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Synthesis of orthogonally protected 1,2-diaminopropanoic acids by ring-opening of 3-unsubstituted N-activated aziridine 2-carboxylates with *para*-methoxybenzylamine: a study of the regioselectivity of the reaction

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ABSTRACT

Orthogonally protected 1,2-diaminopropanoic acids (DAPs) have been synthesised in good yields by the ring-opening of 3-unsubstituted N-activated aziridine 2-carboxylates with *para*-methoxybenzylamine. The choice of both the N-activating group and ester alkyl group had a significant influence on the ratio of attack at the α or β positions of the aziridine. However, the regiochemical outcome is not predictable.

Interest in α,β-diaminopropanoic acids [1,2-diaminopropanoic acids (DAPs)] has expanded over the years, as evidenced by the increase in publications in the area. A recent review,[1] and its update,[2] have highlighted methodologies for their synthesis, as well as their possible applications and biological activities. Natural biologically active molecules, which contain the α,β-diaminopropanoic acid motif, are known and they are stereochemically pure as single enantiomers or diastereoisomers. Therefore methods from the stereoselective synthesis of α,β-diaminopropanoic acids are very important. In this context, the use of α-amino acid derivatives from the chiral pool, where one or more stereocentres are already present, as precursors for α,β-diaminopropanoic acids, is a key method that has been employed. One of the main routes employed for the synthesis of DAPs is the ring-opening of N-activated aziridine 2-carboxylate esters with primary amines. Although there is a large body of literature on the ring-opening of aziridines in general,[3] as well as 2-acyl aziridines[4] and N-activated aziridines,[5] the number of reports on the ring-opening of N-activated aziridine 2-carboxylate esters is fewer. In all such reactions the nucleophile can attack at either the α- or β-position of the aziridine ring to give regioisomeric products (Fig. 1).

In a recent review,[3a] De Kimpe and Ha stated that 'the regioselectivity in the ring-opening reactions of 2-substituted activated aziridines has been shown to be quite straightforward, mostly involving the nucleophilic attack at the less hindered carbon atom, with some exceptional cases comprising the nucleophilic attack at the benzylic position'. An examination of the regioselectivity of these reactions shows that the outcome is not always that predictable,[6] particularly when the nucleophile is a primary amine, and the 2-substituent is also electron-withdrawing (e.g., an ester group). For example, Rich found that reaction of *N*-tosyl aziridine 2-carboxylic acid with methylamine gave a 1:1 ratio of products resulting from α- and β-attack.[7] However, when the steric hindrance at the 2-position was increased, by using the 2-*tert*-butyl ester derivative, the α:β ratio was 1:6.3. The van Boom group found a 3.5:1 ratio, in favour of attack at the less hindered β-position, for the reaction of benzylamine with N-*ortho*-nitrobenzenesulfonyl (*o*-Ns) aziridine 2-*t*-butyl ester, which increased to a 15–17:1 ratio when the primary amine was an α-amino acid ester.[8] When the steric hindrance was increased significantly, by linking the ester group at the aziridine 2-position to a solid support, Olsen found

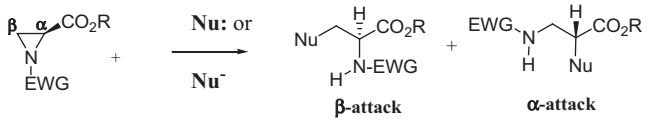

Figure 1. Regiochemistry of nucleophilic ring-opening of N-activated aziridine 2-carboxylates.

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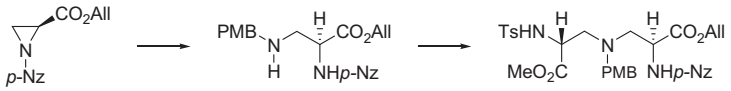
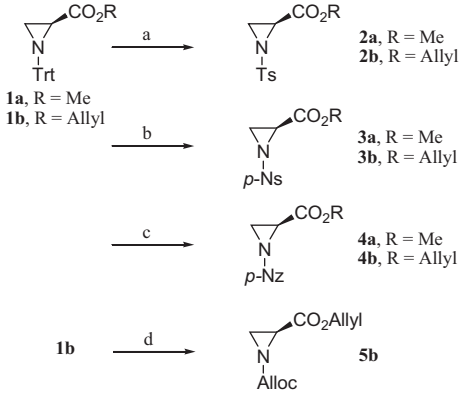


Figure 2. Synthesis of orthogonally protected azalanthionines (lanazanines).[10]

that this led to exclusive attack at the less hindered β-position, with no evidence for any α-attack.[9] The Franzyk group reported a 9:1 ratio, in favour of β-attack, when the ester group of an α-amino ester was linked to a solid support, and it was reacted with N–*p*Ns aziridine methyl 2-carboxylate.[5h]

As part of an ongoing programme of research towards the synthesis of peptides incorporating unusual amino acid residues, we are interested in the synthesis of β-monoalkyl substituted 1,2-diaminopropanoic acids (DAPs). In particular, the use of orthogonally protected DAPs would allow their incorporation into peptide structures and then their subsequent derivatisation. We previously reported the synthesis, and subsequent use, of such orthogonally protected DAPs for the preparation of orthogonally protected azalanthionines (lanazanines), which are nitrogen-linked analogues of the more common amino acid lanthionine (Fig. 2).[10]



