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ENANTIOSELECTIVE ALDOL REACTION OF CHIRAL ACYL THIAZOLIDINE THIONE DERIVED BORON ENOLATES

by

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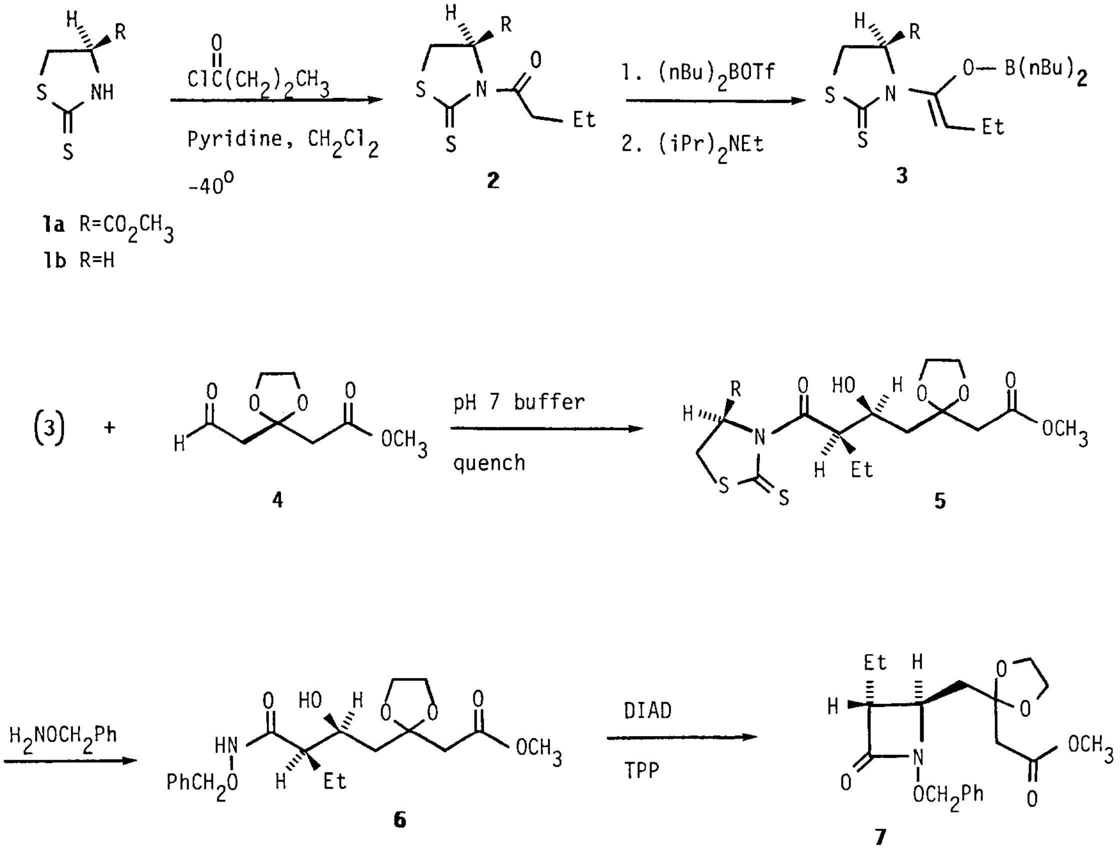
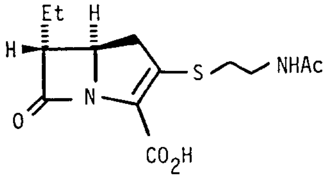
The compatability of an acyl thiazolidine thione as a chiral auxillary in boron enolate chemistry has been demonstrated by an enantioselective aldol condensation. The aldol products provide direct access to chiral β-lactams.

Processes for the diastereoselective and enantioselective formation of carbon-carbon bonds are becoming increasingly practical in organic synthesis.[1] Special emphasis has been given to the development of efficient stereoselective alkylations[2a] and aldol reactions[2b,c,3,4] of chiral metal enolates. Ideally, such asymmetric reactions should employ chiral auxillaries which are readily available, readily acylated, promote efficient enantioselective carbon-carbon bond formation and can be easily removed by solvolysis or aminolysis. The ability to recycle the chiral auxillary would also be desirable. Herein we report an aldol condensation of a chiral acyl thiazolidine thione derived boron enolate which meets all of these requirements. The use of the aldol product for the synthesis of an important chiral β-lactam is also demonstrated.

We were especially attracted to the use of acyl thiazolidine thiones for enantioselective aldol condensations because the acyl thiazolidine thione also serves as an effective active ester for subsequent elaboration.[5] In fact we have previously applied Mukaiyama's tin mediated aldol condensation of non chiral acyl thiazolidine thiones[3c] in a stereoselective synthesis of β-lactams.[6] While chiral versions of tin enolate chemistry have been reported using chiral diamines,[3a,b] we were interested in incorporating the chirality into the thiazolidine thione itself. The ready availability of optically pure 4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione **1a** from L-cysteine[7] and the reported ease of aminolysis (with chiral recognition)[7] of the corresponding acylated derivatives made its consideration for use as a chiral auxillary in aldol condensations very attractive. The high enantioselectivity of aldol reactions of chiral boron enolates[2c] also prompted us to study the previously unreported boron enolate (**3**) of a chiral acyl thiazolidine thione (**2**).

