α-Fluoromethyl Tryptophans via Imino Ene Reaction

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Abstract: A preparative simple synthesis of α-fluoromethyl tryptophans is described. The new method is based on a non-catalytic imine ene reaction of highly electrophilic imines derived from methyl bromodifluoro- and trifluoropyruvate, and 1-sulfonyl-3-methylene indolines.

Keywords: α-fluoromethyl substituted α-amino acids, tryptophans, 3-methylene indoles, fluorinated imines, ene reactions

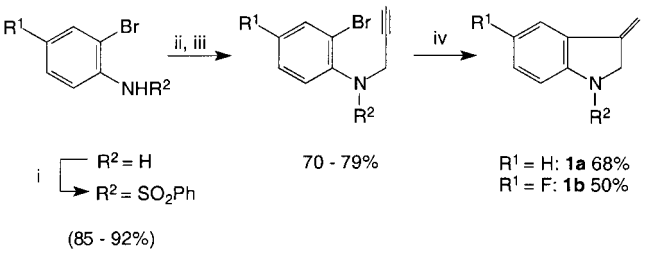
Indole amine 2,3-dioxygenase (IDO) is an interferon-γ-induced protein which is the first enzyme in the degradation pathway of tryptophan in macrophages and other cells.[1] Many inflammatory processes and neurodegenerative diseases have been linked to aberrant L-tryptophan metabolism effected by IDO hyperactivity.[2] It was found, that one class of competitive IDO inhibitors are tryptophan analogues, e.g. β-(3-benzofuranyl)- and β-[3-benzo(b)thienyl] alanines are exhibiting moderate inhibitory activity towards rabbit intestine IDO.[3] Recently it was demonstrated that 1-methyl-L-tryptophan is the most active inhibitor of IDO, known so far, being more active than its D-isomer.[3,4]

Aromatic L-amino acid decarboxylase (AADC) is a pyridoxal phosphate dependent enzyme responsible for the final step in the biosynthesis of both dopamine and seretonin via decarboxylation of L-dopa and L-5-hydroxytryptophan, respectively. In this context, the development of new effective antagonists of serotonin-producing enzymes (tryptophan hydroxylase and AADC), e.g. for chemotherapy of carcinoid tumors, caused by an overproduction of serotonin, is of current interest.[5] During the last two decades a number of α-fluoromethyl α-amino acids, like α-difluoromethyl ornithine,[6] attracted considerable attention of bioorganic and medicinal chemists, due to their ability to inhibit selectively pyridoxal phosphate dependent enzymes via a suicide-type mechanism.[7]

A number of methods for the synthesis of fluoroalkyl substituted tryptophans have been already reported.[5,8-11]

On the other hand, peptidomimetics bearing α-alkylated α-amino acids in strategical positions have recently emerged as important synthetic targets. They are used for the design of highly potent, proteolitically stable, conformationally restricted enzyme inhibitors.[12]

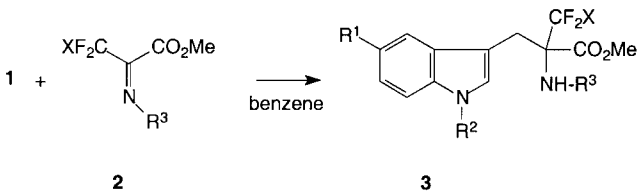
As part of our current investigations directed to the synthesis of new types of peptido-mimetics, we are developing general and highly efficient synthetic routes to non-natural,[13] especially fluorine-containing, conformationally constrained α-amino acids.[14] In connection with these studies, we wish to report herein a short, efficient access to α-bromodifluoromethyl and α-trifluoromethyl tryptophan derivatives, unknown so far. The high electron density of the trifluoromethyl group may be important in the formation of strong hydrogen bonds with enzymes, thereby blocking enzymatic metabolism of the natural substrates. This group is also attractive since it is relatively nontoxic and more stable than the mono- and difluoromethyl analogues.[15]



Scheme 1 Reaction conditions: (i) $PhSO_2Cl$/Py, THF, 80 °C, 2 h; (ii) NaH/DMF, 0 °C, 2 h; (iii) propargyl bromide/DMF, r.t., 8 h; (iv) Bu_3SnH/AIBN, benzene, 80 °C, 4-5 h.

