Pergamon

Tetrahedron Letters 41 (2000) 7577–7581

TETRAHEDRON LETTERS

Polymer supported oxazolidin-2-ones derived from L-serine—a cautionary tale

Sean P. Bew, Steven D. Bull and Stephen G. Davies*

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

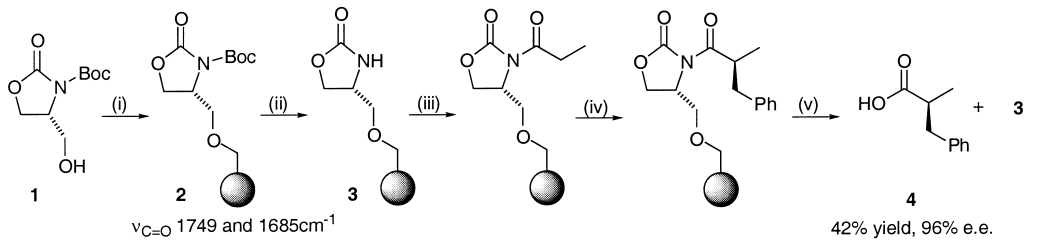
Received 14 June 2000; accepted 28 July 2000

Abstract

The capacity of *N*-Boc-4-hydroxymethyl-oxazolidin-2-ones to undergo rapid *O–O* and *N–O* acyl transfer makes these serine derived chiral auxiliaries unsuitable for attachment to polymers.

There is currently much interest within the synthetic community directed towards the development of polymer supported chiral auxiliaries for the asymmetric synthesis of libraries of homochiral compounds.[1] Within this area, a number of homochiral polymer bound oxazolidin-2-ones derived from tyrosine and serine and attached through the side-chain hydroxyl functionality have been described,[2] although the key issue of polymer recyclability has not been addressed.[3]

As recognised by Allin and Shuttleworth,[2a] serine derived oxazolidin-2-ones have the *potential* for polymer support via attachment of the side-chain hydroxyl group of **1** to Merrifield resin. They have reported that polymer **3** may be employed for the asymmetric synthesis of carboxylic acid **4** in 42% yield and 96% e.e. (Scheme 1).[2a]

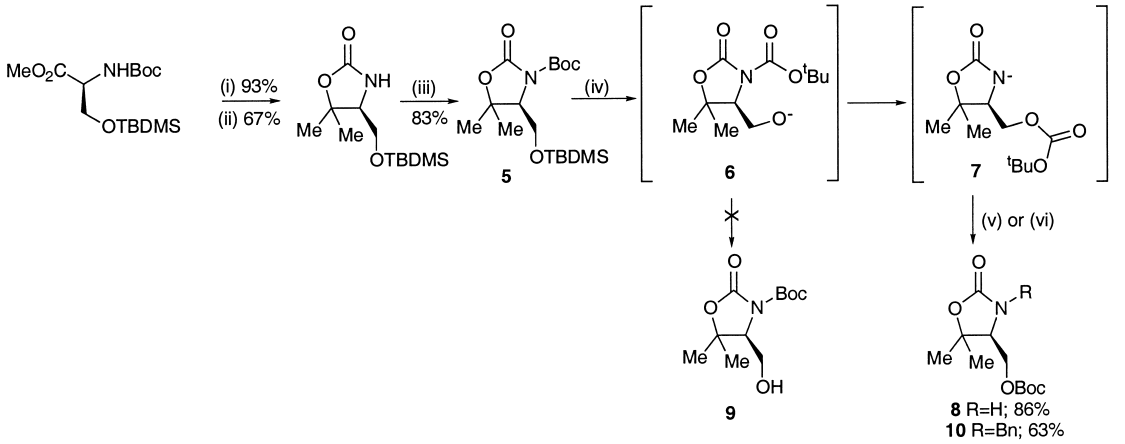


Scheme 1. Allin and Shuttleworth's synthesis of polymer bound oxazolin-2-one derived from L-serine. Reagents and conditions: (i) KH (1.5 equiv.), DMF, 0°C; Merrifield resin, 18-crown-6 (cat.), 80°C, 5 days; (ii) dil. HCl, CH_2Cl_2, Δ, 6 h; (iii) $(CH_3CH_2CO)_2O$, DMAP (10%), Et_3N, THF, Δ, 4 days; (iv) LDA (2 equiv.), THF, 0°C; BnBr (2 equiv.); NH_4Cl (aq.); (v) LiOH, THF, H_2O

* Corresponding author.

