Tetrahedron Letters,Vol.30,No.52,pp 7457-7460,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC SYNTHESIS OF PROTECTED α-FLUOROGLYCINES

Patrick D Bailey,* Andrew N Boa, Gavin A Crofts
Maria van Diepen, Madeleine Helliwell, Robert E Gammon
and Michael J Harrison

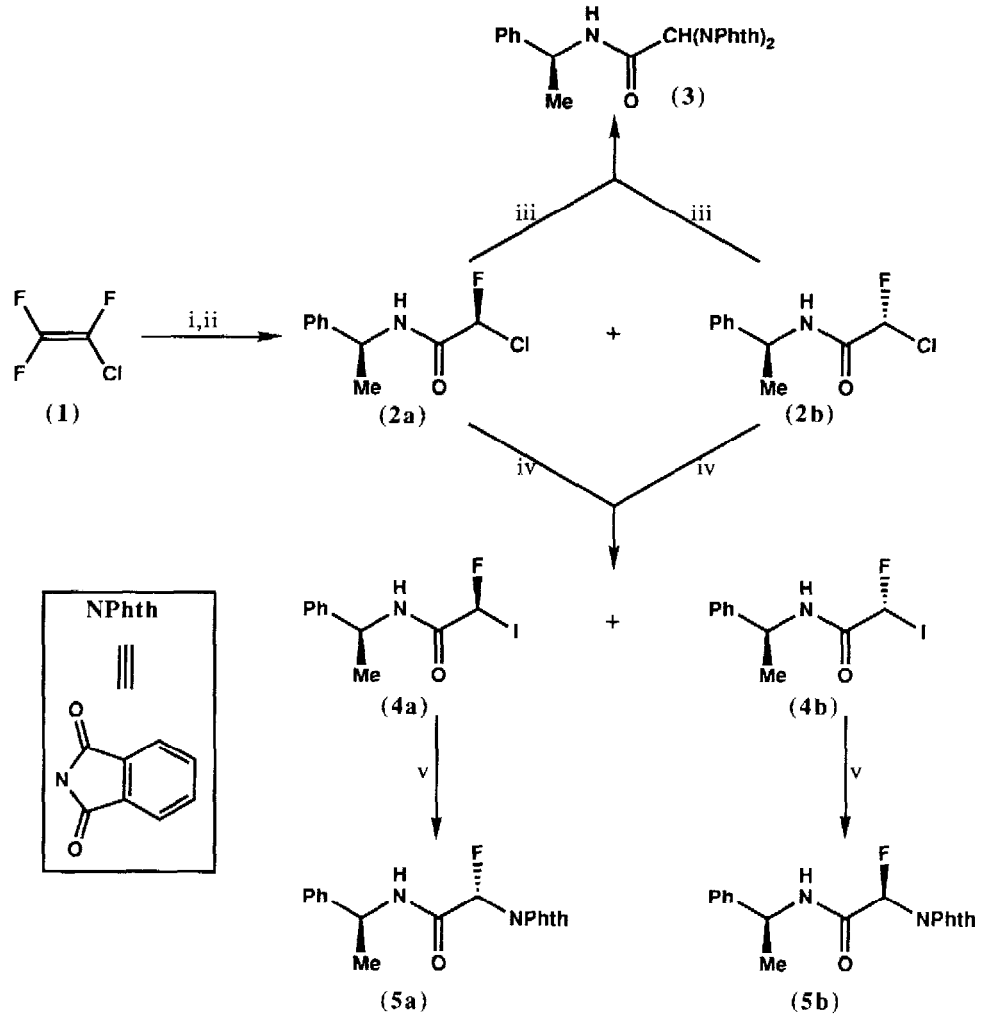
Department of Chemistry, University of York,
Heslington, York YO1 5DD

Summary. Single crystal x-ray structure determination of a key fluoroiodoacetamide gives access to protected α-fluoroglycines of known absolute stereochemistry.

Fluorinated amino acids have been a major synthetic target of medicinal chemists because of the pharmacological potential of these molecules, and of peptides that incorporate them.[1] Nevertheless, there has been no success in the preparation either of free amino acids or of peptides that have been fluorinated at the α-position. This observation is not surprising for amino acids, for which the nitrogen lone pair might be expected to induce the rapid displacement of fluoride ion;[2] but conjugation of the nitrogen (for example, to a carbonyl group) should increase the stability of these compounds, making them viable synthetic targets. Recent results from Takeuchi et al on multifunctional carbons has revealed one route to such molecules from polysubstituted acetates.[3] We report herein an extremely simple asymmetric synthesis of protected α-fluoroglycines, utilising readily prepared chiral fluoroiodoacetamides.

