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A Novel Method for the Preparation of Optically Active Dipeptide. Chemo- and Stereoselective Reduction of 2-Hydroxyimino Amides with Samarium Diiodide

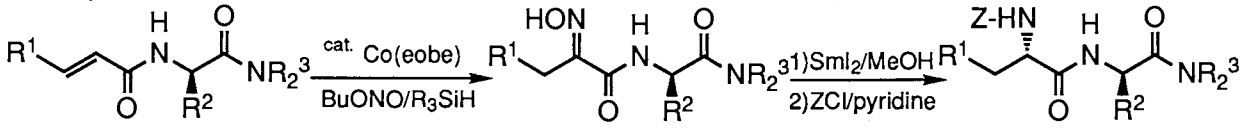
Teruaki MUKAIYAMA,† Kiyotaka YOROZU, Koji KATO, and Tohru YAMADA
Basic Research Laboratories for Organic Synthesis, Mitsui Petrochemical Industries, Ltd.,
Nagaura, Sodegaura, Chiba 299-02

Various α,β-unsaturated amides derived from α-amino acids are converted to the corresponding 2-hydroxyimino amides of α-amino acids by the reaction with butyl nitrite and silane, which are directly reduced with samarium diiodide to the optically active dipeptides in good yields under mild conditions with high chemo- and stereoselectivities.

Dipeptides are one of the most useful intermediates for the preparation of natural products consisted of relatively short peptide chains, and they are given considerable attention because of their strong physiological action.[1] Chemical modifications of the natural peptide chains have led to the developments of highly active analogues of peptides containing unnatural amino acids.[1,2] These peptides are generally prepared from the corresponding amino acids by the conventional coupling methods, such as DCC (*N,N'*-dicyclohexylcabodiimide) method,[3] CDI (*N,N'*-carbonyldiimidazole) method,[4] active ester method,[5] azide method,[6] and mixed anhydride method.[7] According to these methods mentioned above, preparation of optically active unnatural amino acids in advance is required as starting materials.

We have previously reported[8] a method of direct conversion of α,β-unsaturated carboxamides into the corresponding 2-hydroxyimino amides in high yields by the reaction with butyl nitrite and silane in the presence of a catalytic amount of [*N,N'*-bis(2-ethoxycarbonyl-3-oxobutylidene)ethylenediaminato]cobalt(II) complex [Co(eobe)] under mild conditions. Therefore, it could be expected that α,β-unsaturated amides of optically active amino acids are converted to the corresponding 2-hydroxyimino amides by the above mentioned procedures and optically active dipeptides would be yielded by the successive diastereoselective reduction.

In this communication, we would like to report a novel method for preparation of optically active unnatural dipeptides from the α,β-unsaturated amides derived from optically active amino acids by the α-oximation, followed by the chemo- and stereoselective reduction with samarium diiodide (Scheme 1).

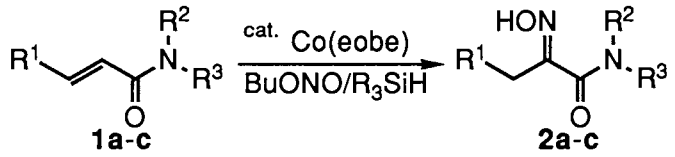


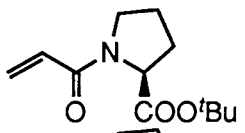
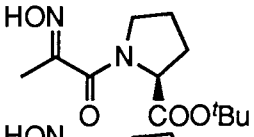
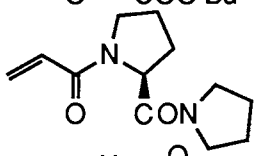
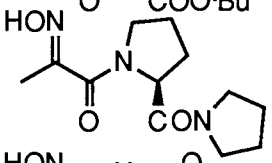
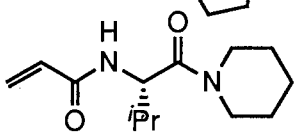
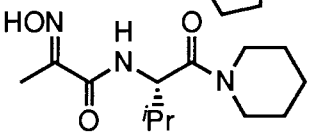
Scheme 1.

† Address: Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162.

In the first place, the α-oximation with butyl nitrite and silane catalyzed by Co(eobe) complex was applied to the α,β-unsaturated amides derived from optically active α-amino acids **1a-1c**. The reactions smoothly proceeded to afford the corresponding α-oximes **2a-2c** in good yields, respectively (see Table 1).

