Pergamon

Tetrahedron Letters 39 (1998) 9211–9214

TETRAHEDRON LETTERS

Lanthanide Triflate-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Polymer-Supported Nitrones with Alkenes for the Preparation of Diverse 2-Isoxazoline Derivatives

Shū Kobayashi*† and Ryo Akiyama

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, and Department of Applied Chemistry, Faculty of Science, Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162-0825

Received 7 September 1998; revised 30 September 1998; accepted 2 October 1998

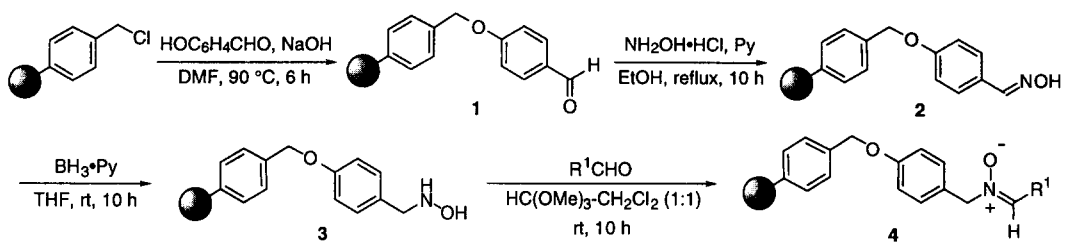
Abstract: *1,3-Dipolar cycloaddition reactions of polymer-supported nitrones with alkenes proceeded smoothly in the presence of a catalytic amount of a lanthanide triflate to afford the corresponding 2-isoxazolines in high yields. Diverse 2-isoxazoline derivatives were prepared based on these solid-phase reactions.* © 1998 Elsevier Science Ltd. All rights reserved.

2-Isoxazolines are found in a number of pharmaceutical agents such as glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors[1] and human leukocyte elastase inhibitors.[2] In addition, they are useful intermediates in the synthesis of many biologically-important compounds.[3] In order to search for and obtain additional bioactive compounds, development of efficient methods for the synthesis of diverse 2-isoxazoline derivatives are strongly in demand. In this paper, we report the lanthanide triflate-catalyzed 1,3-dipolar cycloaddition of polymer-supported nitrones to alkenes for the synthesis of diverse 2-isoxazoline derivatives.

For the preparation of 2-isoxazoline derivatives, use of 1,3-dipolar cycloaddition reactions is the most efficient.[4] There are two pathways: use of nitrones or nitrile oxides. While the cycloadditions are performed under thermal conditions, the same reactions proceed smoothly in the presence of a Lewis acid at room temperature or below. Bearing in mind that dipolarophiles are activated by Lewis acids in most cases in these types of reactions and that solid-phase reactions have many advantages for the synthesis of large numbers of structurally distinct molecules,[5] we decided to immobilize nitrones onto polymers. While 1,3-dipolar cycloadditions using nitrile oxides[6] or nitrones[7] on the solid-phase were reported very recently, they were carried out under thermal conditions (without Lewis acids) and traces of polymer-supports remained even after cleavage from the supports.[8]

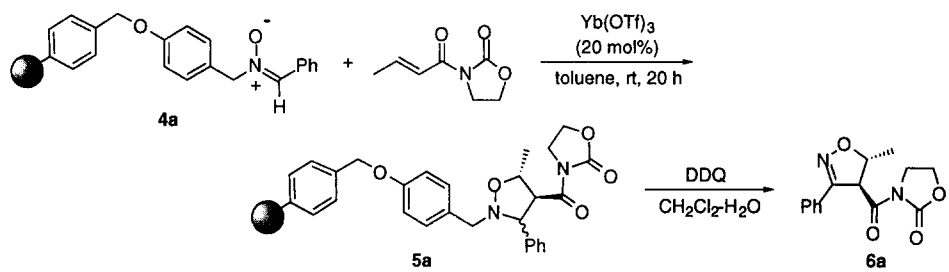
Polymer-supported nitrones were prepared according to Scheme 1. Chloromethyl copoly-(styrene-1%-divinylbenzene) resin (9.25 g, 0.91 mmol/g) was treated with 4-hydroxybenzaldehyde (3.08 g, 25.2 mmol (3 eq.)) in the presence of sodium hydroxide (1.13 g, 28.2 mmol (3.4 eq.)) in DMF (70 ml) at 90 °C for 6 h. Benzyloxy benzaldehyde resin **1** thus obtained was then combined with hydroxylamine hydrochloride (16.0 g, 230.4 mmol (20 eq.)) and pyridine (14 ml) in ethanol (60 ml) under reflux for 10 h to afford oxime resin **2**.[9] Hydroxylamino resin **3** was prepared by reducing **2** using borane-pyridine complex (6.9 g, 74.2 ml (10 eq.)) in THF (100 ml) at room temperature for 10 h.[10] The loading of **3** was calculated by a chlorine titration of hydroxylamino resin hydrochloride. The condensation of **3** (1 mmol) with various aldehydes (5 mmol) was readily performed in CH_2Cl_2-trimethyl orthoformate (1:1, 20 ml)[11] to give polymer-supported nitrones **4**. Characterization of polymers **1-4** were performed using Swollen Resin Magic Angle Spinning NMR (SR-MAS NMR)[12] and IR spectra.