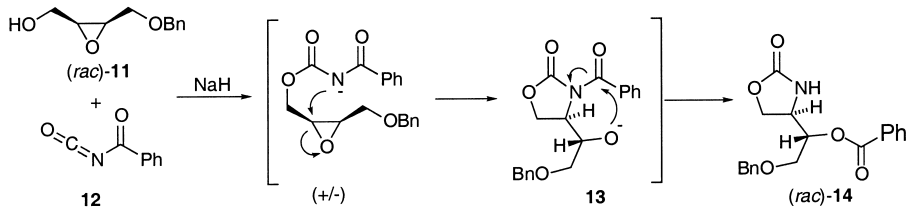
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01301-0

In the SuperQuat series,[4] generation of the fully protected intermediate **5** from L-serine proceeded as planned (Scheme 2). However, treatment of *N*-Boc-*O*-TBDMS-SuperQuat **5** with TBAF did not afford the desired *N*-Boc-oxazolidin-2-one **9** but instead gave homochiral *O*-Boc-oxazolidin-2-one **8** as a single product in a high yield ($[\alpha]_D^{23}$ −53.2, *c* 0.66, $CHCl_3$). Clearly TBAF mediated *O*-deprotection of the silyl protecting group of **5** afforded alkoxide intermediate **6** which readily underwent intramolecular attack at the *N*-Boc carbonyl group to generate **7**, resulting in protecting group migration to afford *O*-Boc-oxazolidin-2-one **8**. Attempts to *O*-benzylate (as a model reaction for Merrifield resin) the intermediate alkoxide anion **6** before *N*-*O*-Boc protecting group migration could occur were also unsuccessful since TBAF deprotection of **5** followed by the immediate addition of a large excess of benzyl bromide afforded *N*-benzyl-*O*-Boc-oxazolidin-2-one **10** (Scheme 2).



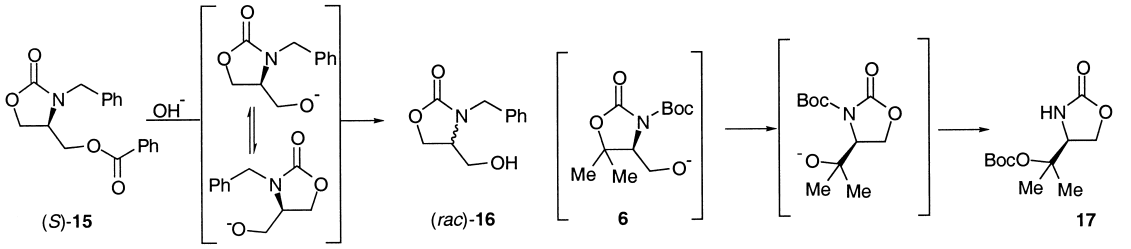
Scheme 2. Reagents and conditions: (i) MeMgBr (4 equiv.), THF, −78°C; (ii) KO^{t}Bu, THF; (iii) Boc_2O, DMAP (cat.), NEt_3, CH_2Cl_2; (iv) TBAF, THF; (v) NH_4Cl (aq.); (vi) BnBr

There is clear literature precedent for this type of *N*–*O* acyl exocyclic rearrangement occurring for serine derived *N*-acyl oxazolidin-2-ones. McCombie et al. have shown that *N*-benzoyl-oxazolidin-2-one **13**, prepared in situ via treatment of (*rac*)-*cis*-epoxide **11** with benzoylisocyanate **12**, is unstable and undergoes an *N*–*O* benzoyl migration to form (*rac*)-*O*-benzoyl-oxazolidin-2-one **14** (Scheme 3).[5]



