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Reinvestigation of a polymer-supported chiral auxiliary derived from serine

Steven M. Allin,[a,*] Cara A. Johnson[a] and Andreas Timm[b]

[a] *Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*
[b] *Rhone-Poulenc Rorer, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

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Abstract—Due to concerns over the reliability of the reported synthesis and application of a polymer-supported chiral auxiliary by our group, we have reinvestigated the preparation of the polymer. Analysis of the resin has now been carried out by MAS ^{13}C NMR spectroscopy, and as a result we now withdraw our previous claim of success.

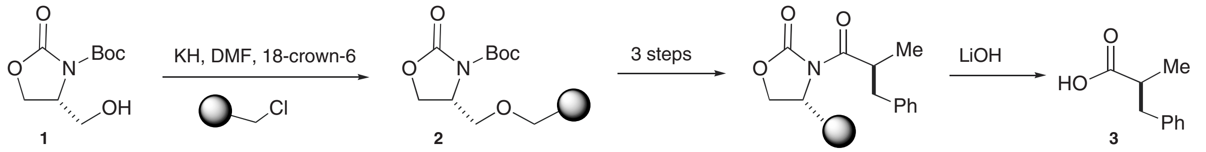
In 1996 our group claimed in this journal the first preparation and application of a polymer-supported oxazolidinone chiral auxiliary, derived from serine.[1] Subsequently, reports have appeared that have described the successful applications of other oxazolidinone auxiliaries derived from tyrosine.[2]

In our approach, key building block **1** was prepared and coupled to Merrifield resin as outlined in Scheme 1. Our interpretation of the FTIR spectra of the resin product **2** suggested to us that the coupling had been successful, and we had believed that proof of concept had been achieved through the isolation of the chiral propionic acid **3**, following a typical reaction sequence.

The identity of product **3** was not in doubt by us since this simple α-substituted propionic acid is a known compound of relatively simple structure. Figure 1 shows the ^{1}H NMR spectrum of the crude reaction mixture, obtained from LiOH-mediated cleavage of products from the resin following the sequence shown in Scheme 1 (Spectrum A), along with a spectrum of the same acid prepared by us by solution phase methods (Spectrum B) [the spectra were, however, recorded on different instruments]. The spectra correspond to those of an authentic sample of **3** supplied to us by Konopelski and co-workers.[3] In addition, ^{13}C NMR spectra and mass spectrometry of our product **3** also provided confirmation of the expected target structure.

Later reports from Davies and co-workers drew attention to the fact that serine derived chiral auxiliaries, particularly the *N*-Boc-4-hydroxymethyl-oxazolidin-2-one **1** prepared by us, were perhaps unsuitable for attachment to polymers due to rapid *O–O* and *N–O* acyl transfer reactions.[4] In light of our own claims, we were clearly worried by these findings and undertook a reinvestigation of our system.

Although we were unable to further examine the resin used in our original study, we repeated the synthesis



Scheme 1.

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* Corresponding author. E-mail: s.m.allin@lboro.ac.uk

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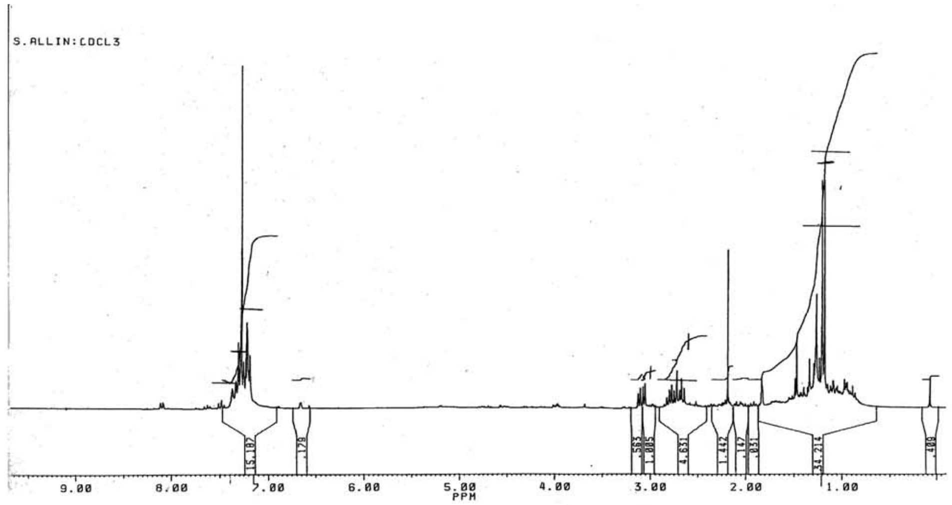
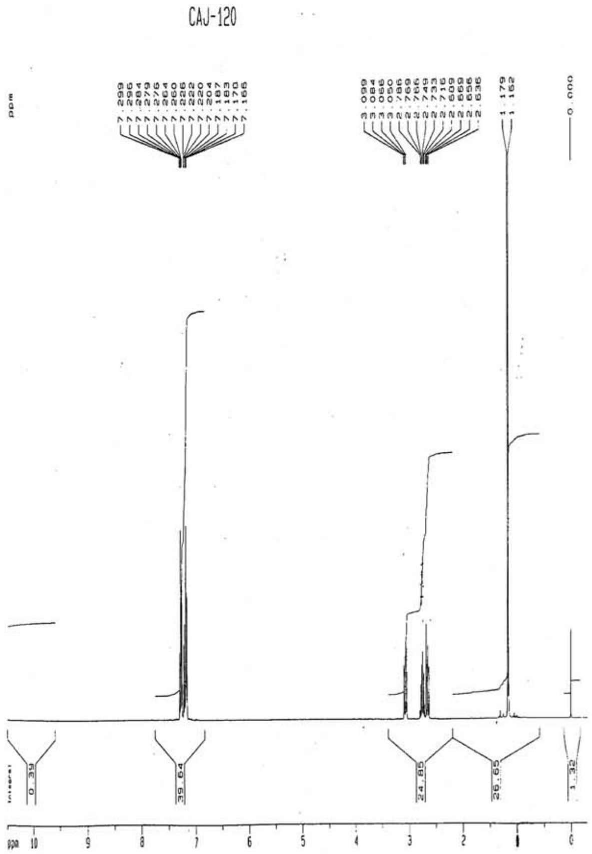


