A facile one-pot solid-phase synthesis of oxazolidin-2-ones using polymer-supported 2-hydroxyalkyl selenide reagent

Qiao-Sheng Hu[a,b], Shou-Ri Sheng[a,b]*, Shu-Ying Lin[a], Mei-Hong Wei[a], Qin Xin[a] and Xiao-Ling Liu[a]

[a]*College of Chemistry and Life Science, Gannan Normal University, Ganzhou, 341000, P. R. China*

[b]*College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 330027, P. R. China*

A simple, efficient and environmentally friendly procedure for one-pot solid-phase synthesis of 2-oxazolidinones in moderate to good yields by reaction of polystyrene-supported 2-hydroxyalkyl selenide with benzoyl isocyanate and subsequent oxidation/cyclisation-hydrolysis using a selenium traceless linker strategy is described.

Keywords: solid-phase organic synthesis, polymer-supported 2-hydroxyalkyl selenide, 2-oxazolidinones

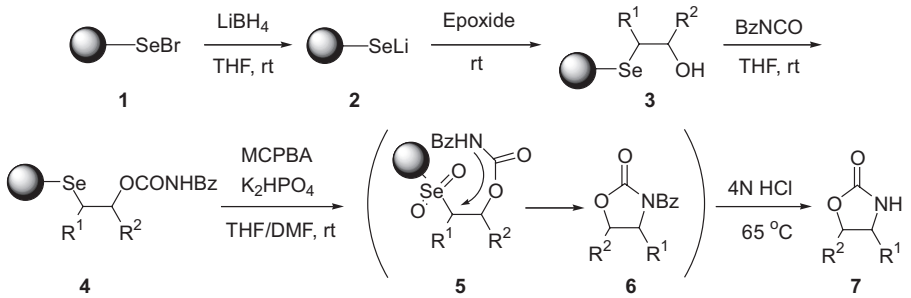
Polymer-supported organic reagents and catalysts have been applied to the preparation of organic molecules. The use of polymer-supported reagents allows the selective removal of excess reagents and by-products by simple filtration rather than liquid–liquid extraction and chromatographic purification. In addition, polymer-supported reagents offer further advantages that include reaction of active intermediates by 'catch-and-release' selectivity and immobilisation of toxic intermediates.[1] Oxazolidin-2-ones are an interesting class of compounds because of their various pharmacological effects,[2] including antibacterial activity.[3] Recently they have also found application as synthetic intermediates, and as chiral auxiliaries.[4] A survey of the literature reveals a variety of starting points for the preparation of oxazolidinones including the reaction of diols with isocyanates, epoxide opening, amino acids, aziridines, oxetanes, 2-oxazolones, hydroxy acids or esters, and perhaps the most common, amino alcohols.[5] Although the synthetic routes to oxazolidinones are well documented, efforts are continuing for the development of more efficient methods with experimental simplicity. Organoselenium reagents are now commonly used as a powerful tool for introducing new functional groups into organic substrates under extremely mild conditions.[6] Recently, the use of the selenium reagents immobilised on a polymer-resin has provided significant advantages, including decreased volatility and simplification of the product work-up.[7] In connection with our interest in solid-phase organoselenium chemistry.[8] We now report a convenient and efficient solid-phase synthetic approach to oxazolidin-2-ones based on the polymer-supported 2-hydroxyalkyl selenide **3** (Scheme 1).

