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Kinetic Resolution of Protected α-Amino Acid Derivatives by a Chiral *O*-Nucleophilic Acyl Transfer Catalyst

Gregory T. Notte and Tarek Sammakia*

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

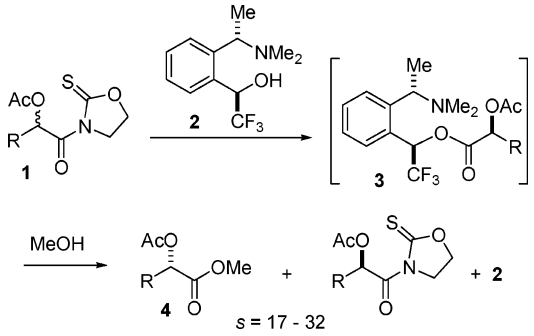
Received November 24, 2005; E-mail: Sammakia@colorado.edu

We recently described a method for the kinetic resolution of (α-acetoxy)oxazolidinethione imides using catalyst **2** (Scheme 1).[1] This catalyst likely operates by an *O*-nucleophilic mechanism[2] wherein the selectivity-determining step involves attack of the hydroxyl group of the catalyst on the active ester of the substrate (**1**) with general base catalysis from the proximal nitrogen of the catalyst to form an acyl-catalyst intermediate (**3**).[2a] Attack of methanol on **3**, again with base catalysis by the proximal nitrogen, provides the methyl ester (**4**) and regenerates the catalyst. In this communication, we describe the use of this catalyst for the kinetic resolution of protected α-amino acid derivatives. The asymmetric synthesis of amino acids is a topic of current interest to the synthetic community.[3,4] In an elegant approach, Deng has recently described the kinetic resolution of *N*-carboxy anhydride derivatives of α-amino acids using modified cinchona alkaloids.[5] While this is an excellent method for the synthesis of acyclic amino acids, the corresponding reaction has not been described for the synthesis of cyclic amino acids, and this class of substrates is generally more difficult to prepare in nonracemic form. Our method is notable in that it provides excellent levels of selectivity with many cyclic substrates and allows for their preparation in high enantiomeric excess.

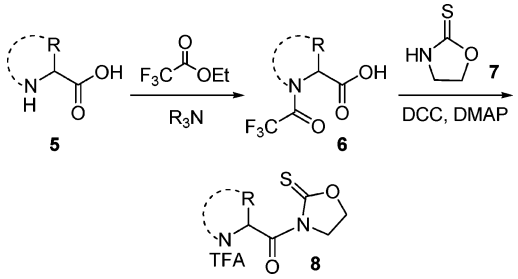
Based on our earlier studies of the methanolysis of α-acetoxy imides,[1] we chose to use *N*-acyl oxazolidinethione imides as our active esters since these compounds were expected to provide higher levels of enantioselectivity than the corresponding *para*-nitrophenyl esters. We also chose to protect the α-amino group as the trifluoroacetamide as this would not only offer a readily removable protecting group[6] but also provide inductive activation of the carbonyl group. The substrates for this study were prepared by first converting the amine to the trifluoroacetamide (ethyl trifluoroacetate and either tetramethylguanidine or triethylamine), followed by activation of the carboxylic acid as the oxazolidinethione imide (DCC, DMAP, and oxazolidinethione **7**, Scheme 2).[7]

We first studied the kinetic resolution of the cyclic substrates shown in Table 1 (entries 1−6) and were pleased to find that the standard reaction conditions from our previous study (5−10% catalyst **2**, 30 equiv of methanol in toluene at 0 °C to room temperature) provide excellent levels of selectivity, with selectivity factors (*s*-factors)[8] ranging from 20 to 86 for all but one substrate. The most selective substrate in this series, the pipecolinic acid-derived substrate (**10**), reacts with an *s*-factor of 86 and provides recovered starting material in greater than 99% ee after only 53% conversion[9] (entry 2). The azepane-2-carboxylic acid-derived substrate (**9**) reacts with an *s*-factor of 20 and provides recovered starting material in 96% ee at 58% conversion (entry 1). Curiously, the azetidine-2-carboxylic acid-derived substrate (**12**) reacts with an *s*-factor of only 1.1 (entry 4). We do not understand the difference in selectivity between this substrate and the other cyclic substrates we have examined which provide high levels of selectivity.

