ORGANIC LETTERS

2003
Vol. 5, No. 24
4649−4652

Use of Selenium-Bound Resin for the Solid-Phase Synthesis of Substituted Isoxazolyl-Substituted (*E*)-Olefins

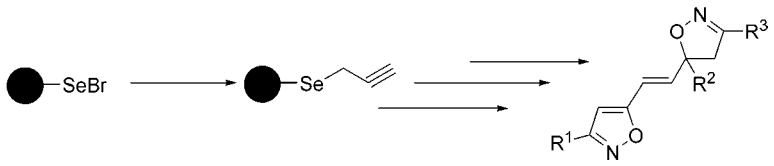
Xian Huang*,[†,‡] and Wei-Ming Xu[†]

Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, Peoples Republic of China, and Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, Peoples Republic of China

huangx@mail.hz.zj.cn

Received September 20, 2003

ABSTRACT



The preparation of isoxazolyl- and isoxazolinyl-substituted olefins, based on polystyrene-supported selenenyl bromide, is described. Key steps include 1,3-dipolar cycloadditions and the α-alkylation reaction of selenium resins. The polystyrene-supported selenium resins used here not only facilitate separation of products, but also assist the crucial reaction of α-alkylation and selenoxide syn-elimination, which ensures the purity of the products.

The application of solid-phase organic synthesis (SPOS) in the preparation of small compound libraries is of considerable significance in the discovery and development of new drug compounds.[1] As the demand for drug-like and natural product-like libraries continues to grow, there is an increasing need for the development of linking strategies that allow complex and diverse targets to be constructed efficiently and reliably. Toward this end, there has been particular interest in developing linking strategies whereby the loading and cleavage steps contribute to the complexity of the target structure rather than merely constituting extraneous manipulations.[2]

Isoxazole and isoxazoline moieties represent two classes of unique pharmacophores that are observed in many therapeutic agents[3] and are versatile intermediates for the synthesis of complex natural products.[4] Therefore, they are interesting targets in the development of new drug leads in solid-phase combinatorial chemistry. Several groups have studied the synthesis of isoxazoles and isoxazolines using solid-phase chemistry.[5] These methods include the condensation of 1,3-dicarbonyl compounds with hydroxylamine,[6] the

[†] Zhejiang University.
[‡] Chinese Academy of Sciences.

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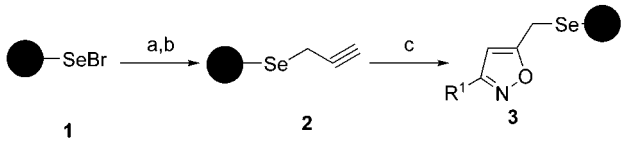
10.1021/ol035816u CCC: $25.00
Published on Web 10/29/2003

addition of nitrile oxides to supported alkynes (alkenes),[7] or the anchoring of a nitrile oxide precursor onto the solid phase.[8] However, most of the solid-phase syntheses rely on the release of carboxylic acids, esters, ethers, or amides from an ester or amide-bound substrate.[5] Alternative methods that allow the cleavage of resin, yet with access to more variable functionalities, are extremely desirable.[9] And also, there are very rare reports[7c] on the construction of isoxazole and isoxazoline scaffolds in one molecule for library production. Since the first organoselenium resin[10] was reported in 1976, several groups have developed organoselenium resins as convenient linkers.[11] Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.[12] We wish to report here convenient syntheses of 3-aryl-5-*E*-substituted-ethenyl isoxazoles **5** and *E*-isoxazolyl- and isoxazolinyl-substituted olefins **8** with evident advantages of easy operations, odorlessness, stability, and good purity of the products. Their syntheses are based on polystyrene-supported selenenyl bromide followed by (i) propargylation of selenenyl bromide resin, (ii) heterocycle-(s) formation by 1,3-dipolar cycloaddition, (iii) α-alkylation of selenium resin, and (iv) cleavage through stereospecific selenoxide syn elimination.[13]

1,3-Dipolar cycloadditions[14] of nitrile oxides in solution are known to suffer from many side reactions including dimerization as a result of the high reactivity of nitrile oxides. Therefore it is synthetically interesting to carry out these reactions on the solid phase, which makes isolation of the product easier. Propargylation of the dark-red resin **1** (Br: 0.99 mmol/g) with $NaBH_4$ and propargyl bromide gave the corresponding pale-yellow resin **2** almost quantitatively (FTIR: 3297 cm^{-1}). Resin **2** reacted smoothly with nitrile oxides to furnish isoxazole-supported selenium resin **3**

Scheme 1. Synthesis of Isoxazole-Supported Selenium Resins[a]

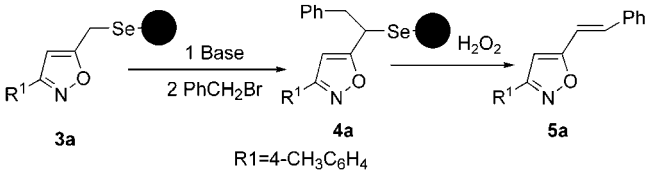


[a] Reagents and conditions: (a) $NaBH_4$ (2 equiv), THF, DMF, 40 °C, 8 h; (b) propargyl bromide (2.2 equiv),THF, rt, 12 h; (c) $R^1CH{=}NOH$ (3 equiv), NCS (3 equiv), CH_2Cl_2, Et_3N (6 equiv), rt, 24 h.

