Pergamon

Tetrahedron Letters, Vol. 38, No. 9, pp. 1593-1596, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00120-2

Facile Synthesis of (*S*)-β-Hydroxy-β-trichloromethylated Aromatic Ketones by the Regioselective Ring Cleavage of Chiral β-Trichloromethyl-β-propiolactone Under the Friedel-Crafts Conditions

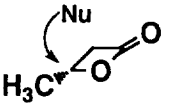
Tamotsu FUJISAWA,* Takatoshi ITO,† Kenji FUJIMOTO, and Makoto SHIMIZU
Department of Chemistry for Materials, Mie University, Tsu, Mie 514, Japan

H. WYNBERG and E. G. J. STARING
Department of Organic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen
The Netherlands

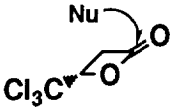
Abstract: The reaction of enantiomerically pure β-trichloromethyl-β-propiolactone (**1**) as a chiral building block with an aromatic compound in the presence of Lewis acid provided an acylated product with a chiral trichloromethyl carbinol moiety. The acylated product was used as an effective chiral synthon for natural product synthesis such as enalapril of ACE inhibitor.

Regioselective ring cleavage of β-lactones with organocuprates has been reported to provide a convenient synthesis of three carbon homologated carboxylic acids by the oxygen-alkyl bond fission.[1] In this type of reaction, it was demonstrated that chiral β-methyl-β-propiolactone (**1**) could serve as an excellent chiral synthon for the synthesis of natural products because the lactone was cleaved completely with cuprate in an S_N2 type fashion.[2] On the other hand, a facile synthesis of enantiomerically pure β-trichloromethyl-β-propiolactone (**2**) from chloral and ketene in the presence of quinidine[3] was reported, which is also useful for the synthesis of (*S*)-malic acid[4] and (*R*)-carnitine[5] via ring cleavage with an oxygen-acyl bond fission by hydrolysis. However, there has been no report that deals with the use of chiral lactone **2** as a chiral building block for carbon-carbon bond formation. Since trichloromethyl group is an equivalent of carboxylic group, the lactone **2** is a very interesting compound as a chiral synthon of natural product synthesis. In this paper we wish to report some of novel findings that reveal the use of (*S*)-**2** as a convenient chiral acylating reagent to aromatics.

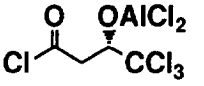
The lactone **2** does not react with organocuprate. The marked contrast of the reactivities between **1** and **2** may be understood in considering the difference of the acidities between acetic acid with pKa of 4.74 and trichloroacetic acid with that of 0.7 owing to the strong electron-withdrawing ability of the trichloromethyl group. Under hot *dil.* alkaline conditions trichloroacetic acid decomposes into chloroform and carbonate,[6] although acetic acid only makes a salt of acetate. When Et_2AlCl was added to a solution of **2** in chloroform, the ^{13}C NMR ($CDCl_3$) showed the shift of carbonyl carbon to δ 173.3 from δ 164.1 of original lactone **2**. The IR



(*R*)-**1**

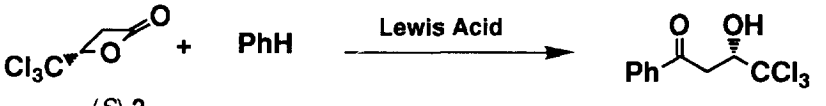


(*S*)-**2**



3

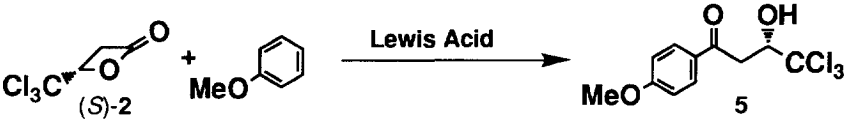
spectrum of the mixture of **2** and Et_2AlCl or $AlCl_3$ showed the new peaks at 1670 and 1570 cm^{-1} due to the complex of acyl chloride and the Lewis acid.[7] These findings indicate that the stable acyl chloride **3** by oxygen-acyl bond fission of **2** is intermediately formed, whereas β-propio-lactone is known to form a polymer in the presence of Lewis acid.[8] While the reaction of β-lactone **1** with organocuprate proceeds with the oxygen-alkyl bond fission, the above facts suggest that an easy oxygen-acyl bond fission would occur rather than the oxygen-alkyl counterpart in the ring cleavage of β-lactone **2**, and that chiral β-trichloromethyl-β-propiolactone **2** would serve as an excellent chiral acylating reagent under the Friedel-Crafts type conditions.