Scheme 1. Kinetic Resolution of α-Acetoxy Imides



Scheme 2. Synthesis of Substrates



We then studied the kinetic resolution of the acyclic substrates shown in Table 1 and found that all substrates examined reacted with excellent levels of selectivity with *s*-factors ranging from 20 to 68 (entries 7−11). The valine-derived substrate (**15**) was the most hindered substrate studied and was found to react with an *s*-factor of 20, whereas the less hindered, unbranched substrates provide *s*-factors of 37 to 68. We also studied the use of a reduced catalyst loading of 5% and found that the reaction proceeds with comparable selectivity but at about half the rate (entries 8 and 9).

The acyclic substrates are significantly more reactive than their cyclic counterparts, and as such, these reactions were conducted at lower temperature (−26 to 0 °C). In our prior mechanistic studies on related systems, we provided evidence that the turnover limiting step of the catalytic cycle is the methanolysis of the acyl-catalyst intermediate.[2a] As such, the greater activity of the acyclic substrates could be attributed to the presence of the acidic N−H of the trifluoroacetamide, which can form a hydrogen bond with the carbonyl of this intermediate and activate it toward methanolysis as shown in Figure 1.[10]

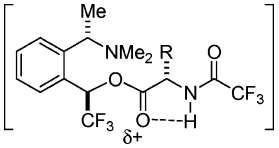


Figure 1. Hydrogen bonding in acyl-catalyst intermediate.

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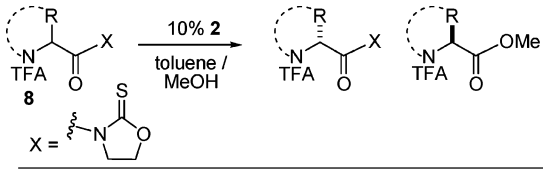
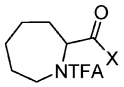
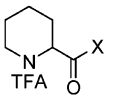
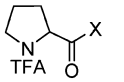
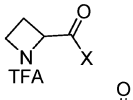
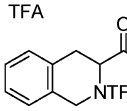
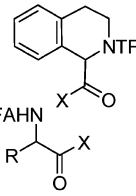
Table 1. Methanolysis of Protected α-Amino Oxazolidinethione Imides



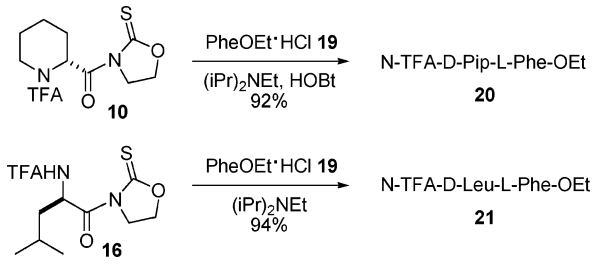
entry	substrate		Temp (°C)	Time (h)	% conv	ee recov sm	s^a
1		**9**	rt	54	58	96%	20
2		**10**	0	70	53	>99%	86
3		**11**	rt	99	58	98%	22
4		**12**	0	30	54	3%	1.1
5		**13**	0	71	52	93%	41
6		**14**	0	55	54	96%	40
7	R = *i*-Pr	**15**	0	39	55	90%	20
8	R = *i*-Bu	**16**	-26	25	55	>99%	68
9[b]	R = *i*-Bu	**16**	-26	50	57	>99%	61
10	R = allyl	**17**	-26	7	52	95%	60
11[c]	R = $MeSCH_2CH_2$	**18**	-26	7	57	>99%	37

[a] All *s*-factors are the average of two runs. [b] 5% catalyst loading. [c] Dichloromethane was used as solvent for solubility purposes.

An important feature of this method is that the recovered starting materials can serve directly as substrates in peptide coupling reactions. Thus, in the presence of Hünig's base and HOBt, the coupling of recovered **10** with phenylalanine ethyl ester proceeds in 92% yield with no detectable racemization (Scheme 3). Similarly, the coupling of **16** and phenylalanine ethyl ester proceeds in the presence of Hünig's base in 94% yield with 3% racemization (unoptimized, starting material of 99% ee provides product in a 98:2 diastereomeric ratio, Scheme 3).

In conclusion, we have described a new method for the kinetic resolution of α-trifluoroacetamido *N*-acyl oxazolidinethiones using a readily prepared catalyst. The reaction has a wide substrate scope and provides material of high enantiomeric excess. The application of this method to the synthesis of complex amino acid derivatives will be described in due course.

Scheme 3. Peptide Coupling with Recovered Oxazolidinethiones



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Supporting Information Available: Experimental procedures for the synthesis and characterization of all new compounds as well as ^1H and ^{13}C spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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