(FTIR: 1635 cm^{-1} with the disappearance of 3297 cm^{-1}) and in this process we found that it was necessary for Et_3N to be slowly added dropwise in 24 h to avoid the dimerization of the nitrile oxides (Scheme 1).

To get the best condition of α-alkylation of isoxazole-supported selenium resin **3** (Scheme 2), we began our efforts

Scheme 2. Optimization of Solid-Phase Conditions of α-Aalkylation



by following the conditions that Reich[15] et al. had devised for allyl selenide in solution phase, but there was very little conversion in the solid-phase reaction under the same conditions (entry 1, Table 1). Upon further investigation, we

Table 1. Optimization of Solid-Phase Conditions of α-Alkylation

entry	base (equiv)	temp (°C)	time (h)	yield (%)[a]	purity (%)[b]
1	LDA (1.0)	−78	0.5	18	>95
2	LDA (1.0)	−60	0.5	55	>95
3	*n*-BuLi (1.0)	−60	0.5	70[c]	
4	LDA (1.2)	−60	1.5	74	99
5	LDA (1.2)	−60	2.5	69[c]	
6	LDA (2.0)	−60	0.5	75[c]	

[a] Yields of the crude product based on the loading of resin **1**. [b] Determined by HPLC [c] Isolated yield.

found that the yield of the desired isoxazole **5a** was increased to 55% with good purity when the reaction temperature was raised to −60 °C (entry 2) and the yield could be improved but with a decrease in purity when a stronger base (*n*-BuLi) was used (entry 3). On the other hand, increasing both the amount of base (LDA) and reaction time to some extent

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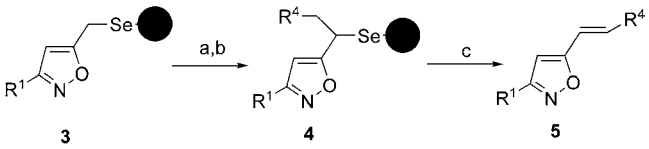
Scheme 3. Synthesis of 3-Aryl-5-*E*-Substituted-Ethenyl Isoxazoles[a]



[a] Reagents and conditions: (a) LDA (1.2 equiv), THF, −60 °C, 1.5 h; (b) R^4CH_2X (4 equiv), THF, −60 to −40 °C, 1 h; (c) H_2O_2, THF, 0 °C, 1 h, then rt, 20 min.

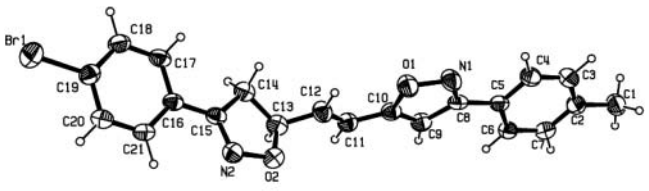
increased the desired yield to 74% with good purity (99%) (entry 4), and the purity of the product was dramatically decreased when too much base, longer time, and stronger base were used (entries 3, 5, and 6). We adopted entry 4 as the best conditions to test the diversity of the α-alkylation reaction with various electrophilic substrates to afford resin **4** followed by selenoxide syn elimination giving 3-aryl-5-*E*-substituted-ethenyl isoxazoles **5** (Scheme 3). Results are described in Table 2 and show that isoxazoles **5** can be obtained in moderate to good yield with good purity.

Table 2. Reagents, Yields and Purities of Substituted Isoxazoles

product	R_1	R_4	yield %)[a]	purity (%)[b]
5a	4-$CH_3C_6H_4$	C_6H_5	74	99
5b	4-$CH_3C_6H_4$	CH_2=CH	78	91
5c	4-$CH_3C_6H_4$	H_3COOC	67	96
5d	4-$CH_3C_6H_4$	HC≡C	69	94
5e	4-$CH_3C_6H_4$		62	90
5f	4-BrC_6H_4	CH_3	76	95
5g	4-FC_6H_4	CH_2=CH	71	94

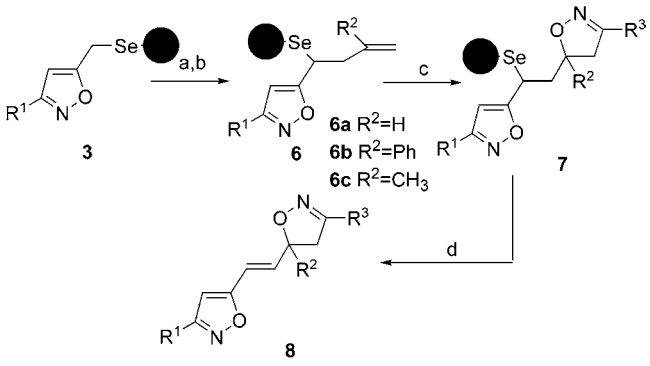
[a] Yields of the crude product based on the loading of resin **1**. [b] Determined by HPLC.

