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S_N2 *vs.* E2 on quaternary centres: an application to the synthesis of enantiopure $\beta^{2,2}$-amino acids†

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S_N2 and E2 competing reactions in cyclic sulfamidates can be modulated by the change of an amide group to an ester group attached to the quaternary carbon activated for the nucleophilic attack, allowing an easy approach to enantiopure α,α-disubstituted β-amino acids.

β-Amino acids have recently attracted a great deal of attention due to their applications in medicinal chemistry and molecular recognition.[1] In addition, peptides containing these amino acids show an extraordinary proteolytic stability.[2] In this area α-substituted β-amino acids are particularly attractive compounds since the presence of an alkyl substituent at the α-position favors folded conformations in the β-peptides.[3]

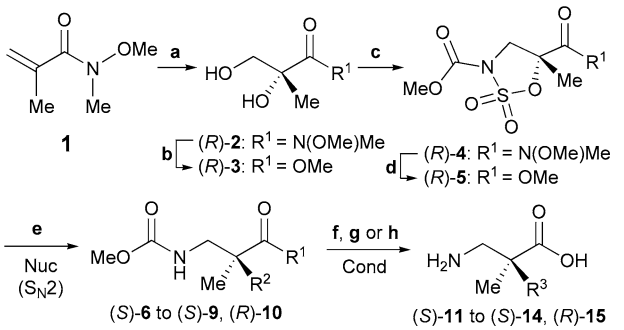
On the other hand, five-membered cyclic sulfamidates have been extensively used as reactive intermediates in organic synthesis,[4] since the majority of ring-opening reactions of cyclic sulfamidates with nucleophiles proceed by the S_N2 pathway with total inversion at the stereogenic centre.[4] The development of both the catalytic asymmetric dihydroxylation (AD) reaction[5] to synthesize chiral 1,2-diols and the efficient method involving the Burgess-type reagent[6] for preparing five-membered cyclic sulfamidates from chiral 1,2-diols has contributed to the expansion of the chemistry of such systems.[7]

In an effort to combine the two aforementioned processes, and in connection with our research into the asymmetric synthesis of conformationally restricted amino acids, we focused our attention on two five-membered cyclic α-methylisoserine-derived sulfamidates (*R*)-**4** and (*R*)-**5**. It was believed that these two compounds would be excellent chiral building blocks for the synthesis of α-methylated β-amino acids by nucleophilic ring-opening reactions (Scheme 1). We report here an easy synthetic approach to a varied collection of $\beta^{2,2}$-amino acids that are not accessible by previously reported methodologies.[8]

Although the synthesis and reactivity of several sulfamidates have been well documented, in all cases these compounds are monosubstituted or α,β-disubstituted. In contrast, little is known about five-membered cyclic sulfamidates that are *gem*-disubstituted at the 5-position—the quaternary carbon activated for nucleophilic attack—and, to the best of our knowledge, it is the first time that such compounds have been opened by nucleophiles *via* S_N2 reaction on the quaternary carbon.

Firstly we synthesised sulfamidates (*R*)-**4** and (*R*)-**5** from chiral diols (*R*)-**2** and (*R*)-**3** in good yield using Burgess' reagent (Scheme 1). Single crystals of (*R*)-**4** and (*R*)-**5** were obtained in order to confirm their structures by X-ray diffraction.‡,[9] Diols (*R*)-**2** and (*R*)-**3** were easily obtained from the Sharpless AD reaction on olefin **1** using AD-mix α.[10] Sulfamidate (*R*)-**5** was also prepared from sulfamidate (*R*)-**4** by the action of TfOH in MeOH. Ring opening of these sulfamidates was examined using nitrogen, sulfur, oxygen, fluorine and carbon nucleophiles (Scheme 1, Table 1).

In our procedure, sulfamidate (*R*)-**4** (1.0 equiv.) and the nucleophile (1.3 equiv.) were heated in DMF at 25–50 °C for 1–12 h. The corresponding sulfamic acid intermediates were hydrolyzed in an acid medium to give the desired S_N2 products (Scheme 1). As the basicity of the nucleophile was increased, for example in the case of oxygen or fluorine nucleophiles, the S_N2 reaction in sulfamidate (*R*)-**4** was accompanied by the elimination product **17**. This problem was solved by changing the amide group to an ester group in the cyclic sulfamidate, therefore on using sulfamidate (*R*)-**5** instead of (*R*)-**4** in the S_N2 reactions, the E2 reaction was



