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The Use of Samarium Enolates, A Novel Alternative in the Addition Reactions to Imines. Synthesis of 3-Amino Esters, Amides and Enantiopure 3,4-Diamino Esters

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Abstract: An efficient reaction of tosylimines with a range of samarium enolates (derived from esters, and amides) is reported. The reaction with the α-dibenzylamino-*N*-*tert*-butanesulfinimine derived from chiral phenylalaninal afforded the corresponding enantiopure 3,4-diamino ester with very high diastereoselectivity.

Keywords: addition to carbonyl compounds; enolates; imines; Mannich reaction; samarium

Considerable effort has been made to develop approaches to 3-amino acids and their derivatives in recent years due to their synthetic importance.[1] In addition, the β-amino acid moiety is present in several biologically active natural products,[2] and pharmacologically important compounds.[3] Moreover β-peptides[4] are present in various drugs.[5]

Thus, many syntheses of 3-amino acids and their derivatives have been reported.[6] Among these methods, the addition reaction of enolates derived from acid derivatives to imines (Mannich-type reaction) constitutes an efficient method to obtain 3-amino acids or their derivatives. The efficiency of a Mannich-type reaction depends on various factors, *inter alia*, the amino component of the imine and the metal of the enolate play important roles. Thus, *N*-sulfonylimines (due to their high reactivity) and the readily available lithium enolates have been extensively used as starting materials. However, the high basicity of lithium enolates sometimes produces undesirable enolization of the starting imines. To overcome this drawback, new less basic enolates derived from other metals have been utilized. In this sense, samarium enolates[7] could be a valuable alternative to the use of lithium enolates due to their lower basicity. However, to the best of our knowledge, the addition reaction of samarium enolates to imines has not been reported.

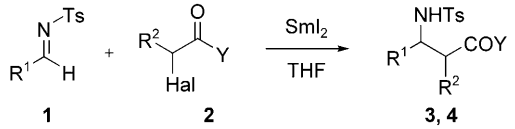
Thus, we report herein the synthesis of 3-amino esters or amides by reaction of imines derived from *p*-toluenesulfonamide with samarium enolates derived from esters or amides. This novel method was also employed to prepare enantiopure 3,4-diamino esters with total stereoselectivity, from chiral 2-amino imines, which were readily available from the corresponding 2-amino aldehydes derived from natural 2-amino acids.

Initially we studied the addition reaction of samarium enolates, derived from esters, to imines. The starting imines **1** derived from *p*-toluenesulfonamide were prepared in high yields according to a method previously reported.[8] The samarium enolates were prepared *in situ*, by treatment of a solution of the corresponding 2-halo ester **2** (1 equiv.) and the imine **1** (1 equiv.) in THF with a solution of 2.5 equiv. of SmI_2 in THF (0.1 M)[9] at room temperature. After 3.5 h of reaction at room temperature, 3-amino esters were obtained, with the yields shown in Table 1.

Products **3** were obtained along with minor by-products with the imines derived from benzaldehyde and phenylacetaldehyde; in the case of *N*-tosylbenzaldimine, the diamine derived from a pinacol coupling reaction was the major product obtained. To overcome these adverse results, the samarium enolate was generated beforehand by reaction of the corresponding chloro esters with SmI_2 at −20 °C for 30 min. Then, imines **1e** or **1f** were added dropwise and the mixture reaction was stirred for 30 min at the same temperature. After stirring for 3.5 additional hours at room temperature the amino esters **3e** or **3f** were obtained in good yields as shown in Table 1.

We also studied the synthesis of 3-amino amides. Thus, the reaction of imines with samarium enolates generated *in situ* from a range of 2-chloroamides in

Table 1. Synthesis of 3-amino esters and amides **3** and **4**.



