Asymmetric Synthesis of β-Lactams using a Pummerer Reaction

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Resolution of 3-phenylsulphinylpropionamide by a cellulose tribenzoate h.p.l.c. column was achieved and the resulting sulphoxides were converted to optically active β-lactams with high efficiency.

We have previously reported syntheses of β-lactams using a Pummerer reaction, in which various 4-(phenylthio)azetidin-2-ones were prepared from the corresponding 3-phenylsulphinylpropionamide derivatives using $CF_3SO_3SiMe_3$ (TMSOTf) and triethylamine under mild conditions.[1] These reactions suggested the use of optically active sulphoxides as possible starting materials to obtain optically active β-lactams. The transfer of chirality from a sulphur atom to the α-carbon was first observed by Allenmark in 1974.[2] Further examples show that the induction occurs in 10—30% enantiomeric excess (e.e.) when acetic anhydride is used to effect this rearrangement.[3] In one case, 70% e.e. (chemical yield 10%) has been reported using acetic anhydride and dicyclohexylcarbodiimide.[4]

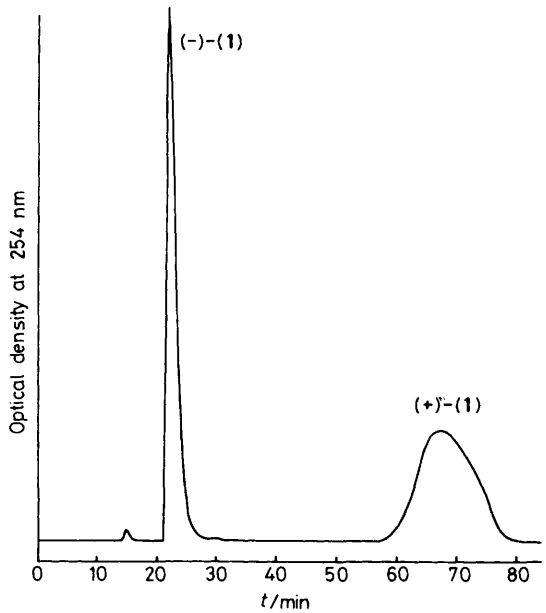
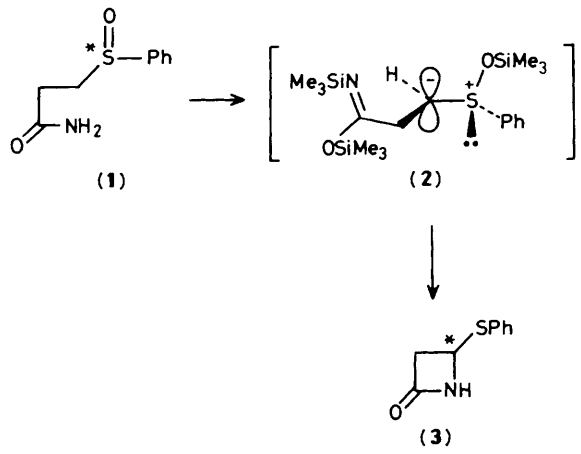


Figure 1. Resolution of (±)-(**1**) on a cellulose tribenzoate column [50 × 2 (i.d.) cm]. Eluent, hexane–propan-2-ol (60:40); flow rate 9.9 ml min^{-1}; (±)-(**1**), 12 mg.

To test this idea, racemic sulphoxide (**1**) was resolved utilizing a chiral stationary material we developed earlier as an h.p.l.c. column.[5] Using hexane–propan-2-ol (60:40) as an eluent, a base-line separation (α = 5.3) of enantiomers was achieved on a column prepared with cellulose tribenzoate absorbed on porous silica gel (Figure 1). Approximately 100 mg of sulphoxide could be separated in one injection.

The resulting enantiomerically pure sulphoxides were subjected to cyclisation conditions. Treatment of (+)-sulphoxide (**1**) {$[\alpha]_{589}^{25}$ + 218°, *c* 0.05 in $CHCl_3$} with TMSOTf and di-isopropylethylamine, 3.6 equiv. of each, at 0 °C in CH_2Cl_2 gave (**3**) in 76% yield, $[\alpha]_{589}^{25}$ −90.3° (*c* 0.5 in $CHCl_3$). The optically pure (4*S*)-(**3**) is reported[6] to have a rotation of −134.6°. Thus, the observed rotation corresponds to a 67% enantiomeric excess. This optical purity was confirmed independently by an h.p.l.c. analysis using the aforementioned chiral column. Use of triethylamine instead of di-isopropylethylamine at −20 °C gave the same optical yield; however, the chemical yield was lower (40%).†

† At −78 °C the reaction (using di-isopropylethylamine) produces little (**3**).



Scheme 1. *Reagents*: $CF_3SO_3SiMe_3$, di-isopropylethylamine. [Only one of the possible structures for ylide (**2**) is depicted.]

The corresponding (−)-sulphoxide (**1**), $\{[\alpha]_{589}^{25}$ −218°, *c* 0.05 in $CHCl_3\}$ gave (+)-(4*R*)-(**3**) in 74% chemical and 67% optical yields. Therefore, this new cyclisation method gives β-lactams with high stereospecificity and high chemical yield. The observed degree of chiral induction is one of the highest reported in Pummerer reactions. Compound (**3**) is an important intermediate for the synthesis of not only monobactams,[7a] but also carbapenems,[7b,c] penems,[7d] and oxapenams.[7e]

Although further work is necessary to elucidate the exact mechanism, the high stereospecificity may indicate that the ring closure is concerted with the S–O bond cleavage and the concomitant electron transfer within the silyloxysulphonium ylide (**2**). We suggest that the stereochemical outcome is the result of orbital control during this process or the steric effect of the ion pair formed in such a process.[8]

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