Pergamon

Tetrahedron Letters 41 (2000) 5069–5072

TETRAHEDRON LETTERS

Solid-phase synthesis of 1,3-oxazolidine derivatives

Heong Sub Oh,[a,*] Hoh-Gyu Hahn,[a] Seung Hoon Cheon[b] and Deok-Chan Ha[c]

[a]*Life Science Division, Korea Institute of Science and Technology, Cheongryang PO Box 131, Seoul 136-791, South Korea*
[b]*Chonnam National University, Kwangju 500-757, South Korea*
[c]*Korea University, Seoul 136-701, South Korea*

Received 14 February 2000; accepted 12 May 2000

Abstract

1,3-Oxazolidines **9** were synthesized by using a solid support. Regioselective ring opening of resin-bound epoxy ether **3** with ammonium chloride followed by nucleophilic substitution with sodium azide gave azido alcohol **7**. Reduction of **7** provided 1-amino-2-alkanol **6**, which was treated with various aldehydes and acyl chlorides or isocyanates to afford the corresponding 1,3-oxazolidines immobilized on Wang resin. Oxidative cleavage with DDQ from the solid support yielded 1,3-oxazolidines as a mixture of **10** (*cis*) and **11** (*trans*).

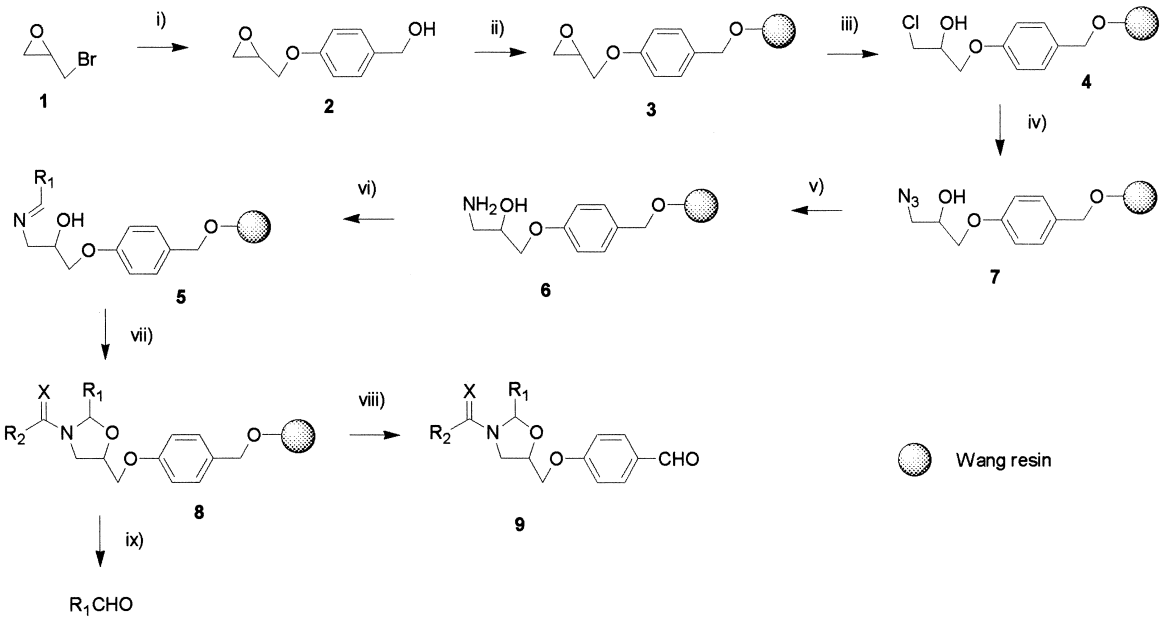
Keywords: 1,3-oxazolidine; solid phase synthesis; oxidative cleavage; diabetes.

