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Syntheses and lipophilicity measurement of N^{α}/*N*-terminus-1, 1-dihydroperfluoroalkylated α-amino acids and small peptides

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Abstract

(1,1-Dihydroperfluoroalkyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imides (**4**, $n = 0$–2) were synthesized and used to transfer the corresponding 1,1-dihydroperfluoroalkyl groups to the α-amino group of (L)tyrosine. The obtained N^{α}-2,2,2-trifluoroethylated (L)tyrosine (**6**, $n = 0$) was further used as the *N*-terminus in the solid phase peptide synthesis of leucine enkephalin analogue. The lipophilicity of the N^{α}-1,1-dihydroperfluoroalkylated (L)tyrosines (**6**, $n = 0$–2) and *N*-terminus-2,2,2-trifluoroethylated leucine enkephalin analogue (**7**), as well as the corresponding parent compounds, was measured.

Keywords: (1,1-Dihydroperfluoroalkyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imides; 1,1-Dihydroperfluoroalkylation; (L)Tyrosine analogue; Leucine enkephalin analogue; Distribution coefficient; Lipophilicity

1. Introduction

Bioavailability is a major concern for peptide based drugs because of their poor biomembrane passage and rapid metabolism in the circulation systems. Examples are the enkephalins, of which the metabolic degradation at all absorptive mucosae and within the body presents a significant barrier to the use of these peptides as drugs [1–4]. Another drawback of enkephalins is that they are too hydrophilic to be absorbed by the transcellular route resulting in poor transport properties [5,6].

To overcome these difficulties, various prodrugs and peptidomimetics, such as 4-imidazolidinone enkephalin analogues [7,8], cyclic and branched enkephalin analogues [9,10], the leucine enkephalin analogues containing unnatural amino acid(s) [11], and glycosylated enkephalin analogues [12,13], have been synthesized. These modifications resulted in the stabilization of enkephalins against different enzymes as well as an improved delivery across bovine BMEC monolayers [6–8,14] or Caco-2 cell monolayers [13,15].

Fluoroalkylation can substantially affect both chemical and physical properties of substrates. For example, because of the inductive effect of CF_3CH_2- group, the lone pair electrons on oxygen in CF_3CH_2OH are less available for hydrogen bonding with the aqueous phase than that in CH_3CH_2OH. Therefore, CF_3CH_2OH ($\log P$ 0.41) is more lipophilic than CH_3CH_2OH ($\log P$ −0.32) [16], though trifluoroethanol (pK_a 12.4) [17] is considerably more acidic than ethanol (pK_a 15.9) [18]. Based on this rationale, it was expected that the attachment of CF_3CH_2- group to the α-amino group of amino acids could change both nucleophilicity [19–22] and lipophilicity of the parent compounds, and possibly, improve their resistance to degradation caused by aminopeptidases.

In this paper, we present the syntheses of (1,1-dihydroperfluoroalkyl)phenyliodonium *N*,*N*-bis(trifluoromethylsulfonyl)imides $CF_3(CF_2)_nCH_2I(C_6H_5)N(SO_2CF_3)_2$ (**4**, $n = 0$–2) and the transfer of the corresponding fluoroalkyl moiety to the α-amino group of (L)tyrosine. The lipophilicity measurements of N^{α}-1,1-dihydroperfluoroalkylated (L)tyrosines (**6**, $n = 0$–2) and the *N*-terminus-2,2,2-trifluoroethylated leucine enkephalin analogue (**7**) are given and compared to that of the corresponding parent compounds.

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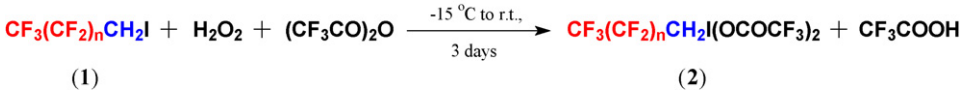


Scheme 1.