The resins **3** were easily prepared in a few steps from cross-linked (1%) polystyrene by reaction of polystyrene-supported lithium selenide **2** with different epoxides.[8d] The IR Spectra of resins **3** showed large hydroxyl absorptions near at 3600 cm^{-1} and 3380 cm^{-1}, and bands (C–O) at 1065–1080 cm^{-1}. Resin **3** can be stored at room temperature for a long time without diminution of capacity or the liberation of disagreeable odours. With the resin **3** to hand, we examined the synthesis of target compounds **7**. First of all, the *O*-acylation reaction was investigated starting from 2-hydroxy-2-phenylethyl selenide resin (**3a**) with benzoyl isocyanate in THF at room temperature for 20 h to afford polystyrene-supported phenyl 2-[(benzoylamino)carbonyl]oxy-2-phenylethyl selenide (**4a**) in 93% yield. This was characterised by its IR spectra featuring a N–H stretch at 3272 and 1515 cm^{-1}, a C=O stretch at 1756 and 1734 cm^{-1}, a C–O–C stretch at 1056 cm^{-1}, and almost complete disappearance of the hydroxyl absorption. Next, treatment of resin **4a** with an excess of MCPBA in DMF/THF solvent in the presence of potassium hydrogenphosphate afforded the corresponding selenone intermediate **5a**. Subsequently the *N*-benzoyl-5-phenyl-oxazolidin-2-one (**6a**) was obtained in 88% yield as a result of the displacement of the selenonyl group by the nitrogen atom of the carbamate. This intramolecular cyclisation reaction occurred easily because of the great leaving ability of the selenonyl group. Finally, *N*-benzoyl-5-phenyl-oxazolidin-2-one (**6a**) was hydrolysed to the corresponding 5-phenyl-oxazolidin-2-one (**7a**) in 84% yield by treatment with 4 N HCl at 65°C for 4 h. In fact, after a series of experiments, we have found it most convenient to

Table 1 Yields of oxazolidin-2-ones

Entry	R^1	R^2	Product	Yield/%[a]
1	H	C_6H_5	**7a**	84
2	H	$C_6H_5CH_2$	**7b**	85
3	H	$C_6H_5OCH_2$	**7c**	83
4	H	$C_6H_5CH_2OCH_2$	**7d**	85
5	H	4-$CH_3C_6H_4OCH_2$	**7e**	82
6	H	CH_3	**7f**	80
7	H	C_2H_5	**7g**	80
8	$(CH_2)_4$		**7h**	75

[a]Overall isolated yield based on polymer-supported selenium bromide (1.18 mmol Br/g).



Scheme 1

* Correspondent. E-mail: shengsr@jxnu.edu.cn

carry out successively the three-step reaction in one-pot from resin **3a** as starting material giving **7a** almost in the same yield without further isolation of selenide resin **4a** and **6a**. With our successful initial studies of the preparation of **7a**, extension of this method to the synthesis of other analogues in moderate to good yields was investigated (Table 1). The residual resin, polystyrene-supported phenylseleninic acid, was obtained as a by-product. Its IR spectrum was identical to the previously reported data.[9] The polystyrene-supported phenylseleninic acid could be converted to polymer-supported selenium lithium for recycling by treatment with $KI/Na_2S_2O_3$[10] followed by $LiBH_4$. For example, 5-phenyl-oxazolidin-2-one (**7a**) was obtained in 80% yield under the same reaction conditions using the recovered selenium lithium resin (second run), and in 75% yield after second recycle (*i.e.* third run). It was shown that recycling 2–3 times led to a gradual deterioration of the resin.

In summary, a novel, convenient, environmentally friendly, one-pot solid-phase traceless synthesis of oxazolidin-2-ones in moderate to good yield from polymer-supported 2-hydroxyalkyl selenide by ester-oxidation/cyclisation-hydrolysis procedure has been developed. This methodology is applicable for the construction to combinatorial libraries of oxazolidin-2-ones.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Mass spectra (EI, 70eV) were recorded on a HP5989B mass spectrometer. Microanalyses were performed with a PE 2400 elemental analyser. THF was distilled under N_2 from sodium/benzophenone immediately prior to use. DMF was refluxed with calcium hydride and distilled under reduced pressure, then dried over molecular sieves 4Å. Other reagents were obtained from commercial suppliers and used without further purification.

