Tandem Michael imino–aldol reactions catalyzed by samarium diiodide

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Abstract—Samarium diiodide catalyzes a one-pot procedure allowing to perform sequentially the Michael addition of a ketene silyl acetal on a cyclic α,β-unsaturated ketone, followed by the addition of a glyoxylic or aromatic imine. The presence of a coordinating group on the imine increases the rate of the reaction. © 2001 Elsevier Science Ltd. All rights reserved.

Tandem or cascade reactions allowing the formation of several carbon–carbon bonds by one pot-procedures are powerful tools for synthetic transformations and are the focus of growing interest.[1,2] The use of metal catalysts in these reactions has been developed for intramolecular sequences, and more recently for three-component reactions. [3–5] The possibility to control the stereo or enantioselectivity of these reactions is an attractive area. Three-component reactions leading to the fixation of two chains on α,β-unsaturated ketones by a Michael–aldol sequence have been described, either by the formation of an intermediate enolate,[6–8] or by the formation of an enoxysilane, followed by reaction with an aldehyde or an unsaturated ketone.[9–14] Similar sequences involving an imine in the second step have not received much attention.

A Mukaiyama–Michael reaction followed by the addition of an imine has been recently published but two different catalysts are needed to perform the two steps.[15] We now report our results for tandem Mukaiyama–Michael, Mannich reactions using samarium diiodide as the sole catalyst.

We have previously investigated the activity of samarium diiodide for Lewis acid-catalyzed reactions such as Mukaiyama aldol or Michael reactions,[16] cycloaddition reactions, or enolization of ketones.[17] We have next found that samarium diiodide can catalyze successively two reactions in a one-pot procedure, a Michael reaction on cyclic α,β-unsaturated ketones followed by an aldol reaction.[18,19] In all these reactions, an aldehyde or a
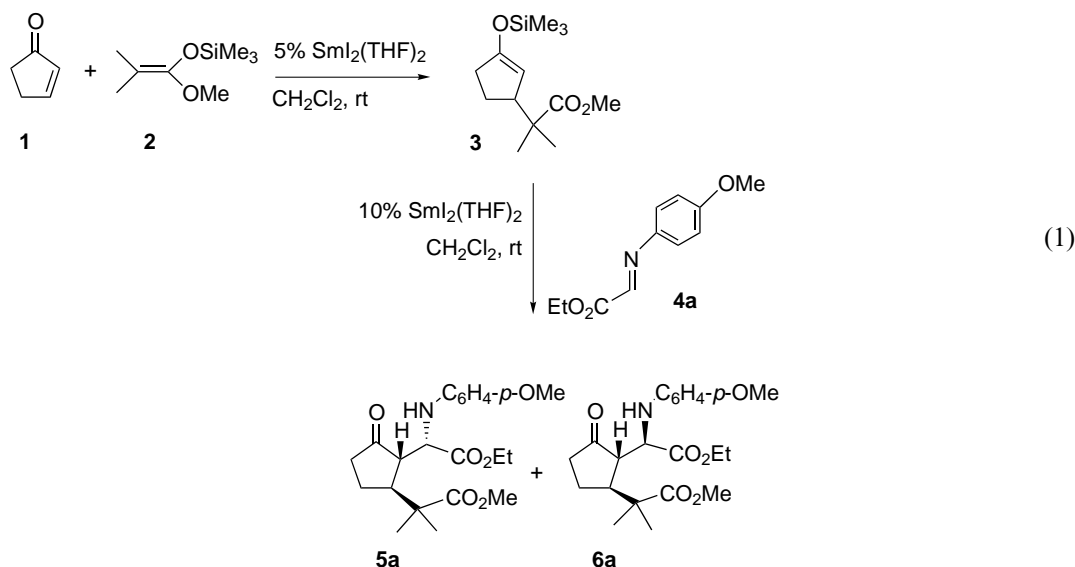

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ketone was used as the electrophile. Recently we studied the reactivity of imines in samarium diiodide catalyzed reactions and described aza Diels–Alder as well as Mannich reactions.[20] Especially imines react with acyclic or cyclic enoxysilanes to yield β-aminoketones under mild conditions. This led us to examine the possibility to realize successively a Michael addition of ketene silyl acetal on α,β-unsaturated ketone leading to enoxysilane followed by a Mannich reaction in a one-pot procedure.

