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Reductive deamination of α-amino carbonyl compounds by means of samarium iodide

Toshio Honda* and Fumihiro Ishikawa

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8051, Japan. E-mail: honda@hoshi.ac.jp

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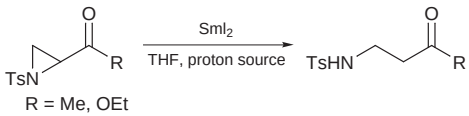
Reaction of α-amino carbonyl compounds with SmI_2 in THF–HMPA in the presence of a proton source afforded the deamination products, where the fragmentation occurred between the nitrogen and the carbon α to the carbonyl group.

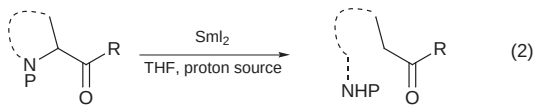
SmI_2 was firstly, introduced as a useful synthetic tool in organic synthesis by Kagan and co-workers,[1] and thereafter, this reagent rapidly became an established reagent for developing a variety of useful and unique transformations.[2] Although much effort has been devoted to studying the reductive deoxygenation of α-hydroxy or α-alkoxy carbonyl compounds employing SmI_2 as a powerful one-electron reducing reagent, its application to the deamination of α-amino carbonyl compounds has received relatively little attention. Attractive examples of the reductive deamination reaction were reported by Molander and Stengel using 2-acylaziridines and 4-acylazetidin-2-one as starting materials [eqn. (1)],[3] where the leaving amino groups were



R = Me, OEt (1)

involved in highly strained three- or four-membered rings. Similar SmI_2-promoted carbon–nitrogen bond cleavage reactions were also employed in the reductive removal of an *N*-substituted benzotriazolyl group,[4] and in the isonitrile–nitrile rearrangement.[5]

In continuation of our work on the synthesis of biologically active natural products using SmI_2,[6] we were interested in researching a general deamination reaction of α-amino carbonyl compounds [eqn. (2)], and here report our successful results

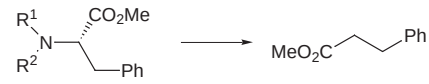


P = alkyl, acyl
R = alkyl, OR′ (2)

concerning systematic investigation of SmI_2-promoted reductive deamination.

Initially, we applied the SmI_2-promoted deamination reaction to phenylalanine derivatives,[7] and the results obtained are summarised in Table 1. Based on the results, it was concluded that reductive deamination with SmI_2 is applicable to the wide variety of amino functions including primary, secondary and tertiary amines, and also amide groups. The deamination usually took place within 30 min in the presence of a proton source, such as MeOH or pivalic acid, to give methyl dihydrocinnamate in high yields, although a relatively prolonged reaction time was required in the case of benzyl-substituted amines as leaving groups. The reductive deamination was typically carried out as follows: a solution of SmI_2 (2.5 mmol) and HMPA (2.5 mmol) in THF (12 cm^3) and a solution of proton source (MeOH or pivalic acid, 1.25 mmol) in THF (5 cm^2) were successively added dropwise to a stirred solution of an α-amino ester (0.5 mmol) in THF (10 cm^3) at 0 °C, and the resulting solution was allowed to warm to room temperature. A stream of air was bubbled through the solution, and an excess of Celite in Et_2O and saturated aqueous $NaHCO_3$ (2 cm^3) were added. The solution was filtered and the filtrate was washed with brine. The organic layer was separated, dried and evaported to give a residue, which was subjected to column chromatography on silica gel.

Table 1 Reductive deamination of phenylalanine derivatives[a]

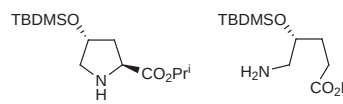
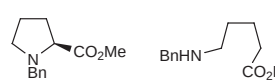
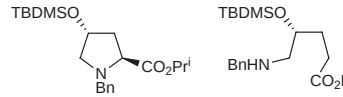


R^1	R^2	Proton source	Reaction time	Yield (%)
H	H	MeOH	30 min	73
H	H	Pivalic acid	15 min	80
H	Me	MeOH	30 min	71
H	Bn	MeOH	2.5 h	85
Me	Me	MeOH	< 5 min	90
Bn	Bn	MeOH	4 h	93
H	Ac	MeOH	15 min	99

[a] Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); proton soruce (2.5 equiv.); solvent (THF); 0 °C to room temperature.

