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A CONVENIENT METHOD FOR THE PREPARATION OF MACROLIDES FROM TRIMETHYLSILYL ω-TRIMETHYLSILYLOXYCARBOXYLATES

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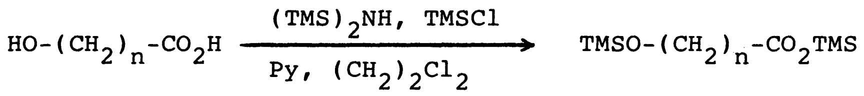
Several macrolides were readily prepared from trimethylsilyl ω-trimethylsilyloxycarboxylates by the use of dipropylboryl trifluoromethanesulfonate (triflate) as a catalyst in good yields.

The lactonization of ω-hydroxycarboxylic acids is one of the most important methods for the preparation of macrolides. Though there have been many reports on the lactonization methods including our recent one,[1] little has been reported about the lactonization of O,O'-diprotected ω-hydroxycarboxylic acid derivatives. Herein we report a very facile method for the preparation of macrolides from O,O'-disilylated ω-hydroxycarboxylic acids.

Trimethylsilyl ω-trimethylsilyloxycarboxylates (2a-d) were prepared in good yields according to the general method[2] as shown in the following.



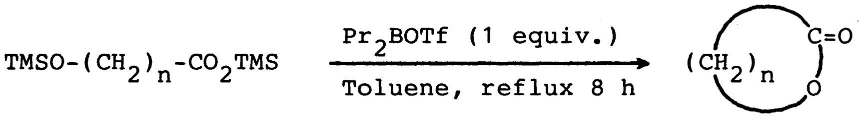
$$HO\text{-}(CH_2)_n\text{-}CO_2H \xrightarrow[\text{Py, }(CH_2)_2Cl_2,\ 60\ ^\circ C,\ \text{overnight}]{(TMS)_2NH,\ TMSCl} TMSO\text{-}(CH_2)_n\text{-}CO_2TMS$$

1a-d 2a-d[3a,b]

2a, n=11, 72%
2b, n=12, 82%
2c, n=14, 97%
2d, n=15, 87%

It has been known that trimethylsilyl triflate (TMSOTf) is a powerful Lewis acid[4] and works as a useful catalyst for a condensation reaction liberating hexamethyldisiloxane instead of water in a dehydration reaction.[5] Treatment of 2a with TMSOTf gave the expected monolide (3a) in 30% yield in refluxing toluene accompanying the diolide (4a) in 28% yield. When a small amount of boron trifluoride etherate was added to the reaction, the yield of 3a was remarkably increased as seen in Table 1. From the fact that boron trifluoride etherate alone did not work effectively, a boron triflate such as F_2BOTf seemed to be formed in the above reaction. Therefore, several dialkylboryl triflates were examined whether they act as a catalyst for the lactonization of 2a. The experimental results are summarized in Table 1.

Consequently, it was found that the use of dipropylboryl triflate in refluxing toluene is the best way for the lactonization of 2a (Entry No.5). Other macrolides (3b-d) were also prepared in good yields in a similar way as shown in below.



2a-d 3a-d[3b]

3a, n=11, 83%
3b, n=12, 89%
3c, n=14, 94%
3d, n=15, 85%

Table 1. Lactonization of 2a Using A Catalyst in Refluxing Toluene[6]

Entry No.	Catalyst	Reflux time/h	Isolated yield/% Monolide 3a	Diolide 4a
1	TMSOTf (1 equiv.)	8	30	28
2	$Et_2O{\cdot}BF_3$ (1.2 equiv.)	10	trace	trace
3	TMSOTf (1.1 equiv.) + $Et_2O{\cdot}BF_3$ (0.2 equiv.)	10	70	30
4	Et_2BOTf[7] (1 equiv.)	8	54	19
5	Pr_2BOTf[7] (1 equiv.)	8	83	17
6	Bu_2BOTf[7] (1 equiv.)	8	50	5

A typical procedure is described for the synthesis of 3a : To a refluxing solution of dipropylboryl triflate (48 mg, 0.2 mmol) in dry toluene (50 ml) was added a solution of 2a (72 mg, 0.2 mmol) in dry toluene (40 ml) dropwise with a mechanically driven syringe in a period of 6 h under nitrogen. After refluxing for an additional 2 h, 10% of $NaHCO_3$ aqueous solution and ethyl acetate were added at room temperature. The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to a preparative TLC (SiO_2, hexane : ether = 8 : 1, v/v) to afford the monolide (3a, 33 mg, 83%) and the diolide (4a, 7 mg, 17%).

Further studies on the detailed mechanism and on the scope and limitation of the present method for the preparation of macrolides are now in progress.

References

1) A. Ahmed, N. Taniguchi, H. Fukuda, H. Kinoshita, K. Inomata, and H. Kotake, Bull. Chem. Soc. Jpn., 57, 781 (1984).

2) C. C. Sweeley, W. W. Wells, and R. Bentley, Methods Enzymol., 8, 95 (1966).

3) a) Distilled with a glass tube oven (Sibata, GTO-250). Bp (oven temperature (°C)/1 Torr) : 2a (190-200), 2b (ca. 230), 2c (ca. 230), 2d (>250) ; b) All of the products gave satisfactory NMR, IR, and Mass spectra for the proposed structures.

4) H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West, and G. Simchen, Synthesis, 1982, 1.

5) T. Tsunoda, M. Suzuki, and R. Noyori, Tetrahedron Lett., 21, 1357 (1980) ; R.Noyori, S. Murata, and M. Suzuki, Tetrahedron, 37, 3899 (1981).

6) Toluene was the best solvent within the examined ones.

7) These compounds were prepared according to the reported procedure : T. Mukaiyama and T. Inoue, Chem. Lett., 1976, 559. Bp (°C/Torr) : Et_2BOTf (54-56/21), Pr_2BOTf (57-59/4), Bu_2BOTf (47-48/0.9).

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