

Note

Catalysis in water: Synthesis of β -amino amides by Sc(III) promoted condensation of silylketene pyridylthioacetal and imines

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Abstract

The scandium (III) catalysed condensation of silylketene thioacetals and pyridylthioacetals with imines in pure water was studied. The reaction of the phenylthioacetal derivatives brings always to β -aminoesters; the reaction of pyridylthioacetals leads to the stereoselective formation of β -lactams in organic solvents, while in the presence of a large amount of water affords β -amino amides in good yields. That represents a new, easy, one-pot catalytic synthesis in water of an interesting class of compounds, direct precursors of 1,3-diamino hydroxy compounds. The possibility of recovering and recycling the catalytic systems was also briefly investigated.

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1. Introduction

The development of new catalytic systems able to efficiently promote stereoselective reactions in water represents a fundamental research activity towards greener synthetic methodologies, alternative to those employing the traditional organic solvents [1]. However, despite the several advantages offered by the use of water as a solvent in terms of cost, safety and environmental impact, only a relatively limited number of organic reactions can be effectively carried out in this solvent [2]. One of the major reasons responsible for this situation is the solubility problem that has been tackled in different ways, including the use of organic cosolvents [3]. It must be noted, however, that a reaction medium with THF or ethanol as predominant component mixed to water, or a system where a large excess of organic reagents is employed in water loses most of its appeal and can be better described as a wet organic system rather than a real aqueous medium [4].

Therefore, the identification of catalytic procedures that can promote stereoselective reactions in pure water is a true challenge [5]. We wish to report here the results of our studies in the scandium (III) catalysed reaction of silyl ketene phenylthioacetals and silyl ketene pyridylthioacetals with imines in water, that was shown to lead to different compounds depending on the substrate and the reaction medium employed. The study is a further demonstration how water may play a decisive role in determining the output of stereoselective organic reactions.

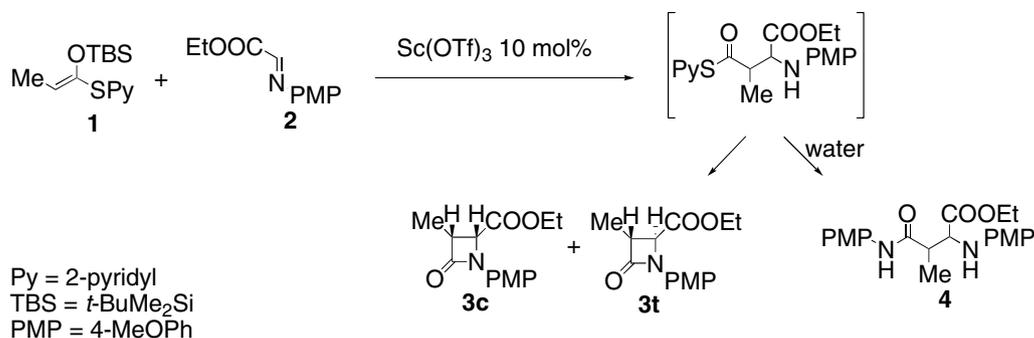
2. Results and discussion

The reaction between silylketene thioacetal (SKTA) (**1**), readily obtained as a single (*E*)-isomer from 2-pyridylthio propanoate [6], and the *N*-4-methoxyphenyl imine of ethyl glyoxylate **2** carried out in the presence of Sc(OTf)₃ [7] was first studied (Scheme 1). The reaction was run for 18 h at room temperature in different solvent systems in the presence of 10% mol cat of scandium (III) species.

The condensation between 2.0 mol equiv. of **1** with imine **2** run in DCM afforded a mixture of *trans* β -lactam **3t** and of its *cis* diastereoisomer **3c**, in a 50:50 ratio and 80% yield as determined by 300-MHz ¹H NMR analysis

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Scheme 1. Sc(III)-catalysed condensation of **1** and **2**.Table 1
Sc(III)-catalysed condensation of **1** and **2**

