



Tetrahedron Letters 44 (2003) 1343-1346

TETRAHEDRON LETTERS

Reaction of lithium eneselenolates derived from selenoamides with ketones: a highly diastereoselective synthetic route to β , β -disubstituted β -hydroxy selenoamides

Toshiaki Murai,* Masato Ishizuka, Akiko Suzuki and Shinzi Kato

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan

Received 20 November 2002; revised 18 December 2002; accepted 20 December 2002

Abstract—The reaction of lithium eneselenolates generated from selenoamides with a variety of ketones proceeded smoothly at -78° C to give the corresponding β , β -disubstituted β -hydroxy selenoamides in moderate to good yields. The reaction showed high diastereoselectivity. The products obtained were converted to the corresponding amides by reacting them with cyclohexene oxide. © 2003 Elsevier Science Ltd. All rights reserved.

The aldol condensation reaction of enolates from amides and thioamides has been studied in great detail.¹ On the other hand, much less attention has been paid to the reaction of these enolates with ketones.² To the best of our knowledge, there has been no report on the stereochemical aspects of this reaction except for the reaction with α -tetralone.^{2d} Meanwhile, syntheses, structure and reaction of compounds with a selenocarbonyl group³ have recently been developed in great depth. Among them, selenium isologues of amides, i.e. selenoamides, have received particular attention.⁴ During the course of our studies on the synthesis and reactivity of selenoamides,⁵ we recently found that selenium isologues of lithium enolates, i.e. lithium eneselenolates generated from selenoamides smoothly underwent Michael addition to α,β -unsaturated ketones.5a We report here the addition reaction of lithium eneselenolates to aliphatic and aromatic ketones with high diastereoselectivity.

Initially, lithium eneselenolate **2a** was generated from selenoamide **1a** and LDA at 0°C in THF (Eq. (1)). To the reaction mixture was then added acetone **3a** and water successively at -78°C. After the usual work-up, β , β -disubstituted β -hydroxy selenoamide **4a** was obtained as a deep yellow oil in 70% yield.⁶ The reaction must be carried out at -78°C. At higher tempera-

tures, the reaction gave a complex mixture along with the recovered starting selenoamide 1a.



Next, a variety of selenoamides 1 and ketones 3 were subjected to the reaction. The results are summarized in Table 1.

A similar reaction of **1a** with cyclic ketones **3b** and **3c** proceeded smoothly to give the corresponding selenoamides **4b** and **4c** in moderate yields (entries 1 and 2). In the reaction with methyl ethyl ketone **3d**, two diastereomers of the products **4d** were obtained in nearly equal amounts (entry 3). On the other hand, the reaction of selenoamides **1a** and **1c** with methyl isopropyl ketone **3e** showed high diastereoselectivity to give exclusively *anti* isomers **4e** and **4j** (entries 4 and 9), whereas the reaction with pinacolone **3f** did not take place and the starting selenoamide **1a** was recovered (entry 5). Aromatic ketones could also be used in the reaction of lithium eneselenolates **2** (entries 6, 7, and 10). As for acetophenone **3h**, *anti* isomers **4h** and **4k** were obtained as sole products (entries 7 and 10).

0040-4039/03/\$ - see front matter @ 2003 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(02)02877-0

Keywords: selenoamides; lithium eneselenolates; β , β -disubstituted β -hydroxy selenoamides; organoselenium compounds; diastereoselectivity.

^{*} Corresponding author. Tel.: +81-58-293-2614; fax +81-58-293-2614; e-mail: mtoshi@cc.gifu-u.ac.jp

Table 1. Reaction of lithium eneselenolates 2 with ketones 3^a

Entry	Selenoamide 1	Ketone 3	Product 4	Yi	eld(%)	^b Ratio ^c
1	Se 1a	о Зь	HO Se	4b	64	-
2	1a	⊖ 3c	HO Se	4c	65	-
3	1a	O 3d	HO Se	4d	59	57 : 43
4 ^d	1a	→ → 3e	HO Se	4e	88	99 : 1
5	1a	→ 3f	HO Se N	4f	0	-
6 ^d	1a	O Ph → Ph 3g	Ph Ph Ph	4g	52	_
7 ^d	1a	Ph 3h	Ph N	4h	75	93 : 7
8	Se NR ₂ 1b R = CH ₂ Ph	Jan Ja	HO Se $R = CH_2F$	4i ²h	100	-
9 ^d	Se 1c	→ ^O 3e	HO Se	4j	70	> 90 : 10
10 ^d	1c	Ph 3h	Ph N	4k	54	> 99 : 1

^a All reactions were carried out by a similar procedure described in the text, unless otherwise noted.