Preliminary to the study of tandem reactions we realized the transformation in two steps, to check the reactivity of an imine in the Mannich reaction with the enoxysilane resulting of the Michael addition. We selected the *N-para*-anisyl ethyl glyoxylic imine **4a** for testing. The enoxysilane **3** resulting from addition of ketene silyl acetal **2** on cyclopenten-2-one **1** was prepared according to the conditions previously described.[16] Then, reaction of isolated **3** with glyoxylic imine **4a** was performed at room temperature in the presence of 10 mol% samarium diiodide in methylene chloride (Eq. (1)). The reaction products were isolated in 44% yield as a mixture of two diastereoisomers that could be separated by column chromatography. These two products were identified by 2D NMR experiments as **5a** and **6a**, (**5a**/**6a**: 71/29). These two diastereomers are the result of the approach of imine *anti* to the substituent on the cycle. Then we carried out the same sequence by a one-pot procedure. After successive additions of ketene silyl acetal **2** and cyclopenten-2-one **1** on a suspension of samarium diiodide in methylene chloride (10 mol%) and 1 h reaction time at room tempera-

ture, the glyoxylic imine **4a** was added (Eq. (2)). We thus obtained the tandem adducts **5a** and **6a** with similar diastereomeric ratio and yield than in the two steps procedure (Table 1, entry 1). We had found formerly that for tandem Mukaiyama–Michael aldol reactions, a decrease of temperature resulted in an increase of both yield, by suppression of by-products, and diastereoselectivity. For the tandem reaction involving imine **4a** a decrease in reaction temperature led to a small increase in diastereoselectivity (entries 1–3) while high yield was obtained at −55°C.

Similar samarium diiodide-catalyzed tandem reactions on various aromatic imines have been carried out at low temperatures to determine the influence of the substituents (Eq. (2), Table 1). The tandem reaction was realized with *N*-phenyl benzyl imine **4b** and afforded adducts **5b** and **6b** with moderate yield and diastereoselectivity (entry 4). With imine **4c** bearing an electrowithdrawing group in *para* position on the aromatic ring fixed on the carbon, a mixture of adducts **5c** and **6c** was similarly obtained (entry 5). In contrast, with imine **4d** bearing an electrodonating group in the same position, the Mannich reaction does not proceed even at room temperature. Imines **4b** and **4c** are less reactive than the glyoxylic imine **4a**, which can be explained by a chelation of this imine on the samarium catalyst. This prompted us to examine the activity of imines with a coordinating group on the aromating ring fixed on the nitrogen atom. Indeed, the presence of an *o*-anisyl group on the imine increases the yields of the Mannich reactions and the reactions with imines **4e** and **4f** could be carried out at lower temperatures than for

$$(2)$$
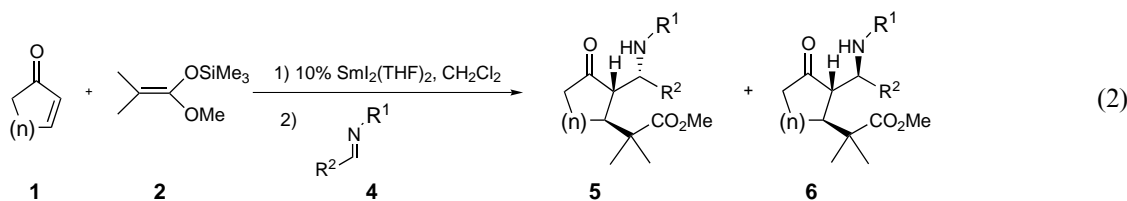
Table 1. Tandem Michael imino–aldol reactions catalyzed by samarium diiodide

Entry	Ketone **1**	Imine			T (°C)	t (h)	Product		
	n		R^1	R^2				Yield[a,b] (%)	5/6[c]
1	1	**4a**	p-CH$_3$OC$_6$H$_4$	CO$_2$Et	rt	3	**5a**+**6a**	50	70/30
2	1	**4a**	p-CH$_3$OC$_6$H$_4$	CO$_2$Et	−55	18	**5a**+**6a**	81	78/22
3	1	**4a**	p-CH$_3$OC$_6$H$_4$	CO$_2$Et	−78	46	**5a**+**6a**	70[d]	85/15
4	1	**4b**	Ph	Ph	0	24	**5b**+**6b**	47	71/29
5	1	**4c**	Ph	p-CF$_3$C$_6$H$_4$	0	24	**5c**+**6c**	42	50/50
6	1	**4d**	Ph	p-CH$_3$OC$_6$H$_4$	rt	48		0	
7	1	**4e**	o-CH$_3$OC$_6$H$_4$	Ph	−40	24	**5e**+**6e**	54	62/38
8	1	**4f**	o-CH$_3$OC$_6$H$_4$	p-CF$_3$C$_6$H$_4$	−40	24	**5f**+**6f**	66	83/17
9	1	**4g**	o-CH$_3$OC$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	0	41	**5g**+**6g**	37	62/38
10	2	**4h**	p-CH$_3$OC$_6$H$_4$	CO$_2$Et	0	24	**5h**+**6h**	46	86/14