Preparation of oxazolidin-2-ones (**7a–7h**); *general procedure*
The polymer-supported 2-hydroxyalkyl selenide **3** was prepared from polystyrene-supported selenium bromide **1** (1.0 g, 1.18 mmol Br/g) according to our reported method.[8d] Under a nitrogen atmosphere, the resin **3** (1.0 mmol) was swelled in THF (10 ml) and DMF (5 ml) at room temperature for 30 min. Benzoyl isocyanate (296 mg, 2.0 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. Then the reaction mixture was treated with *meta*-chloroperoxybenzoic acid (0.69 g, 4.0 mol) and potassium hydrogenphosphate (0.85 g, 5.0 mmol) and stirred for 10 h. Without isolation, 4 N HCl (6.5 ml) was added to the reaction mixture and stirred for 4 h at 65°C, and then the resin was filtered off and rinsed with CH_2Cl_2 (5 × 5 ml). The organic phase was washed with saturated $NaHCO_3$ solution (10 ml), brine (10 ml) and twice with water (2 × 10 ml). It was dried over magnesium sulfate and the solvent was then removed *in vacuo*. The residue was purified by flash silica gel column chromatography (CH_2Cl_2/AcOEt, 80: 20–65: 35) to give pure product **7a–7h**.

5-Phenyl-oxazolidin-2-one (**7a**): White solid; m.p. 91–92°C (Lit.[5b] m.p. 90–91°C); ^{1}H NMR: δ = 3.55 (ddd, *J* = 0.8, 7.6, 8.6 Hz, 1H), 3.98 (ddd, *J* = 0.8, 8.6, 8.6 Hz, 1H), 5.50 (bs, 1H, NH), 5.63 (t, *J* = 8.6 Hz, 1H), 7.34-7.36 (m, 3H), 7.41–7.44 (m, 2H); IR (KBr): ν = 3278, 1721 cm^{-1}.

5-Benzyl-oxazolidin-2-one (**7b**): White solid; m.p. 108–109°C (Lit.[5c] m.p. 107–109°C); ^{1}H NMR: δ = 2.94 (dd, *J* = 6.8, 14.0 Hz, 1H), 3.15 (dd, *J* = 6.0, 14.0 Hz, 1H), 3.33 (ddd, *J* = 0.8, 7.2, 8.4 Hz, 1H), 3.58 (ddd, *J* = 0.8, 8.4, 8.4 Hz, 1H), 4.83–4.90 (m, 1H), 5.59 (bs, 1H, NH), 7.19–7.23 (m, 3H), 7.32–7.36 (m, 2H); IR (KBr): ν = 3286, 1730 cm^{-1}.

5-(Phenoxymethyl)-oxazolidin-2-one (**7c**): Colourless oil; ^{1}H NMR: δ = 3.35 (ddd, *J* = 0.8, 7.0, 8.5 Hz, 1H), 3.62 (ddd, *J* = 0.8, 8.5, 8.4 Hz, 1H), 3.90 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.95 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.83–4.90 (m, 1H), 5.45 (bs, 1H, NH), 6.96–7.01 (m, 2H), 7.26–7.29 (m, 3H); ^{13}C NMR: δ = 46.4, 75.0, 76.1, 115.2, 121.7, 129.4, 135.1, 160.1; IR (KBr): ν = 3283, 1736 cm^{-1}; EIMS: *m/z* (%) = 193 (M^+); Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.23; H, 5.80; N, 7.31.

5-(Benzyloxymethyl)-oxazolidin-2-one (**7d**): Colourless oil; ^{1}H NMR: δ = 3.33 (ddd, *J* = 0.8, 7.0, 8.4 Hz, 1H), 3.61 (ddd, *J* = 0.8, 8.3, 8.1 Hz, 1H), 3.89 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.93 (dd, *J* = 5.2, 9.6 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.85–4.89 (m, 1H), 5.53 (bs, 1H, NH), 7.02–7.08 (m, 2H), 7.31–7.35 (m, 3H); ^{13}C NMR: δ = 41.7, 46.3, 75.1, 78.5, 155.6, 126.7, 128.3, 129.1, 159.5. IR (KBr): ν = 3286, 1738 cm^{-1}; EIMS: *m/z* (%) = 207 (M^+); Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.79; H, 6.38; N, 6.80.

