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N-Acyl-2-benzoxazolinones in titanium-mediated aldol reactions ☆

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Abstract—*N*-Acyl-2-benzoxazolinones readily form trichlorotitanium enolates that react rapidly with aldehydes to provide crystalline *syn*-aldol adducts in high yield. The resulting products are simply converted to amides, esters, and thioesters. A simple, economical synthesis of 3-hydroxy-2-methylpentanoate *N*-propionylcysteamine thioesters based on these findings is presented.

This paper describes the synthesis of key precursors used for the chemo-biosynthesis of previously inaccessible analogues of natural products,[1] now possible through genetic engineering of secondary metabolic pathways.[2] The biosynthesis of novel 6-deoxyerythronolides and erythromycins by feeding synthetic analogues of the initial biosynthetic diketide unit, (2*S*,3*R*)-3-hydroxy-2-methylpentanoate, to suitably engineered microorganisms[3] is a primary example (Fig. 1).

This technology has proven to be broadly applicable, with an astonishing range of synthetic substrates being converted into polyketides. We were faced with the challenge of developing a simple, economical, and general synthesis of *syn*-3-hydroxy-2-methylcarboxylate ('diketide') *N*-acylcysteamine thioesters to support this technology. In developing this synthesis, we were not required to prepare the diketide in optically active form, taking advantage of the ability of the erythromycin polyketide synthase to achieve a kinetic resolution of the racemic diketide.[4] We thus began a search for an economical aldol reaction system that would support high *syn*-diastereoselectivity, be suitable for use in multi-kilogram scale reactions, and provide products that could be directly and simply transformed into thioesters. We report here the use of the trichlorotitanium enolate of *N*-propionyl-2-benzoxazolinone, and demonstrate its use in the preparation of the starting diketide unit in erythromycin biosynthesis.

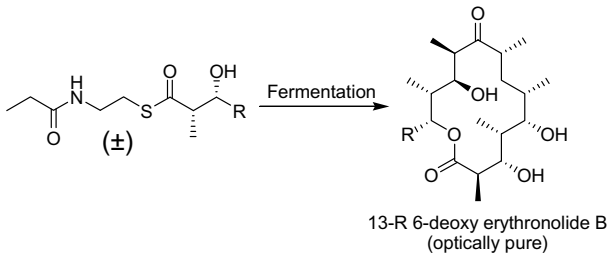

Figure 1.

Titanium tetrachloride-mediated aldol reactions have been shown to provide high levels of *syn*-diastereoselectivity.[5] Excellent enantioselectivities can be obtained through the use of chiral oxazolidinones,[6a] oxazolidinthiones, and thiazolidinethiones in combination with (−)sparteine.[6b] We had hoped that the titanium enolate of the achiral *N*-propionyl oxazolidinone **1** would provide good *syn*-selectivities in the aldol reaction. Interestingly, our initial attempts were unacceptable with respect to both yield and diastereoselectivity (Scheme 1). Both of these parameters were improved significantly with the addition of 2 equiv of (−)sparteine to the reaction mixture prior to addition of the aldehyde. Although this result was satisfying, the use of this costly chiral reagent was unattractive for the large-scale preparation of aldol adducts.

Based on these results we searched for an auxiliary and reagent combination that would be economical and would provide improved *syn*-selectivity. Although we had no knowledge a priori as to the behavior of *N*-acyloxazolones in Ti(IV)-mediated aldol processes, these compounds had other properties that make them

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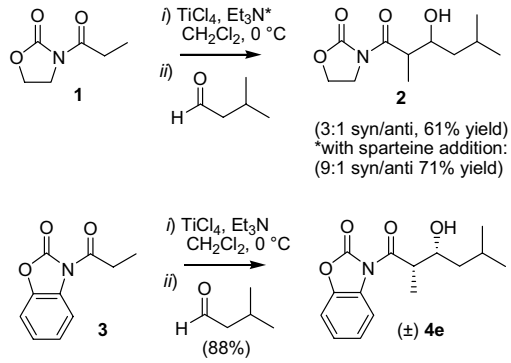


Scheme 1.

quite attractive for large-scale synthesis. They are known to be suitable as acyl donors and can easily be converted to the analogous amides, esters, and thioesters.[7] In addition, the *N*-propionyl derivative of 2-benzoxazolinone is readily crystallized. We expected that the high crystallinity of this compound would be shared by the aldol products that descend from it. Furthermore, it is simply prepared from salicylamide[8] and is commercially available at low cost from a number of sources.