^b Isolated yields.

^c The ratio of diastereomers were determined by NMR analysis of crude products.

^d The reaction mixture was stirred at -78 °C for 1.5 h before the addition of water or CF₃COOH.

The stereochemistry of the product 4h was unequivocally determined by X-ray molecular structure analysis.⁷ The ORTEP drawing of 4h is shown in Fig. 1.

The stereochemistry of the major products 4e, 4j, and

4k was estimated by comparing their ¹³C NMR spectra with that of **4h**.⁸ To compare the stereoselectivity in the present reaction with that of ordinary amides **5**, these compounds were reacted with LDA and ketone **3h** to give a mixture of two diastereomers, albeit in rather low yields (Eq. (2)).



Figure 1. ORTEP drawings of 4h. Selected bond lengths (Å), angles (°), and torsion angles (°): Se(1)-C(1)=1.834(5); C(1)-N(1)=1.318(7). Se(1)-C(1)-N(1)=120.2(4); Se(1)-C(1)-C(6)=121.0(4). Se(1)-C(1)-C(6)-C(7)=60.4(6); C(1)-C(6)-C(7)-O(1)=70.1(6).



The difference in the stereochemical course of the reaction between selenoamides 1 and amides 5 may exit because the reaction of 1 is thermodynamically controlled, and may give more stable products out of two possible diastereomers. The following result may indirectly support this notion. In the reduction⁹ of β , β -disubstituted β -hydroxy selenoamide **4e**, the corresponding amine was not formed. Instead, alcohol **8** and amine **9** were obtained as products in high yields (Eq. (3)).



These products are formed by reduction of the corresponding ketone 3e and lithium eneselenolate 2a, which were derived from the cleavage of 4e via 7.

Finally, the conversion of β -hydroxy selenoamides 4 to amides was examined. Although the conversion of selenoamides to amides with per acids is well known,¹⁰ the reaction of **4h** with MCPBA or Oxone[®] gave a

complex mixture instead of **6b**. The procedure for the deoxygenation of oxiranes to give olefins with selenoamides¹¹ was then used for the conversion of β , β -disubstituted β -hydroxy selenoamides **4**. The reaction of **4h** and **4j** with cyclohexene oxide proceeded with high efficiency to give the corresponding amides **6b** and **6c**¹² in high yields (Eq. (4)).



In summary, we have demonstrated the addition reaction of lithium eneselenolates to ketones. The β , β -disubstituted β -hydroxy selenoamides were obtained in moderate to good yields, and the reaction exhibited high stereoselectivity. Further studies on the present reaction and the synthetic application of the resulting selenoamides obtained are underway.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (C) (No. 12650852) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

- For reviews on the aldol condensation reactions of enolates and thioenolates, see: (a) Heathcock, C. H. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon, Oxford, 1991; Vol. 2, p. 181; (b) Metzner, P. In *Topics in Current Chemistry*; Page P. C. B., Ed.; Springer: Berlin, 1999; Vol. 204, p. 127.
- (a) Hullot, P.; Cuvigny, T.; Normant, M. C. H. Can. J. Chem. 1977, 55, 266; (b) Gaudemar-Bardone, F.; Gaudemar, M. Synthesis 1979, 464; (c) Welch, J. T.; Eswarakrishnan, S. J. Org. Chem. 1985, 50, 5403; (d) Shang, X.; Liu, H.-J. Synth. Commun. 1994, 24, 2485; (e) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. Liebigs Ann. 1996, 881.
- For reviews on selenocarbonyls see: (a) Wu, R.; Hernandez, G.; Dunlap, R. B.; Odom, J. D.; Martinez, R. A.; Silks, L. A. Trends Org. Chem. 1998, 7, 105; (b) Litvinov, V. P. Russ. Chem. Rev. 1999, 68, 737; (c) Chieffi, A.; Comasseto, J. V. Organoselenium Chemistry; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; p. 131; (d) Murai, T.; Kato, S. Topics in Current Chemistry; Wirth, T., Ed.; Springer: Berlin, 2000; Vol. 208, p. 177; (e) Boyle, P. D.; Godfrey, S. M. Coord. Chem. Rev. 2001, 223, 265; (f) Alcami, M.; Mo, O.; Yanez, M. J. Phys. Org. Chem. 2002, 15, 174.

