied Chemistry, Faculty of Science,  
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

The lactonization of silyl  $\omega$ -siloxycarboxylates is successfully carried out under mild conditions in good to high yields by using *p*-trifluoromethylbenzoic anhydride and a catalytic amount of active acidic species generated in situ from  $\text{TiCl}_4$  and  $\text{AgClO}_4$ .

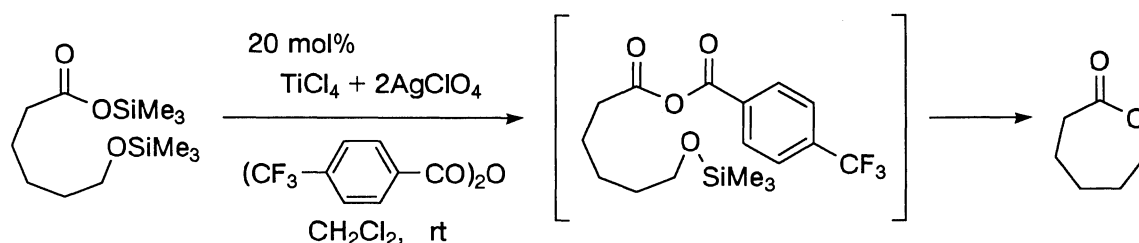
Recently, the chemical synthesis of natural macrolides made great progress owing to the advancement of efficient methods for the ring closure to macrocyclic lactones.<sup>1)</sup> Several methods of macrolactonization have been developed independently from several laboratories.<sup>2)</sup> For example, Corey and Nicolaou introduced a route to synthesize lactones via 2-pyridinethiol ester prepared by the the oxidation-reduction condensation.<sup>3)</sup> 1-Alkyl-2-halopyridinium salts which were developed in our laboratory have been employed as useful reagents for the preparation of lactones in the coexistence of a tertiary amine.<sup>4)</sup> Further, Yamaguchi *et al.* developed a convenient method for the synthesis of lactones via mixed anhydrides using 2,4,6-trichlorobenzoyl chloride and tertiary amines.<sup>5)</sup> According to these procedures, elevated temperatures were generally required; for example, the precursors of lactones, functionally activated derivatives of  $\omega$ -hydroxy carboxylic acids, were refluxed in xylene or toluene solution for a long period. Therefore, it is required to develop an efficient new method of macrolactonization which proceeds under mild condition.

On developing useful synthetic methods for the preparations of carboxylic esters, *S*-phenyl carbothioates and phenyl carboxylates from nearly equimolar amounts of the corresponding starting materials with *p*-trifluoromethylbenzoic anhydride,<sup>6)</sup> it was suggested that the macrolactonization of silyl  $\omega$ -siloxycarboxylates should take place at room temperature via similar mixed anhydrides by the promotion of a catalytic amount of active Lewis acid.

First, in order to examine reactivities of a silyl carboxylate and an alkyl silyl ether toward the anhydride, the following experiment was carried out. To the suspension of a catalytic amount of titanium(IV) salt, generated in situ from 1 mol of  $\text{TiCl}_4$  and 2 mol of  $\text{AgClO}_4$  in dichloromethane, the solution of *p*-trifluoromethylbenzoic anhydride in dichloromethane and the mixture of trimethylsilyl 3-phenylpropionate and 1-methyl-3-phenylpropyl trimethylsilyl ether in dichloromethane were successively added. If the reaction of the alkyl silyl ether proceeds faster than that of the silyl carboxylate, 1-methyl-3-phenylpropyl *p*-trifluoromethylbenzoate should result as a major product. Since 1-methyl-3-phenylpropyl 3-phenylpropionate, which was derived from the mixed anhydride generated in situ from the silyl carboxylate and the anhydride, was exclusively obtained, the reaction of the silyl carboxylate to form the mixed anhydride took place faster than that of the alkyl silyl ether to form the

corresponding *p*-trifluoromethylbenzoate. Therefore, it was expected that the application of this method to silyl  $\omega$ -siloxycarboxylate would provide a new and effective intramolecular ring closure reaction.

Taking the preparation of  $\epsilon$ -caprolactone as a model, the solutions of trimethylsilyl 6-trimethylsiloxyhexanoate and *p*-trifluoromethylbenzoic anhydride in dichloromethane were successively added to the suspension of 20 mol% of titanium(IV) salt, generated in situ from 1 mol of  $\text{TiCl}_4$  and 2 mol of  $\text{AgClO}_4$  in dichloromethane, and the desired lactone was isolated in 41% yield. Then, in order to improve the yield, the mixture of trimethylsilyl 6-trimethylsiloxyhexanoate and *p*-trifluoromethylbenzoic anhydride in dichloromethane was added to the suspension of the catalyst. The reaction smoothly proceeded at room temperature to afford the desired lactone in 71% yield, and the corresponding diolide was not obtained at all.