Table 1. α-Oximation of Various α, β-Unsaturated Amides[a)]

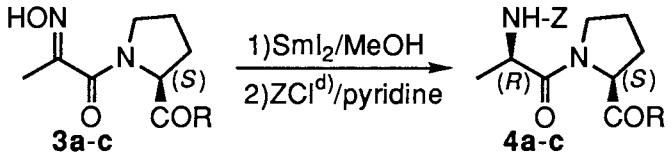


Entry	α,β-Unsaturated Amide		Oxime		Yield /%[b)]
1		**1a**		**2a**	79
2		**1b**		**2b**	70
3		**1c**		**2c**	74

a) Reaction conditions; α,β-unsaturated amide (**1a-1c**) 10.0 mmol, Co(eobe) 10 mol %, butyl nitrite 6.0 equiv., triethylsilane 6.0 equiv., in 2-propanol (30 ml) under argon atmosphere at 60 °C for 5 h. b) Isolated yield.

Next, chemoselective reduction of 2-hydroxyimino amides derived from optically active amino acids into the corresponding dipeptides was examined. After screening various reducing reagents, it was found that

Table 2. Chemo- and Stereoselective reduction of Various Oximes with SmI_2/MeOH[a)]

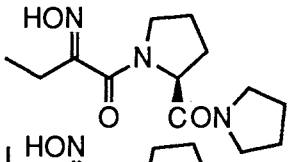
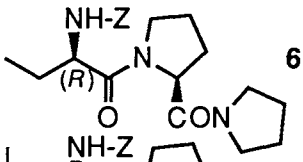
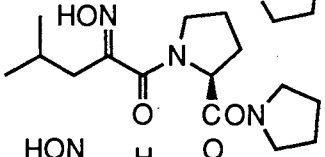
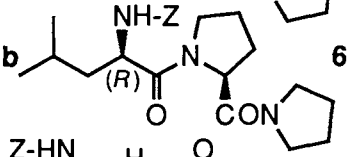
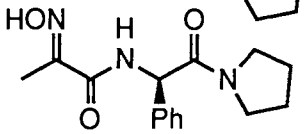
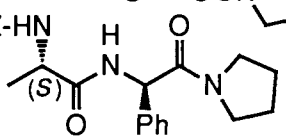
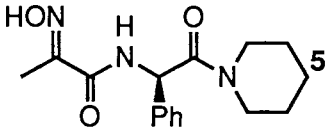
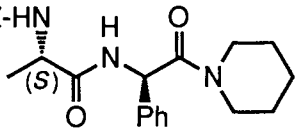
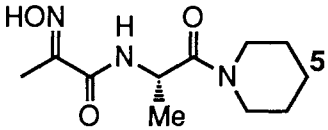
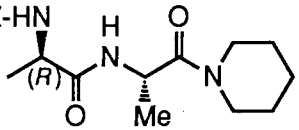
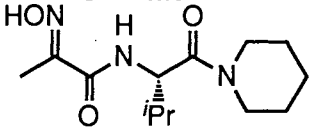
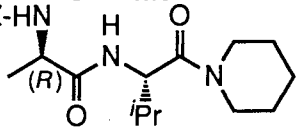
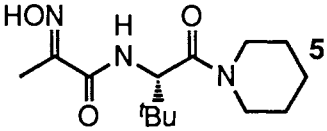
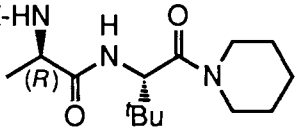


Entry	Oxime R		Dipeptide	Yield /%[b)]	*RS* : *SS*[c)]
1	OMe	**3a**	**4a**	64	85 : 15
2	O^{t}Bu	**3b**	**4b**	67	89 : 11
3		**3c**	**4c**	82	99 : 1

a) Reaction conditions; oxime (**3a-3c**) 0.2 mmol, SmI_2 1.0 mmol (0.1 M THF solution, 10 ml), MeOH 10 ml, in THF (4.0 ml) under argon atmosphere at -40 °C. b) Isolated yield. c) Determined by HPLC analysis. d) ZCl : Carbobenzoxy chloride.

