Tetrahedron Letters,Vol.30,No.9,pp 1083-1086,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

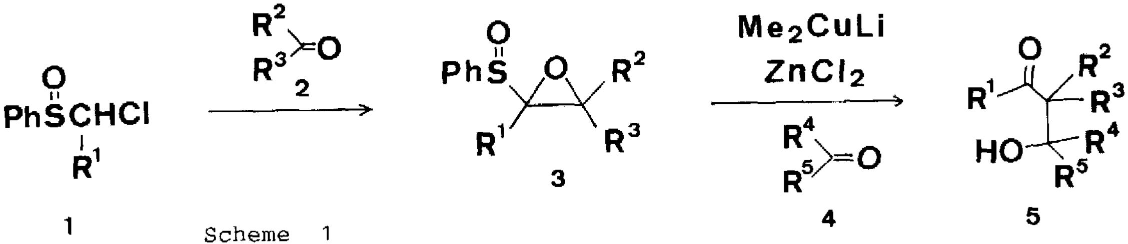
THE REACTION OF α,β-EPOXY SULFOXIDES WITH LITHIUM DIMETHYLCUPRATE GIVING ENOLATES: A NOVEL SYNTHESIS OF ALDOLS[1]

Tsuyoshi Satoh, Atsushi Sugimoto, Masayuki Itoh, and Koji Yamakawa*
Faculty of Pharmaceutical Sciences, Science University of Tokyo,
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Summary The aldols 5 are synthesized from three compoments (1-chloroalkyl phenyl sulfoxide 1 and two kinds of carbonyl compounds 2 and 4) through α,β-epoxy sulfoxides 3 using lithium dimethylcuprate as an electron-transfer reagent.

The nucleophilic ring-opening of oxiranes by organocopper reagents is quite useful method for carbon-carbon bond formation.[2] In fact, numerous papers for syntheses of complex natural products using this reaction have been reported.[3] In some cases, however, the reaction of oxirans with organocopper reagents shows somewhat different aspects by the electron-transferable nature of the reagents.[4] For instance, Tamao *et al.*[5] recently reported a deoxgenation of α,β-epoxy silanes with Grignard reagents catalyzed by copper giving vinylsilanes. This reaction was thought to proceed with one electron transfer from organocopper reagent.

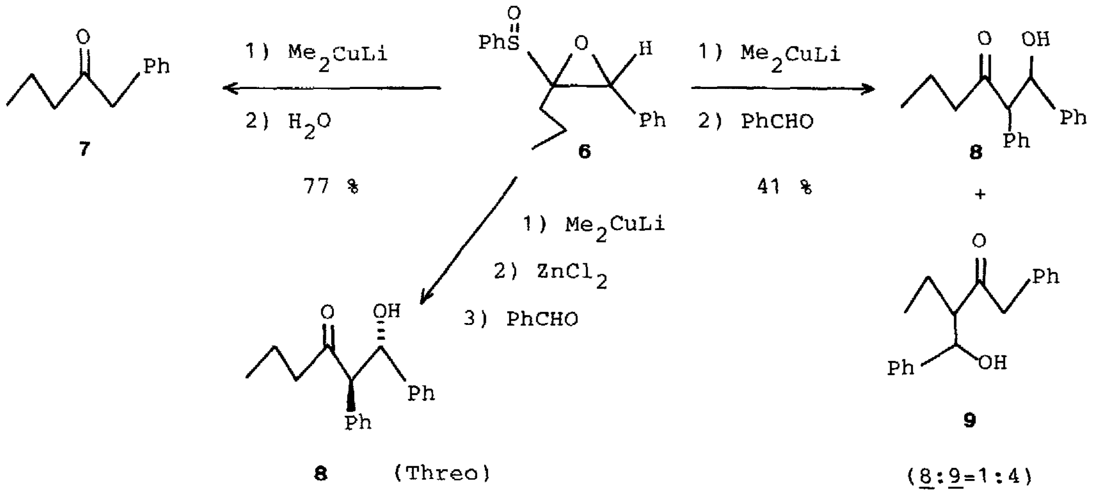
We have recently reported novel synthetic methods from 1-chloroalkyl aryl sulfoxides and carbonyl compounds through α,β-epoxy sulfoxides.[6] In the continuation of our study with α,β-epoxy sulfoxides, it was found that the reaction of α,β-epoxy sulfoxide with lithium organocuprate gave an enolate. This result was completely different from traditional one.[2] In this paper we report a novel synthesis of aldols from 1-chloroalkyl phenyl sulfoxides and two kinds of carbonyl compounds through α,β-epoxy sulfoxides. The whole sequence is shown in Scheme 1.