At first, we had hoped that protected α-fluoroglycines might be directly accessible from the chlorofluoroacetamides (2a/b), prepared using the method of Molines and Wakselman by reaction of chlorotrifluoro--ethene (1) with (S)-1-phenylethylamine, followed by acidic hydrolysis of the resulting fluoro-imine.[4] Separation of the diastereoisomers was initially achieved by careful crystallisation, but flash chromatography[5] (silica) using benzene/ethyl acetate (9:1) as eluant was found to be more

efficient, yielding (2a) (R_F 0.55, m.p. 74-75°C) and (2b) (R_F 0.47, m.p. 52-55°C) as white crystalline solids (c.f. ref. 4).[6] Stereochemical assignment was based on a single crystal x-ray structure determination on the higher R_F component.[7]



Scheme. Reagents: i, (S)-PhCH(Me)NH_2/ Et_2O/ Sealed tube/ r.t./ 140h; ii, 10% H_2SO_4(aq)/ reflux/ 2h (33% overall for i and ii); iii, KNPhth/ DMF/ >40°C; iv, NaI/ Me_2CO/ reflux/ 120h (92%); v, KNPhth/ DMF/ r.t./ 5-6h (50%).

We were disappointed that the chlorofluoroacetamides (2a/b) failed to generate protected α-fluoroglycines when reacted with potassium phthalimide, with the dipththalimide (3) being the only product formed. On the assumption that this must have been generated *via* the desired monophthalimide derivatives, we decided to replace the chlorine with a better leaving group, so that less forcing conditions might be employed. Accordingly, treatment of either (2a) or (2b) with NaI in acetone gave the same mixture (ca. 50:50) of diastereomeric fluoroiodoacetamides (4a/b), which could be readily separated by flash chromatography (silica) using benzene/ethyl acetate (9:1). X-ray crystallography on the higher R_F component[7] enabled the stereochemistries to be assigned as (S,S) for (4a) (R_F 0.59, m.p. 83-84°C), and hence (S,R) for (4b) (R_F 0.51, m.p. 59-61°C).

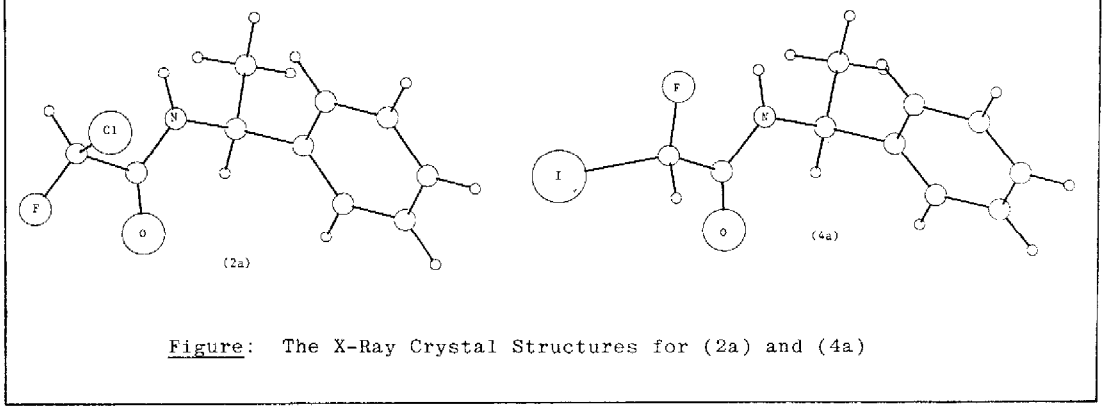


Figure: The X-Ray Crystal Structures for (2a) and (4a)

Treatment of the fluoroiodoacetamides (4a) or (4b) with potassium phthalimide in DMF at room temperature gave, as the major products, the monophthalimides (5a) and (5b) respectively.[8] On the assumption that the formation of (5a) and (5b) proceeded *via* S_N2 pathways,[9] we could infer that (S,S)-(4a)⟶(S,S)-(5a), and that (S,R)-(4b)⟶(S,R)-(5b) [10]. Pure (5a) (m.p. 163-165°C) and (5b) (m.p. 146-148°C) could be obtained by recrystallisation and/or flash chromatography.