5-(4-Methylphenoxymethyl)-oxazolidin-2-one (**7e**): Colourless oil; ^{1}H NMR: δ = 2.31 (s, 3H), 3.34 (ddd, *J* = 0.8, 7.1, 8.6 Hz, 1H), 3.62 (ddd, *J* = 0.8, 8.2, 8.5 Hz, 1H), 3.90 (dd, *J* = 5.1, 9.7 Hz, 1H), 3.95 (dd, *J* = 5.2, 9.7 Hz, 1H), 4.85–4.93 (m, 1H), 5.52 (bs, 1H, NH), 7.52 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR: δ = 20.4, 46.5, 76.8, 76.1, 114.5, 121.2, 129.2, 133.6, 160.2; IR (KBr): ν = 3284, 1740 cm^{-1}; EIMS: *m/z* (%) = 207 (M^+); Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.38; N, 6.81.

5-Methyloxazolidin-2-one (**7f**): Colourless oil (Lit.[5b] Oil); ^{1}H NMR: δ = 1.46 (d, *J* = 6.2 Hz, 3H), 3.21 (ddd, *J* = 0.8, 7.2, 8.4 Hz, 1H), 3.69 (ddd, *J* = 0.8, 8.4, 8.4 Hz, 1H), 4.74–4.82 (m, 1H), 5.57 (bs, 1H, NH); IR (neat): ν = 3298, 1739 cm^{-1}.

5-Ethyl-oxazolidin-2-one (**7g**): White solid; m.p. 51–52°C (Lit.[5c] m.p. 51–53°C); ^{1}H NMR: δ = 1.02 (t, *J* = 7.5 Hz, 3H), 1.66–1.85 (m, 2H), 3.24 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 3.66 (ddd, *J* = 1.2, 8.4, 8.4 Hz, 1H), 4.56–4.62 (m, 1H), 5.32 (bs, 1H, NH); IR (KBr): ν = 3299, 1740 cm^{-1}.

Cis-Cyclohexano[b]-2-oxazolidone (**7h**): White solid; m.p. 55–56°C (Lit.[11] m.p. 55°C); ^{1}H NMR: δ = 1.15–1.46 (m, 4H), 1.60–1.84 (m, 2H), 2.10–2.20 (m, 2H), 3.47 (ddt, *J* = 0.8, 7.5, 8.2 Hz, 1H), 4.72–4.80 (m, 1H), 5.37 (bs, 1H, NH); IR (KBr): ν = 3281, 1740 cm^{-1}.

We gratefully acknowledge financial support from the National Natural Science Foundation of China (No. 20562005) and NSF of Jiangxi Province (No. 0620021).

Received 6 January 2007; accepted 29 January 2007
Paper 07/4397 doi:10.3184/030823407X198267