Scheme 1

Treatment of the α,β-epoxy sulfoxide 6 with three equivalents of lithium dimethylcuprate (Me_2CuLi) in ether at 0 °C for 30 min followed by quenching with sat. aq. NH_4Cl gave 1-phenyl-2-pentanone 7 in 77% yield as a sole product. No methylated product was obtained. We estimated that this reaction took place through an enolate; indeed, quenching the reaction with benzaldehyde instead of water gave a mixture of aldols 8 and 9 (1:4) in 41% yield. Next, this reaction was performed with $ZnCl_2$ as an additive.[7] Thus, 6 was treated with Me_2CuLi at 0 °C for 40 min then two equivalents of a solution of $ZnCl_2$ in ether[7a] was added. After 1 min benzaldehyde was added to the reaction mixture and the reaction was quenched by sat. aq. NH_4Cl to give the aldol 8 in 72% yield as a sole product.

Scheme 2

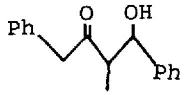
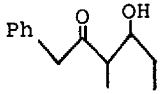
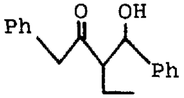
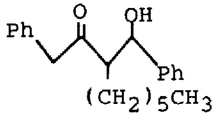
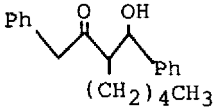
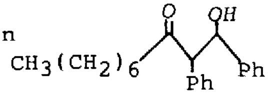
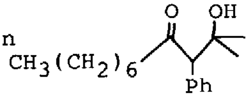
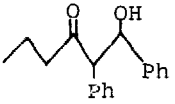


The stereochemical assignment of 8 was made by examination of the vicinal coupling constant in the ^1H NMR. The coupling constant (J=9 Hz) of the protone on the carbon bearing a hydroxyl group clearly indicated that 8 was *threo* diastereomer.[7b,8] Only trace amount of the *erythro* diastereomer was observed on ^1H NMR.

The representative examples of the synthesis of aldols 5 from α,β-epoxy sulfoxides 3 with Me_2CuLi and carbonyl compounds 4 are listed in Table 1. Most notable is the regiochemistry of the aldols. Runs 3, 8 and 4, 6 show that both regioisomers of aldols were synthesized each other in pure form; it must be very difficult to obtain these aldols from 1-phenyl-2-pentanone or 1-phenyl-2-nonanone with high regioselectivity. This reaction is a kind of the directed aldol reaction.[9]

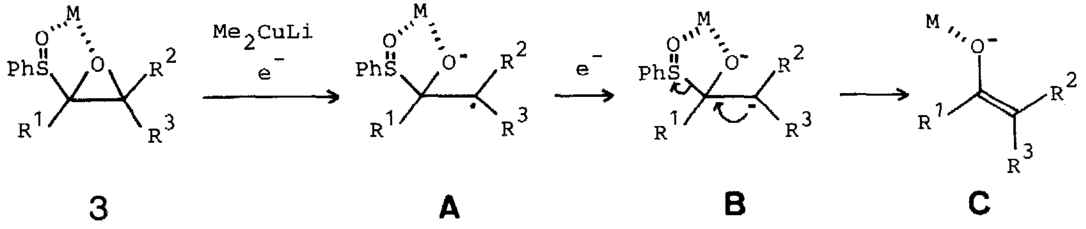
As far as the mechanism of this reaction, the proposed one is as follows (Scheme 3). One electron-transfer from Me_2CuLi to the α,β-epoxy sulfoxide 3 gave an anion radical intermediate A, which received second electron from Me_2CuLi to give a dianion intermediate B. Then elimination of the phenylsulfinyl group of B took place to afford an enolate C, which was trapped with electrophiles (carbonyl compounds) to give the aldols 5.