2. Results and discussion

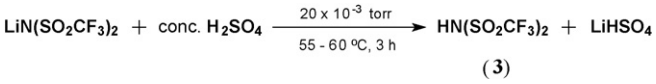
2.1. Preparation of (1,1-dihydroperfluoroalkyl)phenyliodonium N,N-bis(trifluoromethylsulfonyl)imides

Perfluoroalkyl aryliodonium salts were first synthesized by Yagupolskii et al. in the late 1970's [23]. In the early 1980's, Umemoto and Gotoh [24] synthesized perfluoroalkyl and 1,1-dihydroperfluoroalkyl aryliodonium triflates including (2,2,2-trifluoroethyl)phenyl iodonium triflate, which was later prepared using the modified method by Resnati [25] and used for *N*-trifluoroethylation of amino alcohols under dry conditions. In the late 1990's, DesMarteau and Montanari [19] introduced *N*,*N*-bis(trifluoromethylsulfonyl)imide into (2,2,2-trifluoroethyl)phenyliodonium salt to obtain a novel trifluoroethylating agent which has been used to transfer the 2,2,2-trifluoroethyl group to different nucleophiles in aqueous solutions [20–22]. Here, the higher homologues of this reagent are prepared and similarly utilized.

1,1-Dihydroperfluoroalkyl iodides (**1**, $n = 0$–2) were oxidized using hydrogen peroxide (50% aqueous solution) in the presence of excess trifluoroacetic anhydride to form the corresponding iodonium ditrifluoroacetates (**2**, $n = 0$–2) shown in Scheme 1.

N,*N*-Bis(trifluoromethylsulfonyl)imide (**3**) was obtained by sublimation from the corresponding lithium salt in concentrated H_2SO_4 under vacuum (Scheme 2).

The iodonium ditrifluoroacetates (**2**, $n = 0$–2) were reacted with sulfonamide (**3**) and benzene to form the desired 1,1-dihydroperfluoroalkylating agents (**4**, $n = 0$–2) by the elimination of trifluoroacetic acid and Friedel–Crafts like iodonium attachment to benzene ring (Scheme 3).



Scheme 2.

2.2. Preparation of N^{α}-1,1-dihydroperfluoroalkylated (L)tyrosines

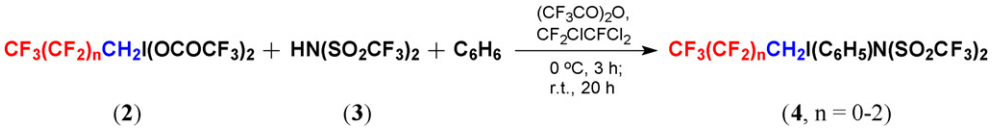
The reaction of (L)tyrosine methyl/ethyl ester with $CF_3(CF_2)_nCH_2I(C_6H_5)N(SO_2CF_3)_2$ (**4**, $n = 0$–2) in two phase solvents CH_2Cl_2/H_2O resulted in ester intermediates (**5**, $n = 0$–2). The esters were then cleaved by basic hydrolysis followed by acidification with conc. HCl to pH 4.5 to give N^{α}-1,1-dihydroperfluoroalkylated (L)tyrosines (**6**, $n = 0$–2) shown in Scheme 4.

2.3. Preparation of N-terminus-2,2,2-trifluoroethylated leucine enkephalin analogue

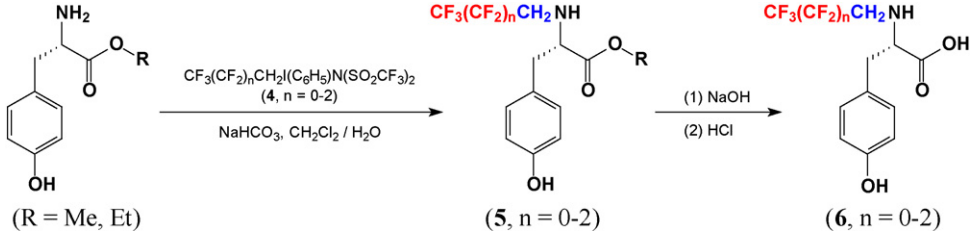
As shown in Scheme 5, Wang resin was used in the solid phase peptide synthesis. The 9-fluorenylmethyloxy carbonyl (Fmoc-) group was used as the N^{α}-protective group. (L)Leucine, (L)phenylalanine, glycine, and the second glycine were attached sequentially onto the Wang resin. N^{α}-2,2,2-trifluoroethylated (L)tyrosine (**6**, $n = 0$) was finally coupled to give the desired *N*-terminus-2,2,2-trifluoroethylated leucine enkephalin analogue (**7**) after the cleavage of pentapeptide from the Wang resin.

2.4. Preparation of N^{α}-ethylated (L)tyrosine

The reaction of (L)tyrosine methyl ester with $(CH_3CH_2)_3OBF_4$ resulted in the N^{α}-ethylated intermediate (**8**). The methyl ester was then cleaved by basic hydrolysis



Scheme 3.



Scheme 4.