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A FACILE METHOD FOR THE STEREOSELECTIVE PREPARATION OF ACYCLIC *syn*-1,3-AMINO ALCOHOLS FROM β-HYDROXY KETONES

Koichi NARASAKA, Shigeru YAMAZAKI, and Yutaka UKAJI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

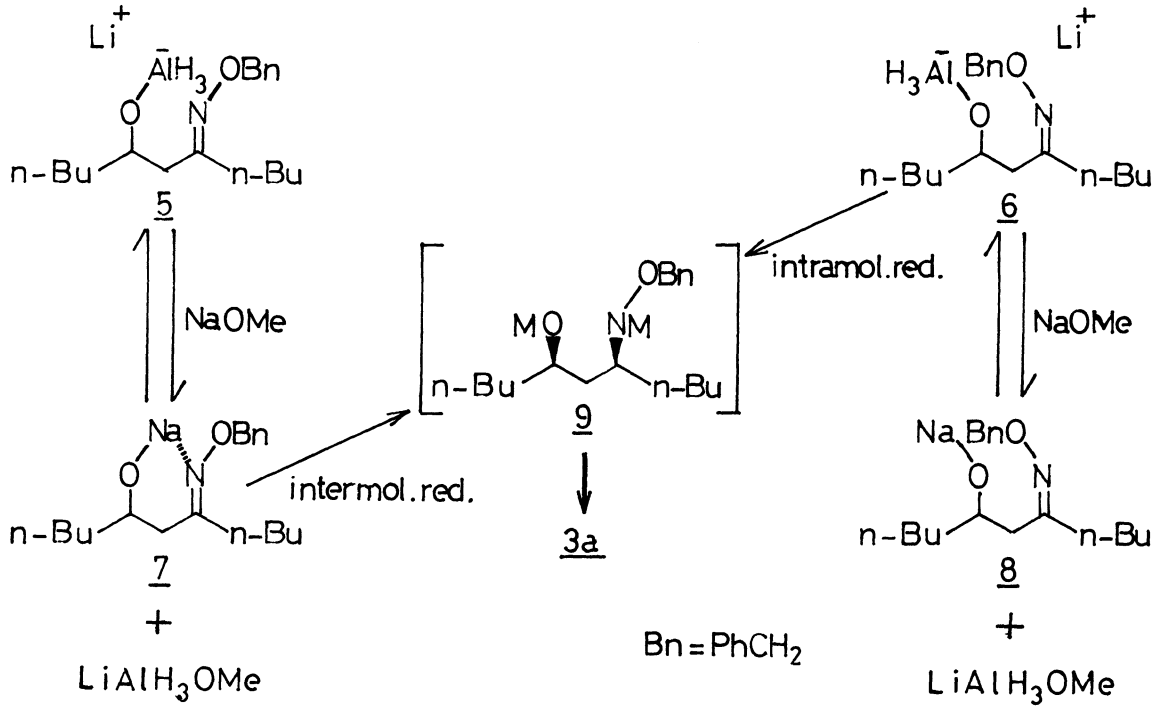
Treatment of acyclic β-hydroxy ketones with O-benzylhydroxylamine hydrochloride gave a mixture of stereoisomers of the corresponding O-benzyloximes. The mixture of the both isomers was reduced with lithium aluminum hydride in the presence of sodium or potassium methoxide to afford *syn*-1,3-amino alcohols in a highly stereoselective manner.

In the preceding communication,[1] we reported a stereoselective preparation of *syn*-1,3-amino alcohols by the reduction of β-hydroxy ketone-*syn*-O-benzyloximes with lithium aluminum hydride [LAH]. Unfortunately, when *anti*-O-benzyloximes were reduced with LAH, the stereoselectivity was not satisfactorily high, therefore, each stereoisomer of O-benzyloximes was obliged to be separated prior to the LAH reduction.

We now report an improved method for the stereoselective preparation of *syn*-1,3-amino alcohols starting from a mixture of *syn*- and *anti*-O-benzyloximes.

