CHEMISTRY LETTERS, pp. 447-448, 1979. Published by the Chemical Society of Japan

ENANTIOSELECTIVE ADDITION OF ACETYLENE TO ALDEHYDE. PREPARATION OF OPTICALLY ACTIVE ALKYNYL ALCOHOLS

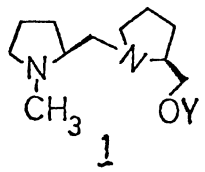
Teruaki MUKAIYAMA, Keisuke SUZUKI, Kenso SOAI, and Toshio SATO

Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Enantioselective addition of acetylene to aldehyde was investigated by the use of (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine as a chiral ligand. The addition of lithium trimethylsilylacetylide to benzaldehyde afforded the corresponding alkynyl alcohol in 92% optical yield.

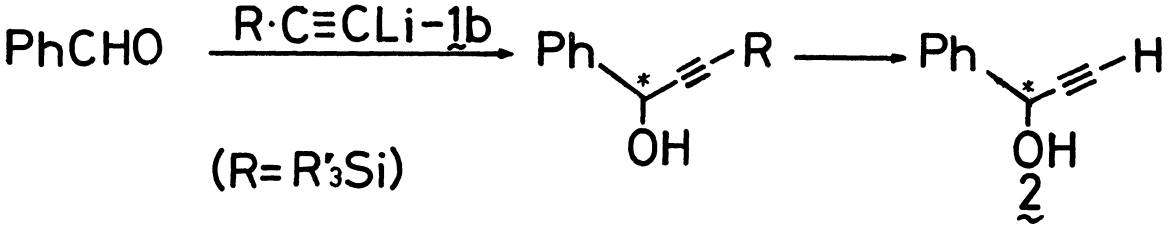
Optically active alkynyl alcohols have been used as versatile intermediates in the synthesis of some optically active natural products such as prostaglandin, vitamin E, and pheromone of dried bean beatle etc.[1] Several methods for the preparation of these alcohols have been so far reported; i) optical resolution of the racemic alcohols,[2] ii) microbial asymmetric hydrolysis of the corresponding acetates,[3] and iii) asymmetric reduction of acetylenic ketones by the use of Darvon alcohol-$LiAlH_4$ complex.[4] However, each of these methods has its limitation in some practical aspects; half of the starting material is essentially wasted in the case of the former two methods, and the latter method involves a tedious experimental procedure; racemic alkynyl alcohols are initially oxidized to the corresponding ketones, which are in turn asymmetrically reduced to form desired optically active alkynyl alcohols.

In this communication, we now wish to report a new and efficient method for the synthesis of the optically active alkynyl alcohols. The method is based on the asymmetric addition of derivatives of lithium acetylide to aldehyde in the presence of (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (1)[5] as a chiral ligand. As illustrated in the following equation, the



1

1a Y=H
b Y=Li



2

present enantioselective ethynylation was investigated using benzaldehyde as the substrate (see Table). It is noted that enantioselectivity of the present reaction depended predominantly on the trialkylsilyl group of the acetylene.

Typical experimental procedure for the reaction utilizing lithium trimethylsilylacetylide is as follows: to a solution of 1 (0.792 g, 4 mmol) in dimethyl ether

Table Enantioselective Ethynylation to Benzaldehyde

Run	R	Temp.(°C)	Yield(%)[a]	Enantiomeric Ratio[b]	Config.
1	H-	- 78	76	77:23	S(+)
2	Me_3Si-	- 78	99	89:11	S(+)
3	Me_3Si-	-123	87	96: 4	S(+)
4	Et_3Si-	-123	93	90:10	S(+)
5	t-$BuMe_2Si$-	-123	67	86:14	S(+)
6	Ph_2MeSi-	-123	88	90:10	S(+)
7	Ph_3Si-	-123	83	88:12	S(+)

a) The silyl groups were removed by the action of methanolic NaOH (run 2,3,4,5) or KF in two phase system in the presence of n-$Bu_4N^+HSO_4^-$ (run 6,7).
b) The optical yield of the resulting 1-phenyl-2-propyn-1-ol (2) was determined by the 100 MHz ^{1}H-NMR measurement of the (S)-(-)-MTPA ester[7] utilizing benzene-d_6 as the solvent.

(20 ml) was added a solution of $(CH_3)_3SiC{\equiv}CH$ (0.268 g, 2.7 mmol) in 2 ml dimethoxymethane, followed by the addition of n-butyllithium (6.7 mmol, 4.3 ml in hexane) at -35°C. After stirring for 30 min at the same temperature, the resulting white suspension was cooled to -123°C. A solution of benzaldehyde (0.106 g, 1 mmol) in 2 ml dimethoxymethane was added dropwise and stirring was continued for an additional 1 h. The reaction mixture was treated with 2N hydrochloric acid, and was extracted with ether. The organic layer was dried over sodium sulfate and concentrated. After the removal of the trimethylsilyl group under basic condition in a usual manner, the resulting 1-phenyl-2-propyn-1-ol (2) was purified by TLC (silica gel). The optical yield of the alcohol 2 thus obtained was determined by 100 MHz NMR analysis of the corresponding ester of (S)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid(MTPA); Mosher's method.[7]

The preparation of various optically active alkynyl alcohols via this asymmetric ethynylation reaction is now under investigation.

Acknowledgment

The authors wish to express hearty thanks to Dr. Tadao Shibanuma, Yamanouchi Pharmaceutical Co., for NMR measurement, and to Shin-etsu Chemical Co., Ltd. for a kind gift of $Ph_2MeSiCl$ and Ph_3SiCl. Thanks are due to Ministry of Education, Japan, for Grant-in-Aid.

References

1) a) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, J. Am. Chem. Soc., 97, 865 (1975). b) K. K. Chan, N. C. Cohen, J. P. De Noble, A. C. Specian, Jr., and G. Saucy, J. Org. Chem., 41, 3497 (1976). c) W. H. Pirkle and C. W. Boeder, J. Org. Chem., 43, 2091 (1978).
2) R. Pappo, P. Collins, and C. Jung, Ann. N. Y. Acad. Sci., 180, 64 (1971).
3) K. Mori and H. Akao, Tetrahedron Lett., 1978, 4127.
4) R. S. Brinkmeyer and V. M. Kapoor, J. Am. Chem. Soc., 99, 8339 (1977).
5) a) T. Mukaiyama, K. Soai, and S. Kobayashi, Chem. Lett., 1978, 219. b) K. Soai, and T. Mukaiyama, Chem. Lett., 1978, 491. c) T. Sato, K. Soai, K. Suzuki, and T. Mukaiyama, Chem. Lett., 1978, 601. d) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, J. Am. Chem. Soc., May issue,1979.
6) I. Iwai and K. Tomita, Yakugaku Zasshi, 80, 160 (1960).
7) J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 95, 512 (1973).

(Received December 23, 1978)