References

1 For recent reviews, see: (a) S.J. Shuttleworth, S.M. Allin and P.K. Sharma, *Synthesis,* **1997**, 1217; (b) F. Guillier, D.Orain and M. Bradley, *Chem. Rev.,* 2000, **100**, 2091; (c) R.E. Sammelson and M.J. Kurth, *Chem. Rev*., 2001, **101**, 137; (d) V.V. Zhdankin and P.J. Stang, *Chem. Rev.,* 2002, **102**, 2523.
2 K. Danielmeier and E. Steckhan, *Tetrahedron*: *Asymmetry,* 1995, **6**, 1181.
3 Some molecules containing the oxazolidin-2-one moiety have shown interesting pharmaceutical activity. For recent leading references, see: (a) S. Ahmed, S. Adat, A. Murrells and C.P. Owen, *Biochem. Biophys. Res. Commun.,* 2002, **294**, 380; (b) A. Mai, M. Artico, M. Esposito, G. Sbardella, S. Massa, O. Befani, P. Turini, V. Giovannini and B. Mondovi, *J. Med. Chem.,* 2002, **45**, 1180; (c) M. Seki and K. Mori, *Eur. J. Org. Chem.,* 1999, **64**, 2965.
4 For some recent selected examples of the use of oxazolidin-2-ones as chiral auxiliary, see: (a) Y.K. Wu, X. Shen, C.J. Tang, Z.L. Chen, Q. Hu and W. Shi, *J. Org. Chem.,* 2002, **67**, 3802; (b) G. Faita, A. Paio, P.Quadrelli, F.Rancati and P.Senesi, *Tetrahedron,* 2001, **57**, 8313; (c) C.Gaul, K. Scharer and D. Seebach, *J. Org. Chem*., 2001, **66**, 3059; (d) H. Yamamoto, S. Watanabe, K. Kadotani, M. Hasegawa, M. Noguchi and S. Kanemasa, *Tetrahedron Lett*., 2000, **41**, 3131.
5 (a) D.J. Ager, I. Prakash and D.R. Schaad, *Chem. Rev.,* 1996, **96**, 835. For some recent developments in 2-oxazolidinone synthesis, see: (b) S.C. Bergmeier and S.J. Katz, *J. Comb. Chem.,* 2002, **4**, 162; (c) B. Gabriele, R. Mancuso, G. Salerno and M. Costa, *J. Org. Chem.,* 2003, **68**, 601; (d) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Org. Lett.,* 2005, **7**, 1983.
6 (a) C. Ed. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press: Oxford, 1986; (e) D. Liotta, Ed. *Organoselenium Chemistry*, Wiley: New York, 1987; (f) A. Krief, *Comprehensive Organic Synthesis*, Pergamon: Oxford, 1991; (g) T.G. Back, *Organoselenium Chemistry*, Oxford University Press: Oxford, 1999; (h) T. Wirth, *Organoselenium Chemistry*, Springer: Berlin, 2000.
7 (a) K.C. Nicolaou, J. Pastor, S. Barluenga and N. Winssinger, *Chem. Commun*., 1998, 1947; (b) T. Ruhland, K. Andersen and H. Pedersen, *J. Org. Chem.,* 1998, **63**, 9204; (c) K.-I. Fujita, S. Hashimoto, A. Oishi and Y. Taguchi, *Tetrahedron Lett*., 2003, **44**, 3793; (d) L. Uehlin and T. Wirth, *Org. Lett.,* 2001, **3**, 2931.
8 (a) X. Huang and S.-R. Sheng, *Tetrahedron Lett*., 2001, **42**, 9035; (b) X. Huang and S.-R. Sheng, *J. Comb. Chem*., 2003, **5**, 273; (c) S.-R. Sheng, X.-L. Liu, X.-C. Wang, Q. Xin and C.-S. Song, *Synthesis,* 2004, 2833; (d) X.-L. Liu, S.-R. Sheng, Q.-Y. Wang, W.-K. Sun, Q. Xin and H.-Y. Ao, *J. Chem. Res(S)*., 2006, 118; (e) B. Huang, S.-R. Sheng, Y.-X. Huang, Q. Xin, L.-Y. Song and N.-H. Luo, *J. Chem. Res(S)*., 2006, 623.
9 G. Zundel, *Angew. Chem., Int. Ed. Engl*., 1969, **8**, 499.
10 (a) F. Ferranti and D.D. Filippo, *J. Chem. Soc. (B)*., 1971, 1925; (b) W.-M. Xu, E. Tang and X. Huang, *Synthesis*, 2004, 2094.
11 A. Hassner, M.E. Lorber and C. Heathcock, *J. Org. Chem.,* 1967, **32**, 540.