Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2271-2274, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00273-0

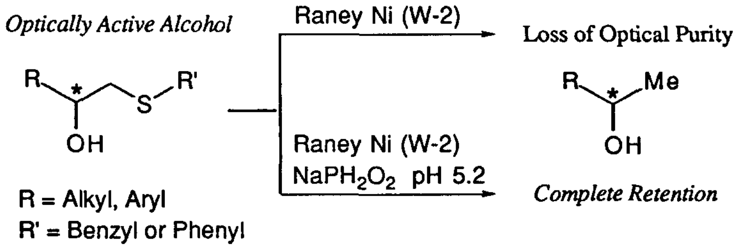
Reductive Desulfurization Using the Raney Nickel - Sodium Hypophosphite Combination System without Racemization of a Secondary Alcohol

Kiyoharu Nishide, Yukihiro Shigeta, Kenichi Obata, Takehisa Inoue,
and Manabu Node*

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract --- Thioethers bearing an optically active secondary alcohol were desulfurized with Raney nickel - sodium hypophosphite - acetate buffer system to give optically active alcohols *without racemization* in high yields. This Raney nickel combination system exhibited a unique desulfurization of benzylthio or phenylthio group in the presence of benzyl ether.

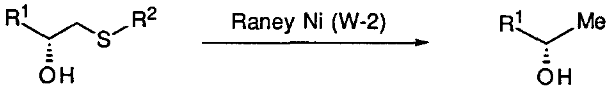
Reductive desulfurization is an important reaction for functional group transformation in organosulfur chemistry.[1] As the reagents for reductive desulfurization, Raney nickel, nickel(0) catalyst, nickel boride, dissolving metal, amalgam, and tin hydride have been used.[2] Among these reagents Raney nickel[3] is most commonly used for the reduction of the carbon-sulfur bonds of sulfides, sulfoxides, and sulfones to the carbon-hydrogen bonds. Secondary alcohols are, however, known to suffer from epimerization with Raney nickel.[4] Racemization of alcohols is thought to involve reversible oxidation-reduction of the alcohols by Raney nickel.[5] Solladié *et al.* protected an alcohol as a benzoate before reductive desulfinylation to retain the configuration of the alcohol.[1e] Alternatively, Ohno *et al.* has presented a protocol to prevent an optically active alcohol from racemization in reductive desulfonylation by the saturation of hydrogen gas in Raney nickel (W-4) suspension,[6] but it seems that the configuration of the alcohol could not be retained completely, even by this method. Here we report the Raney nickel - sodium hypophosphite - acetate buffer system[7,8] to circumvent the racemization problem in the reductive desulfurization of sulfides containing an optically active alcohol.



Optically active (*S*)-4-phenyl-2-butanol (89 %ee) and (*R*)-1,3-diphenyl-1-propanol (76 %ee) were partially racemized to 72 %ee and 5 %ee, respectively, by treatment of Raney nickel (W-2) in ethanol for 1 h at room temperature. A benzylic alcohol was more sensitive to Raney nickel than an aliphatic alcohol. In order to prevent racemization of the alcohol during the reaction, a hydrogen source in the Raney nickel suspension should be added. Sodium hypophosphite in an acetate buffer as a hydrogen source would be promising, because this reagent system has been used for the conversion of nitriles to aldehydes[7] and in the reductive Nef reaction of nitroolefins.[8] We applied this Raney nickel - sodium hypophosphite combination system to the reductive desulfurization. The results are compiled in Table 1. Optically active arylthio- and benzylthioalcohols[9] were easily desulfurized with the Raney nickel combination system to give secondary alcohols in high yields *without any racemization*. The reactions with the Raney nickel combination system were superior to those with Raney nickel itself in yields and optical purities (entries 1, 2 and 5, 6).

