Asymmetric Conjugate Addition of Thiols to Chiral β-Substituted N-Enoylsultams

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Summary: In the presence of 1.5 equiv of $TiCl_4$, the conjugate addition of thiols to chiral β-substituted N-enoylsultams gave the conjugate addition adduct in good chemical yield and a wide range of diastereoselectivity (0–98% de).

The introduction of a new asymmetric center at the β-position of a carboxylic acid containing unit has been a considerable challenge in synthetic organic chemistry.[1] Since the development of asymmetric Lewis acid catalyzed Diels–Alder reactions of chiral α,β-unsaturated N-acyloxazolidinones reported by Evans[2] and conjugated N-enoylsultams by Oppolzer,[3] the application of these concepts to create new stereogenic centers at the α, β, or both positions via nucleophilic addition reactions has been studied widely in the past few years. Representative examples are asymmetric conjugate addition of Grignard reagents[4] and organocuprates[5] to substituted N-enoylsultams, conjugate addition of dialkyl aluminum chlorides to α,β-unsaturated N-acylurethanes,[6] asymmetric nitrile oxide cycloadditions with Oppolzer's chiral sultam,[7] ene reactions,[8] and conjugate addition reactions of allyltrimethylsilanes[9] with α,β-unsaturated N-acyloxazolidinones.

The structure of complex **2a** formed by the treatment of N-crotonoylbornane-10,2-sultam (**1a**) with 1.5 equiv of $TiCl_4$ has been determined by X-ray crystallographic analysis[10] and is thought to be the key intermediate in the asymmetric Diels–Alder addition of cyclopentadiene. This reaction favors addition from the less hindered bottom face and proceeds with >90% asymmetric induction. This model has also been proposed in many other Lewis acid catalyzed asymmetric nucleophilic addition reactions. We therefore anticipated that the addition of a thiol to conjugated N-enoylsultams in the presence of $TiCl_4$ would provide β-mercaptocarboxylic acid derivatives **3** with good asymmetric induction.[11]

Scheme 1

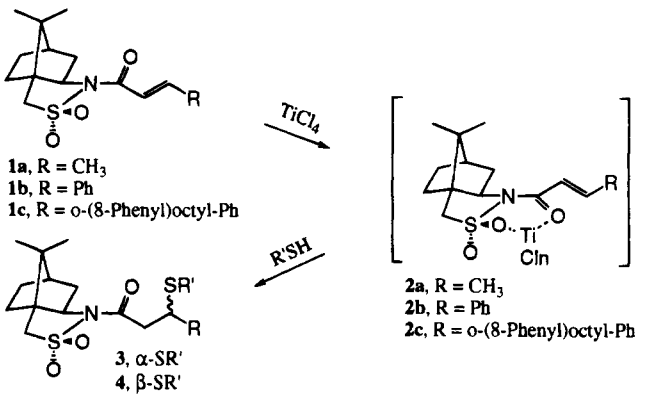

Table 1. Conjugate Addition of Methyl Thioglycolate to 1a[a]

N-acylamide	catalysts	T (°C)/t (h)[b]	ratio of 3a/4a[c]	% yield of 3a and 4a[d]
1a	Et_3N	−78/2	50:50	65
1a	Et_2AlCl	25/5	70:30	51
1a	$BF_3{\cdot}OEt_2$	25/75		NR
1a	$TiCl_4$	−78/3	80:20	96
1a	$LiSCH_2CO_2Me$[e]	−50/5	50:50	86

[a] Methylene chloride as solvent, 1.5 equiv of Lewis acid, and 5 equiv of the thiol was used. [b] T = temperature, t = time. [c] Diastereomeric isomer ratios were determined by using 200 MHz ^1H NMR spectroscopy of the crude products. [d] Isolated yield. NR = no reaction. [e] 10 mol % of the lithium thiolate was used and tetrahydrofuran as solvent.

Initially, we investigated the addition of methyl thioglycolate to chiral N-crotonoylbornane-10,2-sultam (**1a**) in the presence of a variety of Lewis acid catalysts (Scheme 1). The results are summarized in Table 1 and are discussed below. The chiral N-crotonoylbornane-10,2-sultam (**1a**), prepared according to a literature procedure,[12] was treated with 5 equiv of methyl thioglycolate in the presence of 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 3 h. The 1,4-addition adducts **3a** and **4a** were obtained in excellent yield (96%) and with a diastereomeric ratio of 80:20. When Et_2AlCl, a Lewis acid commonly employed for asymmetric conjugate addition reactions, was used in this reaction, the Michael adducts **3a** and **4a** were isolated in 51% yield and in 40% diastereomeric excess. Boron trifluoride etherate was found to be incapable of promoting this 1,4-addition

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Table 2. Titanium Chloride Promoted Conjugate Addition of Thiols to Chiral β-Substituted *N*-Enoylsultams[a]

