Mercuric Triflate·3TMU Catalyzed Cyclization of ω-Alkynoic Acids and Synthesis of a Naturally Occurring γ-Methylene-γ-lactone

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Received 20 December 2005

Abstract: $Hg(OTf)_2$·3TMU showed efficient catalytic activity for the cyclization of ω-alkynoic acid to give ω-methylene-ω-lactone in excellent yield, and the procedure was efficiently applied for the synthesis of naturally occurring γ-methylene-γ-lactone. The absolute structure of the natural product was established by this synthesis.

Key words: catalytic cyclizations, carboxylic acids, alkynes, lactones, mercury

We found that mercury(II) trifluoromethanesulfonate [mercuric triflate, hereafter $Hg(OTf)_2$][1] and $Hg(OTf)_2$-tetramethylurea (hereafter TMU) complex showed potent catalytic activity for the hydration of terminal alkynes to give methyl ketones,[2] hydroxylative 1,6-enyne cyclization to give exomethylene five-membered ring products,[3] arylalkyne cyclization leading to dihydronaphthalene derivatives,[4] cyclization of 1-alkyn-5-ones leading to 2-methylfurans,[5] and biomimetic tandem cyclization of alkynyl polyene affording polycarbocycles.[6,7] These reactions involve a protodemercuration step of the vinylmercury intermediate induced by TfOH that is generated in situ.[6] We describe herein the $Hg(OTf)_2$·3TMU-catalyzed cycloisomerization of alkynoic acids leading to γ-methylene-γ-lactone, δ-methylene-δ-lactone and ε-methylene-ε-lactone in excellent yields with high catalytic turnover of up to 100 times. Although extensive methodologies for the synthesis of the γ-methylene-γ-lactone by the cyclization of alkynoic acid using silver salts,[8] mercuric salts,[9] and transition metals[10] as catalysts have been reported, synthetic methods of δ-methylene-δ-lactone and ε-methylene-ε-lactone are limited. We have also achieved the synthesis of a naturally occurring γ-methylene-γ-lactone[11] by using $Hg(OTf)_2$·3TMU-catalyzed cyclization of alkynyl *tert*-butyl ester as the key step elucidating the absolute structure of the natural product.

First, we examined the reaction of 4-pentynoic acid (**1**) with 2 mol% of $Hg(OTf)_2$ in CD_3CN at room temperature. Yield was determined by ^1H NMR directly by using naphthalene as the internal standard after adding triethylamine to quench the reaction. The starting material was consumed within one minute, affording enol lactone **3** in 42% yield without forming γ-methylene-γ-lactone **2** (Table 1, entry 1). In sharp contrast, 2 mol% of $Hg(OAc)_2$ and $Hg(OTFA)_2$ afforded **2** in 85% and 93% yield, respectively (entries 2 and 3) as reported by Katzenellenbogen.[9] A 2 mol% of $Hg(OTf)_2$·TMU complex, afforded γ-methylene-γ-lactone **2** in 3% yield, and the major product was again isomerized **3** in 62% yield. $Hg(OTf)_2$·2TMU, however, afforded **2** in 94% yield as the sole product (entries 4 and 5). Moreover, $Hg(OTf)_2$·3TMU (2 mol%) afforded **2** in 98% yield after one minute (entry 6). Although the reaction in CD_3NO_2 using $Hg(OTf)_2$·3TMU also afforded **2** in 90% yield after one minute (entry 7), $CDCl_3$ and C_6D_6 did not give satisfactory results (entries 8 and 9). When the quantity of catalyst was reduced to 1 mol%, 15 minutes were required until all starting material was consumed and **2** was obtained in 95% yield (entry 10). A 0.1 mol% of catalyst was not enough to complete the reaction after five hours to give **2** in 66% yield (entry 11).

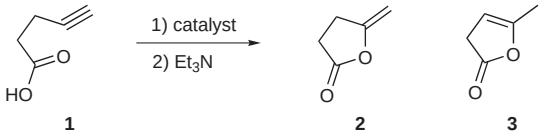
A second substrate was 5-hexynoic acid (**4**) and the reaction with 1 mol% of $Hg(OTf)_2$·3TMU in MeCN at room temperature for 15 minutes afforded δ-methylene-δ-lactone **5** in 99% yield. The yield was also determined by NMR using naphthalene as the internal standard. Thus, the present procedure is highly efficient by comparing it with reported procedures to prepare δ-methylene-δ-lactone.[10a,c]

The procedure is also applicable for the cyclization of 6-heptynoic acid (**6**) to give ε-methylene-ε-lactone **7** in quantitative yield by using 5 mol% of the catalyst in MeCN at room temperature for 20 hours (Scheme 1). It must be pointed out that this is the first practical synthesis of ε-methylene-ε-lactone,[10d] though extra dry conditions (substrate, solvent, and reagent) are critical to get high yield. When the procedure was applied for the cyclization of 7-octynoic acid, ζ-methylene-ζ-lactone was not detected, and the starting material was recovered quantitatively.

