Pergamon

Tetrahedron Letters 40 (1999) 8387–8390

TETRAHEDRON
LETTERS

Triethylborane-induced solid-phase radical cyclization of oxime ethers

Hideto Miyabe, Hirotaka Tanaka and Takeaki Naito *

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

Received 16 July 1999; revised 6 September 1999; accepted 17 September 1999

Abstract

The radical cyclization of oxime ethers anchored to a polymer support proceeded effectively by the use of triethylborane as a radical initiator to provide the functionalized pyrrolidines via a carbon–carbon bond-forming process. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: radical reactions; solid-phase synthesis; oximes.

The free radical-mediated reaction has developed as a particularly powerful method for carbon–carbon bond construction. Although a variety of carbon–carbon bond-forming reactions have been performed on solid support, these are less common than the carbon–heteroatom bond-forming reactions.[1] Therefore, the extension of carbon–carbon bond-forming radical reactions to solid-phase reactions is an important task, and studies on the solid-phase radical reactions using AIBN and SmI_2 have been recently reported.[2–7] We have also demonstrated that triethylborane has the potential to induce intermolecular radical reactions on solid support at below room temperature.[8] As a part of our program directed toward the development of solid-phase radical reactions, we now report the first example of triethylborane-promoted solid-phase radical cyclization of oxime ethers, which provides a new carbon–carbon bond-forming method for the synthesis of the functionalized pyrrolidines.[9]

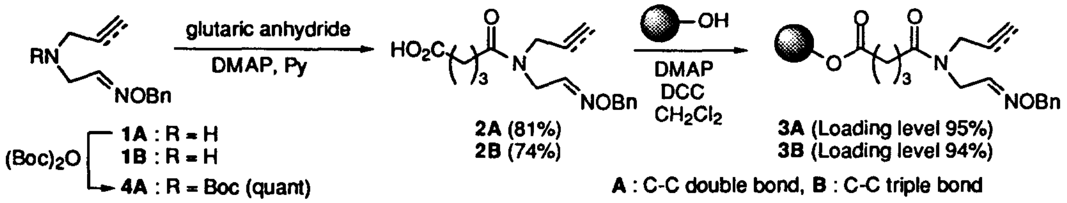
Preparation of oxime ethers **3A** and **3B** anchored to a polymer support is shown in Scheme 1. Treatment of α-chloroacetaldoxime ether[9] with allylamine gave the amine **1A** which was then treated with glutaric anhydride to give the oxime ether **2A**. The oxime ether **2A** was attached to Wang resin by treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20°C for 12 h to give the Wang resin-bound oxime ether **3A** in ca. 95% loading level.[10] The loading level of the Wang resin-bound oxime ether **3A** was determined to be 0.81 mmol/g by quantification of nitrogen by elemental analysis. According to the similar reaction methods, the oxime ether **3B** was also prepared from propargylamine in good loading levels.

Prior to exploring the solid-phase radical cyclization, we first investigated the radical cyclization of oxime ether **4A** in solution under several reaction conditions (Table 1). Treatment of **4A** with Bu_3SnH in the presence of AIBN (1 equiv.) in boiling benzene for 15 min gave the cyclic product **5Aa** in 31% yield

---

* Corresponding author. Fax: +81 78 441 7556; e-mail: taknaito@kobepharma-u.ac.jp

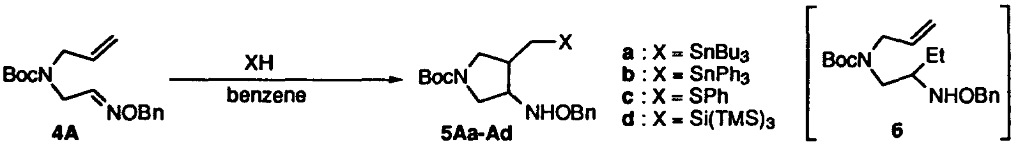
PII: S0040-4039(99)01788-8



Scheme 1.