PII: S0040-4039(98)02100-5



Scheme 1. Synthesis of Polymer-Supported Nitrone **4**

1,3-Dipolar cycloaddition reactions on the solid-phase were successfully carried out using ytterbium triflate ($Yb(OTf)_3$) as a catalyst. In the previous work, we developed the lanthanide triflate-catalyzed three-component coupling reactions of aldehydes, hydroxylamines, and alkenes.[13] In these reactions, alkenes activated by $Yb(OTf)_3$ reacted smoothly with nitrones generated *in situ* from aldehydes and hydroxylamines. A solid-phase version was demonstrated by the reaction of 3-(2-butenoyl)-1,3-oxazolin-2-one with polymer-supported nitrone **4a** (Scheme 2). The reaction proceeded smoothly in the presence of a catalytic amount of $Yb(OTf)_3$ to afford polymer-supported isoxazolidine derivative **5a**. After oxidative cleavage from the support using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[14] 2-isoxazoline derivative **6a** was obtained in an 89% yield.



Scheme 2. 1,3-Dipolar Cycloaddition Reaction on the Solid-Phase

Several examples of the present 1,3-dipolar cycloaddition reactions are summarized in Table 1. Not only aromatic, but also aliphatic and heterocyclic nitrones reacted smoothly under these conditions.[15] Furthermore, an isoxazole was obtained by using an alkyne instead of an alkene (entry 13).

While 1,3-oxazolin-2-one derivatives are the best dipolarophiles in the present reactions, the 1,3-oxazolin-2-one moieties were successfully converted to other functional groups (Scheme 3). Polymer-supported isoxazolidine derivative **5a** was treated with methoxymagnesium bromide (5 eq.) in THF-methanol to afford resin **7a**. After oxidative cleavage, 2-isoxazoline derivative **8a** was obtained in a 67% yield. Furthermore, ester **7a** was reduced on the solid-phase using lithium borohydride (5 eq.) to afford alcohol **9a** in a 77% yield. Similarly, resin **5a** was treated with *N,O*-dimethylhydroxylamine hydrochloride (5 eq.) and trimethyaluminum (5 eq., 1.0 M solution in toluene) in dichloromethane to give an amide resin. After oxidative cleavage, amide **10a** was obtained in a 56% yield. Carboxylic acid **11a** was obtained in a 55% yield using lithium hydroxide (5 eq.) and H_2O_2 (10 eq., 35% solution) in THF-H_2O.

A typical experimental procedure is described for the reaction of 3-(2-butenoyl)-1,3-oxazolin-2-one with **4a**. In the presence of 20 mol% of $Yb(OTf)_3$ and **4a** (0.2 mmol, 0.77 mmol/g), 3-(2-butenoyl)-1,3-oxazolin-

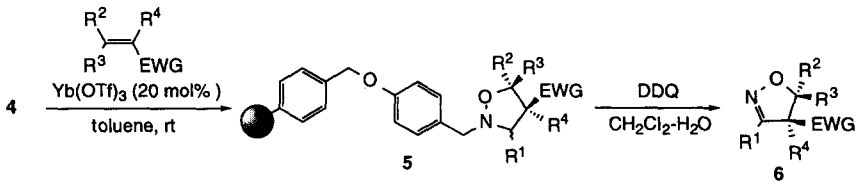
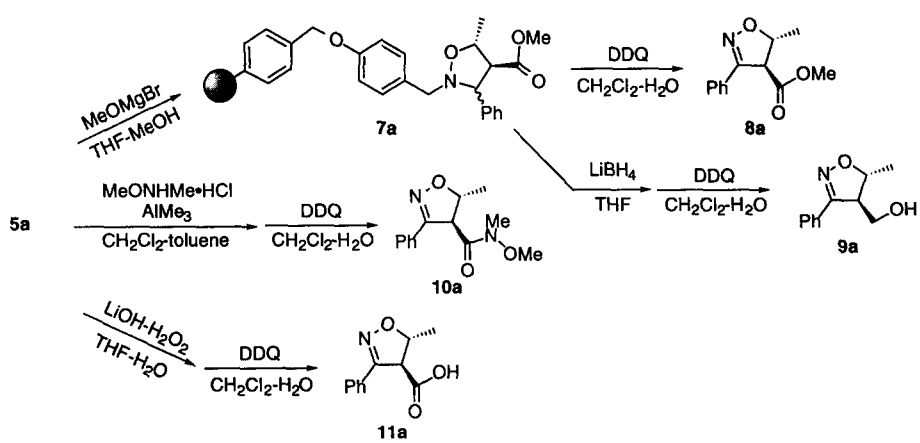


Table 1. Synthesis of 2-Isoxazoline Derivatives

Entry	R^1	Dipolarophile	Yield/%[a]
1	Ph (**4a**)		89
2	(*p*-Cl)Ph (**4b**)		80
3	(*p*-MeO)Ph		61
4	2-Furyl		69
5	2-Thienyl		72
6	1-Naphthyl		85
7	$(CH_3)_2CHCH_2$		74
8	**4a**		79
9	**4b**		80
10	**4b**		77
11	**4a**	MeO_2C	63
12	**4a**		54
13	**4a**	$MeO_2C{-}{\equiv}{-}CO_2Me$	47

[a]Based on the loading of hydroxylamino resin **3**.