The reduction of O-benzyloximes 1 or 2 with LAH is not observed at -78 °C, but proceeds around 0 °C. On the other hand, it was found that the addition of sodium methoxide accelerated the LAH reduction of the *anti*-O-benzyloxime 1a. That is, when 1a was treated with LAH in the presence of sodium methoxide in THF, 1a was consumed smoothly even at -78 °C, and after the reaction mixture was stirred overnight at 0 °C *syn*- and *anti*-1,3-amino alcohols 3a and 4a were obtained in the high stereoselectivity (3a:4a=95:5). To the contrary, in the presence of sodium methoxide, the *syn*-O-benzyloxime 2a was not reduced at -78 °C, but gradually reacted at 0 °C to afford *syn*-1,3-amino alcohol 3a selectively (3a:4a=95:5).

These results suggested that by the addition of sodium methoxide, the aluminum intermediates 5 and 6 are in an equilibrium with the corresponding sodium alkoxides 7 and 8. At this stage, the sodium alkoxide of *anti*-O-benzyloxime 7 is considered to form a six-membered sodium chelate, in which C=N bond is sufficiently activated to be reduced with aluminum hydride at -78 °C generating O-benzylhydroxylamine derivative 9, and the successive reduction progresses around 0 °C to give *syn*-amino alcohol 3a.[2] In the case of *syn*-O-benzyloxime, however, the formation of six-membered chelate like 7 is prevented because of the configuration, therefore, the intramolecular reduction proceeds via aluminum complex 6 at 0 °C.[3]



On the basis of the above observation, we have examined the LAH reduction of the mixture of various *syn*- and *anti*-O-benzyloximes 1 and 2 in the presence of sodium methoxide. The mixture of *syn*- and *anti*-β-hydroxy ketone-O-benzyloximes 1 and 2 was prepared in high yield from the corresponding β-hydroxy ketones by treatment with O-benzylhydroxylamine hydrochloride and pyridine.[4] The following experimemtal procedure for the synthesis of 3a is representative for the stereoselective reduction.

To a THF (125 ml) solution of LAH (30 mmol) and sodium methoxide (20 mmol) was added a 48:52 mixture of 7-hydroxy-5-undecanone-*anti*-O-benzyloxime (1a) and the *syn*-isomer (2a) (total 2 mmol) in THF (6 ml) at -78 °C under an argon atmosphere, and stirred for 6 h at that temperature. After the complete consumption of the *anti*-isomer 1a was indicated by TLC analysis, the reaction mixture was gradually warmed to 0 °C for 6 h, and stirred for 18 h at 0 °C. The mixture was quenched with aqueous sodium sulfate (8.8 ml) and the resulting precipitate was filtered off. The condensed filtrate was purified by preparative tlc on aluminum oxide to give *syn*-7-amino-5-hydroxyundecane (3a) and the *anti*-isomer (4a) (total 92%) in a ratio of 96:4, respectively.[5]

As shown in the table, the high 1,3-asymmetric induction was realized to afford *syn*-1,3-amino alcohols 3 stereoselectively. Furthermore, potassium methoxide was also found to be used effectively instead of sodium methoxide, but the selectivity was decreased when lithium methoxide was employed.

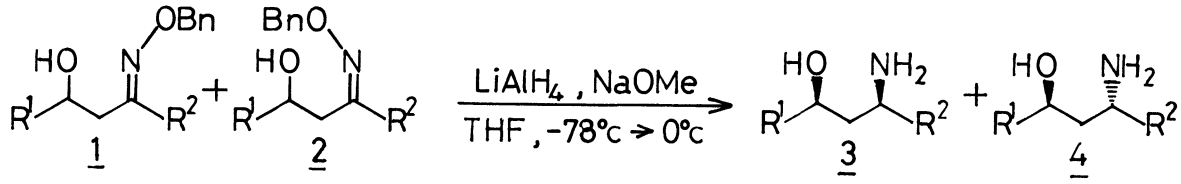


Table 1. Synthesis of 1,3-Amino Alcohls

	R^1	R^2	(1 : 2)	Ratio of 3 : 4 (Total yield)
a	n-Bu	n-Bu	(48:52)	96: 4 (92%)
				97: 3 (92%)[a]
				91: 9 (quant.)[b]
b	i-Bu	i-Bu	(45:55)	95: 5 (92%)
c	$PhCH_2CH_2$	$PhCH_2CH_2$	(49:51)	94: 6 (89%)
d	$PhCH_2CH_2$	CH_3	(66:34)	97: 3 (94%)
e	Ph	CH_3	(72:28)	90:10 (97%)
				92: 8 (93%)[a]

a) Potassium methoxide was used.

b) Lithium methoxide was used.