To expand the diversity of this method, another 1,3-dipolar cycloaddition was performed to furnish isoxazole- and isoxazoline-supported selenium resin **7** when substituted allyl bromide was used as the electrophilic substrate to perform the α-alkylation reaction of resin **3**. Isoxazolyl- and isoxazolinyl-substituted olefins **8** were obtained stereoselectively through selenoxide syn elimination of resin **7** (Scheme 4), and the stereochemistry was established on the basis of the X-ray structure of **8b**, depicted in Scheme 4. Interestingly,



8b

Scheme 4. Synthesis of Isoxazolyl- and Isoxazolinyl-Substitited Olefins[a]



[a] Reagents and conditions: (a) LDA (1.2 equiv), THF, −60 °C, 1.5 h; (b) substituted allyl bromide (4 equiv),THF, −60 ° to −40 °C, 1 h; (c) R^3CH=NOH (3 equiv), NCS (3 equiv), CH_2Cl_2, Et_3N (6 equiv), rt, 24 h; (d) H_2O_2, THF, 0 °C,1 h, then rt, 20 min.

we found that the reactivities of resin **6a** and resin **6b** in the 1,3-dipar cycloaddition are higher than that of resin **6c**. The former reacted smoothly with nitrile oxides to form resin **7** completely. But when resin **6c** was used, incomplete cycloaddition was observed, which resulted in a mixture of the desired isoxazolyl- and isoxazolinyl-substituted olefin **8** and uncyclic substituted isoxazole after the cleavage. However, this could be optimized by repeating the 1,3-dipolar cycloaddition step one more time prior to cleavage. Results are described in Table 3.

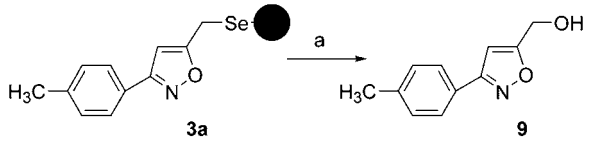
Table 3. Synthesis of Isoxazolyl- and Isoxazolinyl-Substituted Olefins

product	R^1	R^2	R^3	yield (%)[a]	purity (%)[b]
8a	4-$CH_3OC_6H_4$	H	4-ClC_6H_4	76	93
8b	4-$CH_3C_6H_4$	H	4-BrC_6H_4	67	98
8c	4-BrC_6H_4	H	4-$CH_3C_6H_4$	72	93
8d	4-FC_6H_4	H	4-$CH_3C_6H_4$	68	94
8e	4-ClC_6H_4	H	4-BrC_6H_4	74	93
8f	4-ClC_6H_4	H	4-$CH_3OC_6H_4$	72	89
8g	4-$CH_3C_6H_4$	H	4-$CH_3OC_6H_4$	75	88
8h	4-ClC_6H_4	H	4-$O_2NC_6H_4$	56	88
8i	C_6H_5	H	4-$CH_3C_6H_4$	70	93
8j[c]	4-FC_6H_4	CH_3	4-$CH_3C_6H_4$	60	89
8k	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	68	96

[a] Yield of the crude product based on the loading of resin **1**. [b] Determined by HPLC. [c] 1,3-Dipolar cycloaddition step performed twice prior to cleavage.

In conclusion, we developed a method for the preparation of 3-aryl-5-*E*-substituted-ethenyl isoxazoles and *E*-isoxazolyl- and isoxazolinyl-substituted olefins based on polystyrene-supported selenenyl bromide. It is noteworthy that the polymer selenium resins used here not only facilitate separation of products, but also assist the crucial selenoxide syn elimination (Scheme 3, step c) to ensure the purity of

Scheme 5. Unexpected Cleavage from Selenium Resins[a]



[a] Reagents and conditions: (a) H_2O_2, 55 °C, THF, 30 min.

the final products: only the alkylated resins **4**, **6**, and **7** underwent selenoxide syn elimination under mild cleavage conditions. No reaction was observed for the unalkylated resin **3** under the same conditions. An unexpected product **9** was obtained as the major product when the temperature was raised to 55 °C for 30 min (Scheme 5). A further detailed study will be disclosed in due course.

Acknowledgment. We are grateful to the Natural Science Foundation of China (Project No. 29932020).

Supporting Information Available: Characterization data, representative experimental procedures for key compounds, and an X-ray structure report. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035816U