Entry ^a	1:2 (equiv.)	Solvent	Catalyst	Reaction time (h)	4 yield (%) ^b	3 + 4 yield (%) ^b
1	2.0:1.0	DCM	Sc(OTf) ₃	20	–	80
2	2.0:1.0	THF	Sc(OTf) ₃	20	–	61
3	2.0:1.0	Neat	Sc(OTf) ₃	20	–	71
4	2.0:1.0	Water	Sc(OTf) ₃	20	20	33
5	1.0:2.0	Water	Sc(OTf) ₃	72	67	84
6	2.0:1.0	Water	ScTDS	20	23	33
7	2.0:1.0	Water	ScTDS	72	69	83
8	1.0:2.0	Water	ScTDS	40	45	74
9 ^c	1.0:2.0	Water	ScTDS	48	50	77

^a General: all reactions carried out using 10 mol% Sc(III).^b Isolated yields after flash chromatography.^c 2 mol% Sc(III) was used.

of the crude reaction mixture and confirmed after chromatographic purification [8] (Table 1, entry 1).

When THF was used as a solvent after 18 h complete conversion of the imine was observed, and a mixture of *trans*-β-lactam **3t** and of its *cis*-diastereoisomer **3c**, in a 50:50 ratio and 61% isolated yield was gained (Table 1, entry 2).

When **1** was reacted with imine **2** for 20 h at room temperature in the absence of solvent a 50:50 mixture of *trans*- and *cis*-β-lactams **3t** and **3c**, in 71% combined yield was obtained (entry 3). In addition to the products, the spectrum of the crude reaction mixture showed the presence of unreacted SKTA **1** and of the β-aminothioesters precursors of the azetidinones. No traces of the imine could be detected indicating that the reaction proceeded in high conversion [9].

However, the condensation of pyridylthioacetal **1** with **2** in water [10] lead to a different compound as major reaction product, that was identified to be β-amino-amide **4** [11], obtained as a 65/35 mixture of isomers in 20% yield (entry 4). *trans*- and *cis*-β-lactams **3t** and **3c** were obtained as side-products in 13% yield and 50:50 ratio.

We believe that the formation of the amide **4** arises from the peculiar reaction conditions used in the condensation between **1** and **2** in water. The first step is the formation of the β-amino pyridylthioester from the thioacetal **1**

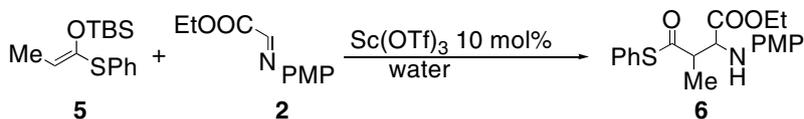
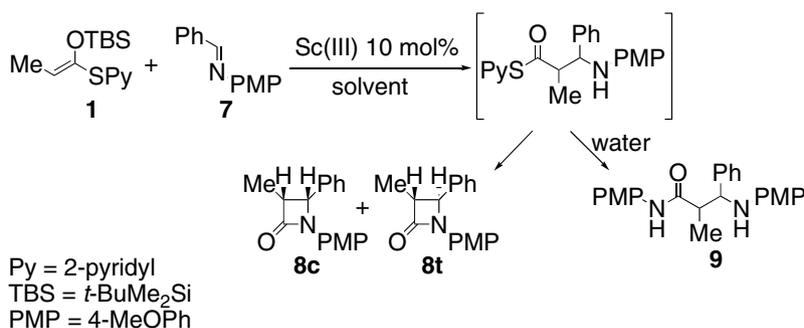
and the imine **2**. The second step in the synthesis of β-lactams is the nucleophilic attack of the nitrogen on the pyridylthio-group. In water, however, a competition might occur between the nucleophilic intramolecular attack of the secondary amine to afford the β-lactam **3** and the nucleophilic attack of *p*-methoxyaniline, derived from the hydrolysis of imine **2**, which would give the amide **4**.

To test this hypothesis, 2.0 mol equiv. of **2** were reacted with **1** for 72 h at room temperature in water and in this case amide **4** was obtained with 67% yield [12] (entry 5).

