One-Step Synthesis Of Optically Active Benzyl
N-Trityl-L-Aziridine-2-Carboxylic Esters

E. Kuyl-Yeheskiely, M. Lodder, G.A. van der Marel and J.H. van Boom
Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Abstract: Benzyl N-trityl-L-serine or threonine esters give upon treatment with sulphuryl chloride the corresponding benzyl (2S)-1-trityl-2-aziridine carboxylate or (2S, 3S)-1-trityl-3-methyl-2-aziridinecarboxylate esters in excellent yields.

In a previous study from this laboratory it was disclosed\(^1\) (see Scheme 1) that the L-serine benzyl ester 1 (R=H) could be smoothly converted into the valuable and versatile benzyl (2S)-1-H-2-aziridinecarboxylate [2, R=H; (2S)-H-Azy-OBn] under the agency of diethoxytriphenylphosphorane. Unfortunately, every attempt to adopt this straightforward and high-yielding method to the preparation of benzyl (2S, 3S)-1-H-3-methyl-2-aziridinecarboxylate [i.e. 2, R=Me; (2S, 3S)-H-3MeAzy-OBn] starting from the L-threonine benzyl ester 1 (R=Me) was abortive.

Scheme 1

\[
\begin{align*}
\ce{O--Bn & Ph_3P(OEt)_2} \\
H_2N & \rightarrow N \ce{O--Bn} \\
1 \ (R = \text{H or Me}) & \quad 2 \ (R = \text{H or Me})
\end{align*}
\]

In 1969, Deyrup et al.\(^2\) found (see Scheme 2) that the reaction of 1-phenyl-2-t-butylaminoethanol (3) with sulphuryl chloride resulted in the isolation, although in a low yield, of the 1-t-butyl-2-phenylaziridine (6). Interestingly, the formation of the expected cyclic sulphamidate 4 could not be established. Instead, an open-chain material, presumably the amino chloride 5, could be isolated and converted into aziridine 6 after attempted chromatographic purification of 5.

Scheme 2

\[
\begin{align*}
\ce{H & t-Bu} \\
\ce{HO & Ph} & \rightarrow \ce{SO_2Cl_2 | Et_3N} \\
3 & \rightarrow 4 & \rightarrow \ce{H & t-Bu} \\
& Ph & \ce{N--O--S} & \ce{Ph & Cl} & \rightarrow \ce{Ph & N--O--S} \\
& Ph & \ce{N--O--S} & \ce{Ph & Cl} & \rightarrow \ce{N--O--S}
\end{align*}
\]

Recently, Baldwin et al.\(^3\) showed that the cyclic sulphamidate 8 (see Scheme 3), prepared from the N-benzyl-L-serine-tert-butyl ester (7) via the Sharpless\(^4\) two-step cyclic sulphate method, was a relatively
stable compound which could be ring-opened by several heteroatomic nucleophiles giving access to valuable β-functionalised α-amino acids (e.g. 9).

**Scheme 3**

In view of the results briefly summarized in Schemes 2 and 3, we anticipated that the presence of a bulky substituent at the nitrogen atom and a non sterically hindered carboxylate protecting group would favour intramolecular ring opening of L-serine (threonine) cyclic sulphonamides giving the respective aziridines.

As part of a program directed towards the assembly of naturally occurring nucleopeptides, we here report that N-trityl-L-serine or threonine benzyl esters (i.e. 10 R=H or Me) can be smoothly transformed via a "one-pot one-step" procedure into the respective aziridines (i.e. 13 R=H or Me).

In order to substantiate our assumption, N-trityl-L-serine benzyl ester (10, R=H) was first converted, as outlined in Scheme 4, into the cyclic sulphonamide 11 (R=H) following a published procedure. Work-up and purification gave homogeneous 11 (R=H; 80%) as a mixture of diastereoisomers. On the other hand, oxidation of 11 with sodium periodate and catalytic ruthenium (III) chloride did not afford cyclic sulphonamide 12 (R=H), but instead (2S)-1-Tr-2-Azy-OBn (13, R=H) as evidenced by its NMR data and optical rotation value. However, it was established that the oxidation of 11 (R=H) was not reproducible.
(i.e. in some cases a drastic decrease in yield was observed). It was anticipated that the use of sulphuryl chloride would be an attractive alternative for the less satisfactory two-step route to compound 13 (R=H).