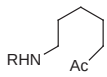
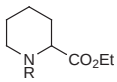
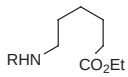
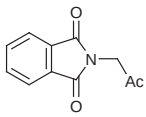
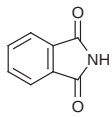
The reactions of proline derivatives[8] (Table 2) and ethyl pipecolinate derivatives[9] (Table 3), where the leaving amino groups were involved in the cyclic systems, under the same reaction conditions as above gave the corresponding deamination products in good yields. The deamination could be applied not only to α-amino esters but also to α-amino ketones. Thus, treatment of α-acetylpiperidine derivatives[10] with SmI_2 also

Table 2 Reductive deamination of proline derivatives[a]

Starting material	Product	Proton source	Reaction time	Yield (%)
		MeOH Pivalic acid	30 min 10 min	62 73
		MeOH	1.5 h	88
		MeOH	9 h	82
		MeOH	7.5 h	99

[a] Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); proton source (2.5 equiv.); solvent (THF); 0 °C to room temperature.

Table 3 Reductive deamination of 2-acetylpiperidine and ethyl pipecolinate derivatives, and a phthalimide derivative[a]

Starting material	Product	R	Reaction time	Yield (%)
		Me	1 min	87
		Bn	1 min	96
		Ac	<5 min	94
		Boc	<5 min	96
		Me	<5 min	86
		Bn	<5 min	89
		Ac	45 min	78
		—	1 min	72

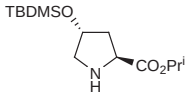
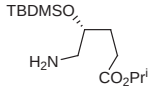
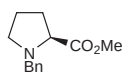
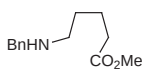
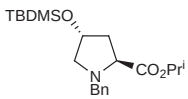
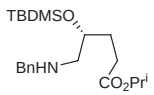
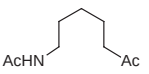
[a] Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); MeOH (2.5 equiv.) was used as a proton source; solvent (THF); 0 °C to room temperature.

provided the desired compounds, in high yields, in which both alkyl and acyl derivatives of amines could be used as leaving groups (Table 3). Interestingly, the reaction of *N*-(2-oxopropyl)phthalimide with SmI_2 in THF–HMPA in the presence of MeOH yielded phthalimide in 72% yield (Table 3). The products obtained were well-characterised by spectroscopic data including microanalysis, or by direct comparison with the authentic samples.

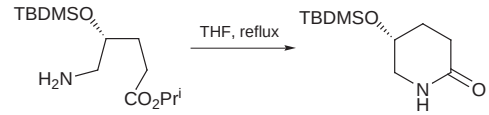
We next investigated the effect of proton sources, and found that *N*,*N*-dimethylaminoethanol (DMAE) was also effective for this reaction as well as MeOH and pivalic acid (Table 4). It should be noted that this reaction can be carried out under neutral reaction conditions in the presence of other functional groups, such as alkyl ester, alkyl ether, imide and amide groups. Moreover, this reaction proceeded in the presence or absence of HMPA, however, the presence of HMPA proved desirable in terms of yields and reaction times (Tables 2, 3 and 4). These results were in agreement with those observed in the reductive deoxygenation reactions, since HMPA was recognised to increase the rate of the reaction of SmI_2.[11]

As can be seen in Table 2, the fragmentation product bearing a primary amino function sometimes afforded the cyclisation compound. This type of conversion will provide a useful route for the synthesis of naturally occurring or biologically interesting piperidine derivatives in optically active forms. Indeed,

Table 4 Investigation of the proton sources and the effect of HMPA in reductive deamination[a]

Starting material	Product	Proton source	Reaction time	Additive	Yield (%)
		MeOH	5 h	none	65
		Pivalic acid	40 min	HMPA	82
		DMAE	45 min	HMPA	90
		MeOH	18 h	none	85
		Pivalic acid	1 h	HMPA	92
		DMAE	2 h	HMPA	78
		MeOH	36 h	none	76
		Pivalic acid	45 min	HMPA	88
		DMAE	1.5 h	HMPA	93
		MeOH	12 h	none	50
		Pivalic acid	<5 min	HMPA	86
		DMAE	10 min	HMPA	71

[a] Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); proton source (2.5 equiv.); additive (5 equiv.); solvent (THF); 0 °C to room temperature.



Scheme 1

heating of isopropyl δ-amino-γ-*tert*-butyldimethylsiloxyvalerate in THF for 2 days gave 5-*tert*-butyldimethylsiloxy-2-piperidone in 75% yield (Scheme 1).

In summary, we have described a general reductive deamination reaction employing SmI_2 in THF–HMPA. This reaction proceeds in relatively high yield under mild reaction conditions and seems to be applicable to the wide variety of α-amino carbonyl compounds. Utilisation of this reaction in the synthesis of natural products is under investigation. This work was supported by the Ministry of Education, Science, Sports and Culture of Japan.

