A Novel Chiral Oxycarbonyl Rearrangement

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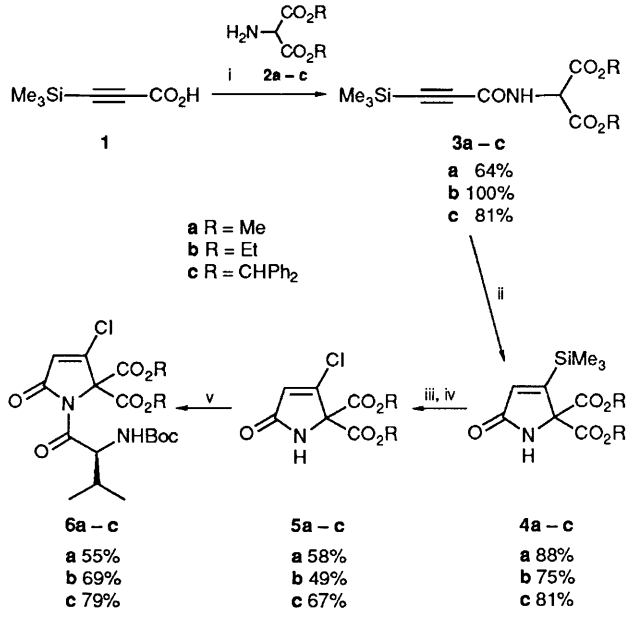
A novel chiral oxycarbonyl rearrangement from carbon to nitrogen was observed and its mechanism is reported.

During a synthetic study towards the antibiotic FR900148,[1–3] we found a novel chiral oxycarbonyl rearrangement. The starting compounds **6a–c** for the rearrangement were prepared as shown in Scheme 1. Acylation of aminomalonates **2a–c** with trimethylsilylprop-2-ynoic acid **1**, followed by cyclization using modified Johnson conditions,[4] gave the desired pyrrolidine derivatives **4a–c** in good yields. Treatment of **4a–c** with chlorine in the presence of *N*-chlorosuccinimide (NCS), followed by treatment with tetrabutylammonium fluoride in tetrahydrofuran (THF), gave the corresponding vinyl chloride derivatives **5a–c** in moderate yields. The structure of **5b**‡ was confirmed by single crystal X-ray analysis as shown in Fig. 1(*a*). *N*-acylation with *N*-Boc-L-valine (Boc = butoxycarbonyl) was carried out by the activated ester method to give the starting compounds **6a–c**.



Scheme 1 *Reagents and conditions*: i, DCC (1.05 equiv.) in CH_2Cl_2; room temp. overnight; or DMF (1.3 equiv.), $POCl_3$ (1.3 equiv.), **1** (1 equiv.), in THF, 0 °C, 30 min; then **2b** (1 equiv.), in aq. THF, at pH 7–7.5, 0 °C, 30 min; ii, $LiN(SiMe_3)_2$ (1.1 equiv.), −78 °C, 20 min; then CuI (1.1 equiv.), TMEDA (1.2 equiv.), −78 °C, 20 min; then Me_3SiCl (1.2 equiv.), room temp. overnight; iii, Cl_2 (4 equiv.), NCS (1 equiv.), in CCl_4–CH_2Cl_2, 0 °C–room temp. 3.5 h; iv, Bu_4NF (2 equiv.), in THF, −78 °C, 20 min; v, NaH (1.2 equiv.), in THF, room temp. 3h; then Boc-L-Val-ONb[5] (1.5 equiv.), room temp. (overnight), reflux (30 min), (DCC = dicyclohexylcarbodiimide, DMF = dimethylformamide, TMEDA = tetramethylethylenediamine, ONb = 5-norbornene-2,3-dicarboxymidoxy)