(*S*)-2 **4**

Thus, acylation of aromatic compounds with (*S*)-**2** in the presence of Lewis acid was investigated. A typical procedure is described as follows: A solution of $AlCl_3$ (3.75 mmol) in benzene (1.0 ml) was stirred for 30 min at room temperature, and to it was added a solution of (*S*)-**2** (0.20 mmol) in benzene (1.0 ml) at 5 °C. The reaction mixture was stirred for 9 h at the same temperature, and then quenched with 2N-HCl. After usual work up, the crude product was purified on silica gel TLC to afford (*S*)-3-hydroxy-1-phenyl-4,4,4-trichloro-1-butanone **4** in 90% yield. Although various Lewis acids, such as $AlBr_3$, $AlCl_3$ and $EtAlCl_2$ were used, the crude product was obtained in almost quantitative yield. The lower temperature of 5 °C increases the yield of the product, and the pure butanone **4** was obtained in yields of 75~90% after purification on silica gel TLC. A better yield was obtained using more than 3 equivalents of Lewis acids, and among the Lewis acids examined the use of $AlCl_3$ gave the adduct **4** in the highest yield. In each case the other enantiomer was not detected by HPLC using a chiral stationary column (Daicel OJ). The product was crystallized from methylcyclohexane with some difficulty, by slowly cooling to 4 °C, yielding pure product as a colorless crystal, mp 62~3 °C, [9] $[\alpha]_D^{23}$ -34.1 (c 0.89, $CHCl_3$). Since the present acylation proceeded by the oxygen-acyl bond fission of **2**, the stereochemical integrity of the hydroxy carbon in the acylated product **4** completely retained as confirmed by HPLC analysis using a chiral column (Daicel OJ) and the derivatization to 2-hydroxy-4-phenylbutanoate, a precursor of enalapril (*vide infra*). The mechanism of this reaction is a kind of the Friedel-Craft acylation through the acyl chloride intermediate **3** initially formed.

To explore the scope of the present method, the reaction using anisole was next examined. As shown in Table 1, the reaction in the presence of $AlCl_3$ in CH_3NO_2 or $FeCl_3$ in anisole gave better yields of **5**, whereas the use of $AlBr_3$, $TiCl_4$ or $EtAlCl_2$ as Lewis acid provided **5** in good yields. The reaction with these Lewis acids without solvent improved the yields, although regioselectivity of **5** was affected to a certain extent under these conditions. The ratio of the acylated product was improved by using Et_2AlCl to give the adduct with high selectivity, although the yield was very poor. The HPLC analysis (Daicel OJ) of the adducts confirmed to retain completely the stereochemical integrity of the starting β-lacton. The *para*-acylated product **5** was further recrystallized from EtOAc-*n*-hexane (mp 89°C; $[\alpha]_D^{23}$ -33.2 (c 1.00, $CHCl_3$)). Although, in general, acylation of anisole was reported to give only *para*-substituted product,[10] the present reaction giving a mixture of



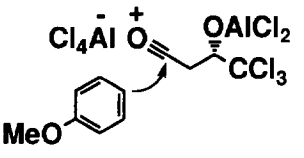
(*S*)-2 **5**

Table 1. Acylation of anisole with (*S*)-2.[a]

