Oxidative decarboxylative synthesis of 2-H-imidazolines from glyoxylic acid and 1,2-diamines†

Kenichi Murai, Maiko Morishita, Ryo Nakatani, Hiromichi Fujioka* and Yasuyuki Kita*

Received (in Cambridge, UK) 8th May 2008, Accepted 27th June 2008
First published as an Advance Article on the web 4th August 2008
DOI: 10.1039/b807810f

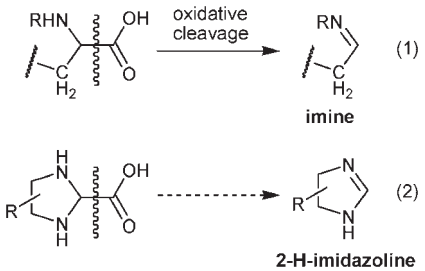
A novel method to prepare 2-H-imidazolines from glyoxylic acid monohydrate and 1,2-diamines is described; the key reaction of this method is the oxidative decarboxylation of the 2-carboxy imidazolidines by NBS.

We recently reported the efficient synthesis of 2-substituted imidazolines.[1] The method involves the condensation of aldehydes and 1,2-diamines without any catalyst. The reaction mixtures are then oxidized by *N*-bromosuccinimide (NBS) to afford the imidazolines in a one-pot operation. This is the first method to prepare imidazolines from aldehydes and 1,2-diamines and has several advantages. Thus the reaction proceeds under mild conditions at low reaction temperature (0 °C–rt) using an almost neutral reagent (NBS). Furthermore, functions such as esters and nitriles can be tolerated, whereas such functions are used for constructing imidazoline rings in previous methods.[2] The utility of this reaction was also demonstrated by our recent total synthesis of spongotine A having the imidazoline-ketone moiety.[3] On the other hand, this method had not been applied to the synthesis of the 2-H-imidazolines.

2-H-Imidazolines are pharmacologically important skeletons.[4] The condensation of 1,2-diamines and an appropriate reagent provides the straightforward and convenient syntheses of 2-H-imidazolines, and several useful methods using 1,2-diamines have been reported. For example, under elevated temperature conditions, condensations with triethyl orthoformate in the presence of a catalytic amount of the acid,[5] *tert*-butyl cyanide using a silver cyanide catalyst,[6] and dimethylformamide dimethyl acetal[7] were reported. On the contrary, at room temperature, condensations with formamidine[4c] or formimidate[4d] reagents are known. In this paper, we describe a novel approach for the synthesis of 2-H-imidazolines by oxidative decarboxylation from glyoxylic acid and 1,2-diamines.

For the synthesis of the 2-H-imidazolines, we initially examined the reaction using formaldehyde. To our delight, the condensation with (±)-1,2-diphenylethylenediamine **1a** followed by oxidation with NBS in CH_2Cl_2 gave compound **2a** in 79% yield. As the yield was not very efficient, we tried to search for a more effective reaction.

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan.
E-mail: fujioka@phs.osaka-u.ac.jp; kita@phs.osaka-u.ac.jp;
Fax: +81 6 6879 8229; Tel: +81 6 6879 8226
† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b807810f

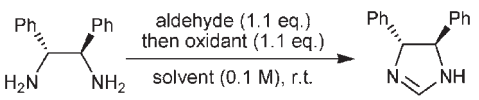


Scheme 1

It is well known that α-amino acids generate imines by oxidative decarboxylation (Scheme 1, (1)).[8] We considered that the 2-carboxy imidazolidines, similar to α-amino acids, could provide the 2-H-imidazolines if their oxidative cleavage could occur (Scheme 1, (2)). Glyoxylic acid bearing a carboxylic acid group at the α position of aldehyde was selected as the coupling partner of the 1,2-diamines.

The results of the reaction with glyoxylic acid monohydrate and diamine **1a** are shown in Table 1. As expected, the condensation of glyoxylic acid monohydrate with diamine **1a** followed by oxidative cleavage by NBS very smoothly proceeded to produce 2-H-imidazoline **2a** in 88% yield in CH_2Cl_2 at room temperature (Table 1, entry 2). MeOH was revealed to be a better solvent and gave an excellent result (98% yield), because of the good solubility of glyoxalic acid in this solvent (Table 1, entry 3). On the other hand, other oxidants such as NaOCl,[8i] $NaIO_4$,[8j] and H_5IO_6,[8k] that are generally used for cleavage of α-amino acids, were not effective (Table 1, entries 4–6).