Solid-phase reactions play an important role in combinatorial chemistry in the area of medicinal as well as agrochemical chemistry, where its potential has emerged due to the possibility of automated synthesis.[1] In particular, access to heterocyclic compounds by solid-phase synthesis is urgently required, since small, substituted heterocycles offer a high degree of structural diversity and they are proven to be exceptionally useful in many applications.[2] In our study aimed at the development of therapeutic agents for the treatment of diabetes mellitus, we were interested in the combinatorial synthesis of 1,3-oxazolidine derivatives.[3] The first concern was selection of a readily cleavable linker since 1,3-oxazolidines were labile even under mild acidic conditions.[4] *p*-Hydroxybenzyl alcohol, immobilized with Wang resin in the form of a benzyl ether, was chosen as a linker. We anticipated that the DDQ oxidation[5] would not only cleave the linker from Wang resin but also generate terminal aldehyde suitable for further functionalization.

Scheme 1 shows an overall synthetic procedure. A nucleophilic displacement of epibromohydrin **1** with *p*-hydroxybenzyl alcohol in the presence of sodium hydride in DMF, followed by treatment with chlorinated Wang resin[6] gave the epoxy ether **3** immobilized on the solid phase in good yield (92%).[7] Ring opening[8] of the epoxide **3** to 1-amino-2-alkanol **6** by treating with methanolic

* Corresponding author. Tel: +82 2 958 5168; fax: +82 2 958 5189; e-mail: oohs@kistmail.kist.re.kr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00775-9



Scheme 1. *Reagents and conditions*: (i) *p*-hydroxybenzyl alcohol, NaH, DMF, 65°C, 19 h, 70%; (ii) chlorinated Wang resin,[6] NaH, DMF, 0°C to rt, 24 h, 92%; (iii) NH_4Cl, DMSO, 80°C, 24 h, quantitative; (iv) NaN_3, DMSO, 80°C, 24 h, 96%; (v) C_6H_5SH, Et_3N, $SnCl_2$, THF, rt, 4 h; (vi) R_1CHO, $CH(OCH_3)_3$, THF, rt, 12 h; (vii) R_2COCl, R_2NCO, or R_2NCS, Et_3N, THF, rt, 24 h; (viii) DDQ, CH_2Cl_2:H_2O (18:1), rt, 3 h; (ix) 1% TFA, CH_2CH_2

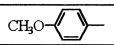
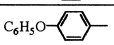
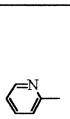
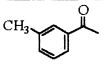
ammonia was unsuccessful, presumably due to the poor swelling ability of the resin in this solvent.[9] Alternatively, the epoxy ether **3** was subjected to ammonium chloride in DMSO at 80°C to give 1-chloro-2-alkanol **4**, which was smoothly transformed to azido alcohol **7** by treatment with sodium azide at room temperature in excellent yield (95%).[10] Direct nucleophilic substitution of the epoxy ether **3** with sodium azide resulted in a low yield (70%) of the azido alcohol **7**. Subsequent reduction of the azido alcohol **7** to an amine using thiophenol:triethylamine:tin chloride (4:5:1) as reported by Bartra and co-workers[11] gave the desired 1-amino-2-alkanol **6** immobilized on the Wang resin. The progress of reaction was monitored by FT–IR following the disappearance of the azide stretch absorption band (2098 cm^{-1}). Condensation of 1-amino-2-alkanol **6** with an aldehyde in the presence of a large excess trimethylorthoformate in THF followed by treatment with acyl chloride, or isocyanate, or isothiocyanate afforded the corresponding polymer-bound 1,3-oxazolidines **8**. No increased yields were observed even though the intermediate imine **5** immobilized on the resin was purified by washing before reacting with electrophiles. The progress of 1,3-oxazolidine formation reaction was monitored by FT–IR following the disappearance of the secondary hydroxyl absorption band (3600–3300 cm^{-1}) and appearance of the C=O or C=S absorption band (1650–1680 cm^{-1} and 2350–1100 cm^{-1}, respectively). It was reported that the 1,3-oxazolidines derived from serine or threonine and benzaldehyde on a Sasrin linker were relatively stable (less than 10% decomposition) under the 95% TFA/water or 5% TFA/CH_2Cl_2.[4] However, in our case, resin bound 1,3-oxazolidines **8**'s were decomposed to give aldehyde (R^1CHO) by the treatment of 1% TFA/CH_2Cl_2 at room temperature. In fact, 1,3-oxazolidine **9** prepared through solution-phase synthesis was easily decomposed even in the presence of a trace amount of acid (TFA) at room temperature. Therefore, other cleavage conditions as a