In an attempt to increase the yield of the amide formation, scandium tris(dodecylsulfate) (ScTDS) was used as a catalyst. ScTDS was first used by Prof. Kobayashi's group as a catalyst in which the Lewis acidic properties were combined with surfactant properties [13]. The catalyst has shown to be specially effective in water due to the presence of long lipophilic chains that form hydrophobic reaction fields, like micelles, in which there is a high concentration of the active scandium and the reaction takes place. Unfortunately in our hands the use of ScTDS did not give any improvement. The reaction between 2.0 mol equiv. of **1** and **2** carried out in the presence of 10% mol ScTDS for 20 h at room temperature afforded the amide **4** in 23% yield (entry 6). The reaction between 2.0 mol equiv. of **1** and **2** carried out in the presence of 10% mol ScTDS afforded the amide **4** in 45% yield after 40 h and 69% yield after 72 h (entries 7 and 8). These values are comparable with those obtained using Sc(OTf)₃ as a catalyst [14].

To further increase the efficiency of the method the catalyst loading was lowered down to 2 mol% of ScTDS; also in this case the reaction between **1** and 2.0 mol equiv. of **2** worked well and afforded amide **4** in 50% yield along with 26% of β-lactams mixture after 48 h reaction time (entry 9).

The unexpected outcome of the reaction might be determined by the combination of the ability of water to interact with the substrates together with a good leaving group as –SPy on the starting material. To prove this hypothesis the reaction between imine **2** and the thioacetal **5**, which does not bear a good leaving group (SPh) was run in the presence of 10% mol Sc(OTf)₃ using water as a solvent. The only isolated product was the β-amino thioester **6** in 47% yield, confirming that both water as a solvent and the 2-pyridylthio group on the starting material are necessary

Scheme 2. Synthesis of β -aminothioester **6**.Scheme 3. Sc(III)-catalysed condensation of **1** and **7**.

for the formation of amino-amide to occur [15] (see Scheme 2).

The scope of the reaction was extended to a unactivated imine, derived from benzaldehyde and 4-methoxy aniline (Scheme 3).

The condensation between 2.0 mol equiv. of pyridylthioacetal **1** and the imine **7**, promoted by 10 mol% of Sc(OTf)₃ gave no reaction after 48 h (Table 2, entry 1). When ScTDS was used as a catalyst 26% of amide **9** [16] in a 70:30 diastereoisomeric ratio along with 21% of a mixture of *cis* and *trans* β -lactams **8c** and **8t** in a 50:50 ratio was obtained after only 18 h reaction time (entry 2). Using 2.0 mol equiv. of **7** gave better results: the condensation promoted by Sc(OTf)₃ afforded amide **9** although in low yield (13% after 72 h, entry 3), while the reaction promoted by ScTDS gave amide **9** in 53% yield after 60 h reaction time (entry 4). It was possible to run the reaction for a shorter reaction time: ScTDS promoted the formation of amide **9** in 42% yield after 32 h (entry 5). Finally, using 2 mol% of ScTDS amide **9** was obtained in 13% yield along with β -lactams **8c** + **8t** in 9% yield after 32 h reaction time [17] (entry 6).

As shown by data collected in Table 2, in the case of imine **7**, a non-activated and less water-soluble imine than

2, ScTDS proved to be a better catalyst than Sc(OTf)₃ to promote the condensation with pyridylthioacetal **1**.

Recovery and recycling of the catalyst was also studied. First, the recycling of the aqueous phase containing ScTDS after separation of the products with an organic solvent was attempted [18]. For example, after the reaction of thioacetal **1** with imine **7**, the crude mixture was extracted with an organic solvent and purified by flash chromatography to give amide **9** in 42% isolated yield. To the aqueous phase new fresh reagents were added and the reaction was run again but no product formation was observed after 72 h reaction time. Probably due to its lipophilic character, ScTDS is soluble in most of the organic solvents and is extracted from the aqueous medium along with the products in the organic phase [19].

It was, then, decided to formally “recycle” the catalyst *in situ* by adding fresh reagents to the reaction vessel without isolating the products to mimic a continuous flow process [20]. Thus, at the end of a first reaction of SKTA **1** with imine **7** in the presence of 10 mol% ScTDS, the same amounts of reagents were added and a second reaction allowed to proceed for 48 h. After three further iterations of this procedure (for a total five reaction cycles) amide **9** was isolated in 31% yield along with 10% β -lactams **8c** and **8t** [21].