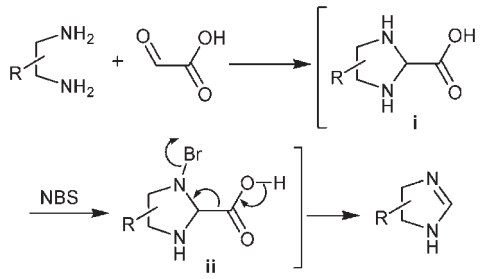
Table 1 Optimization



1a **2a**

Entry	Aldehyde	Oxidant	Solvent	Yield (%)
1	HCHO aq.	NBS	CH_2Cl_2	79
2	$HCOCO_2H·H_2O$	NBS	CH_2Cl_2	88
3	$HCOCO_2H·H_2O$	NBS	MeOH	98
4	$HCOCO_2H·H_2O$	NaOCl	MeOH	N.D.[a]
5	$HCOCO_2H·H_2O$	$NaIO_4$	MeOH	N.D.[a]
6	$HCOCO_2H·H_2O$	H_5IO_6	MeOH	44
7	$HCOCO_2H·H_2O$	NBS + galvinoxyl (1.1 eq.)	MeOH	93

[a] N. D. = Not detected on TLC.



Scheme 2

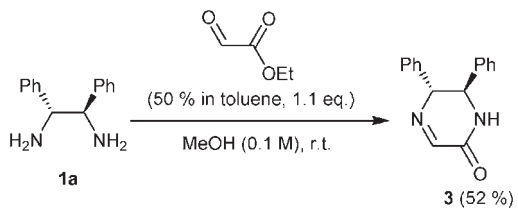
Although it is known that some oxidative cleavages of α-amino acids proceed *via* a radical mechanism,[8c,d,9] the reaction that developed is not a radical reaction, considering the fact that the addition of galvinoxyl, which is a radical scavenger, had little influence on this reaction (Table 1, entry 7). Therefore, as shown in Scheme 2, the reaction proceeds through a sequence involving the formation of aminal **i**, the bromination of the nitrogen atom, and simultaneous elimination of bromine and CO_2 from intermediate **ii** to give 2-H-imidazoline.

It can be assumed that the carboxylic acid of the glyoxylic acid monohydrate plays two important roles in this reaction. First, it increases the reactivity of the aldehyde and makes the formation of the aminal much easier. Secondly, at the oxidation stage, the decarboxylation is a good assistant for the elimination of the bromine. Therefore glyoxylic acid monohydrate effectively produced the 2-H-imidazoline when compared with formaldehyde. Additionally, the carboxylic acid moiety of glyoxylic acid is essential in this reaction, because condensation of the diamine **1a** with ethyl glyoxylate, which has an ester moiety instead of a carboxylic acid formed the 6-membered pyrazinone ring (Scheme 3).[10]

The generality of this reaction is shown in Table 2. *N*-substituted diamines **1b** and **1c** afforded the corresponding 2-H-imidazolines **2b** and **2c** in good yields (Table 2, entries 2, 3). The 2-H-imidazolines **2d** and **2e**, which have a bulky isopropyl or cyclohexyl substitution on the nitrogen atom, were also obtained in high yields (Table 2, entries 4, 5). Furthermore, the diamine **1f** bearing a quaternary carbon can be applicable (Table 2, entry 6).

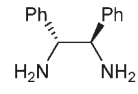
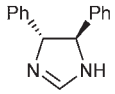
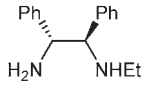
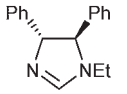
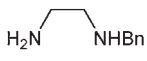
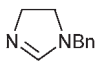
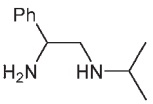
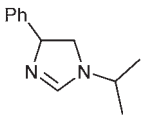
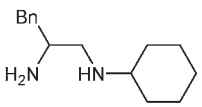
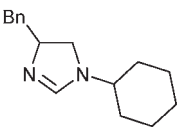
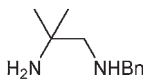
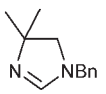
In summary, we have developed a novel method to prepare 2-H-imidazolines from various 1,2-diamines and glyoxylic acid monohydrate. The mild and smooth oxidative decarboxylation of the 2-carboxy imidazolidines is characteristic of this reaction. We believe that this method is useful and will become an alternative method for the synthesis of the 2-H-imidazolines.

This work was financially supported by Grant-in-Aid for Scientific Research (A) and Grant-in-Aid for Scientific Research for Exploratory Research from Japan Society for the Promotion of Science and by Grant-in-Aid for Scientific Research on Priority Areas (17035047) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. K.M. thanks the Japan Society for the Promotion of Science (JSPS) for a Research Fellowship for Young Scientists.