Finally, we planned to achieve the synthesis of natural occurring γ-methylene-γ-lactone **8** that is isolated from Gorgonian *Plexaura flava*,[11] in order to establish the absolute stereochemistry. Known β-ketoester **9**[12] was reduced with (*R*)-Alpine-Borane® in THF to give *R*-alcohol **10** in 21% yield.[13] The *R*-stereochemistry of **10** was confirmed by Kusumi's MTPA method,[14a,b] and the optical purity was established to be 91% ee based on the HPLC experiment using Daicel Chiralcel OD-H column (0.46 × 25 cm) and hexane–2-propanol (15:1) as an eluant. The reduction of **9**

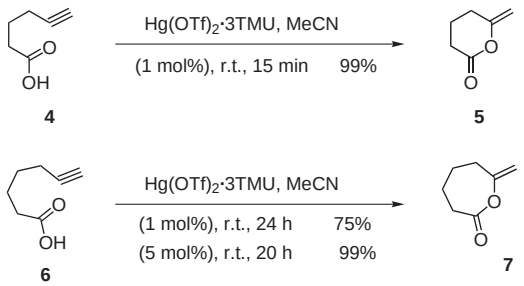
SYNLETT 2006, No. 4, pp 0639–0641
Advanced online publication: 20.02.2006
DOI: 10.1055/s-2006-926257; Art ID: U31705ST

Table 1 Mercuric Salt Catalyzed Cyclization of **1**



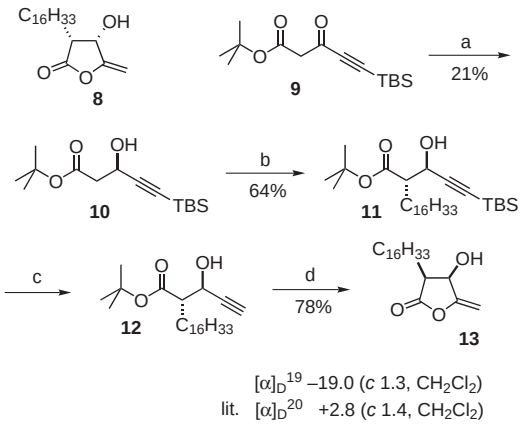
Entry	Catalyst	mol%	Solvent	Time	Yield (%)[a] **2**	**3**
1	$Hg(OTf)_2$	2	CD_3CN	1 min	0	42
2	$Hg(OAc)_2$	2	CD_3CN	1.5 h	85	0
3	$Hg(OTFA)_2$	2	CD_3CN	1 min	93	0
4	$Hg(OTf)_2$·TMU	2	CD_3CN	1 min	3	62
5	$Hg(OTf)_2$·2TMU	2	CD_3CN	1 min	94	0
6	$Hg(OTf)_2$·3TMU	2	CD_3CN	1 min	98	0
7	$Hg(OTf)_2$·3TMU	2	CD_3NO_2	1 min	90	0
8	$Hg(OTf)_2$·3TMU	2	$CDCl_3$	10 min	68	0
9	$Hg(OTf)_2$·3TMU	2	C_6D_6	10 min	75	0
10	$Hg(OTf)_2$·3TMU	1	CD_3CN	15 min	95	0
11	$Hg(OTf)_2$·3TMU	0.1	CD_3CN	5 h	66	0

[a] NMR yield using naphthalene as internal standard.



Scheme 1 $Hg(OTf)_2$·3TMU-catalyzed cyclization of **4** and **6**.

was also examined by using baker's yeast[15] as well as (*R*)-5,5′-diphenyl-2-methyl-3,4-propano-1,3,2-oxazoborolidine-BH_3.[16] The former did not afford reduction product **10** and the latter provided **10** in 67% yield (recovery of starting material 29%) with 23% ee. Frater's *anti*-selective alkylation of **10** using LDA and HMPA afforded *anti*-product **11** in 64% yield.[17] The TBS group was cleaved by TBAF in THF to give terminal alkyne **12**. Then we tried direct cyclization of the alkynyl *tert*-butyl ester **12** using $Hg(OTf)_2$·3TMU (5 mol%) in MeCN at room temperature. (2*R*,3*S*)-γ-Methylene-γ-lactone **13** was obtained in 78% yield after one hour reaction period, and the spectral data of **13** were identical with those of the reported natural product (Scheme 2). Although the rotation value of **13** was different from the reported data, the sign of rotation was opposite. Therefore, we estimated that the absolute stereochemistry of the natural product is 2*R*,3*S* as represented by **8**.[18,19]



Scheme 2 *Reagents and conditions*: (a) (*R*)-Alpine-Borane®/THF, r.t., 90 min; (b) $C_{16}H_{33}I$, LDA, THF, HMPA, –48 °C, 28 h; (c) Bu_4NF, THF, r.t., 1.5 h; (d) $Hg(OTf)_2$·3TMU, MeCN, r.t., 1 h.

Acknowledgment

This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government.

References and Notes

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(14) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) The absolute configuration of β-hydroxyester **10** was established after conversion to the desilylation product by the reaction with TBAF in THF. The resulting desilylated compound was acylated by (*R*)- and (*S*)-MTPA using EDCI and 4-DMAP in CH_2Cl_2. The Δδ (δ_S–δ_R) values of (*R*)- and (*S*)-MTPA esters were shown below (Figure 1).

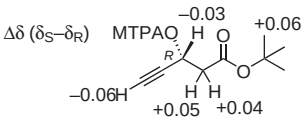

Figure 1

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(18) We could obtain neither the natural product nor NMR spectra and could not check the purity of the natural product.
(19) **General Experimental Procedure.**
To a solution of alkynoic acid (0.30 mmol) in CD_3CN (3 mL, 0.1 M) was added tetramethylurea (0.1 M in CD_3CN, 90 μL, 9.0 μmol) and then a 0.1 M CD_3CN solution of $Hg(OTf)_2$ (30 μL, 3.0 μmol) at r.t. After stirring for 15 min at r.t., Et_3N (100 μL, 0.14 mmol) and naphthalene (internal standard, 0.3 M CD_3CN solution, 0.25 mL, 0.075 mmol) were added. The solution was directly subjected to ^1H NMR analysis, and the yield was calculated from the integral value.