[a] 10% SmI$_2$(THF)$_2$ in 10 mL CH$_2$Cl$_2$; ratio **1**/**2**/**4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratios measured by ^{1}H NMR in crude product.
[d] Yield in crude product.

4b and **4c** (compare entries 4 and 7, and 5 and 8). Reaction with imine **4g** at 0°C allows the isolation of tandem adducts with a moderate yield while no product was observed with **4d**. Influence of the size of the cycle was next examined and the tandem reaction on cyclohexen-2-one with glyoxylic imine **4a** leads to the expected adducts **5h** and **6h**. Since the removal of *N-o*-anisyl or *N-p*-anisyl groups on Mannich products has been already described,[21,22] the samarium diiodide-catalyzed tandem Michael–Mannich reactions should give access to various β-aminoketones or lactams.

In summary we have shown that samarium diiodide catalyzes the formation of two carbon–carbon bonds by successive Michael and Mannich reactions on α,β-unsaturated cyclic ketones to afford β-aminoketones. To the best of our knowledge, no other catalyst has been described for this sequence of tandem reactions. Since we have recently found that iodo samarium binaphthoxides are enantioselective catalysts for Diels–Alder reactions[23] we are currently investigating the use of these catalysts for asymmetric tandem reactions.

Typical procedure: In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). Then CH_2Cl_2 (4 mL), 1-methoxy-2-methyl-1-trimethylsilyloxypropene **2** (203 μL, 1 mmol) and cyclopenten-2-one **1** (125 μL, 1.5 mmol) were successively added under argon. The resulting yellow solution was then stirred for 1 h at room temperature, while the formation of enoxysilane **3** was monitored by GC and reaction mixture was cooled at −55°C. A solution of imine **4a** (270 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) was then added. After 24 h stirring at the same temperature, the reaction mixture was hydrolyzed and extracted by CH_2Cl_2. The crude product was purified on silica gel (heptane/AcOEt: 80/20) and **5a** and **6a** could be separated (**5a+6a,** 317 mg, 81%, **5a/6a**, 78/22).

Analytical data **5a**: ^{1}H NMR (250 MHz, $CDCl_3$) 6.70 (q, $J = 9.2$ Hz, 4H), 4.59 (d, $J = 12$ Hz, 1H), 4.35 (dd, $J = 12$ Hz, $J = 3.4$ Hz, 1H), 4.09 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 2.64 (m, 1H), 2.52 (m, 1H), 2.25 (m, 2H), 2.08 (m, 1H), 1.65 (m, 1H), 1.23 (t, $J = 13$ Hz, 3H), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) 219.6, 177.6, 172.4, 153.2, 140.7, 116.4, 114.6, 61.4, 60.0, 55.6, 52.1, 51.6, 44.8, 44.6, 37.7, 24.2, 22.9, 21.1, 14.0. IR ν cm^{-1}: 3374, 2926, 1731.

Analytical data **6a**: ^{1}H NMR (250 MHz, $CDCl_3$) 6.68 (q, $J = 9.2$ Hz, 4H), 4.35 (d, $J = 10$ Hz, 1H), 4.28 (dd, $J = 10$ Hz, $J = 3$ Hz, 1H), 4.17 (m, 2H), 3.71 (s, 3H), 3.59 (s, 3H), 2.77 (m, 1H), 2.64 (m, 1H), 2.25 (m, 2H), 2.08 (m, 1H), 1.65 (m, 1H), 1.24 (t, $J = 13$ Hz, 3H), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) 218.1, 177.5, 171.8, 152.9, 140.6, 115.4, 114.8, 61.5, 58.4, 55.6, 52.5, 51.9, 45.2, 44.6, 37.7, 23.8, 22.7, 21.6, 14.1.

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