Table 1

Solution-phase radical cyclization of oxime ether **4A**

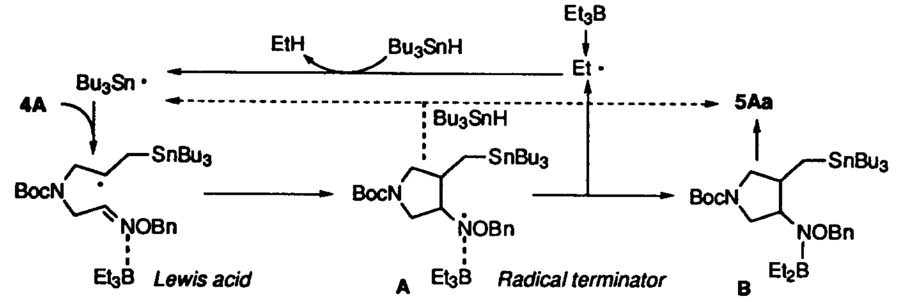


Entry	XH	Radical Initiator	*T* (°C)	Time (min)	Product	Yield (%)[a]
1	Bu_3SnH	AIBN (1.0 eq)	reflux	15	**5Aa**	31 (65)
2	Bu_3SnH	AIBN (1.0 eq)	reflux	120	**5Aa**	84
3	Bu_3SnH	Et_3B (2.5 eq)	reflux	15	**5Aa**	82
4	Bu_3SnH	Et_3B (0.2 eq)	reflux	15	**5Aa**	27 (61)
5	Bu_3SnH	Et_3B (5.0 eq)	20	120	**5Aa**	37 (57)
6	Ph_3SnH	Et_3B (2.5 eq)	reflux	15	**5Ab**	81
7	PhSH	Et_3B (2.5 eq)	reflux	15	**5Ac**	24 (54)
8	Et_3SiH	Et_3B (5.0 eq)	reflux	15	**6**	32 (39)
9	$(TMS)_3SiH$	Et_3B (2.5 eq)	reflux	15	**5Ad**	79

[a] Yields of isolated product; Yields in parentheses are for the recovered starting material **4A**.

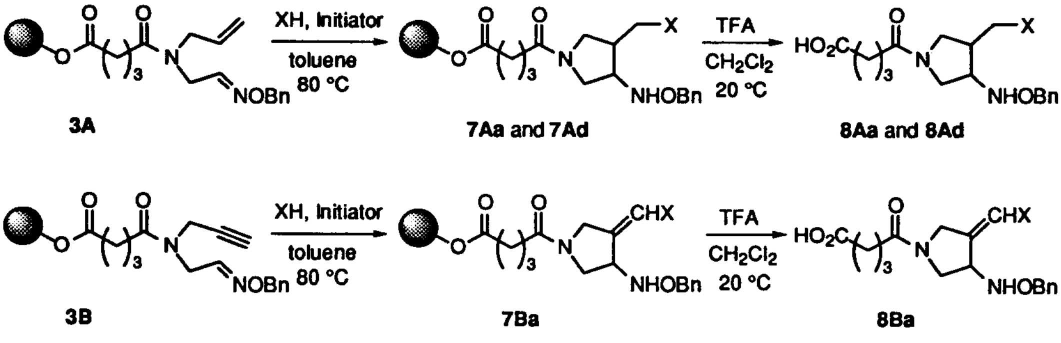
accompanied with 65% yield of the starting material **4A** (entry 1).[11] When triethylborane (2.5 equiv.) was employed as a radical initiator, the cyclic product **5Aa** was obtained in 82% yield within 15 min (entry 3). However, the use of a catalytic amount of triethylborane (0.2 equiv.) was less effective for the radical cyclization (entry 4). The reaction using triethylborane proceeded moderately even at 20°C (entry 5). These results indicate that triethylborane acts as not only a radical initiator but also a Lewis acid and a radical terminator; therefore, more than a stoichiometric amount of triethylborane is required (Scheme 2).[12,13] Thus, the rationale of the major reaction pathway is that the stannyl radical adds to the triethylborane-activated oxime ether **4A** to form the benzyloxyaminyl radical **A** which is then trapped by triethylborane as a radical terminator to give the product **B**.[14] To survey the scope and limitations of the triethylborane-promoted radical cyclization, we investigated the reaction using different radical precursors. High chemical yield was also observed in the radical cyclization using triphenyltin hydride (entry 6). The combination of triethylborane and thiophenol was less effective for the radical cyclization, presumably due to the formation of an unidentified complex from triethylborane and thiophenol (entry 7). The use of the less reactive triethylsilane led to the predominant formation of the ethylated product **6** as a result of the competitive intermolecular addition of an ethyl radical generated from triethylborane (entry 8). In contrast with triethylsilane, the reaction using the more reactive tris(trimethylsilyl)silane proceeded smoothly to give the cyclic product **5Ad** in 79% yield (entry 9).

Based on these results, we next investigated the radical cyclization of oxime ethers **3A** and **3B** anchored to a polymer support (Scheme 3, Table 2). Triethylborane worked well as an effective radical initiator at high temperature for the solid-phase radical cyclization of oxime ethers without interference of the polystyrene skeleton of the resin. To a flask containing oxime ether **3A** and Bu_3SnH in toluene was added (three times) a commercially available 1.0 M solution of triethylborane (13 equiv.) in hexane at



Scheme 2.