Formation of the trichlorotitanium enolate of *N*-propionyl benzoxazolinone **3** and subsequent reaction with 3-methylbutanal gave the *syn*-aldol adduct **4e**, which is crystalline as the racemate[9] (Scheme 1). Investigation of the scope of the reaction[10] using an array of aldehydes with triethylamine as the base (Table 1) revealed consistently high yields and diastereoselectivities.[11] Additionally, extremely base-sensitive aldehydes may be converted into their *syn*-aldol adducts (entries **4h** and **4i**) in good yield, suggesting a very mild enolate.

Reduced selectivity is seen with alkoxy aldehydes and highly hindered systems such as pivalaldehyde. This is to be expected since the stereochemical outcomes of these aldol reactions are expected to be dependent upon coordination of the aldehyde to titanium.[12] The presence of additional ligands, such as pendant ethers on the aldehyde, or solvents, such as THF,[13] which may perturb this coordination, are known to significantly alter diastereoselectivity.[14] The reaction with pivalaldehyde, in fact, favored the *anti*-adduct, presumably due to steric interference with the association of the aldehyde to the titanium.[15] It is of interest that this reversal of diastereoselectivity was noted in the reaction of pivalaldehyde in oxazaborolidinone-promoted aldols, where it was ascribed to hydrogen-bonding interactions between the aldehyde hydrogen and the oxazaborolidinone ring oxygen.[16] In the present case, there can be no such H-bonding interactions at work.

Table 1. Aldol adducts (**4**) resulting from $TiCl_4$-mediated condensation of *N*-propionyl-2-benzoxazolinone (**3**) with RCHO

Entry	R_1	Yield (%)	*syn:anti*
4a	CH_2CH_3	72	>95:5
4b	$CH{=}CH_2$	73	>95:5
4c	Ph	88	>95:5
4d	CH_2OCH_2Ph	60	90:10
4e	$CH_2CH(CH_3)_2$	88	>95:5
4f	$CH_2CH_2CH_3$	80	>95:5
4g	$CH(CH_2)_2$	84	>95:5
4h	CH_2CH_2Cl	63	>95:5
4i	CH_2CH_2F	50	>95:5

Most importantly, the aldol procedure of Scheme 1 is readily amenable to multi-mole scale processes,[17] giving good selectivity at 0 °C using inexpensive reagents. In most cases, the workup procedure is particularly simple, consisting of a quench with aqueous HCl followed by filtration of the organic phase through a pad of silica gel and crystallization of the product.

Simple models indicate that formation of the (*Z*)-enolate of *N*-propionyl-2-benzoxazolinone (Fig. 2) should be enforced by steric interactions between the enolate methyl and H4 of the fused aromatic ring. Additionally, aromatic stabilization of the bi-dentate enolate should help to form a more ordered 'chelated' transition state. Strong preference for the (*Z*)-enolate is expected to result in high *syn*-selectivity in the subsequent aldol addition, as is the case for boron-mediated aldol addition reaction where enolate geometry and product stereochemistry are strongly coupled.[18]

N-Acylbenzoxazolinones have been previously prepared by treatment of carboxylic acids with phosphonate reagents.[19] An improved preparation of **3** was developed based on our observation that acylation by acid anhydrides (but not acid chlorides) is catalytic in base. Thus, treatment of an acetone or acetonitrile solution of 2-benzoxazolinone with propionic anhydride and 0.1 M equiv of potassium carbonate gives **3** in 98% yield after simple precipitation from water.[20]

Displacement of 2-benzoxazolinone from the aldol products occurs under extremely mild conditions and with a wide variety of nucleophiles. Amines react readily with the aldol adducts (**4**). Treatment of an ethereal solution of **4f** with 1.1 equiv of benzylamine resulted in conversion to the corresponding benzylamide in 95%

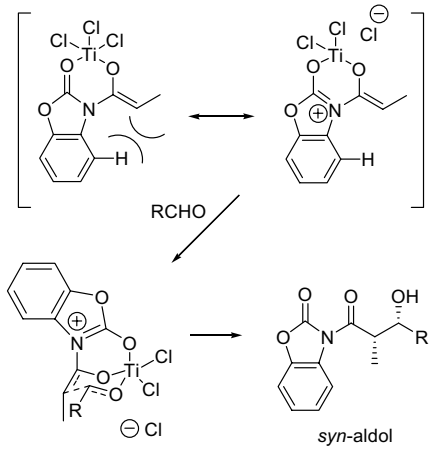
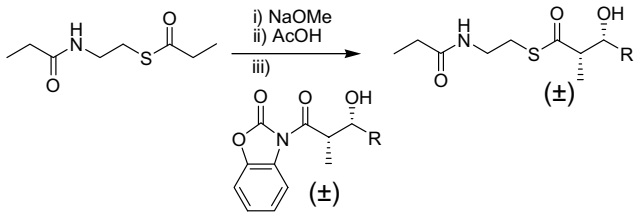


Figure 2.



