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O-Perfluoroalkylation of 4-hydroxyphenylglycine

Short Communication

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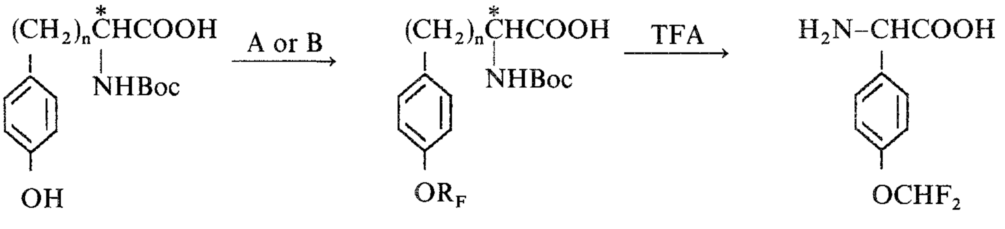
Summary. Racemic N-Boc-4-difluoromethoxyphenylglycine was prepared by O-difluoromethylation of D-N-Boc-4-hydroxyphenylglycine under basic conditions, whereas the hexafluoropropylation reaction gives optically pure D-N-Boc-4-hexafluoropropoxyphenylglycine. D,L-4-difluoromethoxyphenylglycine was obtained by the action of TFA on the corresponding amino acid derivative.

Keywords: Amino acids – Polyfluoroalkylation – 4-Hydroxyphenylglycine

Introduction of polyfluoroalkoxy groups of different sizes modifies the lipophilicity of amino acid residues (Galushko et al., 1991). In our recent paper, (Kolycheva et al., 1991), it was shown that O-polyfluoroalkylation of N-protected L-tyrosine (**1**) is a convenient preparative method for obtaining optically pure ($>99\%$ e.e.) 4-polyfluoroalkoxy containing phenylalanines (**3**a, b) (see scheme), suitable for peptide synthesis.



1,**2** 3a,b; 4a,b **5**

A: $CHClF_2$, 50% KOH, 70°C
B: $CF_3CF=CF_2$, H_2O, Et_3N, 75°C
n = 1 (L-**1**, L-**3**); n = 0 (D-**2**, D,L-**4**a, D-**4**b)

$R_F = CHF_2$ (a), CF_3CFHCF_2 (b)

In order to explore the possibilities of the obtaining of the optically active polyfluoroalkoxy containing phenylglycines (**4a**, b), we have investigated O-polyfluoroalkylation reactions of D-N-Boc-4-hydroxyphenylglycine (**2**). It was found, that in contrast to tyrosine (**1**), phenylglycine (**2**) was completely racemized under the difluoromethylation conditions whereas amino acid (**4b**) was formed in optically active form (> 95% e.e.). The optical purity of the compounds (**4a**, b) was determined with by n.m.r spectrometry application chiral shift reagent Eu(hfc)$_3$.

The different stability of tyrosine and phenylglycine derivatives to racemization under the difluoromethylation conditions can be explained by the greater mobility of the α-proton, since in the case of phenylglycine it is also a benzyl proton.

N-Protected amino acids (4a, b) are oily substances which were purified by silica gel column chromatography (chloroform, R_f 0.15–0.20). Phenylglycine (**5**) was prepared by action TFA on (4a).

Materials and methods

Starting substance (**2**) was prepared by the action of Boc$_2$O on D-4-hydroxyphenylglycine and was purified by silica gel column chromatography. NMR ^{1}H and ^{19}F spectra were recorded using a spectrometer Bruker WP-200 (200 and 188.28 MHz respectively) with TMS and CFCl$_3$ as an internal standard respectively. TLC was carried out using Silufol UV-254 plates.

D,L-N-Boc-4-difluoromethoxyphenylglycine (4a)

The mixture of 1.5 g N-protected amino acid (**2**), 10 ml i-PrOH, 17 g KOH and 20 ml H$_2$O was stirred and heated to 70°C and excess of CHClF$_2$ bubbled through the mixture for 30 min. Then reaction mixture was then cooled and diluted to 100 ml with water. After acidification to pH 4 with 10% aqueous NaHSO$_4$ the product was extracted by ethylacetate (3 x 20 ml). After drying (MgSO$_4$) the solvent was evaporated and residue was purified by silica gel column chromatography (chloroform). Yield 1.5 g (80%), m.p. 119–120°C decomp. (from heptane -ethylacetate 1 : 1). Found C 53.1; H 5.3; F 12.5. $C_{14}H_{17}F_2NO_5$. Required C 53.0; H 5.4; F 12.0. NMR^{19}F spectrum: δ(CDCl$_3$) 81.24d (CHF$_2$, J 74 Hz).

D-N-Boc-4(2-hydro-)perfluoropropoxyphenylglycine (4b)

At 75°C 25 g perfluoropropylene was bubbled through stirred solution of 2 g amino acid (**2**) in 3 ml Et$_3$N and 1 ml H$_2$O for 45 min. The reaction mixture was then treated as amino acid derivative (**4a**). Yield 1.34 g (43%). Found C 46.3; H 3.8; F 27.5. $C_{16}H_{17}F_6NO_5$. Required C 46.1; H 4.1; F 27.3. $[\alpha]_D^{20}$ −84.6° (CHCl$_3$, C 0.86). NMR ^{19}F spectrum: δ [(CD$_3$)$_2$CO] 74.75 m (3F, CF$_3$); 77.8d m and 80.1d m (2F, CF$_2$, J 144 Hz); 212.8 m (F, CHF).

D,L-4-Difluoromethoxyphenylglycine (5)

0.5 g (4a) was dissolved in 10 ml TFA. After one hour at 20°C excess of TFA was evaporated, the residue was dissolved in 10 ml H$_2$O and 2% aqueous NH$_4$OH was added to pH 5. Precipitate was filtered and dried. Yield 0.3 g (90%), m.p. 150–170°C decomp. Found C 49.6; H 4.3; F 17.7. $C_9H_9F_2NO_3$. Required C 49.8; H 4.2; F 17.5. NMR ^{1}H spectrum: δ (D$_2$O) 7.4d (2H, H$_{arom}$); 7.15d (2H, H$_{arom}$); 6.6 t (1H, CHF$_2$, J 73.2 Hz); 5.1 m (1H, α-CH). NMR ^{19}F spectrum: δ (D$_2$O) −80.8 d (CHF$_2$, J 73.2 Hz).

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