Next, this method was applied to syntheses of several large ring lactones. Reaction conditions were examined by taking the reaction of trimethylsilyl 12-trimethylsiloxydodecanoate as a model, and it was shown that a catalyst generated in situ from  $\text{TiCl}_4$  and  $\text{AgClO}_4$  gave a good result (Table 1, entry 6). The above result suggests that the perchlorate anion is more effective compared with the triflate anion as a counter anion of the catalyst for the present intramolecular ring closure reaction. The ratio of the yield of lactone to diolide also increased when the reaction was carried out under highly diluted concentration (entry 7).

Table 1. Effect of Reaction Conditions

<div style="display: flex; justify-content: space-around; align-items: center;"> <div> <math>\text{Me}_3\text{SiO}-(\text{CH}_2)_{10}-\text{OSiMe}_3</math>              solvent, rt         </div> <div> <math>\xrightarrow[\text{solvent, rt}]{10 \text{ mol\% catalyst, } (\text{CF}_3-\text{C}_6\text{H}_4-\text{CO})_2\text{O}}</math> </div> <div>  lactone         </div> <div>+</div> <div>  diolide         </div> </div>						
Entry	Catalyst	Solvent	Concentration / mM	Addition time / h	Yield / % <sup>a)</sup>	
					lactone	diolide
1	$\text{TiCl}_4 + 2\text{AgClO}_4$	toluene	60	4	27	27
2	$\text{TiCl}_4 + 2\text{AgClO}_4$	$\text{CH}_2\text{Cl}_2$	50	4	31	24
3	$\text{Sn}(\text{OTf})_2$	$\text{CH}_2\text{Cl}_2$	6	18	50	18
4	$\text{TiCl}_4 + 2\text{AgSbF}_6$	$\text{CH}_2\text{Cl}_2$	6	18	60	18
5	$\text{TiCl}_4 + 2\text{AgOTf}$	$\text{CH}_2\text{Cl}_2$	6	18	63	9
6	$\text{TiCl}_4 + 2\text{AgClO}_4$	$\text{CH}_2\text{Cl}_2$	6	18	71	12
7	$\text{TiCl}_4 + 2\text{AgClO}_4$	$\text{CH}_2\text{Cl}_2$	4	31	75	7

a) Isolated yield.

Several examples of the present lactonization reaction are demonstrated in Table 2. In entries 1, 5 - 7, the corresponding lactones were obtained in high yields at room temperature under mild conditions. For example, the dodecanolide and the pentadecanolide were isolated in 75% and 89% yields, respectively, at room temperature.<sup>7)</sup> On the other hand, the corresponding diolides were obtained as major products in the case of producing medium size lactones (entries 2, 3).

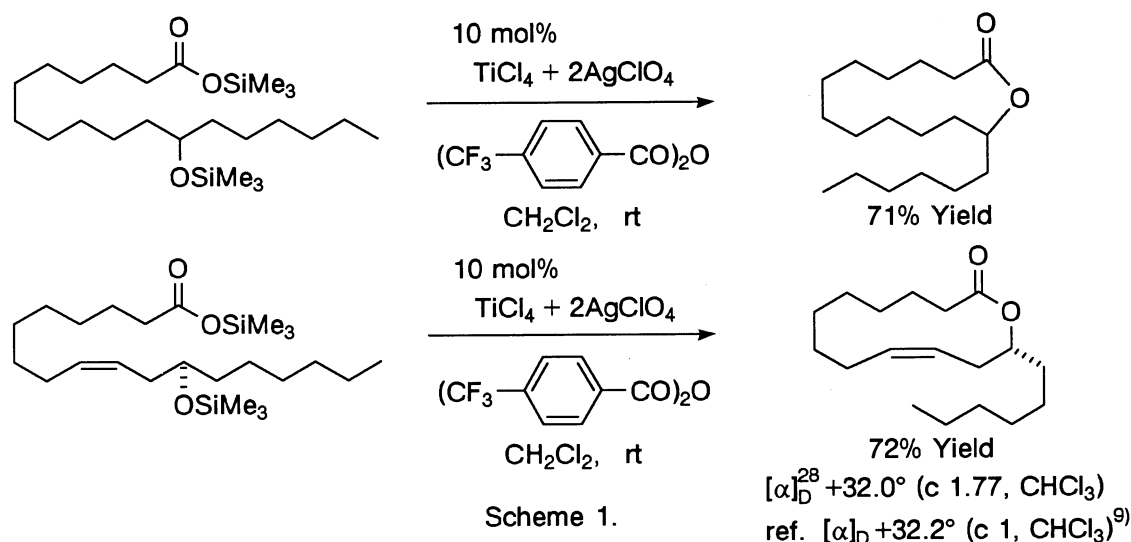
Table 2. Synthesis of lactones

Entry	n	Concentration / mM	Addition time / h	Yield / % <sup>a)</sup> lactone	(Ring number) diolide
1	4	50	at once	70 ( 7)	0 (14)
2	5	5	31	0 ( 8)	50 (16)
3	6	5	31	0 ( 9)	40 (18)
4	7	4	31	33 (10)	47 (20)
5	8	5	31	70 (11)	23 (22)
6	10	4	31	75 (13)	7 (26)
7	13	4	31	89 (16)	4 (32)

a) Isolated yield. Each lactone was identified by GC-MS.