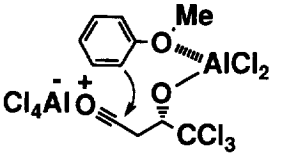
Lewis acid	(eq)	Solv.	Temp. (°C)	5/Yield (%)[b]	*para* : *ortho* [c]
$AlCl_3$	(3.75)	CH_3NO_2	r.t.	77	92 : 8
$AlBr_3$	(3.75)	none	-30~-20	71	70 : 30
$FeCl_3$	(3.75)	none	-30~r.t.	80	81 : 19
$TiCl_4$	(3.3)	none	-30~r.t.	65	71 : 29
$EtAlCl_2$	(3.3)	none	-30~r.t.	72	92 : 8
Et_2AlCl	(3.3)	none	-30~r.t.	16	99 : 1

a) The reaction was carried out according to the typical experimental procedure. b) Isolated yield. c) Determined by HPLC analysis (Hibar Column).

regioisomers of *para*- and *ortho*-substituents seems to be explained in terms of the non-coordinated mechanism **A** and the coordinated analogue **B**; attack of free anisole to the acylium ion intermediate gives a *para*-acylated product due to the least sterically demanding and the most electron-rich position of the aromatic ring (**A**), whereas the coordinated intermediate to aluminum metal (**B**) prefers the proximal *ortho*-attack.

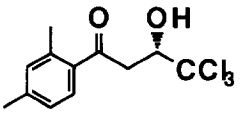


(A)

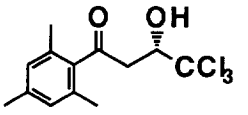


(B)

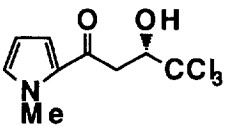
The reaction of more reactive aromatic compound such as *m*-xylene, mesitylene, or *N*-methylpyrrole with (*S*)-β-lactone **2** in the presence of aluminum trichloride gave the acylated products (**6**, **7**, and **8**) as a single regio isomer, respectively, in good yields. All products were confirmed to retain the configuration and enantiomeric purity of the starting β-propiolactone. In contrast to the reaction of β-methyl-β-propiolactone with *N*-methylpyrrole in the presence of Lewis Acid reported recently[11] in which poor regioselectivity was observed, β-trichloromethyl-β-propiolactone gave the chiral β-hydroxy aromatic ketones in good yield with excellent selectivity.



6 Y. 74%
$[\alpha]_D^{23}$-34.2 (c 0.53, $CHCl_3$)

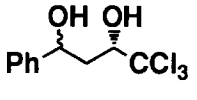


7 Y. 72%
$[\alpha]_D^{23}$-23.0 (c 0.23, $CHCl_3$)

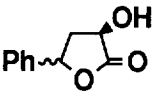


8 Y. 68%
$[\alpha]_D^{23}$-30.6 (c 1.00, $CHCl_3$)

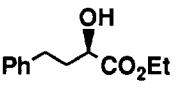
Chiral α-hydroxy acid derivatives are known as important building blocks for many biologically active compounds.[12] (*R*)-2-Hydroxy-4-phenylbutanoate **11**[13] is an important precursor[14] for the synthesis of angiotensin converting enzyme (ACE) inhibitors, *e.g.*, enalapril[15] which has attracted great therapeutic interests in the cardiovascular field. To confirm the absolute configuration, the acylated product **4** obtained in the present study could be easily converted into the precursor **11** of enalapril. Reduction of carbonyl group of **4** with $LiAlH_4$ in THF gave α-trichloromethyl propanediol **9** as a mixture of diastereomers in almost quantitative yield.



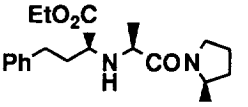
9



10



11



Enalapril

The subsequent hydrolysis of **9** under alkaline conditions gave the butyrolactone **10** with inversion[4,16] of configuration at C_2 in 75% yield. The absolute configuration of the chiral center was established by converting the lactone **10** into 2-hydroxy-4-phenylbutanoic acid by catalytic hydrogenation with 10% Pd-C in acetic acid in quantitative yield. The ethyl ester **11** $[\alpha]_D^{23}$ -25.7 (c 0.08, $CHCl_3$) lit.[14] $[\alpha]_D^{20}$ -20.1 (c 1, $CHCl_3$) was obtained by esterification with diazoethane in 67% yield and confirmed to be enantiomerically pure by HPLC analysis using a chiral column (Daicel OJ).

