COMMUNICATION

One-pot synthesis of α-amino acids based on free radical-mediated carbon–carbon bond formation

Hideto Miyabe, Naoko Yoshioka, Masafumi Ueda and Takeaki Naito *

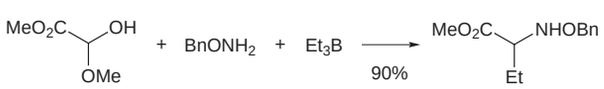
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan
E-mail: taknaito@kobepharma-u.ac.jp

Received (in Cambridge) 8th September 1998, Accepted 16th October 1998

The one-pot reaction of 2-hydroxy-2-methoxyacetic acid methyl ester with benzyloxyamine and an alkyl radical provided a convenient method for preparing the protected α-amino acids *via* a carbon–carbon bond formation by intermolecular carbon radical addition to glyoxylic oxime ether.

In recent years, much attention has been paid to the development of concise and flexible synthetic approaches to α-amino acids, allowing facile incorporation of functional groups and structural variability. Multi-step synthetic routes to α-amino acids are available,[1] however, integration of multi-step chemical reactions into a one-pot reaction is of great significance from both economical and ecological points of view.[2] Thus, the development of one-pot approaches to α-amino acids is a new subject of considerable interest.[3] We recently reported the first example of the preparation of amines and α-amino acids based on the intermolecular carbon radical addition to oxime ethers.[4–6] We now report a novel one-pot procedure for the synthesis of α-amino acid derivatives by the condensation of an α-keto acid derivative with alkoxyamine followed by the addition of an alkyl radical to the resulting oxime ether.

As a preliminary experiment, we chose a combination of commercially available 2-hydroxy-2-methoxyacetic acid methyl ester **1**, benzyloxyamine **2** and triethylborane as an ethyl radical source and investigated the one-pot reaction under several conditions (Scheme 1). Conventional condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **1** with benzyloxyamine **2** proceeded smoothly in the presence of $MgSO_4$ to give the glyoxylic oxime ether **4**. To the reaction vessel was added Et_3B and then the reaction mixture was stirred at 25 °C. This quite simple procedure in one-pot afforded, as expected, the protected α-amino acid **3a** in 90% yield. The reaction proceeds as indicated in Scheme 2. An ethyl radical, initially generated from Et_3B and O_2, adds intermolecularly to the oxime ether group of **4**, which was generated *in situ* from 2-hydroxy-2-methoxyacetic acid methyl ester **1** and benzyloxyamine **2**, to form the intermediate aminyl radical **5**. Since Et_3B acts not only as a radical initiator but also as a terminator to trap the resulting aminyl radical **5**, the radical reaction cycle proceeds through the regeneration of the ethyl radical and the formation of the adduct **6**.[7] The desired ethylated α-amino acid **3a** is obtained as a result of the hydrolysis of the adduct **6**.



1 **2** **3a**

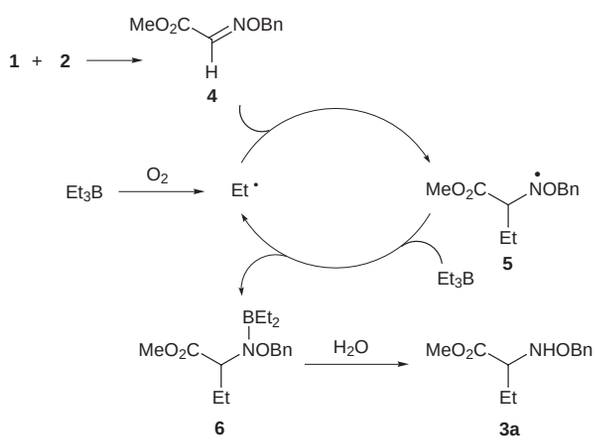
Scheme 1 *Reagents and conditions*: $MgSO_4$, CH_2Cl_2, 25 °C.

In order to investigate the generality and practicality of this one-pot reaction, the present procedure was successfully extended to a three-component reaction using different radical precursors, **7b–h**, as shown in Scheme 3. As in the case of **3a**, to the reaction vessel containing the intermediate oxime ether formed from a 1 : 1 mixture of **1** and **2** were successively added Pr^iI **7b**, Bu_3SnH and Et_3B as a radical initiator. The isopropylated α-amino acid derivative **3b** was obtained in 74% yield (Table 1, entry 1). Not only a secondary alkyl but also the bulky *tert*-butyl radical worked well under similar reaction conditions (entries 1–4). Modest chemical yields were obtained in the reactions using primary alkyl radicals because of the competitive formation of a significant amount of the ethylated product **3a** as a by-product, which would be formed by the reaction with the ethyl radical generated from Et_3B (entries 5–7). As we were expecting that the addition of functionalized radicals would make products more useful building blocks, as