Scheme 3

Table 2 Generality

Entry	Diamine	Product	Yield (%)
1	 **1a**	 **2a**	98
2	 **1b**	 **2b**	95
3	 **1c**	 **2c**	83
4	 **1d**	 **2d**	73
5	 **1e**	 **2e**	91
6	 **1f**	 **2f**	61

Notes and references

1 (*a*) H. Fujioka, K. Murai, Y. Ohba, A. Hiramatsu and Y. Kita, *Tetrahedron Lett.*, 2005, **46**, 2197–2199; (*b*) H. Fujioka, K. Murai, O. Kubo, Y. Ohba and Y. Kita, *Tetrahedron*, 2007, **63**, 638–643; After our report, several groups reported methods to prepare imidazolines from aldehydes by using other oxidants. See: (*c*) P. Gogoi and D. Konwar, *Tetrahedron Lett.*, 2006, **47**, 79–82; (*d*) M. Ishihara and H. Togo, *Synlett*, 2006, 227–230; (*e*) S. Sayama, *Synlett*, 2006, 1479–1484.

2 For the example, see: (*a*) R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, 1954, **54**, 593–613; (*b*) G. Neef, U. Eder and G. Sauer, *J. Org. Chem.*, 1981, **46**, 2824–2826.

3 K. Murai, M. Morishita, R. Nakatani, O. Kubo, H. Fujioka and Y. Kita, *J. Org. Chem.*, 2007, **72**, 8947–8949.

4 (*a*) A. A. Cordi, J.-M. Lacoste, J.-J. Descombes, C. Courchary, P. M. Vanhoutte, M. Laubi and T. J. Verbeuren, *J. Med. Chem.*, 1995, **38**, 4056–4069; (*b*) A. A. Cordi, I. Berque-Bestel, T. Persignard, J.-M. Lacoste, A. Newman-Tancredi, V. Audinot and M. J. Millan, *J. Med. Chem.*, 2001, **44**, 787–805; (*c*) A. A. Cordi, I. Barque-Bestel, T. Persigand, J.-M. Lacoste, A. Newman-Tancredi, V. Audinot and M. J. Millan, *J. Med. Chem.*, 2001, **44**, 787–805; (*d*) A. Hamada, E. L. Yaden, J. S. Horng, R. R. Ruffolo, Jr, P. N. Patil and D. D. Miller, *J. Med. Chem.*, 1985, **28**, 1269–1273.

5 P. K. Martin, H. R. Matthews, H. Rapoport and G. Thyagarajan, *J. Org. Chem.*, 1968, **33**, 3758–3761.

6 Y. Ito, Y. Inubushi, M. Zenbayashi, S. Tomita and T. Saegusa, *J. Am. Chem. Soc.*, 1973, **95**, 4447–4448.
7 Y. Hsiao and L. S. Hegedus, *J. Org. Chem.*, 1997, **62**, 3586–3591.
8 For examples, see: (*a*) A. P. Gledhill, C. J. McCall and M. D. Threadgill, *J. Org. Chem.*, 1986, **51**, 3196–3201; (*b*) G. Apitz and W. Steglich, *Tetrahedron Lett.*, 1991, **32**, 3163–3166; (*c*) A. Boto, R. Hernandez and E. Suarez, *Tetrahedron Lett.*, 1999, **40**, 5945–5948; (*d*) A. Boto, R. Hernandez and E. Suarez, *Tetrahedron Lett.*, 2000, **41**, 2495–2498; (*e*) H. Horikawa, T. Iwasaki, K. Matsumoto and M. Miyoshi, *Tetrahedron Lett.*, 1976, **3**, 191–194; (*f*) T. Nisihitani, H. Horikawa, T. Iwasaki, K. Matsumoto, I. Inoue and M. Miyoshi, *J. Org. Chem.*, 1982, **47**, 1706–1712; (*g*) Y. Harayama, M. Yoshida, D. Kamimura and Y. Kita, *Chem. Commun.*, 2005, 1764–1766; (*h*) Y. Harayama, M. Yoshida, D. Kamimura, Y. Wada and Y. Kita, *Chem.–Eur. J.*, 2006, **12**, 4893–4899; (*i*) H. L. Saltes, D. Taub, C. H. Kuo and N. L. Wender, *J. Org. Chem.*, 1964, **23**, 1424–1429; (*j*) H. O. House and W. F. Berkowitz, *J. Org. Chem.*, 1963, **28**, 2271–2276; (*k*) N. K. Bose and D. N. Chaudhury, *J. Indian Chem. Soc.*, 1966, **43**, 411–415.
9 Synthesis of aldehydes from α-amino acids by using NBS, see: A. Schonberg, R. Moubasher and M. Z. Barakat, *J. Chem. Soc.*, 1951, 2504–2505.
10 Formations of pyrazinone ring from 1,2-diamines and ethyl glyoxylate, see: (*a*) A. V. Zychlinski and I. Ugi, *Heterocycles*, 1998, **49**, 29–32; (*b*) C. Hulme and M.-P. Cherrier, *Tetrahedron Lett.*, 1999, **40**, 5295–2599.