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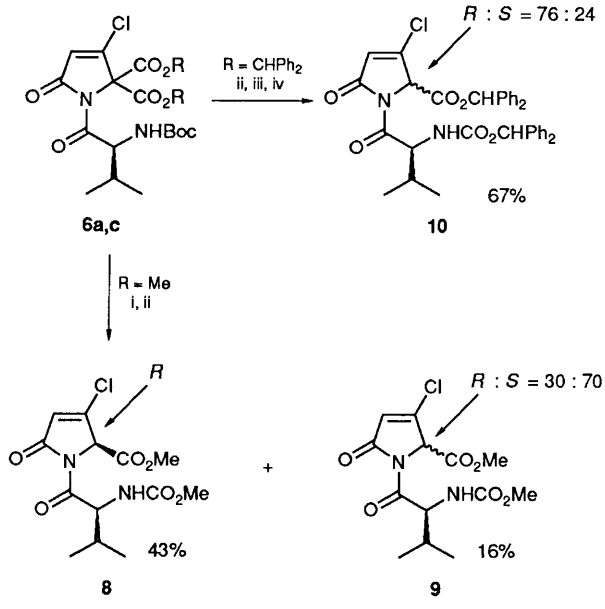
‡ *Crystal data* for: **5b** $C_{10}H_{12}ClNO_5$, monoclinic, $P2_1/c$, M_r = 261.66, a = 11.085(2), b = 7.634(1), c = 14.385(3) Å, β = 91.08(3)°, V = 1217.1(3) Å^3, Z = 4, D_x = 1.429 g cm^{-3}, T = 295 K. R = 0.075 after refinement of 158 parameters from 3678 independent reflections. **8** $C_{13}H_{17}ClN_2O_6$, monoclinic, $P2_1$, M_r = 332.74, a = 10.690(15), b = 9.647(3), c = 7.595(7) Å, β = 92.45(15)°, V = 782.5(14) Å^3, z = 2, D_x = 348 g cm^{-3}, T = 295 K. R = 0.105 after refinement of 199 parameters from 1905 independent reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Novel chiral oxycarbonyl rearrangement from carbon to nitrogen occurred upon selective removal of the Boc moiety from **6a–c** as shown in Scheme 2. Treatment of **6a** with trifluoroacetic acid (TFA) in CH_2Cl_2 in the presence of anisole, followed by neutralization,§ gave spontaneously the *R*-ester **8** in 43% yield as crystals, whose structure was determined by single crystal X-ray analysis‡ as shown in Fig. 1(*b*). An inseparable mixture of *R*- and *S*-esters **9** was obtained from the mother liquors in 16% yield, for which the *R* and *S* ratio was 30:70 by HPLC; total selectivity of the *R*-ester **8** was 81% in 59% chemical yield. In the case of benzhydryl ester **6c**, deprotection was carried out with Me_3SiI. Neutralization followed by treatment with silica gel gave an inseparable *R,S* mixture **10** in 67% yield, for which the *R* and *S* ratio was determined as 76:24 by HPLC.

This reaction was initiated by nucleophilic attack of the primary nitrogen to the carbonyl carbons. Unusual carbon–carbon bond cleavage subsequently occurred to generate a



Scheme 2 *Reagents and conditions*: i, TFA, anisole, in CH_2Cl_2 room temp. 1.5 h; ii, extraction with EtOAc at pH 7.5; iii, Me_3SiI (1.5 equiv.), in CH_2Cl_2, 0 °C, 15 min; iv, silica gel, Et_2O, room temp. overnight

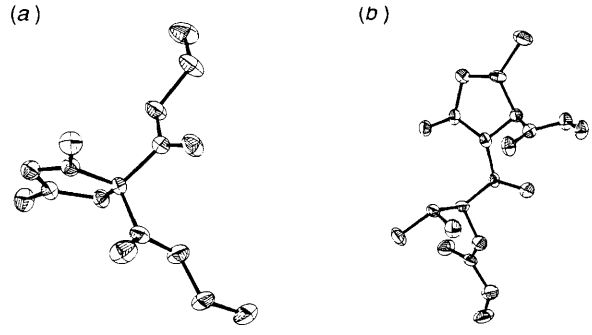


Fig. 1 (*a*) Single crystal X-ray structure of **5b**; (*b*) single crystal X-ray structure of **8**

§ The neutralization was necessary for the rearrangement.

