ORGANIC
LETTERS

2000
Vol. 2, No. 10
1443−1445

Stereocontrol in Solid-Phase Radical Reactions: Radical Addition to Oxime Ether Anchored to Polymer Support

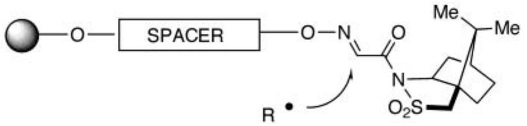
Hideto Miyabe, Chihiro Konishi, and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

taknaito@kobepharma-u.ac.jp

Received March 7, 2000

ABSTRACT



A high degree of stereocontrol in solid-phase radical reactions was achieved by using triethylborane and diethylzinc as a radical initiator at low reaction temperature. Alkyl radical addition to Oppolzer's camphorsultam derivatives of oxime ether anchored to polymer support proceeded smoothly to give the α-amino acid derivatives with excellent diastereoselectivities.

Stereocontrol in free radical-mediated carbon−carbon bond-forming reactions has been of great importance in organic synthesis. In recent years, a high degree of stereocontrol in solution-phase radical reactions has been achieved at low reaction temperature mainly by using triethylborane as a radical initiator.[1] We have recently demonstrated that triethylborane has the potential to induce radical reactions on solid support at below room temperature.[2,3] Thus, employment of triethylborane and its related radical initiators would facilitate the control of stereochemistry in solid-phase reactions and allow further progress in the fields of combinatorial chemistry and drug discovery.[4] As a part of our program directed toward the development of solid-phase radical reactions, we now report the results of experiments to probe the utility of triethylborane and diethylzinc in stereoselective solid-phase radical reactions. As shown below, the radical addition to the chiral oxime ethers anchored to a polymer support proceeded smoothly even at −78 °C to give an α-amino acid derivative with excellent diastereoselectivity.

Our recent studies showed that triethylborane has the potential to induce solid-phase radical reactions on solid support even at −78 °C and acts multiply as a radical initiator, a Lewis acid, and a radical terminator.[2a,5] Recently, Ryu and Komatsu reported that diethylzinc−air system can serve as an initiator of tin hydride-mediated radical reaction as well as triethylborane.[6−8] To test the viability of diethylzinc, we first investigated the simple addition of an ethyl

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(1) For reviews, see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (b) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (d) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996.

(2) (a) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174. (b) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387.

(3) The solid-phase radical reactions using AIBN or SmI_2 as a radical initiator have been reported. See: (a) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61. (b) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678. (c) Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, *38*, 8929. (d) Du, X.; Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 2281. (e) Berteina, S.; De Mesmaeker, A. *Tetrahedron Lett.* **1998**, *39*, 5759. (f) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231. (g) Watanabe, Y.; Ishikawa, S.; Takao, G.; Tour, T. *Tetrahedron Lett.* **1999**, *40*, 3411. (h) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535. (i) Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett.* **1999**, *40*, 7285. (j) Zhu, X.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 157.

(4) For reviews, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) *Chem. Rev.* **1997**, *97*, 347−510 (whole issue of No. 2). (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.

(5) (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569.

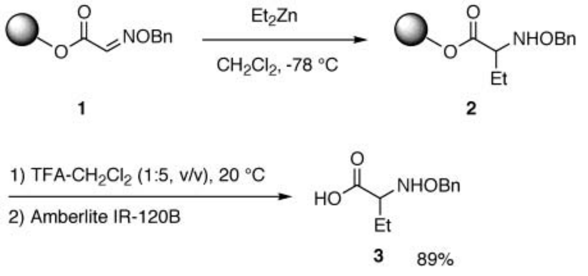
(6) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.

(7) For related examples, see: (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (c) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780.