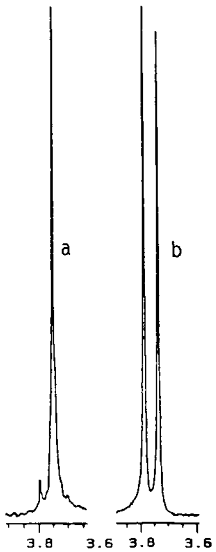
Scheme 1





8, PS-5

Figure 1
300 MHz ^{1}HNMR (with 40 mole % of $Eu(hfc)_3$) of the methyl ester region of a) optically active **7** and b) racemic **7** (prepared by the process described in ref 6 and by use of the boron enolate with **1b**)



We therefore decided to test the compatability of boron enolate chemistry with **1a.** Indeed acylation of **1a** ($[\alpha]_D^{20}$ = -64.5°)[7,8] with butyrl chloride (pyridine, CH_2Cl_2, -40° to 0°) provided the optically active acyl derivative **2a**[9] ($[\alpha]_D^{20}$ = -123.5° (c = 1.9, $CHCl_3$)) in 97% yield. Treatment of **2a** (480 mg, 1.943 mmole) with $(nBu)_2BOTf$ (2.01 mL of a 1.0 M solution in CH_2Cl_2) under N_2 for 5 min at 0° in CH_2Cl_2 (20 mL) followed by slow addition of diisopropyl ethyl amine (350 μl, 2.01 mmole) at 0°C gave a light yellow solution which was stirred for another 30 min at 0°C. The solution was cooled to -78°C and aldehyde **4**[6,10] (368 mg, 1.96 mmole in 3 mL of CH_2Cl_2) was added. The mixture was stirred another 5 min at -78°C and then allowed to warm to 0°C over 20 min. Excess pH 7 phosphate buffer solution was added and the mixture was stirred vigorously at 0°C for 3 min. TLC (EtOAc/hexanes, 1:1) analysis of the crude product solution at this point indicated formation of only one new component (Rf = 0.28). Note that **no H_2O_2 or other oxidative workup was employed.**[11] Instead, the CH_2Cl_2 solution was separated, concentrated and directly chromatographed on silica gel (hexanes/EtOAc, 2:1) to provide the optically active erythro aldol product **5a**[9] (654 mg, 77%, $[\alpha]_D^{20}$ = -83°, c = 3.9, $CHCl_3$). Direct hydroxaminolysis of **5a** with O-benzylhydroxylamine (CH_3CN, 6h) provided the hydroxamate **6a**[9] ($[\alpha]_D^{20}$ = -8.8°, c = 3.7, $CHCl_3$) in 74% yield after chromatography. The chiral auxillary **1a** ($[\alpha]_D^{20}$ = -63.4°) was also recovered in 91% yield. Cyclization of **6** with triphenylphosphine diisopropyl azodicarboxylate (TPP/DIAD)[6,12] gave the β-lactam **7**[9] ($[\alpha]_D^{20}$ = + 21.9°, c = 1.88, $CHCl_3$) in 67% yield. Analysis of the optical purity of this compound was most straightforward. The 300 MHz NMR of **7** was identical to that of racemic **7** prepared previously[6] and by the same route shown in Scheme 1, but with non chiral thiazolidine thione (**1b**, R = H). However, addition of 40 mole % of tris [3-(heptafluoropropyl hydroxymethylene)-d-camphorato] europium(III), $Eu(hfc)_3$, clearly distinguished the racemic and chiral β-lactams (fig. 1) and indicated that **7** was present in at least 93% ee.

Thus, we have demonstrated that the readily available chiral acyl thiazolidine thione **1a** is compatible with boron enolate chemistry and provides products of significant optical purity which are also effective active esters and allow the chiral auxillary **1a** to be regenerated. Studies of the scope of this type of aldol condensation and extensions of this process to the preparation of optically pure carbapenems, like PS-5 **8**[13], and other natural products are in progress.

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9. Representative characterization data includes: **2a**, oil, ^{1}HNMR δ 0.95 (t, J = 7.5 Hz, 3H), 1.65 (quintet, J = 7.5 Hz, 2H), 2.90-3.75 (m, 4H), 3.80 (s, 3H), 5.65 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H); IR (neat) 1750, 1700, 1210, 1150, 770 cm^{-1}. **5a**, oil, ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 8 Hz, 3H), 1.64-1.80 (m, 1H), 1.86-2.00 (m, 1H), 2.05-2.22 (m, 2H), 2.75 (s, 2H), 3.25-3.36 (m, 2H), 3.69 (s, 3H), 3.82 (s, 3H), 4.03 (s, 4H), 4.20 (m, 1H), 4.87 (m, 1H), 5.67-5.70 (dd, J= 8.5 Hz, J = 3 Hz, 1H); IR (neat) 3525, 1720 (broad) cm^{-1}. **6**, oil, ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 8 Hz, 3H), 1.64-1.80 (m, 1H), 1.86-2.00 (m, 1H), 2.05-2.20 (m, 3H), 2.70 (s, 2H), 3.65 (s, 3H), 3.72 (s, broad, 1H), 4.00 (s, broad, 4H), 4.85 (s, 2H), 7.25-7.42 (m, 5H), 8.84 (s, broad, 1H); IR (neat) 3200-3600 (broad), 1730, 1660, 1200, 1010, 730 cm^{-1}. **7**, oil, ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3H), 1.54-1.68 (m, 2H), 2.00 (dd, J = 8.7 Hz, J = 14 Hz, 1H), 2.37 (dd, J= 3.9 Hz. J = 14 Hz, 1H), 2.58 (s, 2H), 2.61 (dt, J = 1.8 Hz, J = 6.6 Hz, 1H), 3.39 (ddd, J = 1.8 Hz, J = 3.9 Hz, J = 8.7 Hz, 1H), 3.69 (s, 3H), 3.82 - 4.02 (m, 4H), 4.95 (s, 2H), 7.30-7.50 (m, 5H); IR (neat) 3750, 3050, 1770, 1750 cm^{-1}.
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