According to this method, various acyclic *syn*-1,3-amino alcohols are prepared by the simple procedures starting from β-hydroxy ketones which are now readily available by a variety of directed aldol reactions.[6]

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References

1) K. Narasaka and Y. Ukaji, Chem. Lett., 1984, 147.

2) The stereochemical outcome arising from the intermolecular reduction of sodium salt 7 might be explained as follows. In the hydride reduction, the chelate 7 exists in a chair conformation (Fig. 1), and the axial attack of hydride toward C=N bond is preferred by steric interaction of the pseudo axial α-hydrogen, torsional strain,[7] and two-election stabilizing interaction.[8]

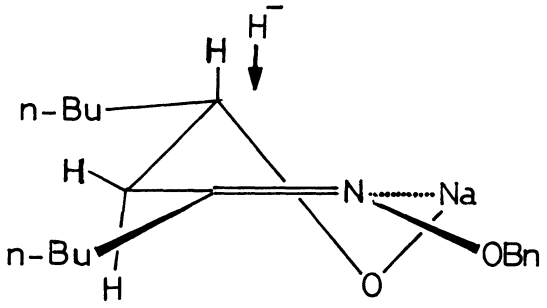

Fig.1.

3) The intramolecular reduction proceeds through 4-membered cyclic transistion states, T1 and T2 (Fig. 2).[9] Non-bonding interaction between two n-Bu groups destabilizes the transition state T2, therefore, the intramolecular reduction proceeds through the transition state T1 to result in the formation of *syn*-1,3-amino alcohol 3a. As compared with the LAH reduction of *anti*-O-benzyloximes, *syn*-isomers were reduced more slowly because of the steric interaction of benzyloxyl group with aluminum group in the transition state T1. The better selectivity in the reduction of *syn*-isomers[1] might be due to the difference of reactivity.

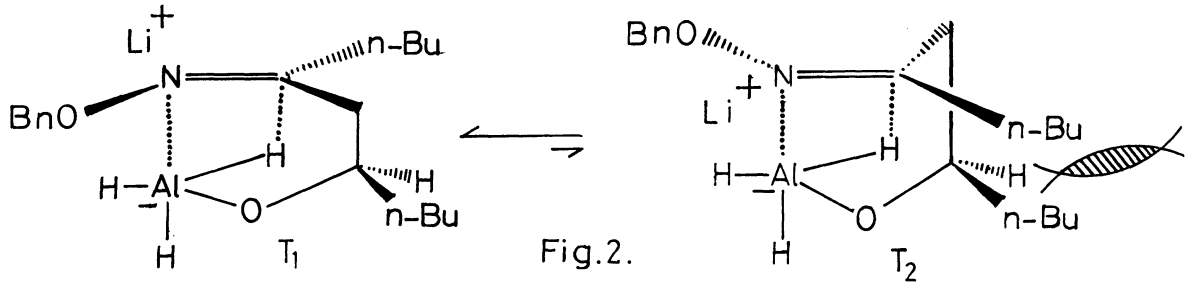

Fig.2.

4) H. Feuer and D. M. Braunstein, J. Org. Chem., 34, 1817 (1969).
5) Isomeric ratio was determined by GLC (OV-101, 135 °C).
6) T. Mukaiyama, "Organic Reactions," ed by W. G. Dauben, John Wiley & Sons, Inc., New York (1982), Vol. 28, Chap. 3.
7) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., Menlo Park, California (1972), Chap. 2, pp.54-70.
8) A. S. Cieplak, J. Am. Chem. Soc., 103, 4540 (1981).
9) E. C. Ashby and J. R. Boone, J. Am. Chem. Soc., 98, 5524 (1976).

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