

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 SmI₂ 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 ether⁹ 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 CH₂Cl₂ 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 Bu₃SnH 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



Scheme 1. Table 1 Solution-phase radical cyclization of oxime ether **4A**

BocN 4A	NOBn t	XH Boch benzene 5A	NHOBn a-Ad	a : X = SnBug b : X = SnPhg c : X = SPh d : X = Si(TM	BocN 3)3	Et NHOBn
Entry	ХН	Radical Initiator	Τ ([°] C)	Time (min)	Product	Yield (%) ^a
1	Bu ₃ SnH	AIBN (1.0 eq)	reflux	15	5Aa	31 (65)
2	Bu ₃ SnH	AIBN (1.0 eq)	reflux	120	5Aa	84
3	Bu ₃ SnH	Et ₃ B (2.5 eq)	reflux	15	5Aa	82
4	Bu ₃ SnH	Et ₃ B (0.2 eq)	reflux	15	5Aa	27 (61)
5	Bu ₃ SnH	Et ₃ B (5.0 eq)	20	120	5Aa	37 (57)
6	Ph ₃ SnH	Et ₃ B (2.5 eq)	reflux	15	5Ab	81
7	PhSH	Et3B (2.5 eq)	reflux	15	5Ac	24 (54)
8	Et ₃ SiH	Et ₃ B (5.0 eq)	reflux	15	6	32 (39)
9	(TMS) ₃ SiH	Et ₃ B (2.5 eq)	reflux	15	5Ad	79

⁴ 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 **Bu₃SnH** in toluene was added (three times) a commercially available 1.0 M solution of triethylborane (13 equiv.) in hexane at



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 CH₂Cl₂, AcOEt followed by MeOH, and the subsequent cleavage of the resin by treatment with TFA:CH₂Cl₂ (1:5, v/v) gave the cyclic product 8Aa in 65% yield.¹⁶ Purification of 8Aa was accomplished by preparative TLC (MeOH:CHCl₃, 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-BBN¹⁷ (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 silvl 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).





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

Entry	Oxime Ether	хн	Radical Initiator	Product	Yield (%) ^a
1	3A	Bu ₃ SnH	Et ₃ B	8Aa	64
2	3A	Bu ₃ SnH	AIBN	8Aa	47
3	3A	Bu ₃ SnH	9-BBN	8Aa	trace
4	3A	(TMS) ₃ SiH	Et ₃ B	8Ad	50
5	3B	Bu ₃ SnH	Et ₃ B	8Ba	77

 Table 2

 Solid-phase radical cyclization of 3A and 3B

⁴ Yields are for the isolated products after purification of the crude products by preparative TLC (CHCl₃/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

- 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.
- 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.
- Our recent studies on the intermolecular radical addition to oxime ethers showed that Et₃B 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 Bu₃SnH 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, ¹H and ¹³C NMR, and HRMS.
- 17. Perchyonok, V. T.; Schiesser, C. H. Tetrahedron Lett. 1998, 39, 5437.