10.1021/ol005771m CCC: $19.00

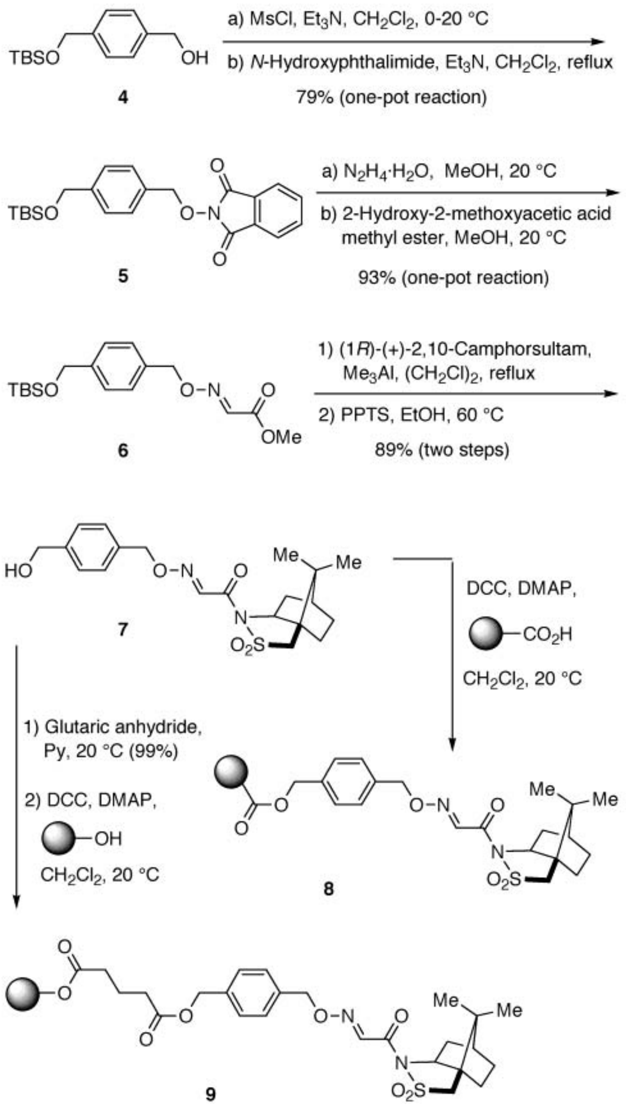
radical, generated from diethylzinc and O_2, to achiral oxime ether **1** anchored to Wang resin (Scheme 1).[9] To a flask containing oxime ether **1** and undegassed CH_2Cl_2 was added a commercially available 1.0 M solution of diethylzinc in hexane (5.1 equiv) at −78 °C, and then the reaction mixture was stirred at the same temperature for 15 min. As expected, the ethylated product **3** was obtained in 89% yield after cleavage of the resin by using TFA followed by purification.[10] Changing the temperature from −78 to 20 °C and the replacement of CH_2Cl_2 with toluene as a solvent were also effective for the reaction. It is noteworthy that diethylzinc works well as an effective radical initiator for the solid-phase radical reaction without interference of polystyrene skeleton of the resin, and good chemical yield was observed even at low reaction temperature.

Scheme 1



On the basis of these results, we next investigated the control of stereochemistry in solid-phase reactions by using triethylborane and diethylzinc at low reaction temperature. The auxiliary of choice was Oppolzer's camphorsultam since it had shown good characteristics in our previous work on solution-phase radical reactions.[5b,8] Additionally, we also expected that the direct comparison of the solid-phase radical reactions with the solution-phase radical reactions would lead to informative and instructive suggestions regarding stereoselection in solid-phase radical reaction. Preparation of chiral oxime ethers **8** and **9** anchored to a polymer support is shown in Scheme 2. Mesylation of the *tert*-butyldimethylsilylated *p*-xylylene glycol derivative **4** in the presence of triethylamine in CH_2Cl_2 followed by treatment with *N*-hydroxyphthalimide in one pot afforded the desired imide **5** in 79% yield.[11] One-pot preparation of oxime ether **6** was achieved by treatment of imide **5** with hydrazine monohydrate in MeOH and subsequent condensation with 2-hydroxy-2-methoxyacetic acid methyl ester.[12] Treatment of oxime ether **6** with (1*R*)-(+)-2,10-camphorsultam in the presence of trimethyl aluminum in boiling dichloroethane gave oxime ether having sultam as a single *E* isomer, which was then treated with pyridinium *p*-toluenesulfonate in EtOH at 60 °C to give deprotected alcohol **7** in 89% yield from **6**. The alcohol **7** could be attached to carboxypolystyrene resin by the treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20 °C for 12 h to give the resin-bound oxime ether **8**.[13] The loading level of the resin-bound glyoxylic oxime ether **8** was determined to be 0.77 mmol/g by quantification of nitrogen by elemental analysis. Treatment of alcohol **7** with glutaric anhydride gave carboxylic acid in 99% yield, which was then attached to Wang resin according to the similar reaction method to give the resin-bound glyoxylic oxime ether **9** in 0.83 mmol/g loading level.

