Pergamon

Tetrahedron Letters 40 (1999) 7389–7392

TETRAHEDRON LETTERS

anti-Aldol selective tandem Michael/aldol reaction with magnesium selenolate and stereoselective preparation of tetrasubstituted tetrahydrofuran

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Received 15 July 1999; accepted 4 August 1999

Abstract

Magnesium selenolate-induced Michael/aldol tandem reaction resulted in the *anti*-aldol selective formation of β-hydroxy-α-(phenylseleno)alkyl esters, which were readily converted into tetrasubstituted tetrahydrofurans in a good 2,3-*cis*-3,4-*trans*-4,5-*trans*-selective manner.

Keywords: Michael reactions; aldol reactions; radical cyclization; selenium; selenium compounds; stereoselection.

The efficiency of organic reaction is recognized as an important problem and a tandem reaction sometimes provides a fascinating solution.[1] The Michael addition and the aldol reaction are acknowledged as the most useful tools for constructing complex organic molecules, and combining the two reactions in one pot has been of interest in current organic synthesis.[2–4] Recently, we have reported that a mixture of lithium thiolate or selenolate, α,β-unsaturated ester and aldehyde gives the Michael/aldol tandem adducts in good yields, and with high *syn*-aldol selectivity.[5] Although magnesium thiolate has been known as a promoter of a similar reaction, the stereochemistry of the reaction has remained unclear.[6] During the course of our examination on the scope and limitation of our tandem strategy, we have found that use of magnesium thiolate or selenolate promotes the tandem reaction with high *anti*-aldol selectivity, which is the reverse of that observed in the reaction promoted by lithium thiolate. In this paper, we report a simple and useful preparation of *anti*-aldols and tetrasubstituted tetrahydrofurans in a highly stereoselective manner.

The procedure of the reaction is shown in Scheme 1. To a yellow solution of diphenyldiselenide was added methylmagnesium bromide in ether at room temperature,[7] and magnesium selenophenolate was precipitated as a white solid. *tert*-Butyl crotonate and benzaldehyde were added to the resulting mixture at −50°C and the reaction mixture was allowed to warm to room temperature for 15 h. Following usual

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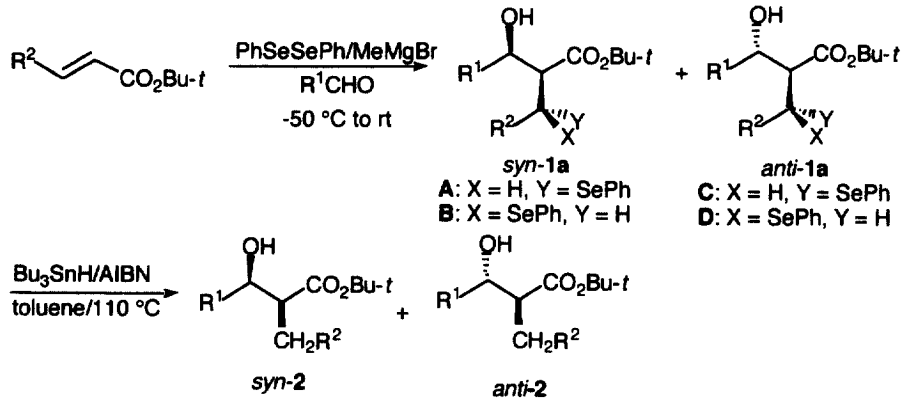
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01516-6

work-up and purification through flash chromatography, tandem adduct **1a** was obtained in a good yield (Scheme 1). The results are summarized in Table 1.



Scheme 1.

Tandem adduct **1a** was isolated in 69–80% yield (entries 1–4). To obtain **1a** in better yield, the aldehyde was added before the ester; the precipitate of magnesium selenolate dissolved and the reaction mixture turned homogeneous. The adduct was usually formed as a mixture of all four possible diastereomers, two of which (**C** and **D**) were formed as major components. The configurations of diastereomers **C** and **D** were found to have the *anti*-aldol configuration (vide infra). Thus, the tandem reaction with magnesium selenolate provides *anti*-aldols selectively. It should be noted that this *anti*-aldol selectivity was the opposite selectivity observed in the Michael/aldol tandem reaction started with lithium thiolate.[5]

The diastereomeric ratio of the four isomers depended on the reaction conditions. The reaction in CH_2Cl_2, for example, gave better **C**+**D** selectivity than that in ether, and diastereomers **C** and **D** were formed predominantly through the reaction performed in toluene (entries 2 and 3). To our surprise, even in THF, an inert solvent for the tandem reaction with lithium thiolate, tandem adduct **1a** was formed in 80% yield (entry 4).[5]