mild and neutral alternative to TFA were examined. Successful oxidative cleavage from the resin was achieved by the treatment with DDQ in methylene chloride at room temperature. Subsequent purification by flash chromatography afforded the corresponding 1,3-oxazolidines **9** with a new functional moiety, aldehyde, which would be suitable for further functionalization.

1,3-Oxazolidines obtained were a mixture of **10** (*cis*) (major) and **11** (*trans*) isomers (minor), which could be separated by flash chromatography. The stereochemistry of the isomers was determined by ^{1}H NOE. Irradiation to the C-5 proton led the signal of the C-2 proton in **10** (*cis*) to a 4.9% enhancement, while no effect was observed in **11** (*trans*) (Fig. 1).

Figure 1. ^{1}H NOE of the isomers: the arrows, which stand for the observed NOE effects point from the irradiated to the observed signal; data of the relative increase in intensity are given in percentages

Table 1
The structures of 1,3-oxazolidines

Entry	R_1	R_2	Yield(%)[a] (*trans/cis*)
1		CH_3CO	54(5/8)
2		C_6H_5NHCO	84(2/5)
3		CH_3NHCS	65(5/6)
4		CH_3NHCS	b
5			b
6		CH_3CO	64(1/2)
7			52(2/3)
8			69(3/4)
9		CH_3CO	57(2/3)
10			73(1/1)
11			59(2/3)
12		C_6H_5NHCO	92(1/3)
13		CH_3NHCS	6(1/4)
14			b
15		CH_3NHCS	b
16		C_6H_5NHCO	b

a. Isolated yields based on polymer-bound azido alcohol 7.

b. A complex mixture including the corresponding aldehyde was obtained.

Table 1 provides structures of the various compounds prepared, the yields, and the ratios of the isomers. The structure and the stereochemistry of the isomers were determined by ^{1}H NMR spectroscopy and mass spectrometry. Some 1,3-oxazolidines, having an electron rich substituent at C-2, could not be prepared by this method. By monitoring their FT–IR spectra, an electron-donating substituent such as the methoxy or phenoxy group in the C-2 phenyl group (entries 4 and 5) made the 1,3-oxazolidine ring unstable under the reaction conditions. In contrast, 1,3-oxazolidines (entries 14, 15, 16) derived from the cinnamaldehyde were stable on the solid support, but they were decomposed during the oxidative cleavage process.

References

1. Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry*: *Synthesis and Application*; John Wiley & Sons: New York, 1997, and references cited therein.
2. Gordeev, M. F.; Pate, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924, and references cited therein.
3. Aicher, T. D.; Balkan, B.; Bell, P. A.; Brand, L. J.; Cheon, S. H.; Deems, R. O.; Fell, J. B.; Fillers, W. S.; Fraser, J. D.; Gao, J.; Knorr, D. C.; Kahle, G. G.; Leone, C. L.; Nadelson, J.; Simpson, R.; Smith, H. C. *J. Med. Chem.* **1998**, *41*, 4556.
4. Ede, N. J.; Bray, A. M. *Tetrahedron Lett.* **1997**, *38*, 7119.
5. (a) Deegan, T. L.; Gooding, O. W.; Baudart, S.; Porco Jr., J. A. *Tetrahedron Lett.* **1997**, *38*, 4973. (b) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345.
6. Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973.
7. The efficiency of loading was determined on the basis of the recovery of pure epoxy ether benzaldehyde obtained by cleavage of resin with DDQ.
8. McManus, S. P.; Larson, C. A.; Hearn, R. A. *Synth. Commun.* **1973**, *3*, 177.
9. Santini, R., Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951.
10. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.
11. Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587.