Finally, the β -amino amide easily prepared by this methodology represents a useful starting point for further synthetic transformations. For example, amide **4** may be reduced to the corresponding 1,3-diamino-alcohol **10** (Scheme 4) [22,23].

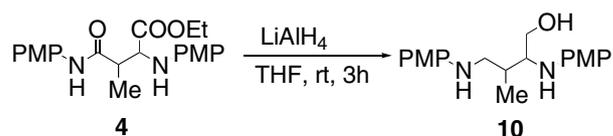
Scheme 4. Functionalisation of amide **4**.

Table 2
Sc(III)-catalysed condensation of **1** and **7**

Entry ^a	1:2 (equiv.)	Catalyst	Reaction time (h)	9 yield (%) ^b	8 + 9 yield (%) ^b
1	2.0:1.0	Sc(OTf) ₃	48	—	—
2	2.0:1.0	ScTDS	18	26	47
3	1.0:2.0	Sc(OTf) ₃	72	13	17
4	1.0:2.0	ScTDS	60	53	65
5	1.0:2.0	ScTDS	32	42	51
6 ^c	1.0:2.0	ScTDS	32	13	23

^a General: all reactions carried out using 10 mol% Sc(III) in water.

^b Isolated yields after flash chromatography.

^c 2 mol% Sc(III) was used.

The reaction of **4** with 2.0 mol equiv. LiAlH_4 in THF at room temperature for 3 h, afforded the expected product **10** in a non-optimised 30% yield. Compound **10** represents a highly functionalised building block, easily prepared in a only 2 step-procedure.

3. Conclusions

In conclusion, a novel synthesis of β -amino-amides was developed by employing a Sc(III) catalysed condensation between pyridylthioacetal and imines in water as a reaction solvent. Amides were obtained in fair to good yields (20–67%) along with mixture of diastereoisomeric β -lactams. Experiments were run in order to elucidate the reaction mechanism and it was concluded that water plays a decisive role in the amide formation, in association with the ability of the pyridylthio group to act as a good leaving group. Preliminary experiments to study further manipulations of the products and recycle of the catalyst were also performed.

Acknowledgements

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- [11] Amide **4**: IR (DCM): ν 3322, 2934, 1732, 1662, 1512, 1244, 1181, 1034 cm^{-1} . ^1H NMR (CDCl_3) (major isomer): δ 1.27–1.40 (m, 6H, Me of ethyl group and Me-C3); 3.00 (m, 1H, H-C3); 3.79, 3.81 (2 s, 3H each, OMe); 4.20 (q, 2H, J 4.0 Hz CH_2 of ethyl group); 4.30 (d, 1H, J 2.6 Hz, H-C4); 6.80–6.88 (m, 6H, aromatic protons); 7.39 (m, 2H, aromatic protons). ^{13}C NMR (CDCl_3): δ 13.4, 14.1, 43.7, 55.4, 55.6, 61.3, 61.5, 114.0, 114.5, 117.6, 121.6, 131.0, 139.6, 154.3, 156.3, 171.4. Elem. Anal. Calc. for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.31; H, 6.76; N, 7.23%.
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- [16] Amide **9** m.p. = 133–136 $^\circ\text{C}$; IR (DCM): ν 3054, 2986, 1676, 1510, 1265, 740 cm^{-1} . ^1H NMR (CDCl_3) (major isomer): δ 1.38 (d, 3H, J 10.3 Hz Me-C3); 2.85 (m, 1H, H-C3); 3.80 (s, 3H, OMe); 4.50 (d, 1H, J 7.7 Hz, H-C4); 6.70–6.85 (m, 4H, aromatic protons); 7.11–7.27 (m, 4H, aromatic protons); 7.32–7.37 (m, 5H, aromatic protons). ^{13}C NMR (CDCl_3): δ 16.1, 48.6, 55.4, 55.6, 62.1, 114.0, 114.5, 114.8, 122.5, 126.6, 127.4, 127.5, 128.8, 130.0, 141.2, 142.3, 151.8, 156.7, 172.5. Elem. Anal. Calc. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.79; H, 6.72; N, 7.19%.
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