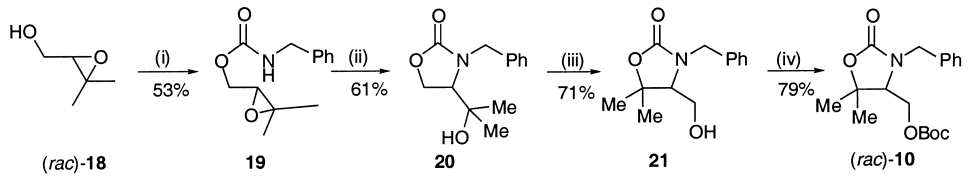
Scheme 3.

It is also known that alkoxides of serine derived oxazolidin-2-ones have the capacity to undergo a competing endocyclic rearrangement via intramolecular attack of the alkoxide anion at the oxazolidin-2-one carbonyl. For example, Katsumura et al. have shown that alkaline hydrolysis of homochiral (*S*)-*N*-benzyl-*O*-benzoyl-oxazolidin-2-one **15** (LiOH in THF/H_2O; Cs_2CO_3 in MeOH; or K_2CO_3 in MeOH) results in *racemic N*-benzyl-oxazolidin-2-one **16**, via intramolecular attack of the primary alkoxide at the C_2 carbonyl of the oxazolidin-2-one (Scheme 4).[6] This implied that our structural assignment of **8** and **10** might be incorrect since alkoxide **6** had the capacity to undergo this type of endocyclic rearrangement to afford oxazolidin-2-one **17**.



Scheme 4.

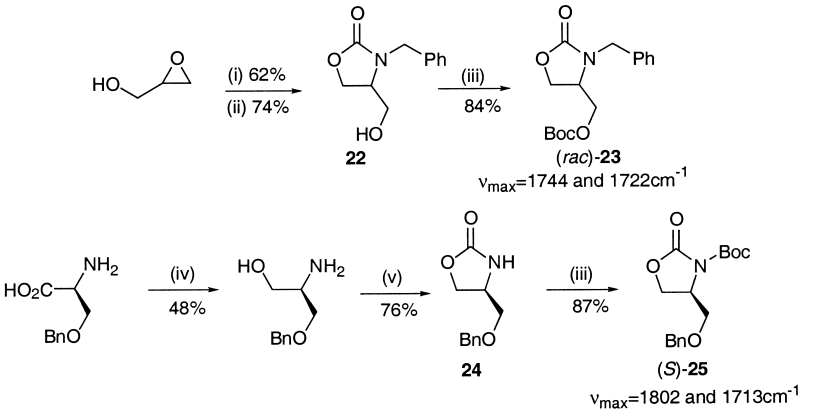
In order to resolve this structural problem an authentic sample of oxazolidin-2-one **10** was prepared according to the protocol described in Scheme 5. Thus, treatment of (*rac*)-epoxide **18** with benzylisocyanate in the presence of a catalytic amount of bis-(dibutylchlorotin)oxide afforded epoxy-carbamate **19** which was cyclised to oxazolidin-2-one **20** via treatment with *n*-BuLi at −20°C. Subsequent treatment of **20** with NaH at room temperature led to equilibration of **20** to the thermodynamic rearranged product **21** which was *O*-Boc protected to generate (*rac*)-**10** (Scheme 5).