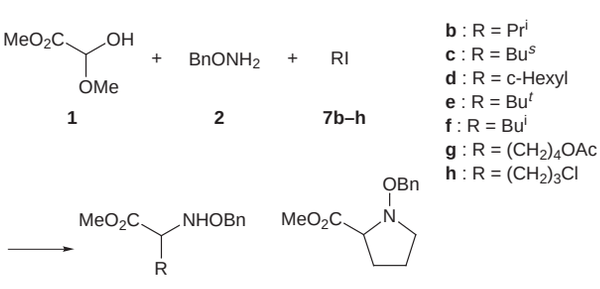
Table 1 One-pot synthesis of α-amino acid derivatives **3b–g** and **8h**

Entry	RI	Product[a]	Yield[b] (%)
1	Pr^iI	**3b**	74
2	Bu^sI	**3c**	71
3	c-HexylI	**3d**	72
4	Bu^tI	**3e**	86
5	Bu^iI	**3f**	49
6	$AcO(CH_2)_4I$	**3g**	57
7	$Cl(CH_2)_3I$	**8h**	46

[a] The ethylated product **3a** was obtained in *ca.* 5–10% yields (entries 1–4) or *ca.* 10–25% yields (entries 5–7). [b] Isolated yields.



Scheme 2



Scheme 3 *Reagents and conditions*: Bu_3SnH, Et_3B, $MgSO_4$, CH_2Cl_2, 25 °C.

exemplified by the recent progress in the fields of combinatorial chemistry and drug discovery, we investigated the reaction employing bifunctional halides as an alkyl radical precursor. As was expected from the nature of the radical reaction, alkyl iodides containing an ester moiety or a chlorine atom underwent smooth radical addition reactions to give the correspondingly functionalized α-amino acid derivatives **3g** and **8h** (entries 6 and 7). In the case of 1-chloro-3-iodopropane **7h**, the proline derivative **8h** was obtained as a result of the concomitant intramolecular *N*-alkylation of **3h** which was preformed by the one-pot reaction of the chloropropyl radical.

The advantages of this one-pot procedure are that the tedious isolation of the intermediate oxime ether is unnecessary and the crucial radical addition proceeds under very mild conditions to give *C*-alkylated products with high levels of regioselectivity. Therefore, the radical addition approach complements the nucleophilic addition of organometallic reagents giving a mixture of *C*- and *N*-alkylated products.[8,9]

In addition to the previously reported multi-step synthesis of amines and α-amino acids *via* alkyl radical addition to oxime ethers, the newly found one-pot procedure disclosed a broader aspect of the potentiality of an alkyl radical addition to oxime ethers, thus establishing the one-pot synthesis as a simple and useful methodology for the construction of various types of α-amino acid derivatives.

General procedure

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **1** (80 mg, 0.67 mmol) in CH_2Cl_2 (1 cm^3) were added benzyloxyamine **2** (82.4 mg, 0.67 mmol) in CH_2Cl_2 (0.5 cm^3) and $MgSO_4$ (10 mg) under a nitrogen atmosphere at 25 °C. After the reaction mixture was stirred at the same temperature for 1 day, RI **7** (3.35 mmol), Bu_3SnH (0.45 cm^3, 1.68 mmol) and Et_3B (1.0 M in hexane, 1.68 cm^3, 1.68 mmol) were added. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt 15:1, two repeats) followed by preparative TLC (chloroform) afforded the α-amino acid derivatives **3**.

Acknowledgements

We thank the Ministry of Education, Science, Sports and Culture of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

References

1 (*a*) R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989; (*b*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.
2 (*a*) P. A. Tempest, S. D. Brown and R. W. Armstrong, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 640; (*b*) G. H. Posner, *Chem. Rev.*, 1986, **86**, 831.
3 (*a*) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1997, **119**, 445; (*b*) N. A. Petasis, A. Goodman and I. A. Zavialov, *Tetrahedron*, 1997, **53**, 16463.
4 (*a*) H. Miyabe, R. Shibata, C. Ushiro and T. Naito, *Tetrahedron Lett.*, 1998, **39**, 631; (*b*) H. Miyabe, C. Ushiro and T. Naito, *Chem. Commun.*, 1997, 1789; (*c*) H. Miyabe, R. Shibata, M. Sangawa, C. Ushiro and T. Naito, *Tetrahedron*, 1998, **54**, 11431.
5 Oxime ethers are well known to be excellent radical acceptors because of the extra stabilisation of the intermediate aminyl radical provided by the adjacent oxygen atom. See H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi and T. Naito, *J. Org. Chem.*, 1998, **63**, 4397 and references cited therein.
6 For a related example, high 1,3-stereoinduction in radical additions to glyoxylate imines has recently been reported. See M. P. Bertrand, L. Feray, R. Nouguier and L. Stella, *Synlett*, 1998, 780.
7 K. Nozaki, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 403.
8 (*a*) Y. Yamamoto and W. Ito, *Tetrahedron*, 1988, **44**, 5415; (*b*) T. Kolasa, S. K. Sharma and M. J. Miller, *Tetrahedron*, 1988, **44**, 5431; (*c*) J.-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.*, 1971, 1019; (*d*) J.-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.*, 1970, 1813.
9 For recent examples, the nucleophilic addition of allylic zinc reagents to glyoxylic oxime ethers proceeds regioselectively to give the *C*-alkylated products. See (*a*) S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 8997; (*b*) S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5273.

Communication 8/07017B