The addition order of the reagents (Raney nickel, and sodium hypophosphite) to the solution of the starting material was essential to perform the desulfurization in this combination system. The following procedure was successful: Raney nickel (ethanol suspension) was added to an acetate buffer and ethanol (1 : 2) solution of the starting material, followed by the addition of an aqueous sodium hypophosphite solution immediately (see A Typical Procedure below). Combinations of the starting material, Raney Nickel, and sodium hypophosphite in other addition orders were unsuccessful.

Table 1. Reductive Desulfurization of Thioethers Bearing a Hydroxy Group

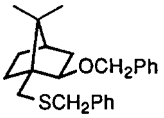
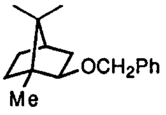
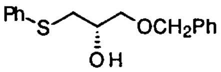
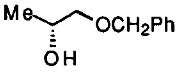
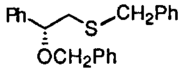
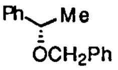


Entry	Method ^{a}	Substrate			Product	
		R^1	R^2	o.p. (%)^{b}	yield (%)^{c}	o.p. (%)^{b}
1	A	Ph	Bn	99 ^{d}	84	99 ^{e}
2	B	Ph	Bn	99 ^{d}	54	68 ^{e}
3	A	Ph	Ph	99 ^{d}	89	99 ^{e}
4	A	Ph	*p*-Tol	99 ^{d}	82	99 ^{e}
5	A	*n*-Hex	Bn	91 ^{f}	85	91 ^{g}
6	B	*n*-Hex	Bn	91 ^{f}	75	89 ^{g}
7	A	*n*-Hex	Ph	91 ^{f}	84	91 ^{g}
8	A	*n*-Hex	*p*-Tol	91 ^{f}	82	91 ^{g}

a) Method A: Raney Ni (W-2) - Sodium hypophosphite - Acetate buffer (pH 5.2) - EtOH, r. t., 0.5 h. Method B: Raney Ni (W-2) - EtOH, r. t., 0.5 h. b) Optical purity c) GC yield [Hewlett PACKARD HP-5890A, OV-1701 (25 m x 0.20 mm id), col. 120 °C, 1.0 ml He, split ratio 1 / 50] d) DAICEL CHIRALPAK AS (hexane / *i*-PrOH = 99 / 1) e) DAICEL CHIRALCEL OB (hexane / *i*-PrOH = 90 / 10)[10] f) DAICEL CHIRALCEL OF (hexane / *i*-PrOH = 99 / 1) g) DAICEL CHIRALCEL OF (hexane) after benzoylation

Another aspect of the utility of Raney nickel was debenzylation.[11] Raney nickel (W-2) is very useful in selective hydrogenolysis of benzyl ethers in the presence of other functional groups, such as 4-methoxybenzyl, methoxymethyl, and silyl ethers, isolated or conjugated olefins, and acetals.[12] We found that the desulfurization of benzylthio- and phenylthioethers in the presence of benzyl ether using the Raney nickel combination system was possible. The results are summarized in Table 2. This unique chemoselectivity showed the mildness of this Raney nickel combination reagent system.

Table 2. Reductive Desulfurization of Thioethers Bearing a Benzyl Ether with the Raney Nickel Combination System[a]

Entry	Substrate	Product	Yield[b] (%)
1			87
2			84
3			83

a) Starting material (0.2 mmol) was used in the same procedure as described in the typical procedure for desulfurization. b) Isolated yield.

A Typical Procedure for Desulfurization (Table 1, entry 1): To a solution of (*R*)-2-benzylthio-1-phenyl-1-ethanol (74 mg, 0.30 mmol, 99 %ee) in an acetate buffer (pH 5.2) and ethanol (1 : 2, 9 ml) was added freshly prepared Raney Ni (W-2) (suspension in ethanol, 5 ml), followed by the addition of sodium hypophosphite monohydrate (321 mg, 3.0 mmol, in 2 ml water solution) immediately, and the resultant solution was stirred for 0.5 h at room temperature. The reaction mixture was filtered with celite. To this solution was added water (20 ml), then the aqueous layer was extracted with dichloromethane (30 ml x 3), washed with brine, dried ($MgSO_4$). The GC yield (84 %) was calculated using α-methylnaphthalene (5.0 mg) as an internal standard. After the usual work-up, the preparative TLC of the residue gave (*S*)-(-)-*sec*-phenethyl alcohol, whose ee (99 %) was determined by a chiral HPLC analysis.