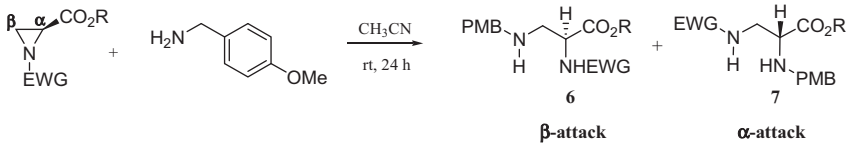
Scheme 1. Synthesis of N-activated aziridine 2-carboxylate esters.[10,12] Reagents and conditions: (a) (i) 50% TFA in CH_2Cl_2/MeOH (1:1), rt, 30 min, (ii) $NaHCO_3$, H_2O, rt, (iii) *p*-TsCl, EtOAc, rt, 24 h, (**2a** 85%, **2b** 83%); (b) (i) 50% TFA in CH_2Cl_2/MeOH (1:1), rt, 30 min, (ii) $NaHCO_3$, H_2O, rt, (iii) *p*-nitrobenzenesulfonyl chloride, EtOAc, rt, 24 h (**3a** 85%, **3b** 80%); (c) (i) 50% TFA in CH_2Cl_2/MeOH (1:1), rt, 30 min, (ii) $NaHCO_3$, H_2O, rt, (iii) *p*-nitrobenzyl chloroformate, EtOAc, rt, 24 h (**4a** 82%, **4b** 82%); (d) (i) 50% TFA in CH_2Cl_2/MeOH (1:1), rt, 30 min, (ii) $NaHCO_3$, H_2O, rt, (iii) allyl chloroformate, EtOAc, rt, 24 h, 34%.

The required DAPs were prepared by the ring-opening of 3-unsubstituted N-activated aziridine 2-carboxylate esters with benzylamines, or by the Mitsunobu reaction of serine derivatives.[11] During the aziridine ring-opening reactions it was found that there were issues with the regioselectivity of the reactions, depending on the choice of the N-protecting group and ester group at the aziridine 2-position. Since the initial results showed that the regiochemical outcome was not straightforward, an extended study was undertaken to determine whether the regioselectivity was in any way predictable. The required N-activated aziridine 2-carboxylates were prepared as shown in Scheme 1.[10,12]

In each case the protecting groups chosen were those that have been used previously in solid-phase peptide syntheses, particularly in the preparation of lanthionine containing peptides and their analogues.[12] Thus the N-protecting groups used were Ts, *para*-nitrobenzenesulfonyl (*p*-Ns), and *para*-nitrobenzyloxycarbonyl (*p*-Nz), while the methyl and allyl esters were chosen for the aziridine 2-position. Preparation of a DAP with the β-amino group also being protected was achieved by ring-opening of aziridine **2a** with *para*-methoxybenzylamine (PMB-NH_2) following the method of Kim.[13] This involved heating the reaction to 80 °C in acetonitrile for 24 h with two molar equiv of PMB-NH_2, which gave the two regioisomeric products from nucleophilic attack at either the α- or β-positions of the aziridine. The PMB group was chosen because it can be easily removed in solid-phase synthesis. The yield of the product (Table 1) from attack at the less hindered β-position was 32%, while attack at the α-position gave a 41% yield (entry 1).

Conducting the reaction at room temperature for 24 h gave a reversal in the observed selectivity, with the β-attack giving a yield of 70% and α-attack of 23% (entry 2). The selectivity observed at higher temperatures was not unexpected, but the 23% yield of the compound isolated from attack at the hindered α-position, at room temperature, was somewhat of a surprise. Since the conditions required to remove the tosyl group are very harsh for solid-phase peptide synthesis the alternative N-activating, peptide-friendly, *p*-Ns and *p*-Nz groups were chosen, for comparison with the *N*-tosyl aziridine **2a**. (Note: the N-Fmoc protected aziridine was not chosen because it was felt that the

Table 1
Regioselectivity of the ring-opening of aziridines with *p*-methoxybenzylamine



Entry	Aziridine	% β-attack[a]	% α-attack[a]
1	**2a** (R = Me, EWG = Ts)	32 (**6a**)[b]	41 (**7a**)[b]
2	**2a** (R = Me, EWG = Ts)	70 (**6a**)	23 (**7a**)
3	**3a** (R = Me, EWG = *p*-Ns)	63 (**6b**)	21 (**7b**)
4	**4a** (R = Me, EWG = *p*-Nz)	56 (**6c**)	—
5	**2b** (R = Allyl, EWG = Ts)	—	—
6	**3b** (R = Allyl, EWG = *p*-Ns)	—	—
7	**4b** (R = Allyl, EWG = *p*-Nz)	66 (**6d**)	—
8	**5b** (R = Allyl, EWG = Alloc)	—	—

[a] Product number is in parentheses.
[b] Reaction conducted at 80 °C.