A New Method for the Synthesis of β-Amino–β′-Hydroxy Ketones by the Samarium(II) Iodide-mediated Aldol Reaction of Aldehydes with Aryl or Alkyl Aziridinyl Ketones

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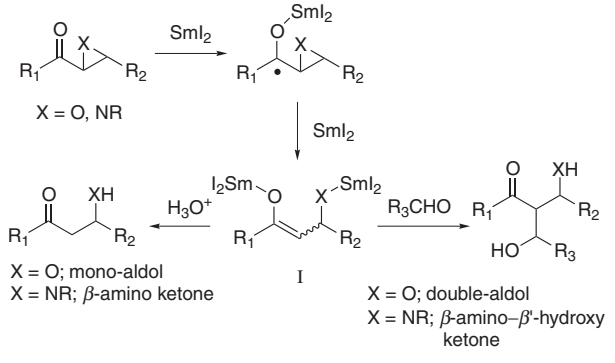
(Received August 3, 2004; CL-040919)

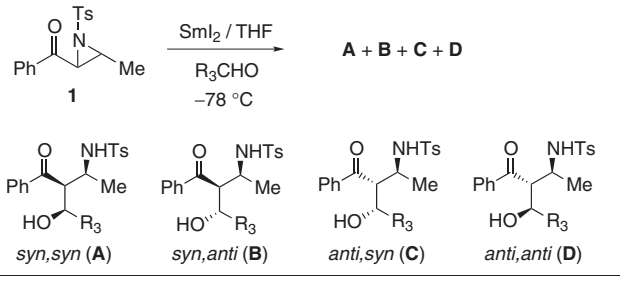
β-Amino–β′-hydroxy ketones were synthesized by the aldol reaction of aldehydes with samarium enolates generated by aziridine fragmentation of aryl or alkyl aziridinyl ketones with two moles of samarium(II) iodide.

Samarium(II) iodide (SmI_2) is a powerful one-electron reducing agent[1] and various α-hydroxy-, α-acetoxy-, α-alkoxy-, α-alkylthio-, or α-halo ketones are reduced with two moles of SmI_2 under mild conditions to form the corresponding deoxygenated, desulfurated, or dehalogenated ketones, respectively.[2] Also, it is reported that reduction of alkyl or aryl oxiranyl ketones or aziridinyl ketones with SmI_2 in the presence of protic compounds such as methanol afforded mono-aldols or β-amino ketones through samarium enolates as shown in Scheme 1.[3] The samarium enolates **I**, are the same nucleophilic enolates as those generated by deprotonation at α-position of mono-aldols or β-amino ketones. These results prompted us to study on the preparation of 3-hydroxy-2-(1-hydroxyalkyl)alkyl ketones (double-aldols) by the SmI_2-mediated aldol reaction of aldehydes with oxiranyl ketones.[4] This reaction is useful and is successfully applied to synthesis of taxane skeleton.[5] Then, the use of aziridinyl ketones instead of the above mentioned oxiranyl ketones became our next target to seek for its newer application to synthetic chemistry. Thus formed aldol adducts are expected to be 3-amino-2-(1-hydroxyalkyl)alkyl ketones (β-amino–β′-hydroxy ketones). In recent years, synthesis of β-amino acids has attracted considerable attention.[6] Because of their similarity to serine and other unusual amino acids, various substituted β-amino acids, especially β′-hydroxy derivatives actually constituted an important class of molecules with interesting chemical and biological properties. Therefore, β-amino–β′-hydroxy ketones are considered as important analogues of β-amino–β′-hydroxy acids and are expected to work as building blocks for the synthesis of biologically important compounds; however, methods for their synthesis have not yet been reported. In this communication, we would like to describe a new and efficient method for synthesis of β-amino–β′-hydroxy ketones.



Scheme 1.

Table 1. SmI_2-mediated aldol reaction of aziridinyl ketone (**1**) and various aldehydes



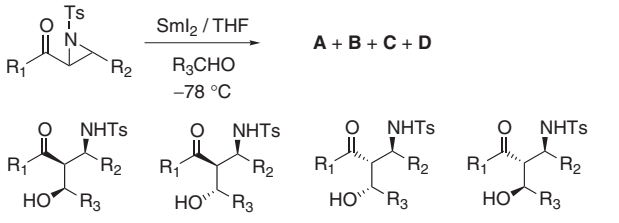
Entry	Aldehyde R_3	Product	Yield /%[a]	(**A** / **B** / **C** / **D**)[b]
1	Ph	**1a**	80	(0 / 67 / 0 / 33)
2	Et	**1b**	95	(0 / 34 / 0 / 66)
3	$Ph(CH_2)_2$	**1c**	91	(0 / 40 / 0 / 60)
4	*i*-Pr	**1d**	98	(0 / 28 / 0 / 72)
5	*c*-Hex	**1e**	95	(0 / 28 / 0 / 72)

[a]Isolated yield.
[b]The ratio was determined by ^{1}H NMR.

