Pergamon

Tetrahedron Letters 39 (1998) 7755–7758

TETRAHEDRON LETTERS

Synthesis of α-Heterosubstituted Glycine Derivatives from Dihaloethanamides

Patrick D. Bailey,[a] S. Richard Baker,[b] Andrew N. Boa,[c] Joanne Clayson,[a] and Georgina M. Rosair[a]

[a] *Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, UK EH14 4AS*
[b] *Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, UK GU20 6PH*
[c] *Department of Chemistry, Hull University, Hull, UK HU6 7RX*

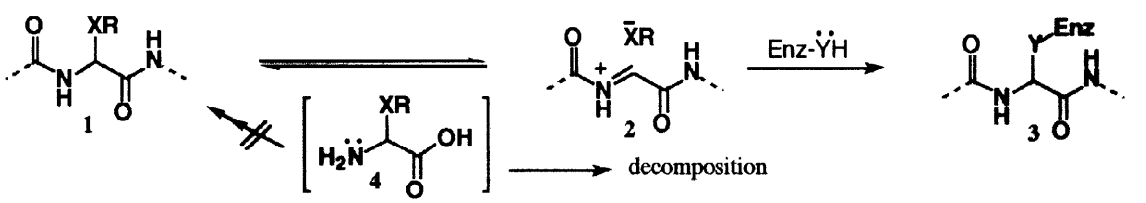
Received 30 June 1998; accepted 3 August 1998

Abstract

A range of protected α-heterosubstituted analogues of glycine were synthesised from starting materials of the type CHFX-CONHR [X = Cl, Br, I; R = CH_2Ph, (*S*)-CHMePh]; the final products included derivatives of glycine possessing *N*, *O*, *F* or *S* in the α-position, and the first example of a free α-fluoro-α-amino acid (α-fluorobetaine) whose structure was confirmed by X-ray crystal structure determination.

Keywords: amino acids and derivatives, peptide analogues/mimetics

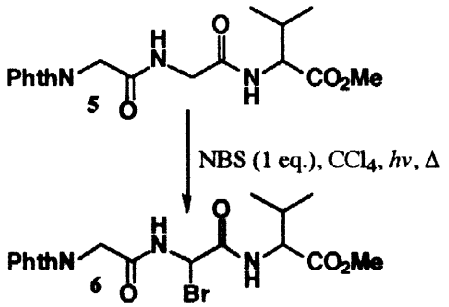
Peptides in which the α-position of one of the residues is substituted with a heteroatom group (XR) have important pharmaceutical potential; whilst they can closely mimic a parent peptide and hence bind to an enzyme or receptor, the heteroatom can be readily displaced and the resulting acyl iminium intermediate trapped, thereby blocking the enzyme or receptor (Scheme 1). Access to such compounds is not trivial, as the parent amino acids are inherently unstable, so that standard peptide synthesis is not viable.



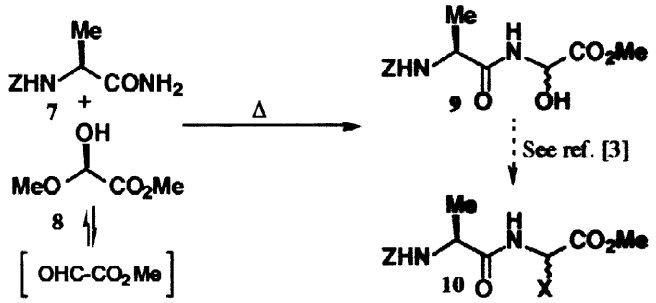
Scheme 1 The pharmacological potential of α-hetero-substituted peptides.

Synthetic progress to these targets has been made by brominating amino acids in the α-position after peptide bond formation (Scheme 2) [1], and by the coupling of some amino acid amides to reactive glyoxamide derivatives (Scheme 3) [2]. However, the number of ways of accessing such compounds is somewhat limited [3], and we therefore explored the possibility of extending our work on α-fluoroglycine derivatives [4], to provide routes to a wider range of α-hetero-substituted glycine derivatives.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01658-X

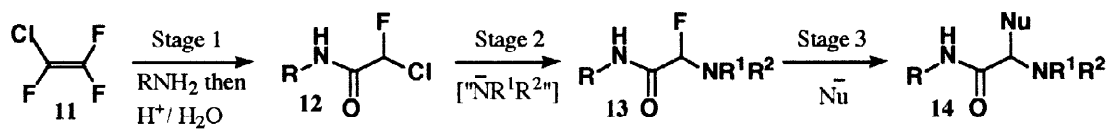


Scheme 2 Route to α-bromo-peptides [1].