1 + **2** → **3, 4**

Entry	**1**[a]	**3** or **4**	R^1	R^2	Y	Yield[%][b]
1	**1a**	**3a**	$PhCH_2CH_2$	H	OEt[c]	69
2	**1b**	**3b**	*s*-Bu	H	OEt[c]	63
3	**1c**	**3c**	*c*-C_6H_{11}	H	OEt[c]	67
4	**1d**	**3d**	*n*C_7H_{15}	Me	OEt	67
5	**1e**	**3e**	Ph	Me	OEt	60
6	**1f**	**3f**	$PhCH_2$	*n*-C_5H_{11}	OEt	61
7	**1a**	**4a**	$PhCH_2CH_2$	H	NEt_2	81
8	**1c**	**4b**	*c*-C_6H_{11}	H	[d]	85
9	**1e**	**4c**	Ph	H	NEt_2	80
10	**1f**	**4d**	$PhCH_2$	Me	[d]	74
11	**1b**	**4e**	*s*-Bu	Me	[d]	73
12	**1d**	**4f**	*n*-C_7H_{15}	Ph	[d]	73

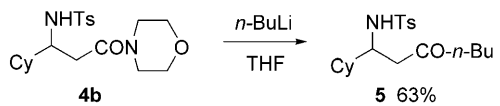
[a] Unless otherwise noted, Hal = Cl.
[b] Isolated yield after column chromatography based on compounds **1**.
[c] Hal = Br.
[d] From morpholine amide.

THF at room temperature for 3.5 h gave the corresponding 3-amino amides **4** in high yields (>73%). In all cases, the yields obtained from amides were higher (10–20%) than those obtained from ester enolates (Table 1).

The synthesis of 3-amino esters or amides was general. In both cases, no differences were observed starting from linear, branched or cyclic aliphatic and aromatic imines, or when the structure of the starting enolates was changed (R^2, the halogen atom in the esters and the amine group of amides). The starting halo compounds **2** ($R^2 \neq H$) allowed the formation of a diastereoisomeric mixture of **3** or **4**, (*dr* ranged between 1:1 and 3:1).

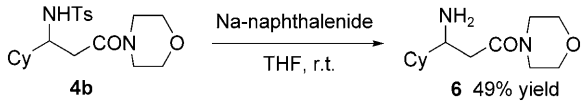
Taking into account that amides derived from morpholine can be readily transformed into ketones by reaction with organolithium reagents,[10] butyl ketone **5a** was directly obtained from compound **4b**. So, treatment **4b** with *n*-butyllithium at −78 °C for 1 h afforded amino ketone **5** in 63% yield (Scheme 1).

Furthermore, the *N*-substituent on 3-amino carboxylic acid derivatives was easily removed by using sodium naphthalenide, following a method previously reported.[11] Thus, compound **4b** was deprotected to give **6** in 49% isolated yield after purification (Scheme 2).



4b → **5** 63%

Scheme 1. Synthesis of 3-amino ketone **5**.



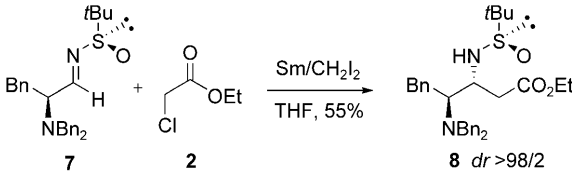
4b → **6** 49% yield

Scheme 2. Deprotection of *N*-tosyl-3-amino amide **4b**.

Synthesis of enantiopure 3,4-diamino esters 8: 3,4-Diamino acids[12] are a type of amino acid that has been the subject of growing interest, due to their capacity to modify biological properties in small peptides,[13] and their pharmacological activity.[14] In addition 3,4-diamino acid derivatives are precursors of various organic compounds, for example 2-aminopyrrolidinones or 3-aminopyrrolidines.[15] However, very few preparative methods have been reported,[15,16] and, in general, the described syntheses took place through multi-step reactions in low overall yields.