Scheme 3. Transformations on the Solid-Phase

2-one (1 mmol) in toluene (4 ml) was added and the mixture was stirred for 20 h at room temperature. After saturated $NaHCO_3$ aq. was added to quench the reaction, the polymer was filtered and washed. The resulting polymer **5a** was combined with DDQ (3 eq.) in CH_2Cl_2-H_2O (10:1, 4 ml), and the mixture was stirred for 12 h. After L-ascorbic acid was added to reduce excess DDQ, the organic layer was washed with saturated $NaHCO_3$ aq. and brine. The organic layer was dried with Na_2SO_4 and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel to afford 2-isoxazoline derivative **6a**.

In summary, 1,3-dipolar cycloaddition reactions of polymer-supported nitrones with alkenes were successfully carried out using a catalytic amount of $Yb(OTf)_3$ to afford the corresponding 2-isoxazoline derivatives in high yields. Moreover, the 3-acyl-1,3-oxazolin-2-one group could be converted to various functional groups on the solid-phase. Thus, the present 1,3-dipolar cycloaddition reactions on the solid-phase would provide an efficient methodology for the preparation of large numbers of 2-isoxazoline derivatives. Further investigations to examine the biological activities of the synthetic and related compounds as well as to develop catalytic asymmetric 1,3-dipolar cycloaddition reactions[16] on the solid-phase are now in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, and a SUT Special Grant for Research Promotion.

References and Notes

1 (a) Zang, L. -H.; Chung, J. C.; Costello, T. D.; Valvis, I.; Ma, P.; Kauffman, S.; Ward, R. *J. Org. Chem.* **1997**, *62*, 2466-2470. (b) Zang, L. -H.; Anzalone, L.; Ma, P.; Storace, L.; Ward, R. *Tetrahedron Lett.* **1996**, *37*, 4455-4458. (c) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jinag, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 1292. (d) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jinag, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50-60.

2 Groutas, W. C.; Venkataman, R.; Chong, L. S.; Yoder, J. E.; Epp, J. B.; Stanga, M. A.; Kim, E. -H. *Bioorg. Med. Chem.* **1995**, *3*, 125-128.

3 Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley & Sons: New York, 1984, Vols. 1 and 2.

4 Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH: Weinheim, 1988.

5 (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555, and references cited therein. (b) Révész, L.; Bonne, F.; Manning, U.; Zuber, J. -F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 405-408. (c) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291-1294. (d) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295-1298. (e) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708-718. (f) Hone, N. D.; Davies, S. G.; Taylor, S. L.; Baxter, A. D. *Tetrahedron Lett.* **1998**, *39*, 897-900. (g) Bhalay, G.; Blaney, P.; Palmer, V. H.; Baxter, A. D. *Tetrahedron Lett.* **1997**, *38*, 8375-8378. (h) Scialdone, M. A. *Tetrahedron Lett.* **1996**, *37*, 8141-8144. (i) Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783-7786. (j) Tortolani, D. R.; Biller, S. A. *Tetrahedron Lett.* **1996**, *37*, 5687-5690. (k) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809-2812.

6 (a) Shankar, B. B.; Yang, D. Y.; Ganguly, A. K. *Tetrahedron Lett.* **1998**, *39*, 2447-2448. (b) Cheng, J. -H.; Mjalli, A. M. M. *Tetrahedron Lett.* **1998**, *39*, 939-942.

7 Haap, W. J.; Kaiser, D.; Walk, T. B.; Jung, W. G. *Tetrahedron* **1998**, *54*, 3705-3724.

8 Intramolecular 1,3-dipolar cycloaddition on the solid-phase was reported. Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204-4212.

9 DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295-1300.

10 Kawase, M.; Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1979**, 643-645.

11 Ruhland, B.; Bahandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253-253.

12 Kobayashi, S.; Akiyama, R.; Furuta, T.; Moriwaki, M. *Molecules Oneline* **1998**, *2*, 35-39.

13 Kobayashi, S; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039-1040.

14 (a) Oikawa, Y.; Yoshioka, T. *Tetrahedron Lett.* **1982**, *23*, 885-888. (b) Li, P.; Gi, H. -J.; Sun, L.; Zhao, K. *J. Org. Chem.* **1998**, *63*, 366-369.

15 Nonpolymer-supported aliphatic nitrones are known to be unstable and sometimes difficult to employ in 1,3-dipolar cycloadditions.

16 Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840-5841.