Notes and references

1 P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693.

2 Reviews: J. Inanaga, *J. Org. Synth. Chem.*, 1989, **47**, 200, J. A. Soderquist, *Aldrichim. Acta*, 1991, **24**, 15; D. P. Curran, T. L. Fevig, C. P. Jasperse and M. J. Totleben, *Synlett*, 1992, 943; G. A. Molander, *Chem. Rev.*, 1992, **92**, 29: G. A. Molander and C. R. Harris, *Chem. Rev.*, 1996, **96**, 307; G. A. Molander and C. R. Harris, *Tetrahedron*, 1998, **54**, 3321 and references cited therein.

3 G. A. Molander and P. J. Stengel, *J. Org. Chem.*, 1995, **60**, 6660; G. A. Molander and P. J. Sangel, *Tetrahedron*, 1997, **53**, 8887; N. H. Kawahara and M. Goodman, *Tetrahedron Lett.*, 1999, **40**, 2271.

4 J. M. Aurrecoechea and A. Fernandez-Acebes, *Tetrahedron Lett.*, 1993, **34**, 549; J. M. Aurrecoechea and A. Fernandez-Acebes, *Synlett*, 1996, 39; A. R. Katritzky, M. Qi, D. Feng and D. A. Nichols, *J. Org. Chem.*, 1997, **62**, 4121.

5 H.-Y. Kang, A. N. Pae, Y. S. Cho, H. Y. Koh and B. Y. Chung, *Chem. Commun.*, 1997, 821.

6 T. Honda, S. Yamane, K. Naito, K. and Y. Suzuki, *Heterocycles*, 1994, **37**, 515; T. Honda, F. Ishikawa and S. Yamane, *J. Chem. Soc., Chem. Commun.*, 1994, 499; T. Honda, S. Yamane, K. Naito and Y. Suzuki, *Heterocycles*, 1995, **40**, 301; T. Honda, F. Ishikawa and S. Yamane, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1125; T. Honda, S. Yamane, F. Ishikawa and M. Katoh, *Tetrahedron*, 1996, **37**, 12177; T. Honda, M. Katoh and S. Yamane, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2219; T. Honda and M. Katoh, *Chem. Commun.*, 1997, 369.

7 The starting phenylalanine derivatives were prepared from the methyl ester by the known procedures; *N*-methyl derivative: M. C. Allen, W. Fuhrer, B. Tuck, R. Wade and J. M. Wood, *J. Med. Chem.*, 1989, **32**, 1652; *N*,*N*-dimethyl derivative: T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki and M. Kumada, *J. Org. Chem.*, 1983, **48**, 2195; *N*-benzyl derivative: F. Effenberger, U. Burkard and J. Willfahrt, *Liebigs Ann. Chem.*, 1986, 314; *N*,*N*-dibenzyl derivative: B. D. Gray and P. W. Jeffs, *J. Chem. Soc., Chem. Commun.*, 1987, 1329; *N*-acetyl derivative: M. J. Burk, J. E. Feaster, E. H. Harlow and L. Richard, *Tetrahedron: Asymmetry*, 1991, **2**, 569; *N*-Boc derivative: M. Sakaitani and Y. Ohfune, *J. Org. Chem.*, 1990, **55**, 870.

8 *N*-Benzylproline methyl ester was prepared from methyl prolinate: V. Ferey, P. Vedrenne, L. Toupet, T. L. Gall and C. Mioskowski, *J. Org. Chem.*, 1996, **61**, 7244; isopropyl 4-*tert*-butyldimethylsiloxyprolinate was prepared by silylation of the corresponding ester, which on *N*-benzylation with BnBr and NaH gave the *N*-benzyl derivative.

9 *N*-Substituted pipecolinates were prepared from ethyl pipecolinate by alkylation with the suitable alkyl halide and Pr^i_2NEt or by acetylation with Ac_2O.

10 2-Acetyl-*N*-alkylpiperidine derivatives were prepared from ethyl pipecolinate *via* four steps involving *N*-alkylation with alkyl halide, hydrolysis of the ester, conversion of the acid to the Weinreb's amide (S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815), and treatment of the amide with MeMgBr; the *N*-acetyl compound was derived from the *N*-benzyl derivative by reductive debenzylation over Pd/C in the presence of Ac_2O; the *N*-Boc derivative was prepared according to the known procedure: S. Aoyagi, T.-C. Wang and C. Kibayashi, *J. Am. Chem. Soc.*, 1993, **115**, 11393.

11 J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.*, 1987, 1485.

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