Scheme 1 (a) Ref. 10: AD-mix α, $MeSO_2NH_2$, $^tBuOH/H_2O$ (1 : 1), 0 °C, 12 h, 81%, ee = 93%; (b) i) $LiOH{\cdot}H_2O$ (5 equiv.), H_2O/MeOH (1 : 3), rt, 2 h; ii) AcCl, MeOH, reflux, 12 h, 85%; (c) Burgess' reagent, THF, rt, 24 h, 96%; (d) TfOH, MeOH, 60 °C, 3 h, 97%; (e) i) Nuc (1.3 equiv.), DMF, 25–50 °C, 1 to 12 h, ii) 20% H_2SO_4 (aq.)/CH_2Cl_2 (1 : 1), rt, 12 h; (f) i) H_2, Pd–C, MeOH, rt, 12 h, ii) 6 M HCl (aq.), 100 °C, 12 h, iii) propylene oxide, EtOH, reflux, 2 h; (g) The same conditions described in steps ii) and iii) of (f); (h) i) $LiOH{\cdot}H_2O$ (10 equiv.), H_2O/MeOH (2 : 3), reflux, 48 h, ii) Dowex H^+.

† Electronic supplementary information (ESI) available: experimental details, spectroscopic characterization of all compounds, crystal structure data and tables of electronic energies, enthalpies, entropies, Gibbs free energies and coordinates for the conformations of structures. See http://www.rsc.org/suppdata/cc/b4/b400282b/

Table 1 Synthesis of $\beta^{2,2}$-amino acids (β-aa) from sulfamidates (Sul)

Entry	Sul	R^2	Nuc (*T*, °C)	S_N2 (%)[a]	Cond	R^3	β-aa (%)[b]
1	(*R*)-**4**	N_3	NaN_3 (50)	(*S*)-**6** (86)	**f**	NH_2	(*S*)-**11** (70)
2	(*R*)-**4**	SMe	NaSMe (25)	(*S*)-**7** (93)	**g**	SMe	(*S*)-**12** (81)
3	(*R*)-**5**	PNB-O[c]	PNB-OH[c]/ CsF (50)	(*S*)-**8** (99)	**g**	OH	(*S*)-**13** (85)
4	(*R*)-**5**	F	NBu_4F (25)	(*S*)-**9** (97)	**g**	F	(*S*)-**14** (83)
5	(*R*)-**5**	CN	NaCN (25)	(*R*)-**10** (96)	**h**	CN	(*R*)-**15** (98)

[a] Yield of S_N2 product after column chromatography. [b] Overall yield corresponding to the transformations of S_N2 product into β-aa. [c] PNB-OH = *p*-nitrobenzoic acid.

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suppressed (Table 1, entries 3–5). This functional groups exchange has already been studied in order to modulate the regioselectivity in the S_N2 reaction on cyclic sulfates.[11] Interestingly, an elimination reaction on substrates (*R*)-**4** or (*R*)-**5** can be directed by the action of DBU in THF at reflux, cleanly giving products **17** and **18**, respectively (Table 2). Some derivatives of these α-methylene-β-alanines have been used as starting materials in the asymmetric synthesis of β-amino acids,[12] and as monomers in the production of polymers with a high isotacticity.[13]

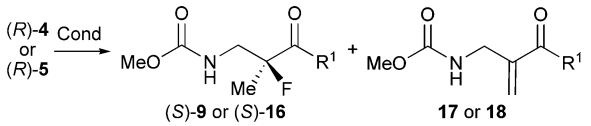
The approaches shown in Scheme 1 can be used to synthesize $\beta^{2,2}$-amino acids with a variety of substituents in addition to the methyl group. In this way we obtained, in enantiomerically pure form, the following $\beta^{2,2}$-amino acids: (*S*)-**11**, (*S*)-**12**, (*S*)-**13**, (*S*)-**14** and (*R*)-**15** (Table 1). The synthesis of β-amino-α-methylalanine[14] (*S*)-**11** was achieved from the S_N2 product (*S*)-**6** by hydrogenation of the azide group and subsequent acid hydrolysis. The hydrolysis of (*S*)-**7** gave the new $\beta^{2,2}$-amino acid *S*,α-dimethylisocysteine (*S*)-**12**. In the same way, the known α-methylisoserine[15] (*S*)-**13** and α-fluoro-α-methyl-β-alanine[16] (*S*)-**14** were obtained from (*S*)-**8** and (*S*)-**9**, respectively. Moreover, the new $\beta^{2,2}$-amino acid 2-(aminomethyl)-2-cyanopropanoic acid (*R*)-**15** was obtained from (*R*)-**10** by basic hydrolysis. Among these compounds it is worth highlighting $\beta^{2,2}$-amino acid (*S*)-**14**; considering the significant effects of the C–F bond on the activity of an HIV protease inhibitor,[17] the availability of α-fluorinated derivatives will serve to aid studies in this field. The absolute configuration and the enantiomeric purity of known $\beta^{2,2}$-amino acids were established by comparison of the optical rotations with literature values.[14,15] The enantiomeric purity of the rest of the amino acids was determined by GC–MS analysis using α- or γ-DEX™ chiral capillary columns.