In conclusion, we have found that the Raney nickel - sodium hypophosphite - acetate buffer system was an excellent reagent for 1) reductive desulfurization of optically active sulfur-containing alcohols to give secondary alcohols in high yields *without any loss of the optical purity*, 2) a unique chemoselective desulfurization of benzylthio- and phenylthioethers in the presence of benzyl ether. These features of the Raney nickel combination system would be useful in asymmetric syntheses using organosulfur reagents. Further applications of this reagent system to optically active alcohols containing sulfoxide, sulfone, or other chalcogens are in progress.

ACKNOWLEDGMENT

Partial financial support (Grant-in-Aid No. 07672301 to KN) for this research by the Ministry of Education, Science and Culture, Japan is gratefully acknowledged. We thank Associate Professor Keiji Hashimoto of this university for his kind help with the GC experiments. Also, we thank Messrs. Takashi Ohtsuki and Hiroaki Shiraki for their technical assistance.

REFERENCES AND NOTES

1. a) Pizey, J. S. *Synthetic Reagents*, Vol. 2, chapter 4, John Wiley & Sons Inc., New York, 1974. b) Boekelheide, V.; Anderson, P. H.; Hylton, T. A. *J. Am. Chem. Soc.* **1974**, *96*, 1558-1564. c) Kondo, K.; Negishi, A.; Matsui, K.; Tunemoto, D.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1311-1312. d) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1976**, 855-858. e) Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982**, *23*, 5047-5050.
2. Caubère, P.; Coutrot, P. 'Reduction of Sulfur-Carbon Bonds and of Other Heteroatoms Bonded to Tetrahedral Carbon' in "Comprehensive Organic Synthesis", Vol. 8, p 835-870, Ed. by Trost, B. M.; Fleming, I., Pergamon Press, Oxford, 1991.
3. Mozingo, R. *Organic Syntheses, Coll. Vol. III* **1955**, 181-183.
4. Epimerization: a) Peppiatt, E. G.; Wicker, R. J. *J. Chem. Soc.* **1955**, 3122-3125. b) Eliel, E. L.; Schroeter, S. H. *J. Am. Chem. Soc.* **1965**, *87*, 5031-5038. c) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. I* **1985**, 605-609. d) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95-102.
5. Bonner, W. A. *J. Am. Chem. Soc.* **1952**, *74*, 1033-1034.
6. Nakamura, K.; Ushio, K.; Oka, S.; Ohno, A.; Yasui, S. *Tetrahedron Lett.* **1984**, *25*, 3979-3982.
7. a) Billek, G.; Kindl, H.; Schimpl, A.; Schmook, F. P. *J. Label. Compounds* **1969**, *5*, 3-7. b) Montgomery, J. A.; Hewson, K.; Laseter, A. G. *Carbohyd. Res.* **1973**, *27*, 303-308. c) Passannanti, S.; Paternostro, M. P.; Piozzi, F.; Savona, G. *J. Heterocyclic Chem.* **1977**, *14*, 103-106.
8. Monti, D.; Gramatica, P.; Speranza, G.; Manitto, P. *Tetrahedron Lett.* **1983**, *24*, 417-418.
9. Optically active arylthio- and benzylthioalcohols were prepared from (*R*)-styrene oxide or (*R*)-epoxyoctane with lithium thiolate in tetrahydrofuran in high yields.
10. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709-6716.
11. Debenzylation with Raney nickel: Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis, 2nd ed.," John Wiley & Sons, Inc., 1991, New York. Also see ref. 4c and 4d.
12. a) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021-3028. b) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397-5400.

(*Received in Japan* 12 *January* 1996; *revised* 1 *February* 1996; *accepted* 8 *February* 1996)