Based on this background, we performed the synthesis of the enantiopure 3,4-diamino ester **8** by reaction of the samarium enolate with the imine derived from L-*N,N*-dibenzylphenylalaninal. Unfortunately, the reaction of the samarium enolate with the tosylimine derived from phenylalaninal[17] afforded the expected 3,4-diamino ester in only 5% yield. To improve the yields, we performed the reaction with imine **7** prepared by reaction of phenylalaninal with (*R*)-2-methyl-2-propanesulfinamide.[18] However, no higher yields of the diamino ester were obtained under the same reaction conditions as those employed to obtain compounds **3** or **4**. The best results were obtained when samarium diiodide was generated *in situ*

from a Sm/CH_2I_2 mixture.[19] Thus, the addition of diiodomethane to the mixture of imine **7** [derived from phenylalaninal, and (*R*)-2-methyl-2-propanesulfinamide], ethyl chloroacetate and samarium powder in THF at 0 °C and further stirring at room temperature for 6 h gave the corresponding diamino ester **8** in 55% yield (Scheme 3).

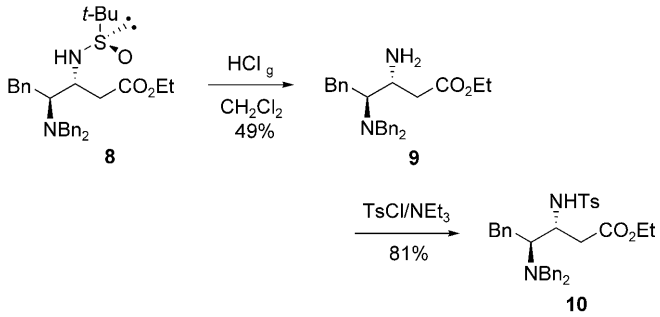


Scheme 3. Synthesis of enantiopure 3,4-diamino ester **8**.

The total stereoselectivity ($dr > 98:2$) of the addition reaction was established based on the ^1H NMR data and of crude reaction product **8** which revealed the presence of only one stereoisomer. The absence of the other stereoisomer proved that no racemization took place in the reaction.

The absolute configuration of the 3,4-diamino ester **8** was established after its transformation into ethyl (3*R*,4*S*)-5-phenyl-4-(*N*,*N*-dibenzylamino)-3-(tosylamino)pentanoate **10**, following the synthetic pathway described (Scheme 4). The spectroscopic data of **10** were identical with those of the same product, previously prepared and characterised (X-ray analysis) by Reetz.[20]

This absolute configuration is in agreement with that obtained in the previously reported addition of



Scheme 4. Synthesis of enantiopure 3,4-diamino esters **9** and **10**.

organometallic reagents to 2-dibenzylamino aldehydes,[21] chloromethyl ketones[21] or the reduction of chloromethyl ketimines.[22] Thus the stereochemical course of the addition reaction of samarium enolate **11** could be controlled by the bulky dibenzylamino group. In this case the addition of samarium enolate to imine **7** could take place under non-chelation control in which the most favoured transition state has the larger substituent (dibenzylamino group) *anti* to the attack of the samarium enolate (Scheme 5). A similar stereochemical course was observed in the addition of other anions to *N*-(3-*p*henyl-2-dibenzylaminopropylidene)-*tert*-butanesulfylamide.[18,23] However, additional studies to confirm this mechanism and to clarify the stereochemical effect of the sulfinyl group, should be carried out.

In conclusion, a novel addition reaction of samarium enolates derived from esters, and amides to imines derived from *p*-toluenesulfonamide is reported, as an alternative to the use of enolates derived from other conventional metals, to obtain 3-amino esters or amides. The reaction with *N*-(3-*p*henyl-2-dibenzylaminopropylidene)-*tert*-butanesulfylamide afforded the corresponding enantiopure 3,4-diamino ester with very high diastereoselectivity. Generalization of this reaction and studies to delineate all the factors involved in these transformations, including the mechanism, are currently under investigation in our laboratory.