A theoretical study was carried out in order to shed light on the different reactivities of sulfamidates (*R*)-**4** and (*R*)-**5** with the fluoride anion in the S_N2 and E2 reactions. All ground state and transition state (TS) geometries were located using hybrid density functional theory (B3LYP)[18] and the 6-31+G(d) basis implemented in Gaussian 98.[19] All the TS geometries were fully optimized and characterized by frequency analysis. The energetic results of the different TS with the fluoride anion and some relevant features of the TS are shown in Fig. 1.

As far as substrate (*R*)-**4** is concerned, the TS obtained for the E2 reaction (**TS4_e**) was slightly lower in energy (0.60 Kcal mol^{-1} more stable) than that resulting from the nucleophilic attack of the fluoride anion (**TS4_s**). This situation is in qualitative agreement with the chemoselectivity experimentally observed. In contrast, with (*R*)-**5** the difference in energy between the TS (**TS5_e** and **TS5_s**) is considerably higher, with the S_N2 route now being favored by *ca.* 2 Kcal mol^{-1}. This fact can be explained by considering the electrophilic character of C_α. Thus, whereas the net charge at C_α in (*R*)-**5** is +0.54 electrons, this value is only +0.29 in (*R*)-**4**.

Finally, in terms of geometry the hydrogen of the methyl group in **TS4_e** (Fig. 1) is perfectly aligned *anti* with respect to the C–O breaking bond. This feature is not possible with any of the diastereotopic hydrogens of the ring, which explains the experimental finding that only olefin **17** was formed as a product of the E2 reaction with sulfamidate (*R*)-**4**.

Table 2 S_N2 *vs.* E2 on cyclic sulfamidates (Sul)



Entry	R^1	Sul	Cond[a]	S_N2 (%)	E2 (%)
1	N(OMe)Me	(*R*)-**4**	**A**	(*S*)-**16** (32)	**17** (68)
2	OMe	(*R*)-**5**	**A**	(*S*)-**9** (97)	—
3	N(OMe)Me	(*R*)-**4**	**B**	—	**17** (88)
4	OMe	(*R*)-**5**	**B**	—	**18** (80)

[a] Conditions: **A**: i) NBu_4F (1.2 equiv.), DMF, 50 °C, 12 h, ii) 20% H_2SO_4 (aq.)/CH_2Cl_2 (1 : 1), rt, 12 h. **B**: DBU (2.0 equiv.), THF, reflux, 12 h.

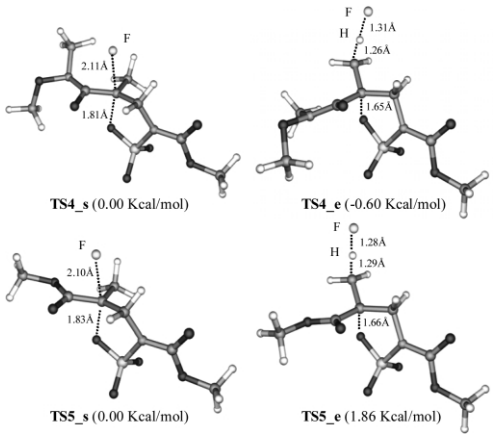


Fig. 1 TS calculated with (*R*)-**4** and (*R*)-**5** and fluoride anion.

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Notes and references

‡ (a) *Crystal data* of (*R*)-**4**: $C_8H_{14}N_2O_7S$, *Mw* = 282.28, colorless prism, *T* = 173 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 8.8646(3), *b* = 10.9014(4), *c* = 12.4336(5) Å, *V* = 1201.54(8) $Å^3$, d_{calc} = 1.561 g cm^{-3}, *F*(000) = 592, λ = 0.71073 Å (Mo-Kα), μ = 0.299 mm^{-1}, Nonius kappa CCD diffractometer, θ range 3.7–27.9°, 2787 unique reflections, full-matrix least-squares (SHELXL97),[9] R_1 = 0.0400, wR_2 = 0.1029, goodness of fit = 1.04, residual electron density between 0.26 and −0.29 e $Å^{-3}$; CCDC 228173. (b) *Crystal data* of (*R*)-**5**: $C_7H_{11}NO_7S$, *Mw* = 253.24, colorless prism, *T* = 173 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 8.2367(3), *b* = 8.9543(4), *c* = 14.8873(7) Å, *V* = 1098.0(8) $Å^3$, d_{calc} = 1.532 g cm^{-3}, *F*(000) = 528, λ = 0.71073 Å (Mo-Kα), μ = 0.316 mm^{-1}, Nonius kappa CCD diffractometer, θ range 3.4–35.0°, 4609 unique reflections, full-matrix least-squares (SHELXL97),[9] R_1 = 0.0591, wR_2 = 0.1591, goodness of fit = 1.02, residual electron density between 0.41 and −0.51 e $Å^{-3}$. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). CCDC 227600. See http://www.rsc.org/suppdata/cc/b4/b400282b/ for crystallographic data in .cif or other electronic format.

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