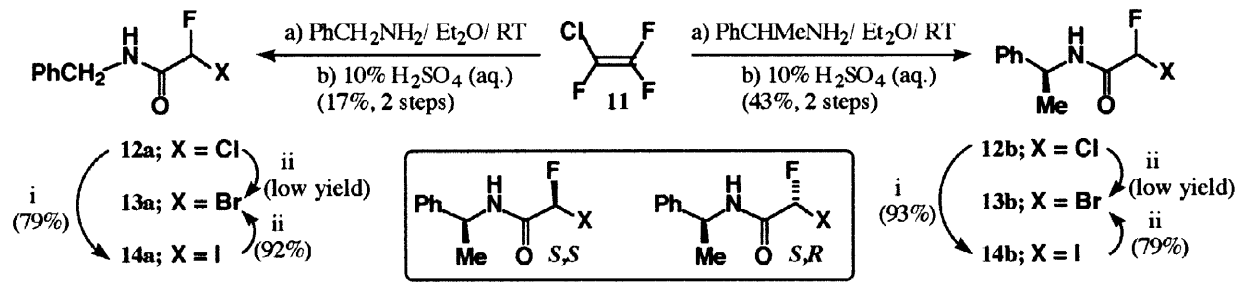
Scheme 3 Route to α-hydroxypeptides [2].

Our basic strategy is outlined in Scheme 4. The first stage [5] involved formation of chlorofluoroethanamide derivatives **12**; the differential leaving group ability of the halogens was to be exploited in subsequent S_N2 reactions, and we also planned to replace the chlorine with other leaving groups. The second stage involved displacement of the more labile halogen with an *N*-nucleophile, to generate the glycine skeleton **13**, followed by displacement of the fluorine by a second nucleophile. An important feature of this approach was the ease with which the absolute stereochemistry might be controlled, by simply replacing benzylamine by α-methylbenzylamine in the first step, and separating the diastereoisomers at some stage in the synthesis.



Scheme 4 The proposed route to protected α-hetero-substituted glycine derivatives.

We decided to prepare a range of dihaloethanamides, so that we could try to match them with appropriate nucleophiles, and to explore the possibilitites for stereocontrol. The optimised reactions are summarised in Scheme 5. All of the halogen exchange reactions proceeded without diastereocontrol [i.e. single diastereomeric starting materials such as (*S,S*)-**12b** gave *ca* 50:50 diastereomeric products (*S,S*)- and (*S,R*)-**13b**]; however, all of the diastereoisomeric products **12b/13b/14b** were separable by flash chromatography. The stereochemistry of (*S,S*)-**12b** and (*S,S*)-**14b** had already been determined by single crystal X-ray structure determinations [4]; for the bromo-analogue **13b**, its synthesis from (*S,S*)-**14b** was quenched at various time intervals, and ^1H NMR spectra showed one predominant diastereoisomer of **13b** early in the conversion, which was assigned as the (*S,R*)-isomer due to S_N2 inversion.