Scheme 2



We first investigated the simple addition of an ethyl radical, generated from triethylborane and O_2, to the carboxypolystyrene resin-bound oxime ether **8** in CH_2Cl_2 at −78 °C (Scheme 3). Although the radical reaction might proceed smoothly, the difficulty in achieving the subsequent cleavage

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(8) For our related example, see: (a) Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789. (b) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176.

(9) Oxime ether **1** was readily prepared from glyoxylic oxime ether ($HO_2CCH{=}NOBn$) and Wang resin. See ref 2a.

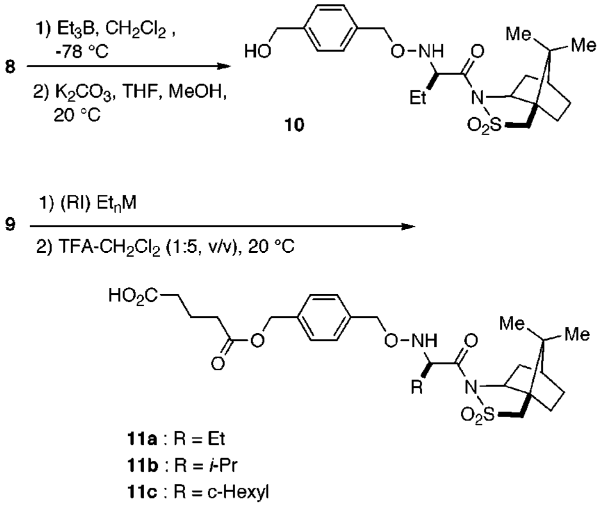
(10) Purification was accomplished by a combination of Amberlite IR-120B (eluting with MeOH) and the preparative TLC ($MeOH/CHCl_3$, 1:10, v/v).

(11) Diether, R. K.; Datar, R. *Can. J. Chem.* **1993**, *71*, 814.

(12) Moody, C. J.; Gallagher, P. T.; Lightfoot, A. P.; Slawin, A. M. Z. *J. Org. Chem.* **1999**, *64*, 4419.

(13) Carboxypolystyrene and Wang resins purchased from Novabiochem were used in all experiments.

Scheme 3



of the resin has remained unresolved; thus, a trace amount of the ethylated product **10** was only isolated.[14] We next investigated the ethyl radical addition to Wang resin-bound oxime ether **9** in CH_2Cl_2 (Table 1). Triethylborane and diethylzinc worked well as an effective radical initiator at −78 °C for the solid-phase radical reaction of oxime ether **9**. To a flask containing oxime ether **9** and undegassed CH_2Cl_2 was added a commercially available 1.0 M solution of triethylborane in hexane, and then the reaction mixture was stirred at −78 °C for 30 min. The resin was then filtered and washed successively with CH_2Cl_2 and AcOEt, and the subsequent cleavage of the resin with TFA/CH_2Cl_2 (1:5, v/v) gave the crude ethylated α-amino acid derivative as a TFA salt. The diastereomeric purity was found to be not less than 95% de.[15] The diastereoselectivity of solid-phase radical reaction was better than that obtained by solution-phase radical reaction shown in our recent report, probably due to lower reactivity of oxime ether anchored to a polymer support.[8] The absolute configuration of the major product was assigned to be *R* since their ^1H NMR data showed similarity with that of major product in the solution-phase radical reaction showed in our recent report.[8] Purification of the resulting α-amino acid derivative was accomplished by preparative TLC (hexane/AcOEt 2:3, v/v) to afford the free amino acid derivative **11a** in 74% isolated yield (entry 1). Diethylzinc could also be utilized to achieve a high degree of stereocontrol in solid-phase radical reaction of **9** to afford the ethylated product **11a** in 67% isolated yield with excellent diastereoselectivity (entry 2).

