ORGANIC LETTERS

2004
Vol. 6, No. 18
3139−3141

Synthesis of a New *N*-Acetyl Thiazolidinethione Reagent and Its Application to a Highly Selective Asymmetric Acetate Aldol Reaction

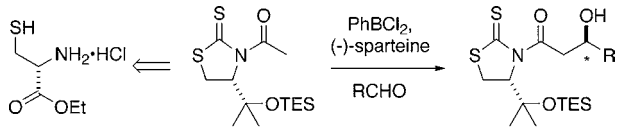
Yingchao Zhang and Tarek Sammakia*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215.

sammakia@colorado.edu

Received June 22, 2004

ABSTRACT

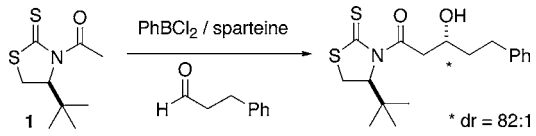


*dr = 9.5:1 to 89:1

A new *N*-acetyl thiazolidinethione reagent, which undergoes highly diastereoselective aldol reactions upon enolization with dichlorophenylborane and (–)-sparteine and subsequent treatment with a variety of aldehydes, is described. This reagent is pseudoenantiomeric to an L-*tert*-leucine-derived reagent recently described by us and is useful because it avoids the prohibitively costly D-*tert*-leucine.

We recently described a new method for performing diastereoselective acetate aldol reactions[1,2] using the chiral *N*-acetyl thiazolidinethione reagent **1** (Scheme 1).[3] In this reaction, enolization is accomplished using phenyldichloroborane and sparteine, and high yields and excellent selectivities are observed in additions to a variety of aldehydes. The chiral auxiliary for this reagent is derived from L-*tert*-leucine, and the reaction benefits from the bulk of the *tert*-butyl group as other less bulky groups provide significantly lower diastereoselectivities. However, this method suffers from the

Scheme 1



(1) (a) For selected reviews on the aldol reaction, see: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917. Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353. Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley: New York, 2000. (b) For recent advances in asymmetric synthesis with chiral imide auxiliaries, see: Evans, D. A.; Shaw, J. T. *Actualité Chimique* **2003**, 35.

(2) (a) For reviews of asymmetric acetate aldol reactions, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (b) For selected references of asymmetric acetate aldol reactions, see: Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297. Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397. Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. Oppolzer, W.; Starkemann, C. *Tetrahedron Lett.* **1992**, *33*, 2439; *24*, 874. Yan, T. H.; Hung, H. C.; Hung, A. W.; Lee, H. C.; Chang, C. S. *J. Org. Chem.* **1994**, *59*, 8187. Yan, T. H.; Hung, A. W.; Lee, H. C.; Chang, C. S. Liu, W. H. *J. Org. Chem.* **1995**, *60*, 3301. González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949. Bond, S.; Perlmutter, P. *J. Org. Chem.* **1997**, *62*, 6397. Palomo, C.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Oliarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 180. Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, *4*, 2253.

(3) Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org Lett.* **2004**, *6*, 23.

10.1021/ol048810t CCC: $27.50 © 2004 American Chemical Society
Published on Web 07/31/2004

significant limitation that only the L-enantiomer of *tert*-leucine is available at reasonable cost. We, therefore, wished to devise a new reagent that is the functional equivalent of D-*tert*-leucine, and in this communication, we describe the synthesis of such a reagent and its application to diastereoselective acetate aldol addition reactions using our previously described procedure.

In considering the design of reagents which bear steric bulk, we sought to replace the *tert*-butyl group with a protected tertiary alcohol and wished to study the thiazolidine thione reagent **2** shown in Figure 1. Tertiary alcohols are

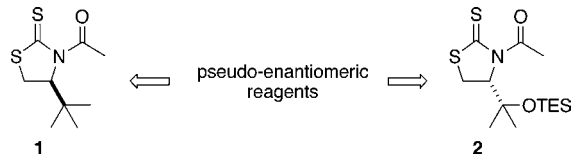
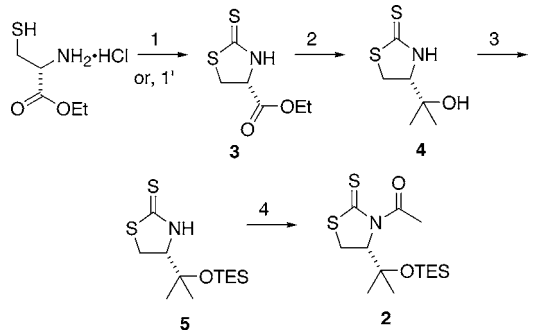