80°C (entry 1).[15] After the reaction mixture was stirred at 80°C for 8 h, the resin was then filtered and washed successively with CH_2Cl_2, AcOEt followed by MeOH, and the subsequent cleavage of the resin by treatment with TFA:CH_2Cl_2 (1:5, v/v) gave the cyclic product **8Aa** in 65% yield.[16] Purification of **8Aa** was accomplished by preparative TLC (MeOH:$CHCl_3$, 1:20, v/v) to afford the product **8Aa** in 64% isolated yield.[11] In contrast with the solution-phase radical cyclization of **4A**, the solid-phase cyclization of **3A** using triethylborane at 80°C did not go to completion within 15 min. We also examined the reaction using triethylborane at 20°C; however, **8Aa** was obtained only in low yield after prolonged reaction of around 3 days. Treatment of oxime ether **3A** with Bu_3SnH in the presence of AIBN (1.0×3 equiv.) in toluene at 80°C for 20 h was also found to be effective for the solid-phase cyclization and gave the cyclic product **8Aa** in 47% isolated yield after cleavage of the resin (entry 2). In agreement with the general advantages of the solid-phase methodology over the reaction in solution, the tedious workup to remove tin residues from the reaction mixture is eliminated by ready washing of the resin with solvents. The use of 9-BBN[17] (6.5×3 equiv.) as a radical initiator was less effective for the solid-phase radical reaction of **3A** in the present study (entry 3). A silyl centered-radical, generated from tris(trimethylsilyl)silane and triethylborane, could also be utilized to achieve the cyclization of **3A** to give the cyclic product **8Ad** in 50% isolated yield under similar reaction conditions (entry 4). Reaction of oxime ether **3B** having a C–C triple bond with a stannyl radical also proceeded effectively to give the cyclic product **8Ba** in 77% isolated yield (entry 5).



a : X = $SnBu_3$, **d** : X = $Si(TMS)_3$

Scheme 3.

In conclusion, we have shown the first example of the triethylborane-induced radical cyclization of oxime ethers on solid support, providing a novel method for preparing the functionalized pyrrolidines via a carbon–carbon bond-forming process. In this reaction, triethylborane plays multiple roles as a Lewis acid, a radical initiator, and a terminator. Additionally, the direct comparison of the solid-phase reaction

Table 2
Solid-phase radical cyclization of **3A** and **3B**

Entry	Oxime Ether	XH	Radical Initiator	Product	Yield (%)[a]
1	**3A**	Bu_3SnH	Et_3B	**8Aa**	64
2	**3A**	Bu_3SnH	AIBN	**8Aa**	47
3	**3A**	Bu_3SnH	9-BBN	**8Aa**	trace
4	**3A**	$(TMS)_3SiH$	Et_3B	**8Ad**	50
5	**3B**	Bu_3SnH	Et_3B	**8Ba**	77

[a] Yields are for the isolated products after purification of the crude products by preparative TLC ($CHCl_3$/MeOH 20:1).

with the solution-phase reaction indicated that the reactivity of oxime ethers anchored to a polymer support was slightly lower than that of oxime ethers in solution.

Acknowledgements

We wish to 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.

References

1. For reviews, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) *Chem. Rev.* **1997**, *97*, whole issue of No. 2, pp. 347–510. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.
2. Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61.
3. (a) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678. (b) Du, X.; Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 2281.
4. Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, *38*, 8929.
5. (a) Berteina, S.; De Mesmaeker, A. *Tetrahedron Lett.* **1998**, *39*, 5759. (b) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231.
6. Watanabe, Y.; Ishikawa, S.; Takao, G.; Tour, T. *Tetrahedron Lett.* **1999**, *40*, 3411.
7. Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535.
8. Miyabe, H.; Fujishima, U.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174.
9. Oxime ethers are well known to be excellent radical acceptors. See: (a) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (b) Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883.
10. Wang resin purchased from Novabiochem was used in this study.
11. Cyclic products **5Aa–Ad** and **8Aa–Ba** were obtained as a *cis/trans* mixture in ca. 1:1–1:2 ratio.
12. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403. (b) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.
13. Our recent studies on the intermolecular radical addition to oxime ethers showed that Et_3B works as not only a radical initiator but also as a Lewis acid and a terminator. See: (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569.
14. Another possible route to the product **5Aa** from **A** via the reaction with Bu_3SnH would not be excluded.
15. The reaction conditions have not been optimized. All reactions were run on scale 200–250 mg beads in commercially available solvents and with reagents without requiring any special precautions.
16. Compounds **8Aa–Ba** were characterized by IR, ^{1}H and ^{13}C NMR, and HRMS.
17. Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron Lett.* **1998**, *39*, 5437.