Table 1. Synthesis of Aldol 5 from 1, 2 and 4 through 3

Run	1	2		4		Me$_2$CuLi	Time	5	
	R^1	R^2	R^3	R^4	R^5	(equiv.)			Yield/%[a)](T/E)[b)]
1	PhCH$_2$	CH$_3$	H	Ph	H	4	1.5 h		80 (2/1)
2	PhCH$_2$	CH$_3$	H	CH$_3$CH$_2$	H	4	1.5 h		79 (2/1)
3	PhCH$_2$	CH$_3$CH$_2$	H	Ph	H	3	2 h		53 (1/0)
4	PhCH$_2$	CH$_3$(CH$_2$)$_5$	H	Ph	H	3	7 h		60 (1/0)
5	PhCH$_2$	CH$_3$(CH$_2$)$_4$	H	Ph	H	3	4 h		74 (1/0)
6	CH$_3$(CH$_2$)$_6$	Ph	H	Ph	H	3	30 min		84 (9/2)
7	CH$_3$(CH$_2$)$_6$	Ph	H	CH$_3$	CH$_3$	3	30 min		52[c)]
8	CH$_3$(CH$_2$)$_2$	Ph	H	Ph	H	3	40 min		72[d)]

a) The yield from α,β-epoxy sulfoxide 3. Isolated yield. b) The ratio of threo/erythro-isomer. Measured by ^{1}H NMR. c) This reaction gave the aldol with 39% yield of 1-phenyl-2-nonanone. d) With trace amount of erythro isomer.

Scheme 3



The scope and limitation, and further extention of this reaction to novel synthetic methods are underway in these laboratories.

References and Notes

1. α,β-Epoxy sulfoxides as useful intermediates in organic synthesis. 20. Part 19: T. Satoh, A. Sugimoto, and K. Yamakawa, Chem. Pharm. Bull., 37, 184 (1989).
2. R. W. Herr, D. M. Wieland, and C. R. Johnson, J. Am. Chem. Soc., 92, 3813 (1970); G. H. Posner, Org. React., 22, 253 (1975); J. P. Marino and D. M. Floyd, Tetrahedron Lett., 1979, 675; A. Alexakis, G. Cahiez, and J. F. Normant, Tetrahedron, 36, 1961 (1980); A. Ghribi, A. Alexakis, and J. F. Normant, Tetrahedron Lett., 25, 3075 (1984); B. H. Lipshutz, R. S. Wilhelm, J. A Kozlowski, and D. Parker, J. Org. Chem., 49, 3928 (1984); J. M. Chong and K. B. Sharpless, Tetrahedron Lett., 26, 4683 (1985).
3. M. R. Johnson, T. Nakata, and Y. Kishi, Tetrahedron Lett., 1979, 4343; Y. Kishi, Aldrichimica Acta, 13, 23 (1980); B. H. Lipshutz and J. A. Kozlowski, J. Org. Chem., 49, 1147 (1984); J. G. Millar and E. W. Underhill, *ibid.*, 51, 4726 (1986); R. D. Tung and D. H. Rich, Tetrahedron Lett., 28, 1139 (1987); J. A. Marshall and J. D. Trometer, *ibid.*, 28, 4985 (1987); J. M. Chong, D. R. Cyr, and E. K. Mar, *ibid.*, 28, 5009 (1987); T. Hanamoto, T. Katsuki, and M. Yamaguchi, *ibid.*, 28, 6195 (1987); A. Alexakis and D. Jachiet, *ibid.*, 29, 217 (1988).
4. H. O. House, Acc. Chem. Res., 9, 59 (1976).
5. K. Tamao, E. Nakajo, and Y. Ito, J. Org. Chem., 53, 414 (1988).
6. T. Satoh, Y. Kaneko, and K. Yamakawa, Bull. Chem. Soc. Jpn., 59, 2463 (1986); T. Satoh, T. Kumagawa, A. Sugimoto, and K. Yamakawa, *ibid.*, 60, 301 (1987); T. Satoh, M. Itoh, T. Ohara, and K. Yamakawa, *ibid.*, 60, 1839 (1987); T. Satoh, T. Oohara, Y. Ueda, and K. Yamakawa, Tetrahedron Lett., 29, 313 (1988); T. Satoh, T. Oohara, and K. Yamakawa, *ibid.*, 29, 2851 (1988); T. Satoh, K. Iwamoto, A. Sugimoto, and K. Yamakawa, Bull. Chem. Soc. Jpn., 61, 2109 (1988) and references cited therein.
7. a) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973); b) K. K. Heng and R. A. J. Smith, Tetrahedron, 35, 425 (1979).
8. R. Baker, J. L. Castro, and C. J. Swain, Tetrahderon Lett., 29, 2247 (1988).
9. T. Mukaiyama, Org. React., 28, 203 (1982).

(Received in Japan 11 October 1988; accepted 23 December 1988)