Spectrum A



Spectrum B

Figure 1. ^{1}H NMR Spectra of compound **3** obtained by supported synthesis (Spectrum A) and solution phase methods (Spectrum B).

under identical conditions to those reported by us in 1996 in order to access the derivatized resin **2**.

In our original paper we had reported the following IR data and characterization (KBr): 1749 (oxazolidinone) and 1685 cm^{-1} (Boc-carbonyl). We had observed complete disappearance of the peak corresponding to the Boc-carbonyl group on treatment of the resin with aq. HCl, and subsequent reappearance of a carbonyl group peak (1652 cm^{-1}) on reacylation with the propionyl side chain during the synthesis of acid **3**.

The group of Davies, and now ourselves, have prepared solution phase analogues of possible resin-bound species that could presumably be formed during the chemistry outlined in Scheme 1, in order to compare IR spectral data (Fig. 2).

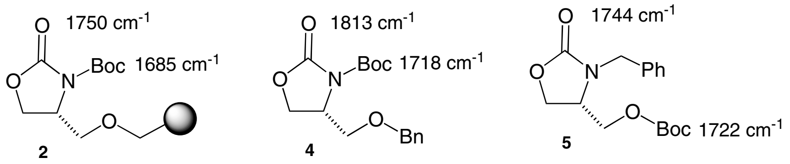


Figure 2. FTIR data for the reported resin-bound serine oxazolidinone, **2**, and solution phase equivalents of the possible alternatives.

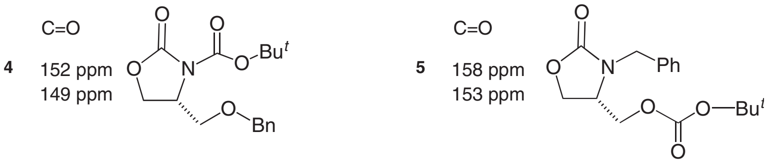


Figure 3. ^{13}C data obtained for the carbonyl region of solution phase models.[4]

Clearly the reported oxazolidinone carbonyl absorption of our original resin-bound species is closer to the *N*-benzyl-*O*-Boc model **5**, raising suspicions at this point about the true identity of this resin-bound material. The absorption attributed by us to the *N*-Boc carbonyl group (1685 cm^{-1}) in our original resin remains significantly different to solution phase model systems, **4** and **5**. We are still unable to account for this observation.

A resynthesis of resin **2** was undertaken by us and analysis of this resin by FTIR spectroscopy revealed a much more complex mass of peaks in the carbonyl region than observed with our original resin, ranging from 1655 cm^{-1} to >1800 cm^{-1} (>10 peaks). Worried that the FTIR analysis of the resin would not prove conclusive, we moved to examine this resin by MAS ^{13}C NMR spectroscopy (Varian nano-probe, 125 MHz), reasoning that comparison of the ^{13}C data obtained from the resin and from models **4** and **5** would give greater insight. This analytical procedure was unavailable to us at the time of our initial work. Figure 3 highlights the ^{13}C shifts (ppm) observed for the carbonyl groups of solution phase models **4** and **5**.

As can be appreciated, the more downfield shift (158 ppm) of one carbonyl group of the *N*-benzyl *O*-Boc oxazolidinone **5** should prove diagnostic. MAS ^{13}C NMR spectroscopy of our derivatized resin, **2**, showed that the main species attached to the resin displayed carbonyl group shifts at 158 and 153 ppm, matching perfectly the solution phase model of the *N*-benzyl-*O*-Boc derivative **5**, thus confirming the identity of the resin-bound material produced in this reinvestigation. Other (very) minor peaks were apparent in this region of the spectrum, between 145 and 160 ppm, but it would perhaps not be wise for us to postulate further on this fact at this present juncture.

In summary, we have reinvestigated the preparation of a polymer-supported oxazolidinone derived from serine and have now confirmed the identity of the resin-bound material by MAS NMR methods. We can conclude that, as suspected by Davies, the application of our previously reported method does not produce the desired resin-bound auxiliary **2**. Davies has already shown that the *N*-benzyl-*O*-Boc model **5** is not suitable for the preparation of chiral acids such as **3**,[4] and therefore we are also unable to satisfactorily explain our previously reported success in this arena. Given the new MAS ^{13}C NMR evidence provided in this paper we should therefore wish to withdraw our previous claim of success.[1]

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