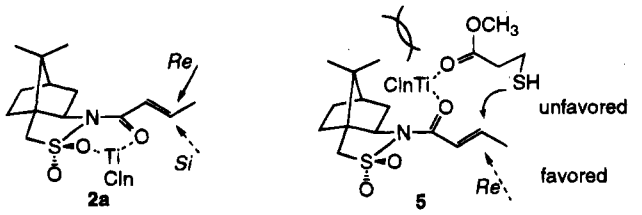
entry	*N*-enoylsultam	thiols	*T*(°C)/*t*(h)[b]	products	ratio of **3** and **4**[c]	% yield of **3** and **4**[d]
1	**1a**	CH_3COSH	25/24	**3b/4b**	86:14	56
2	**1a**	$HSCH_2CH_2CO_2Me$	−78/6	**3c/4c**	89:11	89
3	**1a**	$PhCH_2SH$	−78/48	**3d/4d**	65:35	79
4	**1a**	PhSH	25/24	**3e/4e**	60:40	98
5	**1a**	*o*-$(CO_2Me)C_6H_4SH$	−78/3	**3f/4f**	99:1	67
6	**1a**	$HSCH_2CO_2Et$	−60/1	**3g/4g**	85:15	85
7	**1b**	$HSCH_2CO_2Me$	−78/24	**3h/4h**	87:13	72
8	**1c**	$HSCH_2CH_2CO_2Me$	−45/16	**3i/4i**	95:5[e]	98

[a] Methylene chloride as solvent, 1.5 equiv of $TiCl_4$, and 5 equiv of the thiol were used. [b] T = temperature, t = time. [c] Diastereomeric isomer ratios were determined by using 200 (or 400) MHz ^1H NMR spectroscopy of the crude products. [d] Isolated yield. [e] This ratio was determined by HPLC.

reaction. In the presence of 1 equiv of Et_3N, the reaction went more rapidly, but a 50:50 mixture of diastereomers was obtained. Poor stereoselectivity was also observed in the same reaction catalyzed by 10 molar % of lithium thiolate derived from methyl thioglycolate. The configuration of the newly formed stereogenic center is unknown at this point.

Under the optimal reaction conditions, addition of methyl thioglycolate to the more electron rich olefin **1b** derived from cinnamic acid, a longer reaction time (24 h) is required to obtain 99% yield of the 1,4-addition products **3i** and **4i** as a 87:13 mixture of diastereomers (entry 7, Table 2). We also found that a variety of thiols will react in a 1,4-fashion with chiral *N*-crotonoylbornane-10,2-sultam (**1a**) to give Michael adducts in good chemical yield. Interestingly, the use of benzylmercaptan and thiophenol as nucleophiles under the described reaction conditions gave very poor asymmetric induction (<15% de) (entries 3 and 4, Table 2). The major stereoisomers of these two runs were not determined. However, the reaction of methyl 3-mercaptopropionate with *N*-crotonoylbornane-10, 2-sultam (**1a**) in the presence of 1.5 equiv of $TiCl_4$ gave an 89% yield of Michael adducts **3c** and **4c** as a 89:11 mixture of diastereomers (entry 2, Table 2). The structure of **3c** was unambiguous determined by X-ray crystallography which indicated the absolute configuration at C(β) to be R.[13] This result is completly opposite to our expectation based on the reactive intermediate **2a**. The unexpected facial stereoselectivity in the formation of **3c** and the significant difference of asymmetric induction between using methyl 3-mercaptopropionate and thiophenol as nucleophiles could be explained by transition states **2a** and **5** (Scheme 2). Since the β-position of conjugated *N*-enoylsultam is quite remote from the chiral auxiliary, the steric interaction between the chiral auxiliary and the nucleophile from either the *Si* or *Re* face during nucleophilic addition is not severe for nucleophiles such as benzylmercaptan and thiophenol as shown in transition state **2a**. However, when methyl 3-mercaptopropionate was used as a nucleophile, coordination between the ester group of the nucleophile and titanium of complex **2a** would bring the hydrocarbon moiety of the nucleophile closer to the chiral auxiliary and increase the steric interaction if addition

Scheme 2



occurs from the top face (*Si* face) as shown in transition state **5**. Therefore, nucleophilic addition favors attack from the bottom face (*Re* face) and proceeds with 78% asymmetric induction. The same argument can be applied to the reactions when thioacetic acid and methyl thioglycolate were used as nucleophiles but through different ring size (8- and 9-membered rings instead of 10-membered ring) of the transition state. The coordination between the ester functionality and titanium seems to be the major factor in obtaining high asymmetric induction. To test this hypothesis, the reaction of *N*-crotonylbornane-10,2-sultam (**1a**) with methyl thiosalicylate was carried out (entry 5, Table 2). As expected, this reaction gave the conjugate addition adducts as almost one single isomer (>98% de). The absolute configuration of **3f** at C(β) was also determined to be R by X-ray crystallography.[13]

In conclusion, we have developed a new and highly enantioselective syntheses of β-mercaptocarboxylic acid derivatives. The reaction mechanisms and application of this methodology to the synthesis of optically pure sulfur-containing medicinals and natural products are now under investigation.

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Supplementary Material Available: Experimental procedures, spectral data for conjugate addition adducts **3a-3j**, and an ORTEP drawing of **3f** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) X-ray crystallographic data of compounds **3c** and **3f** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.