Figure 1. Reagent **2**, the pseudoenantiomer of the L-*tert*-leucine-derived reagent **1**.

readily prepared by nucleophilic additions to esters, and our synthesis begins with the ethyl ester of cysteine (Scheme 2). Conversion of commercially available cysteine ethyl ester·

Scheme 2[a]

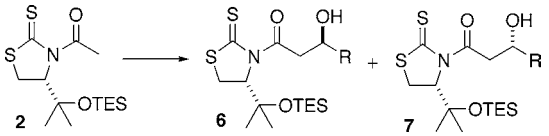


[a] Conditions: (1) NEt_3 (1 equiv), thiocarbonyldiimidazole (1 equiv), THF, 90%; (1′) NEt_3 (1 equiv), CS_2 (1.1 equiv), CH_2Cl_2, 75%. (2) MeLi (3.5 equiv), $CeCl_3$ (4 equiv), THF, −78 °C, then ester **3** was added at −40 °C, recrystallization from toluene 80%. (3) TESOTf, (2 equiv), DMAP (2 equiv), CH_2Cl_2, 0 °C to room temperature, 95%. (4) *n*-BuLi (1.2 equiv), −78 °C, then CH_3COCl (1.2 equiv), THF, 90%.

HCl to the corresponding thiazolidine thione **3** was accomplished in 90% yield by treatment with triethylamine and thiocarbonyldiimidazole.[4] Alternatively, this reaction can be performed using the less costly reagent combination of carbondisulfide and triethylamine in 75% yield.[5] The addition of methyllithium to **3** was then studied, and while the reaction provides good yields, it proceeds with partial racemization to provide the product in a maximum of 62% enantiomeric excess under a variety of conditions.[6] This is presumably due to enolization under the reaction conditions, and we therefore studied the use of the corresponding organocerium reagent[7] (prepared from MeLi and $CeCl_3$). Addition of this reagent to **3** proceeds in high yields and provides the highly crystalline **4** with an enantiomeric excess of 94%. A single recrystallization of **4** from toluene provided material with an enantiomeric purity of 99.4% in an overall yield of 80% (after crystallization). This material was protected as the triethylsilyl ether to provide **5** and then acylated to provide **2**. The overall yield of this four-step process is 61% (or 51% if the thiazolidinethione is prepared using CS_2), and we have prepared 6 g of **2** in a single batch.

With compound **2** in hand, we carried out a survey of the scope of this reagent in reactions with representative aldehydes (Table 1).[8] As expected, the results are similar to the

Table 1. Aldol Reactions of Thiazolidinethione **3** with Representative Aldehydes[a]



entry	aldehyde	dr (6:7)[b]	yield (%)[c]
1	$PhCH_2CH_2CHO$	49:1	86
2	$(CH_3)_2CHCHO$	57:1	88
3	$CH_3(CH_2)_3CHO$	59:1	91
4	$(CH_3)_2CHCH_2CHO$	89:1	92
5	$BnOCH_2CHO$	59:1	86
6	$TBSOCH_2CH_2CHO$	31:1	80
7	PhCHO	16.5:1	80
8	*trans*-PhCH=CHCHO	9.5:1	63

[a] Conditions: compound **2** (1.3 equiv), $PhBCl_2$ (1.3 equiv), (−)-sparteine (2.6 equiv), CH_2Cl_2, 0 °C to room temperature, then RCHO, −78 °C to 0 °C. [b] Ratios were determined by 500 MHz ^1H NMR spectroscopic analysis of the crude reaction mixtures. [c] Yield of the major diastereomer after purification.

tert-leucine derived *N*-acetyl thiazolidine thione reagent **1**. Straight-chain and α- or *β*-branched aliphatic aldehydes react with high selectivities (diastereomeric ratios range from 49:1 to 89:1) and in excellent yields (86−92%, entries 1−4). Aldehydes that are oxygenated at the α- or *β*-position such as benzyloxyacetaldehyde and 3-(*tert*-butyldimethylsilyloxy)-propanal are also excellent substrates for this reaction (entries

(4) Soai, K.; Ishizaki, M. *Heterocycles* **1984**, *22*, 2827.

