Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1503-1506, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00183-2

Diastereoselective Addition-elimination Reactions of Lithium Enolates of Chiral N-Acyloxazolidinones with 2-methylene-3-phenoxyalkanoates

Hideyuki Kanno* and Ken Osanai

Exploratory Research Laboratories II, Daiichi Pharmaceutical Co., Ltd.,
Kita-Kasai, Edogawa-ku, Tokyo 134, Japan

Abstract: Addition-elimination reactions of lithium enolates **2** of N-acyloxazolidinones with 2-methylene-3-phenoxyalkanoates **3** and **10** proceeded diastereoselectively and regiospecifically to give chiral N-[(*E*)-4-alkoxycarbonyl-4-pentenoyl]oxazolidinones **4** and **12a**, which are useful intermediates for the synthesis of enzyme inhibitors.

Chiral 4-alkylidene-2-substituted glutarates **1** are useful synthetic intermediates of inhibitors[1] of metallopeptidases such as neutral endopeptidase and matrix metalloproteinase. We, therefore, studied asymmetric addition-elimination reactions[2,3] of lithium enolates **2** of N-acyloxazolidinones with 2-(diphenoxymethyl)acrylates **3** by application of the Evans method[4] to control the stereochemistry of the α-position of the acyl group attached to chiral 1,3-oxazolidinones. The addition-elimination reactions of **2** with **3** gave predominantly chiral N-[(*E*)-alkoxycarbonyl-4-pentenoyl]oxazolidinones **4**, which are the precursors of **1** (Scheme 1).

Scheme 1

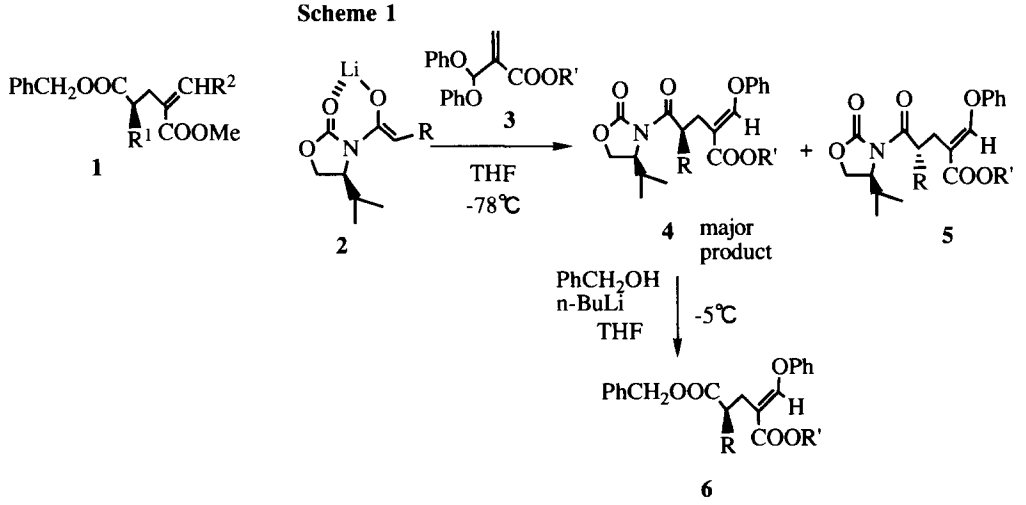


Table 1. Reactions of enolates 2 with 2-(diphenoxymethyl)acrylates 3 and conversions of 4 into benzyl esters 6

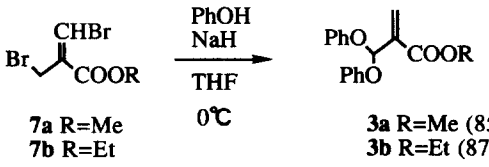
	enolate 2		3			product 4				benzyl ester 6		
entry		R		R'	diastereomeric ratio (4:5)[a]		yield[b] %	diastereomeric excess % d.e.	$[\alpha]_D$ (c, 1.0)		yield[b] %	$[\alpha]_D$ (c, 1.0)
A	**2a**	$PhCH_2$	**3a**	Me	94:6	**4a**	70	96	+105.5[c]	**6a**	91	+21.1[c] (c=0.95)
B	**2b**	Ph-  -CH_2	**3a**	Me	94:6	**4b**	71	>99	+102.7[c]	**6b**	78	+24.5[c]
C	**2b**	Ph--CH_2	**3b**	Et	97:3	**4c**	84	>99	+105.6[d]	**6c**	74	+25.1[d]
D	**2c**	Ph-  -O	**3a**	Me	86:14	**4d**	40	98	+71.8[c]	**6d**	47	-5.0[c]
E	**2d**	Ph	**3a**	Me	>99:<1	**4e**	83	>99	+152.2[c]	**6e**	78	+46.0[c] (c=1.1)

a) Ratios were determined by HPLC (ref. 5). b) In all cases, yields are reported on chromatographed material whose diastereomeric purity is noted in the next column. c) Rotations were determined in methylene chloride. d) Rotations were determined in chloroform.

Lithium enolates **2** were prepared by treatment of the corresponding N-acyloxazolidinones (1.0 equiv.) with lithium diisopropylamide (1.1 equiv.) in THF at -78 °C. Reaction of **2** with **3** (1.5 equiv.) in THF at -78 °C for 60 min afforded **4** together with small amounts of diasteroisomers **5**. Diastereomer analysis of these compounds was carried out by HPLC.[5] Analysis showed that all reactions proceeded regiospecifically and diastereoselectively to afford N-[(*E*)-alkoxycarbonyl-4-pentenoyl]oxazolidinones **4** (Table 1). In particular, the reaction of **2d** with **3a** was highly stereoselective giving **4e** (entry E) as the sole product. The reaction mixture was separated by silica gel column chromatography to isolate **4** in high diastereomeric excess (>96% d.e.). The resulting derivatives **4** were converted into the benzyl esters **6** by treatment with $PhCH_2OH$ (2.0 equiv.) / n-BuLi (1.5 equiv.) at -5 °C (Table 1).