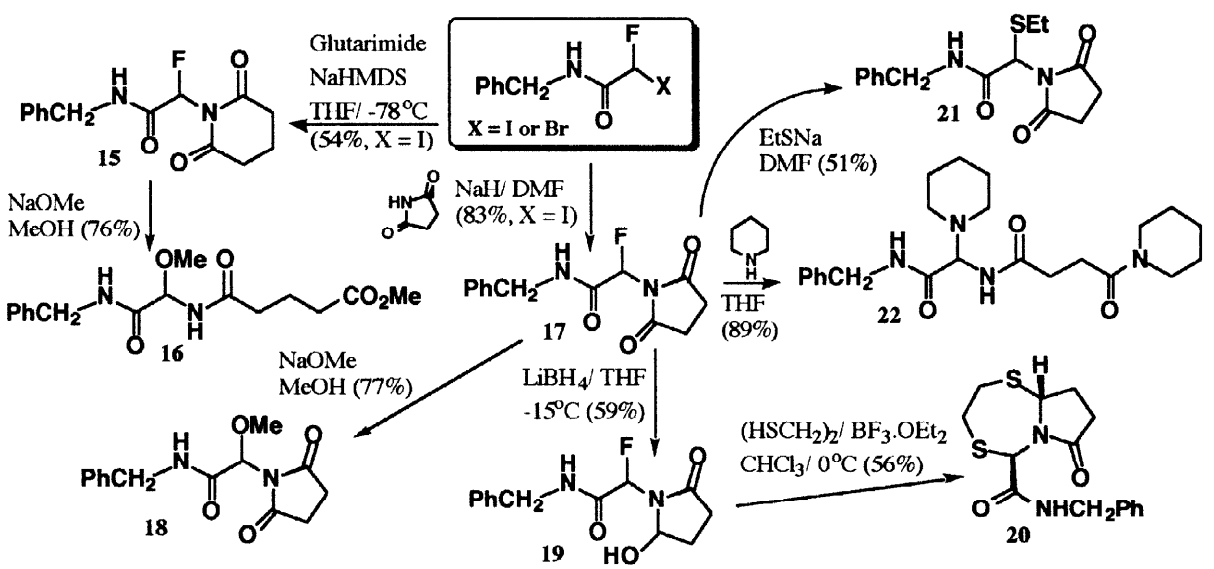
Scheme 5 The formation and interconversion of α,α-dihaloethanamide derivatives.
Conditions: i) NaI (8 eq.), Me_2CO, reflux; ii) EtBr (70 eq.), NaBr (0.2 eq.), NMP, 40°C [6].

Usefully, a range of other physical data demonstrated reliable correlation with stereochemistry for all of the dihaloethanamides, as summarised in Table 1. Such correlations may prove valuable for the assignment of absolute stereochemistry to chiral amines derivatised as the (*R*)- or (*S*)-dihaloethanamides, and Takeuchi has been developing similar multifunctionalised compounds for this purpose [7,8]; it is worth noting that compounds such as **12a/b** can be converted into the acid chlorides with retention of optical integrity [5].

	(*S*,*S*)-**12b**	(*S*,*R*)-**12b**	(*S*,*S*)-**13b**	(*S*,*R*)-**13b**	(*S*,*S*)-**14b**	(*S*,*R*)-**14b**
R_f[a]	0.47	0.41	0.49	0.42	0.53	0.43
m.p. (°C)	74-75	52-55	79-80	oil	83-84	59-61
δ_H (α-H)	6.24	6.27	6.57	6.60	7.11	7.14
δ_F	-144.19[b]	-144.05[b]	-148.31	-148.23	-157.12	-157.04
δ_C (α-C)	94.14	94.18	84.55	84.63	62.35	62.39
δ_C ($CHCH_3$)	49.21	49.05	49.24	49.01	49.19	48.91
δ_C ($CHCH_3$)	21.13	21.30	21.02	21.38	20.70	21.41

Table 1 Data for diastereoisomers of **12-14b**. [a] Silica, PhH/EtOAc 9:1 [b] ^{35}Cl isomer (^{37}Cl isomer peak also seen, Δδ 0.01)

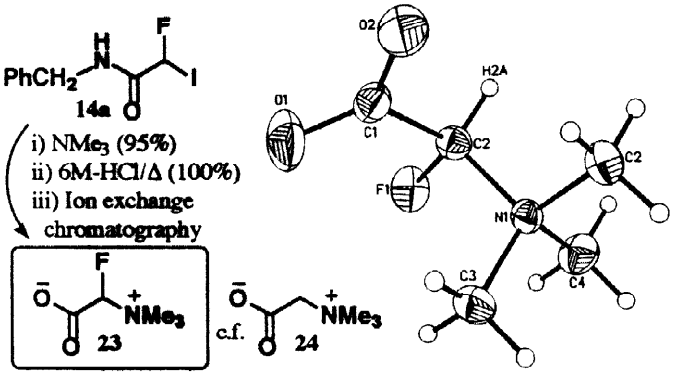
With the dihaloethanamides **12-14a/b** in hand, displacement reactions to generate protected α-fluoroglycine derivatives were studied, and the results for the *N*-benzyl derivatives are summarised in Scheme 6. In particular, it is noteworthy that our approach provides short, efficient routes to a range of derivatives of this type (including *N*, *O*, *F*, and *S* analogues), and that straightforward extension to peptides should be possible.



Scheme 6 Transformations of **13a/14a** into α-substituted α-amino acid derivatives (all RT unless otherwise stated).