(5) (a) Rufino, A. R.; Biaggio, F. C. *Tetrahedron Lett.* **2001**, *42*, 8559. (b) Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E. *J. Org. Chem* **1985**, *50*, 4072. (c) Hsiao, C. N.; Liu, L.; Miller, M. *J. Org. Chem.* **1987**, *52*, 2201.

(6) Reaction was studied in THF and ether, at temperatures ranging from −78 °C to room temperature, and using methyl Grignard in THF, ether, or dichloromethane at the same temperature ranges with no improvement in the results.

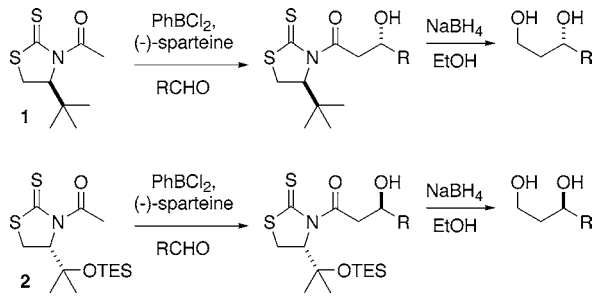
(7) For reviews on organocerium reagents, see: (a) Liu, H. J.; Shia, K. S.; Shang, X.; Zhu, B. Y. Tetrahedron **1999**, *55*, 3803. (b) Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228. (c) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, p 231.

(8) For experimental details, see Supporting Information.

5 and 6). Aldolization with benzaldehyde provided the products in good yield, but with slightly diminished selectivity (16.5:1, entry 7), and the use of *trans*-cinnamaldehyde provided diminished, but useful, yields and selectivities (63% yield, 9.5:1 selectivity, entry 8).

The stereochemistry of the products was determined by reductive cleavage of the aldol adducts obtained in entries 1 and 5 of Table 1 to produce the known compounds (*S*)-5-phenylpentane-1,3-diol and (*R*)-1-*O*-benzyl-1,2,4-butanetriol.[9] All other entries were assigned by analogy. The sense of asymmetric induction is as expected and consistent with our prior studies using the L-*tert*-leucine-derived auxiliary **1**. Thus, the pseudoenantiomeric reagents **1** and **2** provide the enantiomeric aldol adducts and diols upon reductive cleavage of the auxiliary (Scheme 3).

Scheme 3



In conclusion, we have developed a readily synthesized thiazolidinethione auxiliary that provides high levels of diastereoselection in acetate aldol reactions with a variety of aldehydes in excellent yields. This, together with the L-*tert*-leucine-derived thiazolidinethione reagent, affords a powerful method for the synthesis of either isomeric acetate aldol adduct in high enantiomeric purity and excellent yield. This work also further highlights the practical utility of phenyldichloroborane and (−)-sparteine for the enolization of *N*-acyl thiazolidinethione reagents and their subsequent highly selective acetate aldol reactions. Furthermore, the strategy behind the synthesis of this auxiliary should prove to be useful for the synthesis of analogues of other L-*tert*-leucine-derived reagents and catalysts. The application of this reagent to the synthesis of natural products is underway and will be reported in due course.

Acknowledgment. We wish to thank Professor Andrew Phillips for insightful discussions. This work was supported by the National Institutes of Health (GM48498) and Array Biopharma. NMR instrumentation used in this work was supported in part by the National Science Foundation CRIF program (CHE-0131003).

Supporting Information Available: Experimental procedures for the synthesis of reagent **2**, a representative procedure for conducting the aldol reaction, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048810T

(8) (*S*)-5-Phenylpentane-1,3-diol: $[\alpha]_D = -12.8$ (*c* 1.96, EtOH), lit. $[\alpha]_D = -7.2$ (*c* 1.52, EtOH). See: Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928. (*R*)-1-*O*-Benzyl-1,2,4-butanetriol: $[\alpha]_D = +9.64$ (*c* 0.85, MeOH), lit. $[\alpha]_D = +7.9$ (*c* 7.56, MeOH). See: Takano, S.; Hirama, M.; Seya, K.; Ogasawara, K. *Tetrahedron Lett.* **1983**, *24*, 4233.