Table 1. Solid-Phase Radical Addition to **9**

entry	initiator	R	product	% yield[a]	selectivity
1[b]	Et_3B	Et	**11a**	74	>95% de
2[b]	Et_2Zn	Et	**11a**	67	>95% de
3[c]	Et_3B	*i*-Pr	**11b**	69	92% de
4[c]	Et_3B	c-Hexyl	**11c**	58	92% de
5[c]	Et_2Zn	*i*-Pr	**11b**	53	90% de
6[c]	Et_2Zn	c-Hexyl	**11c**	41	90% de

[a] Isolated yields of major diastereomer **11a**−**c**. [b] Reactions were carried out with Et_3B or Et_2Zn (5.0 equiv) in CH_2Cl_2 at −78 °C. [c] Reactions were carried out with Et_3B or Et_2Zn (10 equiv) in *i*-PrI/toluene (4:1, v/v) at 0 °C.

To test the generality of the solid-phase radical reaction of **9**, we next investigated the reaction using different radical precursors under the iodine atom-transfer reaction conditions.[16] However, the reactivity of oxime ether anchored to polymer support was quite different from that of oxime ethers in solution-phase reactions. General reaction procedures established in the solution-phase radical reactions did not give the good results.[8b] In the case of the solid-phase addition of isopropyl radical to **9** using triethylborane, the addition of ethyl radical, generated from triethylborane, competed with the iodine atom-transfer process to give a large amount of the ethylated product **11a** and a small amount of the isopropylated product **11b**.[5a,7b] Selective formation of the desired isopropylated product **11b** was observed in the reaction using triethylborane in *i*-PrI/toluene (4:1, v/v) at 0 °C (entry 3). After purification by preparative TLC, the isopropylated product **11b** was obtained in 69% isolated yield with good diastereoselectivity. Additionally, in the solid-phase reactions, the often tedious workup to remove excess reagents from reaction mixture was eliminated by washing the resin with solvents. The addition of a bulky cyclohexyl radical proceeded in slightly lower chemical efficiency under the same reaction conditions to give the cyclohexylated product **11c**, obtained in 58% isolated yield (entry 4). Diethylzinc worked well under similar reaction conditions to give the alkylated products with good selectivity (entries 5 and 6).

In conclusion, we have demonstrated that triethylborane and diethylzinc can be applied to the stereoselective solid-phase radical reactions.

Acknowledgment. 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. Partial support for this work was also provided to H.M. by the Nissan Chemical Industries Award in Synthetic Organic Chemistry, Japan. H.M. gratefully acknowledges the financial support from Takeda Science Foundation, Japan.

Supporting Information Available: General experimental procedures and characterization data for all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] The screening of several methods for the cleavage of the resin under the basic reaction conditions did not show good results because of the competitive reactions such as removal of the sultam and the formation of unidentified products.

[15] Diastereoselectivities were determined by ^1H NMR analysis.

[16] Bertrand's group and our group have reported that the solution-phase radical addition to imino groups proceeded in the absence of Bu_3SnH by using Et_3B or Et_2Zn. In this reaction, Et_3B and Et_2Zn act multiply as a Lewis acid, a radical initiator, and a terminator. See refs 5, 7, and 8.