In the first place, SmI_2-mediated aldol reaction of (3*SR*, 2*RS*)-3-methyl-1-tosylaziridin-2-yl phenyl ketone (**1**), an aryl aziridinyl ketone,[7] with several aldehydes was examined (Table 1).[8] The reaction of **1** with benzaldehyde gave the corresponding β-amino–β′-hydroxy ketone (**1a**) in good yield (67/33 mixture of *syn*, *anti* (**B**) and *anti*, *anti* (**D**) isomers) along with a small amount of β-*N*-tosylamino ketone (Entry 1). The yield of **1a** slightly decreased because benzaldehyde was partly reduced at the same time. On the other hand, the reaction of **1** with aliphatic aldehydes proceeded smoothly to give the corresponding β-amino–β′-hydroxy ketones (**1b–1e**) in excellent yields (Entries 2–5). All entries afforded the *syn*, *anti* (**B**) and *anti*, *anti* (**D**) isomers as major products among the four possible diasteromers. These results are similar to those of SmI_2-mediated double-aldols formation from epoxy ketones with aldehydes.

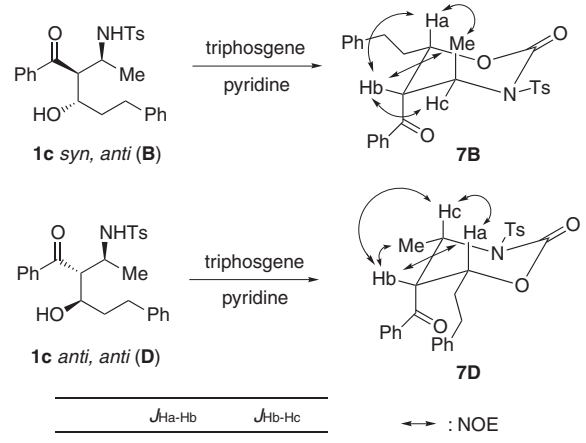
Next, the SmI_2-mediated aldol reaction of various aziridinyl ketones with various aldehydes was further examined (Table 2). The reaction between aryl aziridinyl ketones and aldehydes also proceeded smoothly and afforded the corresponding β-amino–β′-hydroxy ketones in excellent yields (Entries 1–8). In this reaction, the substituents at C-3 position (R_2) play an important role on the control of stereoselectivity. It is noteworthy that, in the case of aziridinyl ketone **3** having a bulky substituent (R_2 = *i*-Pr), the reactions afforded the corresponding products with

Table 2. SmI_2-mediated aldol reaction of various aziridinyl ketones and various aldehydes



Entry	Aziridinyl ketone			Aldehyde	Product	Yield /%[a]	
		R_1	R_2	R_3			(**B** / **D** / others)[b]
1	**2**	Ph	*n*-Pr	$Ph(CH_2)_2$	**2a**	88	(29 / 71 / 0)
2		Ph	*n*-Pr	*i*-Pr	**2b**	92	(14 / 86 / 0)
3	**3**	Ph	*i*-Pr	$Ph(CH_2)_2$	**3a**	98	(<5 / >95 / 0)
4		Ph	*i*-Pr	*i*-Pr	**3b**	99	(<5 / >95 / 0)
5	**4**	Ph	Ph	$Ph(CH_2)_2$	**4a**	96	(28 / 65 / 7)
6		Ph	Ph	*i*-Pr	**4b**	97	(13 / 81/ 6)
7	**5**	Ph	H	$Ph(CH_2)_2$	**5a**	86	—[c]
8		Ph	H	*i*-Pr	**5b**	83	—[c]
9	**6**	Me	Ph	Ph	**6a**	73	(70 / 30 / 0)
10		Me	Ph	$Ph(CH_2)_2$	**6b**	88	(29 / 71 / 0)
11		Me	Ph	*i*-Pr	**6c**	99	(38 / 62 / 0)

[a]Isolated yield.
[b]The ratio was determined by ^1H NMR.
[c]The *anti* isomer was only obtained.



	J_{Ha-Hb}	J_{Hb-Hc}
7B	4.0 Hz	2.5 Hz
7D	3.5 Hz	6.0 Hz

Scheme 2.

high diastereoselectivity (Entries 3, 4). In addition to aryl aziridinyl ketones, alkyl aziridinyl ketone **6** reacted with aldehydes to give the corresponding products in high yields (Entries 9–11).

The relative configuration at newly created stereocenters of the diastereomers was determined by chemical transformation and NOE experiment (Scheme 2). Namely, treatment of **1cB** and **1cD** with triphosgene in pyridine afforded the carbamates **7B** and **7D**, which were analyzed by NOE difference spectroscopy.

In summary, a new method for the synthesis of β-amino–β'-hydroxy ketones from aryl or alkyl aziridinyl ketones and aldehydes by using two moles of SmI_2 via the samarium enolates was thus developed. Further investigation of this reaction is now in progress.

The present work was partially supported by Grant of the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References and Notes

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8 Typical experimental procedure is as follows (Table 1, Entry 3): to a mixture of **1** (51.5 mg, 0.162 mmol) and 3-pheny propanal (23.9 mg, 0.178 mmol) in THF (2 mL) at −78 °C under an argon atmosphere was added a solution of SmI_2 in THF (0.1 M, 4.05 mL, 0.405 mmol). After the reaction mixture was stirred for 1 h at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride and was diluted with ethyl acetate. It was extracted with ethyl acetate, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, crude product was purified by thin-layer chromatography to afford *syn*, *anti* adduct (26.6 mg, 36%), and *anti*, *anti* adduct (39.8 mg, 54%), respectively.

Published on the web (Advance View) October 16, 2004; DOI 10.1246/cl.2004.1472