Indeed, treatment of 10 (R=H) in toluene (-50°C) with sulphuryl chloride and excess triethylamine furnished, after workup and purification, homogeneous 13 (R=H; 90%), the optical rotation value of which was in good accord with the reported value [i.e. $\alpha_1^D = -95.5$ (c 1, THF)] of the same aziridine derivative. Fortunately, it was also established that the highly reproducible one-step sulphuryl chloride method could be applied successfully toward the preparation of (2S, 3S)-1-Tr-3MeAzy-OBn (13, R=Me). Thus, reaction of N-trityl-L-threonine benzyl ester (10, R=Me) with sulphuryl chloride gave the chirally pure aziridine 13 (R=Me) in 94% yield. In addition, detritylation of 13 (R=Me) proceeded in a nearly quantitative yield affording homogeneous (2S, 3S)-1-H-3MeAzy-OBn (14, R=Me) which, in turn, was smoothly converted into benzoxycarbonyl chloride (Z-Cl) into the homogeneous compound 15 (R=Me).

In conclusion, the one-step synthesis of the valuable aziridines 13 (R=H or Me) is in several aspects superior over the well-established Okawa two-step procedure. For example, the aziridine 13 (R=Me) could be obtained after prolonged heating (48 h, 80°C) of the O-tosyl threonine derivative 10 (R=Me) with triethylamine in THF. At present, the use of aziridines 14 (R=H or Me) in the preparation of naturally occurring nucleopeptides is in progress.

**EXPERIMENTAL PROCEDURE**

** Benzyl (2S)-1-trityl-2-aziridinecarboxylate (13, R=H).

Compound 10 (R=H) (2.29 mmol, 1.0 g) was dissolved in anhydrous dioxane (2x25 ml) and the solvent was removed by evaporation. Toluene (50 ml) and triethylamine (6.86 mmol, 0.96 ml) were added and the mixture was cooled to -50°C. Sulphuryl chloride (2.86 mmol, 0.286 ml) in toluene (25 ml) was then added dropwise during a period of 15 min. and the mixture was left for 1 hr at -50°C. The temperature was allowed to rise to room temperature and the solution was diluted with ethyl acetate. The combined organic phases were extracted with brine (NaCl 10% solution, 50 ml), dried (MgSO$_4$) and concentrated. Crude compound 13 (R=H) was purified by silica gel flash chromatography (ethyl acetate/n-hexane, 1/4, v/v) to yield an oil which crystallized (H$_2$O/acetone/MeOH) as 13 (R=H). Yield: 90% (2.06 mmol, 864 mg). Rf 0.65 (Ethyl acetate/n-hexane, 1/5, v/v). $\alpha_1^D = -91.7$ (c 0.92, THF). M.p. 106-107°C. MH$^+$ 420.

$^1$H NMR (200 MHz in CDCl$_3$): $\delta = 7.51-7.21$ (m, 9H, Aromatic H); 5.22-5.21 (d, 2H, J 2.0 Hz, CH$_2$, Bn); 2.29-2.27 (dd, 1H, J 1.5 and 3.0 Hz, PCH$_2$ Azy); 1.95-1.91 (dd, 1H, J 3.0 and 6.0 Hz, aCH$_2$ Azy); 1.43-1.39 (dd, 3H, J 1.5 and 6.0 Hz, CH$_3$ Azy). $^{13}$C NMR (50.1 MHz in CDCl$_3$): $\delta = 171.17$ (GO, Azy); 143.37-126.29 (Aromatic C); 74.20 (C-N); 66.43 (CH$_2$, Bn); 31.60 (aCH, Azy); 28.59 (KHz, Azy).

** Benzyl (ZS)-1-trityl-3-methyl-2-aziridinecarboxylate (13, R=Me).

In a similar fashion, compound 10 (R=Me, 2.29 mmol, 1.03 g) was converted into 13 (R=Me) as described for the synthesis of (ZS)-Tr-Azy-OBn. Crude compound 13 (R=Me) readily crystallized from methanol. Yield: 94% (2.15 mmol, 932 mg). Rf 0.69 (ethyl acetate/n-hexane, 1/5, v/v). $\alpha_1^D = -108.9$ (c 1.54, CHCl$_3$). M.p. 99-101°C. MH$^+$ 434. $^1$H NMR (200 MHz in CDCl$_3$): $\delta = 7.53-7.16$ (m, 9H, Aromatic H); 5.22-5.21 (d, 2H, J 2.0 Hz, CH$_2$, Bn); 2.29-2.27 (dd, 1H, J 1.5 and 3.0 Hz, $\beta$CH, Azy); 1.95-1.91 (dd, 1H, J 3.0 and 6.0 Hz, aCH, Azy); 1.43-1.39 (dd, 1H, J 1.5 and 6.0 Hz, $\beta$CH, Azy). $^{13}$C NMR (50.1 MHz in CDCl$_3$): $\delta = 171.17$ (C=O, Azy); 143.37-126.29 (Aromatic C); 74.20 ($\phi_3$-C-N); 66.43 (CH$_2$, Bn); 31.60 (aCH, Azy); 28.59 ($\beta$CH$_2$, Azy).