samarium diiodide is quite effective in the reduction of 2-hydroxyimino amides to the corresponding dipeptides. The diiodide reduced no coexisted functional groups such as ester and amide ones, while the other available reductants, such as $LiAlH_4$, $NaBH_4$, BH_3, etc., reduced the above functional groups at the same time to yield the complex products. Thus 2-hydroxyimino amide **3a** was stereoselectively and cleanly reduced to the corresponding dipeptide with samarium diiodide (5.0 equiv.) in MeOH and THF at -40 °C in 64% yield (Diastereomer ratio *RS* : *SS* = 85 : 15) (Entry 1 in Table 2). And the diastereoselectivity was increased upto 89 : 11 in the case of oxime **3b** with *t*-butyl ester instead of methyl ester **3a** (Entry 2). The diastereoselectivity in the present reduction was remarkably improved upto 99 : 1 and dipeptide was obtained in 82% yield when *t*-butyl ester group was substituted by pyrrolidino amides group in the above amide **3b** (Entry 3).

Table 3. Reduction of Various Oximes with SmI_2/MeOH[a)]

Entry	Oxime		Dipeptide		Yield /%[b)]	*R* : *S*[c)]
1		**5a**		**6a**	71	97 : 3
2		**5b**		**6b**	75	92 : 8
3		**5c**		**6c**	84[d)]	18 : 82
4		**5d**		**6d**	80[d)]	10 : 90
5		**5e**		**6e**	70[d)]	80 : 20
6		**5f**		**6f**	77[d)]	90 : 10
7		**5g**		**6g**	73[d)]	91 : 9

a) Reaction conditions; oxime (**5a-5g**) 0.2 mmol, SmI_2 1.0 mmol (0.1 M THF solution, 10 ml), MeOH 10 ml, in THF (4.0 ml) under argon atmosphere at -40 °C. b) Isolated yield. c) Determined by HPLC analysis. d) SmI_2 (1.5 mmol) was used.

As shown in Table 3, the above procedure was successfully applied to the reduction of various 2-hydroxyimino amides, such as 2-hydroxyimino amides derived from (*S*)-proline, which were smoothly reduced

into the corresponding dipeptides in good yields and with extremely high diastereoselectivities without accompanying any reduction of other functional groups (Entries 1 and 2). According to the present procedure, oximes derived from pyrrolidino and piperidino amides of D-phenylglycine were also converted into the corresponding dipeptides in high yields with good diastereoselectivities, respectively (Entries 3 and 4). In particular, oxime derived from piperidino D-phenylglycine gave the best result with respect to the diastereoselectivity. 2-Hydroxyimino groups in the amides derived from piperidino L-alanine, L-valine, and L-*t*-butylleucine were smoothly reduced into amino groups to afford the corresponding dipeptides in good yields and in high diastereoselectivities (Entries 5-7). It is noted that the bulky substituent in amino acid moiety is effective improving the diastereoselectivity in the present reduction.

A typical procedure is described for the reduction of oxime **3c** : To a solution of oxime **3c** (51.0 mg, 0.20 mmol) in MeOH (10 ml) and THF (4.0 ml) was successively added 0.1 M-samarium diiodide in THF solution (10 ml, 1.0 mmol) under argon atmosphere at -40 °C, the resulting mixture was stirred for 1 h. Then the reaction mixture was quenched with a mixture of buffer (pH 7, 2.5 ml) and MeOH (2.5 ml) solution at -40 °C. The reaction mixture was poured into 10% aqueous potassium carbonate solution, and extracted with dichloromethane. Organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Then dichloromethane (10 ml) was added to the residue, and carbobenzoxy chloride (ZCl) (0.04 ml, 0.3 mmol) and pyridine (0.03 ml, 0.3 mmol) were added to this solution. After stirring for 1 h at 0 °C, the reaction mixture was quenched with brine and extracted with dichloromethane. Organic layer was dried over anhydrous magnesium sulfate. Subsequently, the solvent was removed, and the crude product was purified by silica gel TLC (AcOEt), dipeptide **4c** was obtained (60.8 mg, 82% yield).

It is noted that, α,β-unsaturated amides derived from α-amino acids are converted with BuONO to the corresponding 2-hydroxyimino amides, which were smoothly reduced with samarium diiodide into the corresponding optically active unnatural dipeptides in good yields with high chemo- and diastereoselectivities. Thus, the present procedure provides a useful method for preparation of dipeptides containing unnatural α-amino acids.

References

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