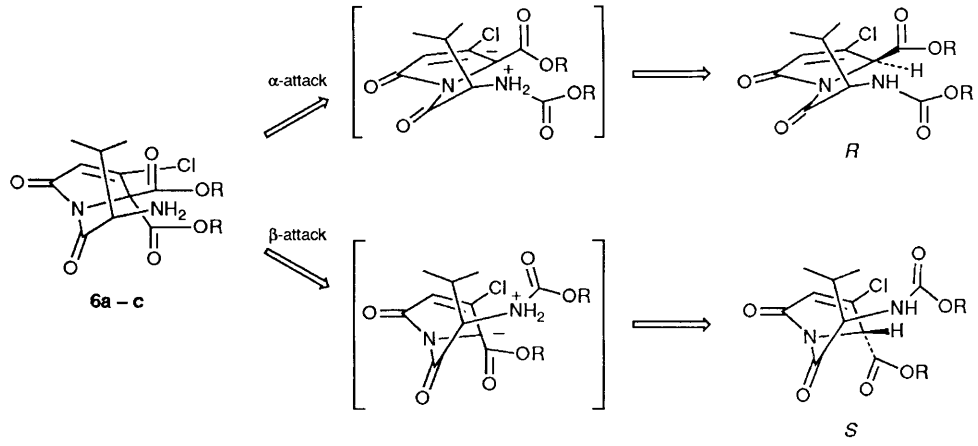


Fig. 2 Reaction pathway for novel oxycarbonyl rearrangement

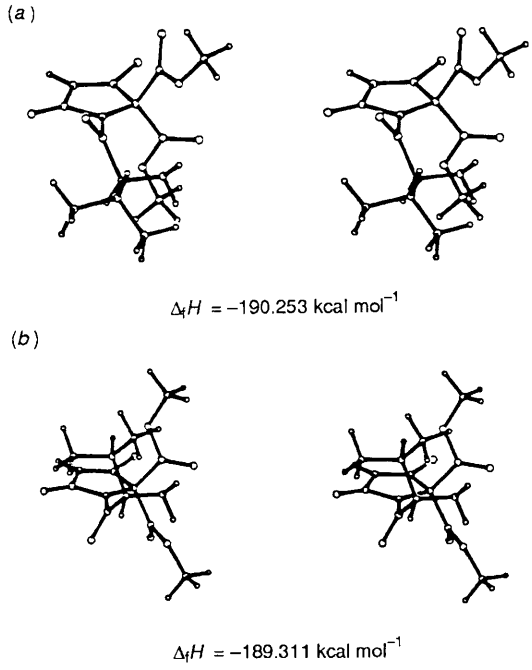


Fig. 3 (*a*) Stereoview of conformer *A*; (*b*) stereoview of conformer *B* (MNDO calculations)

highly stabilized carbanion, which would be immediately protonated from the resultant oxycarbonylammonium species, as shown in Fig. 2. Therefore, the stereochemistry at the newly formed chiral centre would be determined by the orientation of nucleophilic attack of the free nitrogen. In order to determine this orientation, we attempted an MNDO conformational analysis. In the case of attack at the α-carbonyl carbon, a chair-like conformer (*A*), containing the bulky isopropyl moiety (Pr^i) in a pseudoequatorial orientation, is the most favoured conformation and leads to the *R*-ester. In the case of attack at the β-carbonyl carbon, a chair-like conformer (*B*) containing Pr^i in a pseudoaxial orientation is the preferred one and leads to the *S*-ester. Their MNDO-calculated optimized conformations and heats of formation are shown in Fig. 3 (*a*) and (*b*). As a result, *A* is the most favoured conformation, and the energy difference between *A* and *B* was calculated to be 0.942 kcal mol^{-1} (1 cal = 4.184 J). This energy difference corresponds well with the stereoselectivity (*ca.* 80% at room temp.) in this reaction.

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