Trimethylsilyl  $\omega$ -trimethylsilyloxycarboxylates were prepared from  $\omega$ -hydroxy carboxylic acids on treatment with trimethylsilylchloride and triethylamine in dichloromethane and purified by distillation. A typical experimental procedure is described for the synthesis of pentadecanolide: to a suspension of  $\text{AgClO}_4$  (0.08 mmol) in dichloromethane (90 ml), was added a solution of  $\text{TiCl}_4$  (0.04 mmol) in toluene (0.08 ml). Then, a mixture of trimethylsilyl 15-trimethylsilyloxypentadecanoate (0.4 mmol) and *p*-trifluoromethylbenzoic anhydride (0.4 mmol) in dichloromethane (10 ml) was slowly added to the suspension over 31 h at rt. The reaction mixture was further stirred for 3 h at rt, and then quenched with aq. sat.  $\text{NaHCO}_3$ . After usual work up, the crude product was purified by column chromatography on silica gel to afford lactone and diolide in 89% and 4% yields, respectively.

The reactions of silyl derivatives of secondary  $\omega$ -hydroxy carboxylic acids afforded the corresponding lactones in high yields at room temperature as shown in Scheme 1. It is noteworthy to refer that (+)-(Z)-9-octadecen-12-olide is exclusively obtained in high yield without accompanying isomerization of the double bond and racemization.<sup>8)</sup>



Thus, the lactonization of silyl  $\omega$ -siloxycarboxylates proceeded under extremely mild conditions to afford the corresponding lactones in good to high yields except in cases of 8, 9, and 10 membered lactones, wherein diolides were obtained as major products. Further investigation of catalytic lactonization of silyl  $\omega$ -siloxycarboxylates is now in progress.

#### References

- 1) "Recent Progress in the Chemical Synthesis of Antibiotics," ed by G. Lukacs and M. Ohno, Springer-Verlag, Berlin (1990).
- 2) For review see: E. Haslam, *Tetrahedron*, **36**, 2409 (1980). Acidic conditions; (CF<sub>3</sub>CO)<sub>2</sub>O: W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, **1952**, 1447. AgClO<sub>4</sub>, AgBF<sub>4</sub>: H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, **57**, 2661 (1974). Hg(OCOCF<sub>3</sub>)<sub>2</sub>: S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975). BF<sub>3</sub>·Et<sub>2</sub>O: L. T. Scott, *Synthesis*, **1976**, 738. <sup>n</sup>Bu<sub>2</sub>SnO: K. Steliou, M. A. Poupart, *J. Am. Chem. Soc.*, **105**, 7130 (1983). (<sup>n</sup>Bu<sub>2</sub>ClSnOSn<sup>n</sup>Bu<sub>2</sub>OH)<sub>2</sub>: J. Otera, T. Yano, Y. Himeno, and H. Nozaki, *Tetrahedron Lett.*, **27**, 4501 (1986). Hydrous ZrO<sub>2</sub>: H. Kuno, M. Shibagaki, K. Takahashi, I. Honda, and H. Matsushita, *Chem. Lett.*, **1992**, 571.
- 3) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); E. J. Corey and D. J. Brunelle, *Tetrahedron Lett.*, **1976**, 3409.
- 4) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, **1976**, 49; T. Mukaiyama, K. Narasaka, and K. Kikuchi, *ibid.*, **1977**, 441; K. Narasaka, K. Maruyama, and T. Mukaiyama, *ibid.*, **1978**, 885.
- 5) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
- 6) T. Mukaiyama, I. Shiina, and M. Miyashita, *Chem. Lett.*, **1992**, 625; T. Mukaiyama, M. Miyashita, and I. Shiina, *ibid.*, **1992**, 1747.
- 7) According to the method of Corey and Nicolaou, the lactones were isolated in 66% and 80% yields, respectively. In the case of using 1-methyl-2-chloropyridinium iodide, the lactones were isolated in 69% and 84% yields, respectively.
- 8) In this reaction, phosphate buffer (pH=7) was used as a reagent for quenching.
- 9) H. Yamada, S. Ohsawa, T. Sugai, H. Ohta, and S. Yoshikawa, *Chem. Lett.*, **1989**, 1775.

(Received February 19, 1993)