Scheme 2.

yield. The corresponding methyl ester of **4f** was formed in 74% yield using catalytic dimethylaminopyridine in methanol.

Application of the aldol adducts to the synthesis of *N*-propionylcysteamine thioesters is equally direct. The sodium salt of the *N*-acylcysteamine is prepared in situ by reaction of the air-stable donor thioester (in this case, an *N*,*S*-diacylcysteamine) with sodium methoxide in methanol. The thiolate is then partially quenched by addition of acetic acid, followed by addition of the aldol products **4**. This procedure avoids oxidative formation of disulfides commonly observed with free thiols and results in clean, efficient thiolate generation. The main side reaction is in situ methanolysis of the thioester product. We have found that quenching approximately 80% of the free thiolate prior to addition of the aldol product significantly reduces methyl ester formation and provides yields of 80–85% typically (Scheme 2).[21]

In summary, chlorotitanium enolates of *N*-propionyl-2-benzoxazolinone react with a variety of aldehydes to give crystalline aldol products of high yield and *syn*-diastereoselectivity. Additionally, a simple procedure for acylation and purification of the parent benzoxazalinone has been developed. This coupled with extremely mild thiolysis conditions provides an economical synthesis of racemic *syn*-diketide thioesters that is practical from the 100-mg scale up to tens of kilograms. This process should greatly facilitate the production of novel polyketides through bioconversion using genetically manipulated polyketide synthases.

Acknowledgements

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9. To date, all of the aldol products have been crystalline.
10. General procedure for aldol condensations: $TiCl_4$ (1.1 equiv) is added over 5 min to a 0.5 M solution of **3** (1.0 equiv) in anhydrous CH_2Cl_2 at 0 °C under an N_2 atmosphere and the resulting yellow slurry is stirred vigorously for 15 min. Triethylamine (1.1 equiv) is added over 5 min and the resulting deep red solution and is stirred for 60 min. Freshly distilled aldehyde (1.1–1.5 equiv) is added rapidly, and the reaction is stirred for 90 min. The excess reagents are quenched by addition of one volume of 2 N HCl. The phases are separated, and the organic phase is processed using one of two procedures. (A) The organic phase is filtered through a pad of silica gel, the silica was rinsed with ether, and the organic eluents are combined. (B) One volume of ether is added and the mixture is washed sequentially with 2 N HCl (2×), satd aq $NaHCO_3$ (2×), and brine. The organic layers from either method are dried over $MgSO_4$, filtered, and concentrated under vacuum to give the crude product, which typically crystallizes upon standing. The product is purified either by recrystallization or by flash chromatography.
11. In most cases none of the *anti*-isomer could be observed by NMR, suggesting a diastereoselectivity of >95:5.
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15. Reaction with pivalaldehyde under standard conditions (i.e., rapid addition of the aldehyde to the enolate) gave a 1:1 mixture of *syn* and *anti* adducts. Slow addition of pivalaldehyde gave a 86:14 ratio of *anti* and *syn* products. The major product was identified as the *anti*-diastereomer by reduction with $LiAlH_4$ and conversion to the acetonide, which gave a product identical to the *anti*-isomer described by Kiyooka, S.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511–5523.
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20. A solution of 2-benzoxazolinone (135 g, 1.0 mol) in acetone (750 mL) was treated with potassium carbonate (14 g, 0.1 mol) and with propionic anhydride (130 mL, 1.0 mol) at ambient temperature with stirring. After 4 h, the mixture was poured into 3 L of water with vigorous stirring. The precipitated product was collected by vacuum filtration, washed with water, and air dried to yield 187 g (98%) of light tan-colored product suitable for further use; mp = 88–90 °C (uncor). Recrystallization from ether yields the pure product, 172 g (90% yield).

21. To a solution of *N*,*S*-dipropionylcysteamine (1.1 equiv, 1 M) in methanol and is added a sodium methoxide solution (25%, 1.1 equiv) with stirring. Upon consumption of starting material (~15–20 min as monitored by TLC) acetic acid (0.8 equiv) is added, followed by addition of the aldol product. The reaction is monitored by TLC until complete (~10 min) and quenched with acetic acid (0.6 equiv). The reaction mixture is concentrated and purified by column.