Scheme 5. Reagents and conditions: (i) Benzylisocyanate, cat. $[(n\text{-Bu})_2SnCl]_2O$, CH_2Cl_2; (ii) *n*-BuLi (1 equiv.), THF, −20°C; (iii) NaH, THF, rt; (iv) Boc_2O, DMAP, CH_2Cl_2

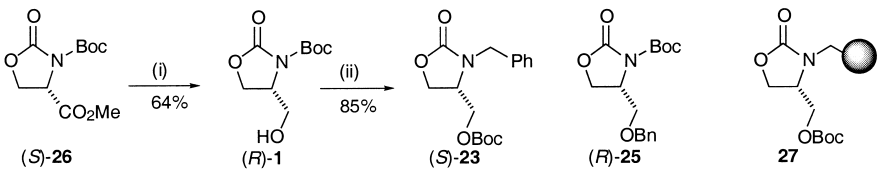
Clearly the above *endo*- or *exo*-cyclic migrations potentially render serine derived SuperQuat oxazolidin-2-ones unsuitable for attachment to polymer support via the hydroxymethyl side-chain. Furthermore, the report by Allin and Shuttleworth (Scheme 1) of the generation of an alkoxide from **1** (KH, DMF, 0°C) and clean attachment of Merrifield resin {DMF, 18-crown-6 (cat.), 80°C, 5 days} without apparent racemisation (endocyclic rearrangement), or Boc migration (exocyclic rearrangement), is remarkable and merited investigation. Firstly authentic samples of (*rac*)-*N*-benzyl-*O*-Boc-**23** and (*S*)-*N*-Boc-*O*-benzyl-4-hydroxymethyloxazolidin-2-ones **25** were prepared as shown in Scheme 6. Thus, (*rac*)-glycidol was treated with benzylisocyanate, and the resulting carbamate deprotonated with *n*-BuLi to afford *N*-benzyl

oxazolidinone **22**, which was protected on oxygen to afford (*rac*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **23** (Scheme 6). Alternatively, reduction of *O*-benzyl-L-serine with borane, followed by treatment with CDI, afforded *O*-benzyl-oxazolidin-2-one **24**, which was protected on nitrogen to afford (*S*)-*N*-Boc-*O*-benzyl-oxazolidin-2-one **25** (Scheme 6).



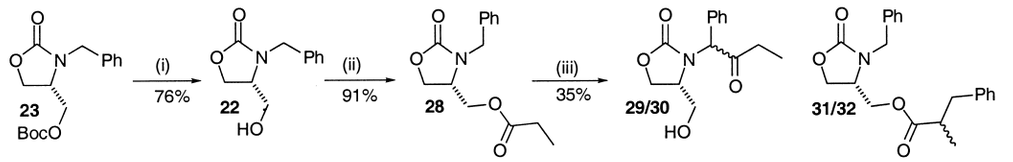
Scheme 6. Reagents and conditions: (i) Benzylisocyanate, cat. $[(n\text{-Bu})_2SnCl]_2O$, CH_2Cl_2; (ii) *n*-BuLi (1 equiv.), THF, −20°C; (iii) Boc_2O, DMAP, CH_2Cl_2; (iv) BH_3, THF; (v) CDI, CH_2Cl_2

The infra-red carbonyl absorptions cited by Allin and Shuttleworth for the polymer bound auxiliary **2** (1749 and 1685 cm^{-1}) were clearly incompatible with the *N*-benzyl-*O*-Boc derivative **23** (1744 and 1722 cm^{-1}) or the *N*-Boc-*O*-benzyl-derivative **25** (1802 and 1713 cm^{-1}). The chemistry in Scheme 1 was then reinvestigated. (*R*)-*N*-Boc-4-hydroxymethyloxazolidin-2-one **1** was prepared by reduction of the known ester (*S*)-**26** with $NaBH_4$ and shown to be enantiomerically pure by ^1H NMR chiral shift experiments ($[\alpha]_D^{23}$ −45.6, *c* 0.83, $CHCl_3$) with (+)-$Eu(tfc)_3$ in comparison with (*rac*)-**1**.[6] Treatment of homochiral (*R*)-**1** with KH in DMF at 0°C in DMF, followed by excess BnCl (as a model reaction for Merrifield resin) and 18-crown-6 (cat.) in DMF at room temperature, led to the clean formation of homochiral (*S*)-*N*-benzyl-*O*-Boc derivative **23** (Scheme 7). This result is consistent with the mechanism described in Scheme 3 whereby the alkoxide of (*R*)-**1** undergoes a very rapid *N*- to *O*-Boc migration to generate a nitrogen anion, which is subsequently benzylated. Since *N*-benzyl-*O*-Boc derivative (*S*)-**23** was isolated in homochiral form ($[\alpha]_D^{23}$ +10.5, *c* 1.54, $CHCl_3$) the observed exocyclic migration described in Scheme 3 must occur at a much faster rate than the corresponding endocyclic attack of the alkoxide at the oxazolidin-2-one carbonyl described in Scheme 3. No trace of the *N*-Boc-*O*-benzyl derivative (*R*)-**25** was observed in this reaction.