- For recent examples of selenoamides, see: (a) Zhang, P.-F.; Chen, Z.-C. Synthesis 2000, 1219; (b) Koketsu, M.; Kanoh, M.; Itoh, E.; Ishihara, H. J. Org. Chem. 2001, 66, 4099; (c) Koketsu, M.; Takenaka, Y.; Ishihara, H. Synthesis 2001, 38, 503; (d) Zhang, P.-F.; Chen. Z.-C. J. Heterocyclic Chem. 2001, 38, 503; (e) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. J. Am. Chem. Soc. 2001, 123, 8408; (f) Koketsu, M.; Takenaka, Y.; Hiramatsu, S.; Ishihara, H. Heterocycles 2001, 55, 1181; (g) Bhattacharyya, P.; Woollins, J. D. Tetrahedron Lett. 2001, 42, 5949; (h) Koketsu, M.; Okayama, Y.; Aoki, H.; Ishihara, H. Heteroatom Chem. 2002, 13, 195; (i) Zhao, H.-R.; Zhao, X.-J.; Huang, X. Synth. Commun. 2002, 32, 3383.
- (a) Murai, T.; Suzuki, A.; Ezaka, T.; Kato, S. Org. Lett.
 2000, 2, 311; (b) Murai, T.; Mutoh, Y.; Kato, S. Org. Lett. 2001, 3, 1993; (c) Murai, T.; Suzuki, A.; Kato, S. J. Chem. Soc., Perkin Trans. 1 2001, 2711; (d) Murai, T.; Aso, H.; Kato, S. Org. Lett. 2002, 4, 1407 and references cited therein.
- 6. Typical experimental procedure for the reaction of a lithium eneselenolate with a ketone: In a 20-mL two-necked flask, to a THF solution (2 mL) of LDA (1.2 mmol) was added selenoamide 1a (0.19 g, 1.0 mmol) at 0°C, and the mixture was stirred at 0°C for 10 min under a nitrogen atmosphere. Acetone (3a) (0.15 mL, 2 mmol) was then added to the reaction mixture, followed by water. The reaction mixture was poured onto water and extracted with Et₂O (20 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was

purified by column chromatography on silica gel using hexane– Et_2O as an eluent to give 0.171 g (70%) of **4a** as a yellow oil.

- 7. Crystal data of **4h**: $C_{15}H_{21}NOSe$, $F_W = 310.30$, triclinic, space group $P2_1/c$ (#14), a = 8.804(2), b = 13.605(3), c = 12.211(1) Å, $\beta = 91.74(1)^\circ$, V = 1461.8(4) Å³, Z = 4, $D_{calcd} = 1.410$ g cm⁻³, μ (Mo K α) = 25.58 cm⁻¹, T = 296 K, R = 0.143, $R_1 = 0.057$, 1271 reflections, GOF = 1.00. Crystallographic Data for **4h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 197594.
- 8. The signals due to the carbon atom of the C=Se group of *anti* isomers were observed in higher fields than those of *syn* isomers.
- 9. As in the reduction of amides, the reaction of selenoamides with $LiAlH_4$ has been known to give amines.^{5c}
- Shimada, K.; Akimoto, S.; Itoh, H.; Nakamura, H.; Takikawa, Y. *Chem. Lett.* **1994**, 1743.
- 11. Ogawa, A.; Miyake, J.; Murai, S.; Sonoda, N. Tetrahedron Lett. 1985, 26, 669.
- As an alternative procedure for the synthesis of β,β-disubstituted β-hydroxy amides, the addition of organometallic reagents to β-oxo amides has been reported. See: (a) Taniguchi, M.; Oshima, K.; Utimoto, K. Chem. Lett. 1992, 2135; (b) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. Bull. Chem. Soc. Jpn. 1994, 67, 2514; (c) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. Tetrahedron Lett. 2001, 42, 6093.