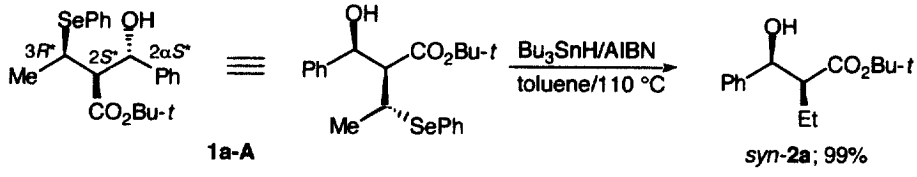
Table 1
Preparation of tandem adduct **1** with magnesium selenolate

entry	R^1	R^2	solvent	**1**;Yield (%)[a]	**A:B:C:D**[b]	**2**;Yield (%)[a]	*syn:anti*[c]
1	Ph	Me	ether	**1a**;73	11:3:48:38		
2	Ph	Me	CH_2Cl_2	**1a**;70	5:1:56:38		
3	Ph	Me	toluene	**1a**;69	3:0:52:45	**2a**; 89	3:97
4	Ph	Me	THF	**1a**;80	27:12:56:5		
5	*p*-Me-C_6H_4-	Me	toluene	**1b**;77	6:2:57:36	**2b**; 93	4:96
6	*p*-Cl-C_6H_4-	Me	toluene	**1c**;52	4:0:57:38	**2c**; 95	2:98
7	*m*-MeO-C_6H_4-	Me	toluene	**1d**;59	5:1:53:41	**2d**; 99	5:95
8	*p*-MeO-C_6H_4-	Me	toluene	**1e**;75	21:6:55:18	**2e**; 92	21:79
9	C_5H_{11}-	Me	toluene	**1f**; 8	n/d		
10	Ph	C_3H_7-	toluene	**1g**;38	4:0:46:50	**2g**; 91	2:98
11	*p*-Me-C_6H_4-	C_3H_7-	toluene	**1h**;63	9:1:50:40	**2h**; 97	6:94

a. Isolated yield. b. Determined by HPLC analyses. c. Determined by ^{1}H-NMR analyses.

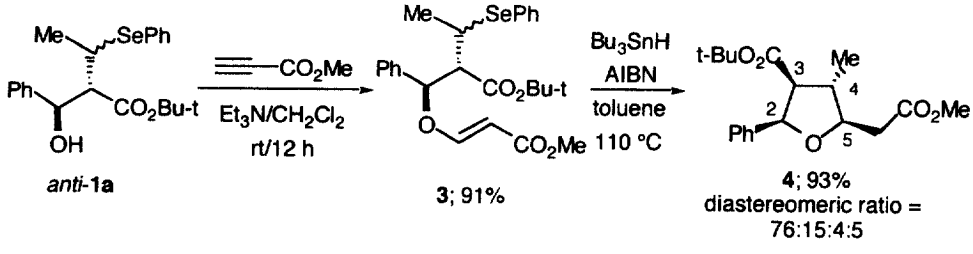
The present reaction conditions were useful for the reaction of other aromatic aldehydes and crotonate or 2-hexenoate ester, giving tandem adducts **1** in good yields *anti*-aldol-selectively (entries 5–8 and entries 10–11). In contrast, the reaction of aliphatic aldehydes resulted in the formation of **1** in poor yield (entry 9). The tandem adducts **1** obtained were readily converted into *anti*-aldols **2** on treatment with Bu_3SnH; the reduced product contained almost single isomer. Thus, the present two-step method provides a useful preparation of *anti*-isomer of β-hydroxyl esters.

Relative stereochemistries of the diastereomers were determined in the following way (Scheme 2). Single crystal of **1a-A** revealed its configuration to be 2*S**,3*R**,2α*S** by X-ray crystallographic analysis.[8] Reductive removal of the phenylseleno group gave diastereomerically pure *syn*-aldol **2a**,[9] which was the opposite diastereomer of **2a** obtained from the reaction shown in Table 1, entry 3, in which **2a** was isolated in 89% yield in 3:97 of diastereomeric ratio. Thus, the major isomer of this **2a** should have *anti*-aldol configuration, and diastereomers **C** and **D** have the same *anti*-aldol configuration between C2 and C2α position.



Scheme 2.

The present tandem adducts act as useful precursors for stereoselective preparation of tetrasubstituted tetrahydrofuran derivatives (Scheme 3). For example, *anti*-**1a** was converted into vinylether **3** in a good yield via the conjugate addition to methyl propiolate, and subsequent radical cyclization of **3** afforded tetrahydrofuran **4** in a highly stereoselective manner. The configuration of **4** was determined to be 2,3-*cis*-3,4-*trans*-4,5-*trans* on the basis of NOE study and X-ray crystallographic analysis.[10] This stereochemical preference of 2,3,5-*cis* configuration in the radical cyclization process is reasonable in comparison with the previous results.[11]



Scheme 3.

In conclusion, the tandem Michael/aldol reaction with magnesium selenolate and subsequent reductive removal of the seleno group provides a useful formation of *anti*-aldols in high stereoselectivity. This is the opposite stereoselectivity to that observed in the reaction with lithium cation. Reductive removal of the phenylseleno group leads to the formation of diastereomerically pure *anti*-aldol or tetrasubstituted tetrahydrofuran. Further investigation and studies of the application of the reaction are now underway in our laboratory.

Acknowledgements

We thank the UBE foundation for financial support (to A.K.). The present work was partially supported by a Grant-in-Aid for Scientific Research (C-11640536) from the Ministry of Education, Science, Sports and Culture, Japan.

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