Scheme 7. Reagents and conditions: (i) $NaBH_4$, EtOH, 0°C; phosphate buffer pH 4.0; (ii) KH, DMF, 0°C; 18-crown-6 (cat.), BnCl

In light of these observations we must conclude that the material described by Allin and Shuttleworth as the *O*-bound homochiral polymeric auxiliary **2** was in fact *N*-bound polymeric auxiliary **27**. In order to investigate the possibility that this class of ester might prove useful for the asymmetric synthesis of homochiral acid **4** we prepared *N*-benzyl-*O*-acyl-oxazolidin-2-one **28** ($[\alpha]_D^{23}$ +10.0, *c* 1.35, $CHCl_3$) from homochiral (*S*)-**23** ($[\alpha]_D^{23}$ +29.0, *c* 1.66, $CHCl_3$) according to the protocol described in Scheme 8 and investigated its performance under enolate alkylation conditions. Thus, deprotonation of *O*-acyl-*N*-benzyl-**28** with 2 equivalents of LDA at −78°C in THF followed by addition of 2 equivalents of benzyl bromide resulted in a mixture of the epimeric ketones **29**/**30** in good yield, with no evidence of the expected product of enolate benzylation **31**/**32**, an authentic sample (0% d.e.) of which was prepared by acylation of the hydroxyl functionality of **22** with (*rac*)-**4**. Employing conditions in which the enolate of **28** was generated at 0°C, afforded a more complex mixture of reaction products containing the epimeric ketones **29**/**30**, with no evidence of any **31**/**32** having been formed.



Scheme 8. Reagents and conditions: (i) 2 M HCl; (ii) $(CH_3CH_2CO)_2O$, DMAP, Et_3N, CH_2Cl_2; (iii) LDA (2 equiv.), −78°C, THF; BnBr

In light of these results further work is necessary to explain the success of Allin and Shuttleworth in employing polymer supported oxazolidin-2-ones for the generation of carboxylic acid **4** with a 96% e.e.[2a]

All new compounds were fully characterised including elemental analysis or HRMS.

The successful attachment of the SuperQuat chiral auxiliary derived from tyrosine via its phenolic hydroxyl will be reported elsewhere.

References

1. Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small Molecular-Weight Compound Libraries*; Tetrahedron Organic Chemistry Series; Elsevier: Oxford, 1998; Vol. 17.
2. (a) Allin, S. M.; Shuttleworth, S. J. *Tetrahedron Lett*. **1996**, *37*, 8023. (b) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett*. **1997**, *38*, 8777; (c) Burgess, K.; Lim, D. *J. Chem. Soc., Chem. Commun*. **1997**, 785. (d) Phoon, C. W.; Abell, C. *Tetrahedron Lett*. **1998**, *39*, 2655.
3. In a recent report on the use of a polymer supported oxazolidin-2-one derived from L-tyrosine for asymmetric 1,3-dipolar cycloadditions the authors reported on 'a diminished enantioselectivity of up to 14% e.e.' upon recycling; Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett*. **2000**, *41*, 1265.
4. (a) Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671. (b) Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett* **1998**, 519. (c) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans 1* **1999**, 387.
5. McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett*. **1987**, *28*, 5395.
6. Katsumura, S.; Kondo, A.; Han, Q. *Chem. Lett*. **1991**, 1245, and references cited therein.