In summary, an efficient acylating reaction is demonstrated where chiral β-trichloromethyl-β-propiolactone **2** is used as a convenient chiral acylating reagent of aromatic compounds *via* the Friedel-Crafts acylation. The easy availability of chiral β-trichloromethyl-β-propiolactone makes the present reaction of high value. The acylated products retain completely the stereochemical integrity of the starting β-trichloromethyl-β-propiolactone. Accordingly chiral β-trichloromethyl-β-propiolactone can be used as an effective chiral synthon for the synthesis of optically active natural products as demonstrated in the synthesis of an important precursor of enalapril of ACE inhibitor.

References and Notes

† Present address: Osaka Municipal Technical Research Institute.

1. Fujisawa, T.; Sato, T. *J. Synth. Org. Chem. Jpn.*, **1982**, *40*, 618-628. Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.*, **1980**, *21*, 935-938. Fujisawa, T.; Sato, T.; Kawara, T.; Kawashima, M.; Shimizu, H.; Itoh, Y. *Tetrahedron Lett.*, **1980**, *21*, 2181-2184. Sato, T.; Kawara, T.; Kawashima, M.; Fujisawa, T. *Chem. Lett.*, **1980**, 571-574. Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A.; Obinata, T. *Tetrahedron Lett.*, **1980**, *21*, 2553-2556. Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron*, **1989**, *45*, 403-412.
2. Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.*, **1980**, *21*, 3377-3380. Fujisawa, T.; Sato, T.; Kawara, T.; Ohhashi, K. *Tetrahedron Lett.*, **1981**, *22*, 4823-4826. Sato, T.; Itoh, T.; Hattori, C.; Fujisawa, T. *Chem. Lett.*, **1983**, 1391-1394.
3. Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.*, **1982**, *104*, 166-168. Wynberg, H.; Staring, E. G. J. *J. Org. Chem.*, **1985**, *50*, 1977-1979. Song, C. E.; Ryu, T. H.; Roh, E. J.; Kim, I. O.; Ha, H. J. *Tetrahedron Asymm.*, **1994**, *5*, 1215-1218.
4. Wynberg, H.; Staring, E. G. J. *J. Chem. Soc., Chem. Commun.*, **1984**, 1181-1182. Ketelaar, P. E. F.; Staring, E. G. J.; Wynberg, H. *Tetrahedron Lett.*, **1985**, *26*, 4665-4668.
5. Song, C. E.; Lee, J. K.; Lee, S. H.; Lee, S. *Tetrahedron Asymm.*, **1995**, *6*, 1063-1066.
6. Pollock, J. R. A.; Stevens, R. *Dictionary of Organic Compounds*, **1965**, *5*, 3109-3110.
7. Susz B. P.; Wuhrmann J.-J. *Helv. Chim. Acta*, **1957**, *40*, 971-980. Cook, D. *Can. J. Chem*, **1959**, *37*, 48-53.
8. Yasuda, T.; Aida, T.; Inoue, S. *Macromolecules*, **1983**, *16*, 1792-1796.
9. For the racemate; Koenigs, W., *Chem. Ber.* **1892**, *25*, 792-802.
10. Noller, C. R.; Adams, R. *J. Am. Chem. Soc.*, **1924**, *46*, 1889-1896, and the references cited therein.
11. Harrowven, D.; Dainty, R. F. *Tetrahedron Lett.*, **1995**, *36*, 6739-6742.
12. See for example, Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*, John Wiley & Sons: New York, 1987, and the references cited therein.
13. Sugai, T.; Ohta, H. *Agric. Biol. Chem.*, **1991**, *55*, 293-294. Bradshaw, C. W.; Wong, C. H.; Hummel, W.; Kula, M. R. *Bioorg. Chem.*, **1991**, *19*, 29-39.
14. Yanagisawa, H.; Ishihara, S.; Ando, A; Kanazawa, S.; Miyamoto, T.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.*, **1989**, *30*, 1984-1991.
15. Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirshmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature*, **1980**, *288*, 280-283.
16. Corey, E. J.; Link, J. O. *Tetrahedron Lett.*, **1992**, *33*, 3431-3434. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.*, **1992**, *114*, 1906-1908.

(*Received in Japan* 9 *December* 1996; *revised* 13 *January* 1997; *accepted* 16 *January* 1997)