Fluorinated analogues of amino acids and peptides have been studied extensively, primarily because the small highly electronegative fluorine atom can significantly affect the medicinal properties [9]. Whilst there are examples of α-amino acids and peptides fluorinated in the side-chain, there are no reports of α-fluorinated α-amino acids or peptides. The latter derivatives may be particularly valuable because of their potential effect on the α-amino and α-carbonyl groups, and examples of protected α-fluoro amino

acids have been prepared [10]; unfortunately, free α-fluoro α-amino acids have never been isolated, presumably due to spontaneous decomposition (see Scheme 1). We were keen to see if it were possible to prepare α-fluoroglycine derivatives by our dihaloethanamide route, but our earlier results indicated that this might be impossible.



Scheme 7 Synthesis of **23**.

Figure 1 X-ray structure of **23**.

Bond lengths (Å)		Bond angles (°)	
F(1)-C(2)	1.372(3)	F(1)-C(2)-N(1)	105.9(2)
N(1)-C(2)	1.514(3)	F(1)-C(2)-C(1)	110.2(2)
O(1)-C(1)	1.228(3)	N(1)-C(2)-C(1)	113.3(2)
O(2)-C(1)	1.228(3)	O(2)-C(1)-O(1)	128.9(2)

Table 2 Selected X-ray data for **23**.

Consequently, we decided to explore whether α-fluorobetaine **23** might be prepared, in which there is no nitrogen lone pair available to displace fluoride ion. This target was attractive for two reasons. Firstly, the betaine **24** is of biological and medicinal importance, as it is the methylating agent in the biosynthesis of methionine. Secondly, the *N*-termini of peptides are protonated at physiological pH; peptides containing *N*-terminal betaine would therefore mimic glycyl-peptides in terms of charge and side-chain.

Our synthesis of α-fluorobetaine is summarised in Scheme 7, and was surprisingly straightforward given that there are no such compounds in the literature. The X-ray crystal structure of **23** (Figure 1) confirmed the synthesis of this unusual amino acid, and provided some interesting structural observations (see Table 2 - c.f. betaine **24** [11]).

These results provide a flexible entry to wide range of α-heterosubstituted glycine derivatives, including access to chiral targets by use of *N*-1-phenylethyl derivatives.

We thank Dr A S F Boyd and Dr R Ferguson for NMR and mass spectra, and EPSRC and Lilly Research for financial support.

References

[1] Easton CJ, Hutton CA, Rositano G, Tan EW. J. Org. Chem. 1991;56:5614.
[2] Shiono S, Harada K. Bull. Chem. Soc. Jpn. 1985;58:1061.
[3] Bailey PD, Clayson J, Boa AN. Contemporary Org. Syn. 1995;2:173.
[4] Bailey PD, Boa AN, Crofts GA, Van Diepen M, Helliwell M, Gammon RE, Harrison MJ. Tetrahedron Lett. 1989;30:7457.
[5] Molines H, Wakselman C. Synthesis 1984;84:838.
[6] Willy WE, McKean DR, Garcia BA. Bull. Chem. Soc. Jpn. 1976;49:1989.
[7] Takeuchi Y, Itoh N, Kawahara S-I, Koizumi T. Tetrahedron 1993;49:1861.
[8] Takeuchi Y, Itoh N, Koizumi T, Yamaguchi K. J. Org. Chem. 1993;58:1812.
[9] Welch JT. Tetrahedron 1987;43:3123.
[10] Takeuchi Y, Nabetani M, Takagi K, Hagi T, Koizumi T. J. Chem. Soc., Perkin Trans. 1 1991:49.
[11] Mak TCW. J. Mol. Struct. 1990;220:13.

Footnote: Crystal data – colourless crystal (0.4 x 0.35 x 0.3 mm) from water, $C_5H_{10}FNO_2$, M = 135.14, monoclinic, space group $P2_1/n$, a = 5.7708(4), b = 10.9160(9). c = 10.6794(8) Å, β = 105.550(6)°, V = 648.11(9) Å^3, Z = 4, D_C = 1.385 g cm^{-3}, μ = 0.123 mm^{-1}, absorption corrections (ψ scans) were applied; $R1$ = 0.0439, $wR2$ = 0.0951 and goodness of fit 1.057 for 783 unique observed data and 82 parameters. Full data has been deposited with the Cambridge Crystallographic Data Centre.