The readily prepared chiral fluoroiodoacetamides (4a and 4b) are therefore valuable intermediates for the preparation of α-fluoroglycine derivatives of known absolute stereochemistry, and we are currently investigating whether α-fluoroglycyl peptides are accessible using this methodology.

We thank Dr. T.A. Dransfield, Mr. B. Glennie and Mrs. B. Chamberlain for NMR and mass spectra, S.E.R.C. for an earmarked quota award, and the Yorkshire Cancer Research Campaign for a Career Development Award (to PDB).

REFERENCES AND NOTES

1. For recent reviews, see J. Mann, Chem. Soc. Rev., 1987, 16, 381, and J.T. Welch, Tetrahedron, 1987, 43, 3123.

2. Although most amines are predominantly protonated at pH < 9, it is likely that the presence of small amounts of free amine in equilibrium would cause decomposition of α-fluoroamines at most pHs.

3. Y. Takeuchi, M. Asahina, K. Nagata, and T. Koisumi, J. Chem. Soc., Perkin Trans. I, 1988, 1149, and references therein.

4. H. Molines and C. Wakselman, Synthesis, 1984, 84, 838.

5. W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, 43, 2923.

6. All compounds were homogeneous by HPLC and/or TLC, and showed satisfactory spectral data including high resolution mass spectra.

7. Crystal data for (2a): $C_{10}H_{11}ClFNO$, M = 215.7, orthorhombic, space group $P2_12_12_1$, a = 5.418, b = 12.030, c = 15.387 Å, U = 1032.23 Å^3, Z = 4, D_c = 1.39 gcm^{-3}, μ(Cu-K$_\alpha$) = 30.14 cm^{-1}. Using Cu-K$_\alpha$ radiation (λ = 1.5418 Å), and the ω/2θ scan mode (2θ ≤ 100°), a total of 684 unique reflections were measured. The structure was solved for all non-hydrogen atoms by direct methods using MULTAN86 (with SAYTAN option),[11] and was refined using SHELX76,[12] converging at R = 0.0645 (R_w = 0.0712) for the correct isomer, and R = 0.0753 (R_w = 0.0866) for the enantiomer.

Crystal data for (4a): $C_{10}H_{11}FINO$, M = 307.1, monoclinic, space group $P2_1$, a = 5.264, b = 8.309, c = 13.227 Å, β = 94.161°, U = 577.01 Å^3, Z = 2, D_c = 1.77 gcm^{-3}, μ(Mo-K$_\alpha$) = 25.6cm^{-1}. Using Mo-K$_\alpha$ radiation (λ = 0.71069 Å), with the ω/2θ scan mode (2θ ≤ 54°), a total of 1272 unique reflections were measured. The iodine atom was located from a Patterson synthesis, and the remaining non-hydrogen atoms were located by successive difference maps. Refinement using SHELX76[12] converged at R = 0.0476 (R_w = 0.0552) for the correct isomer, and R = 0.0515 (R_w = 0.0591) for the enantiomer (this relatively small difference in R values probably being due to the proximity of the iodine to the origin).

Both structures were solved using data collected on a specially upgraded Hilger and Watts 4-circle diffractometer. All data were corrected for absorption/Lorentz-polarisation effects, and have been deposited at the Cambridge Crystallographic Centre.

8. The crude α-fluoroglycine derivatives (5a) and (5b) were always contaminated with ca. 15% of their epimers [i.e. crude (5a) contained ca. 15% of (5b) and *vice versa*]. As small amounts of recovered starting materials showed 0% d.e. [i.e. equal amounts of (4a) and (4b)], we concluded that iodide generated during the reaction caused some epimerisation of the starting material.

9. Gabriel's reagent generally proceeds via the S_N2 pathway, leading to inversion of configuration - see M.S. Gibson and R.W. Bradshaw, Angew. Chem. Int. Ed., 1968, 7, 919 (especially pp. 920-921, and references therein). As the auxiliary did not influence the stereochemical outcome of the reaction [i.e. (4a)→(4b) but (4b)→(5b)], and as there are no reported cases of retention of configuration from similar Gabriel transformations, it seems certain that inversion must have occurred.

10. i.e. Inversion, although the R/S notation is unaltered because of priority rules.

11. T. Debaerdemaeker, C. Tate, and M.M. Woolfson, Acta Crystallogr., Sect. A, 1985, A41, 286.

12. G.M. Sheldrick, SHELX76, Program for Crystal Structure Determination, University of Cambridge, 1976.

(Received in UK 2 November 1989)