Although the reagent **3a** has been prepared as a mixture with methyl 3-phenoxy-2-(phenoxymethyl)-acrylate **8** from methyl 3-bromo-2-(bromomethyl)acrylate **7a** by Gopal et al,[6] we found that reaction of freshly prepared **7a** (1.0 equiv.) with PhOH (1.5 equiv.) / 60% NaH (1.5 equiv.) in THF at 0 °C selectively gave **3a** in 85% yield. In the same manner, **3b** was prepared from ethyl 3-bromo-2-(bromomethyl)acrylate **7b** in 87% yield (Scheme 2). The reaction of enolate **2b** with **8** did not proceed at all and the starting material was recovered unchanged.

Scheme 2

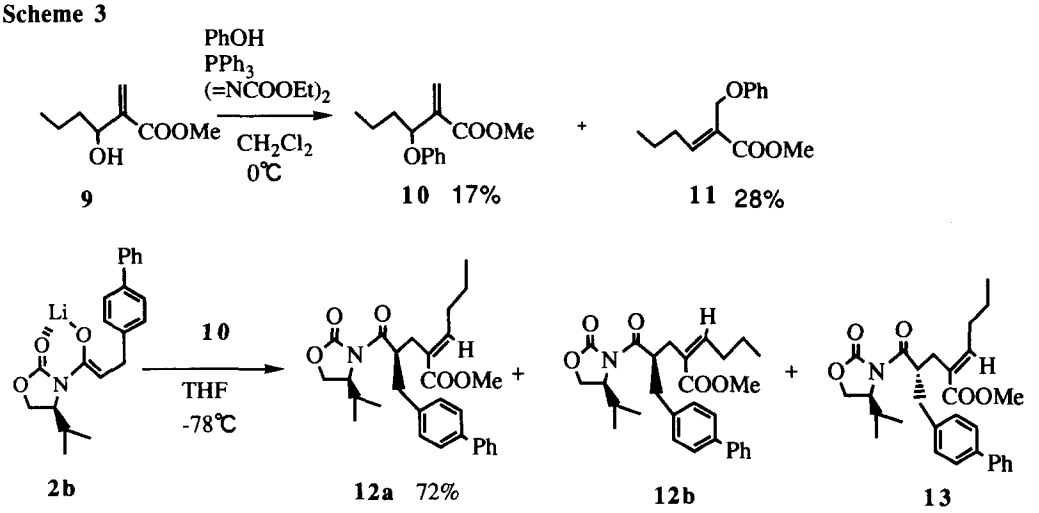


7a R=Me
7b R=Et

3a R=Me (85%)
3b R=Et (87%)

We also studied the addition-elimination reaction of **2b** with methyl 3-phenoxy-2-methylenehexanoate **10** instead of diphenoxy derivatives **3** (Scheme 3). A mixture of methyl 3-hydroxy-2-methylenehexanoate **9** and phenol was treated with triphenylphosphine and diethyl azodicarboxylate at 0 °C in methylene chloride, followed by separation by silica gel column chromatography to give **10** and methyl 2-(phenoxymethyl)-2-hexenoate **11** in 17% and 28% yields, respectively. The reaction of enolate **2b** with **10** proceeded smoothly at -78 °C to afford **12a** regio- and diastereoselectively. The ratio of products **12a**, **12b** and **13** was 91.4: 0.4: 8.2.[5] Compound **12a** was separated by silica gel column chromatography in 72% yield in diastereomerically pure form.

Scheme 3



Thus, we have developed an efficient and diastereoselective route for **6**, intermediates for the synthesis of enzyme inhibitors by addition-elimination reactions of chiral enolates **2** with 2-(diphenoxymethyl)-acrylates **3**. Furthermore, we have expanded the addition-elimination methodology to the reaction of **2** with 2-methylene-3-phenoxyalkanoates **10**.

References and Notes

1. Neutral endopeptidase inhibitors: Ksandar, G. M.; Diefenbacher, C. G.; Yuan, A. M.; Clark, F.; Sakane, Y.; Ghai, R. D. *J. Med. Chem.*. **1993**, *36*, 2420. Matrix metalloproteinase inhibitors: Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Esser C. K.; Hagmann, W. K.; Kopka, I. E. *PCT Int. Appl. WO* 9412169.

2. Michael addition and subsquent elimination reaction has been reported as a mechanistic account in α,α'-annulation process; Jung, M. E.*"Comprehensive Organic Synthesis," ed. by Trost, B. M.; Fleming, I.; Semmelhack, M. F. Pergamon Press, Oxford,* **1991**,*Vol 4*, p 1.
3. For recent examples of Michael addition and elimination reaction; a) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 4979; b) Sharma, S.; Mesic, T. M.; Martin, R. A. *Tetrahedron* **1994**, *50*, 9223.
4. a) Evans, D. A. *"Asymmetric Synthesis," ed. by Morrison, J. D. Academic Press, New York.* **1984**, *Vol. 3*, 1; b) Evans, D. A. *Aldrichimica Acta.* **1982**, *15*, 23; c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737; d) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.
5. Analysis of diastereomeric purity was performed using a SSC Silica-4301-N column (1.0 cm x 30 cm) with 20% ethyl acetate in hexane for elution at a flow rate of 5 ml per min.
6. Gopal, D.; Rajagopalan, K. *Tetrahedron Lett.* **1987**, *28*, 5327.

(*Received in Japan* 19 *April* 1995)