** Benzyl (2S, 3S)-1-Trityl-3-methyl-2-aziridinecarboxylate (13, R=Me).

In a similar fashion, compound 10 (R=Me, 2.29 mmol, 1.03 g) was converted into 13 (R=Me) as described for the synthesis of (2S)-Tr-Azy-OBn. Crude compound 13 (R=Me) readily crystallized from methanol. Yield: 94% (2.15 mmol, 932 mg). Rf 0.69 (ethyl acetate/n-hexane, 1/5, v/v). $\alpha_1^D = -108.9$ (c 1.54, CHCl$_3$). M.p. 99-101°C. MH$^+$ 434. $^1$H NMR (200 MHz in CDCl$_3$): $\delta = 7.53-7.16$ (m, 9H, Aromatic H); 5.31-5.25 (d, 1H, J$_{AB}$ 12.0 Hz, CH$_2$, Bn); 5.16-5.10 (d, 1H, J$_{AB}$ 12.0 Hz, CH$_2$ Bn); 1.95-1.92 (d, 1H, J 6.0 Hz, aCH, Azy); 1.69-1.56 (m, 1H, $\beta$CH, MeAzy); 1.37-1.34 (d, 3H, J 5.0 Hz, CH$_3$).

$^{13}$C NMR (50.1 MHz in CDCl$_3$): $\delta = 170.00$ (C=O, MeAzy); 143.75-126.70 (Aromatic C); 74.84 ($\phi_3$-C-N); 66.31 (CH$_2$, Bn); 35.92 and 34.87 (aCH and $\beta$CH, MeAzy); 13.20 (CH$_3$, MeAzy).
Benzyl (2S, 3S)-1-H-3-methyl-2-aziridinocarboxylate (14, R=Me).

To a solution of compound 13 (R=Me, 1.42 mmol, 615 mg) in absolute methanol (10 ml) was added formic acid (5.0 ml) at 0°C. After stirring the mixture for 1.5 h at 0°C and 1.5 h at room temperature, TLC analysis indicated complete detritylation. Toluene (30 ml) was added and the mixture was concentrated. The evaporation procedure was repeated twice to ensure complete removal of formic acid. Crude compound 14 (R=Me) was used without further purification for the preparation of (2S, 3S)-Z-3MeAzy-OBn. ¹H NMR (200 MHz in CDCl₃): δ = 7.47-7.18 (Aromatic H); 5.20 (s, 2H, CH₂, Bn); 3.05 (s, CH₂, OCH₂); 2.69-2.66 (d, 1H, J 6.0 Hz, CCCH₂, MeAzy); 2.37-2.25 (m, 1H, βCH, MeAzy); 1.29-1.26 (d, 3H, J 6.0 Hz, CH₃).

ACKNOWLEDGEMENT

We thank the Dutch Cancer Society for financial support.

REFERENCES AND NOTES

8. Relevant data of compound 11:
   ¹H NMR (200 MHz in CDCl₃): δ = 4.71-4.65 (d, 1H, JAB 12.0 Hz, CH₂, Bn); 4.52-4.46 (d, 1H, JAB 12.0 Hz, CH₂, Bn); 4.25-3.98 (m, 2H, βCH₂, Ser); 3.91-3.82 (dd, 1H, J 4.0 and 6.0 Hz, αCH, Ser).
   ¹³C NMR (50.1 MHz in CDCl₃): δ = 171.55 (C=O, Ser); 145.36-126.44 (Aromatic C); 71.01 and 70.93 (2xCH₂ of Z and Bn); 66.86 (CH₂, Bn); 64.18 and 63.71 (2xβCH₂, Ser); 55.89 (αCH, Ser).
11. Yield of 15 (R=Me) was 81%. Rf 0.45 (ethyl acetate/n-hexane, 1/4, v/v). [α]D 0.20-63.7 (c 1.13, MeOH).

(Received in UK 12 March 1992)