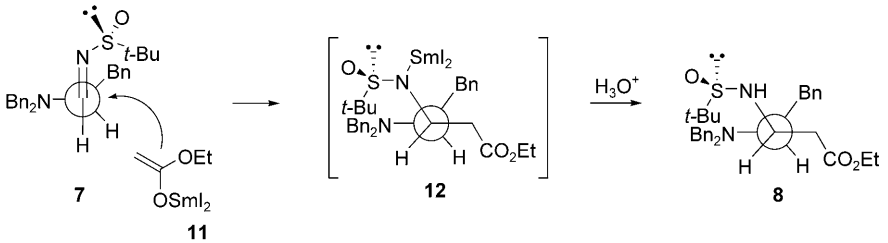
Experimental Section

General Procedure for the Synthesis of Compounds 1

Imines **1** were synthesized following the method reported in ref.[8]

General Procedure for the Synthesis of Compounds 3 and 4

To a stirred solution of the requisite imine **1** (0.4 mmol) and compounds **2** [ester or amide (0.4 mmol)] in THF (2 mL), a solution of SmI_2 in THF (10 mL, 2.5 equiv., 1.0 mmol) was added at room temperature. After stirring at the same temperature for 3.5 h, the excess of SmI_2 was removing by bubbling a stream of air through the solution. An aqueous solu-



Scheme 5. Mechanism of the addition to amino aldimines **7**.

tion of 0.1 N HCl (10 mL) was then added and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compounds **3** or **4**.

In the case of compound **3e**, the samarium enolate was previously formed at −20 °C and the imine **1e** was added subsequently. The reaction mixture was stirred at the same temperature for 30 min and then was left to reach room temperature for 3 h. After the corresponding hydrolysis and the purification the product **3e** was isolated in the pure state.

Synthesis of 5 from 4b

To a stirred solution of **4b** (0.4 mmol) in THF (2 mL), *n*-BuLi (1 mmol) was added at −78 °C. After stirring at the same temperature for 1 h, the reaction mixture was quenched with an aqueous solution of 0.1 N HCl (10 mL) and the aqueous phase was extracted with diethyl ether (3× 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compound **5**.

Synthesis of 6 from 4b

Deprotection of compound **4b** was carried by using the conditions described in ref.[11]

General Procedure for the Synthesis of Compounds 8

α-Amino imines **7** were synthesized following the method reported in ref.[17]

To a stirred solution of Sm(0) (3 equiv., 1.2 mmol), previously activated by heating, and THF (2 mL), the imine **7** (0.4 mmol), ester (0.4 mmol) and THF (10 mL) were added at room temperature. Then, CH_2I_2 (3 equiv., 1.2 mmol) was added and the reaction mixture was stirred at the room temperature for 6 h. The excess SmI_2 was removing by bubbling an stream of air through the solution and further treatment with an aqueous solution of 0.1 N HCl (10 mL). The aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 2:1) provided pure compound **8**.

General Procedure for the Synthesis of Compound 9

To a stirred solution of crude material **8** in CH_2Cl_2, was bubbled a stream of HCl (gas) for 15 min. The aqueous phase was extracted with CH_2Cl_2 and the organic layer was washed with $NaHCO_3$ and dried over Na_2SO_4. After removing the solvents, a crude mixture was obtained and purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to yield **9** as a pure compound.

General Procedure for the Synthesis of Compound 10

Triethylamine (1,1 equiv., 0.44 mmol) and tosyl chloride (1.1 equiv., 0.44 mmol) were added to a stirred solution of **9** (0.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was left to stir at room temperature for 12 h. An aqueous solution of 1 N HCl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with 1 N HCl, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography on silica gel (hexane/EtOAc, 3:1) provided pure compound **10** with the same spectroscopic data to those shown by the same product prepared by Reetz, see ref.[20]

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