3-Methylene-1-(phenylsulfonyl)indolines **1a**[16] and **1b**[17] (Scheme 1) obtainable in good yields in a three-step procedure starting from *ortho*-bromoanilines, which are commercially available with a vast variety of substituents at the aromatic ring, readily react with highly electrophilic imines derived from methyl bromodifluoro and trifluoropyruvates[18] in an ene-type reaction (Scheme 2, Table).

The *N*-phenylsulfonyl amines **1** easily react with sulfonylimines **2** derived from methyl trifluoropyruvate[19] at room temperature to give the protected tryptophan derivatives **3a-c**, **f**.[20] The progress of the reaction was monitored by ^{19}F NMR spectroscopy, to obtain optimal yields. Heteroaromatization of the indoline moiety to give the indole system is the driving force of the ene reaction. Since the starting material 3-methylene-1-(phenylsulfonyl)indoline **1** itself is susceptible to heteroaromatization,[21] protic solvents have to be avoided, because they readily catalyze this process. So far, best results were obtained using dry benzene.



2 3

Scheme 2

Table Synthesis of α-Fluoromethyl Tryptophans **3**

	X	R^1	R^2	R^3	Yield [%]
3a	F	H	SO_2Ph	SO_2Ph	98
3b	F	H	SO_2Ph	Ts	91
3c	F	H	SO_2Ph	SO_2Me	84
3d	F	H	SO_2Ph	Boc	50
3e	Br	H	SO_2Ph	Boc	39
3f	F	F	SO_2Ph	Ts	45

As expected, less electrophilic imines like **2d** and **2e** and **1** react only at elevated temperatures (80 °C). However, yields were low (18−24%), especially when equimolar amounts of the starting materials were used. Under these reaction conditions, *N*-phenylsulfonyl-3-methylindole, formed on heteroaromatization from **1** was the main product of the reaction. When starting materials **2d**/**2e** and **1** were treated in a 2:1 ratio at 60 °C and the progress of the reaction was carefully monitored by ^{19}F NMR spectroscopy, yields could be improved to 39-50%.

In conclusion, we have demonstrated that the imino ene reaction is a useful tool for the construction of α-trifluoromethyl and α-bromodifluoromethyl tryptophan derivatives. Experiments to adapt this methodology for the synthesis of a series of α-fluoroalkyl substituted heterocyclic α-amino acids as building blocks for the construction of new types of peptidomimetics and for modification of natural products are in progress.

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(17) 5-Fluoro-3-methylene indoline **1b** was unknown. ^1H NMR ($CDCl_3$) δ = 4.56 (t, J = 3.0 Hz, 2H, NCH_2), 5.02 (t, J = 2.4 Hz, 1H, *trans*-C = CH), 5.34 (t, J = 3.0 Hz, 1H, *cis*-C = CH), 7.0-7.9 ppm (m, 8H, Ar). ^{19}F NMR ($CDCl_3$) δ = -42.4 ppm (m, 1F).
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(20) **General procedure for the preparation of 3:** A mixture of 3-methylidene-*N*-(phenylsulfonyl)indoline **1** (0.4 mmol) and *N*-protected imine of pyruvate **2** (0.4 mmol) in 5 mL of benzene was stirred at r.t. (80 °C for **3d, e**). The solvent was removed in vacuo, and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether). Selected data for **3a**: ^1H NMR (D_6-acetone) δ = 3.32 (s, 3H, OMe), 3.61 (d_{AB}, *J* = 12.4 Hz, 1H, CH_2), 3.65 (d_{AB},

J = 12.4 Hz, 1H, CH_2), 7.29 (t, *J* = 3.6 Hz, 1H, arom.), 7.34 (t, *J* = 3.6 Hz, 1H, arom.), 7.48 (d, *J* = 4.0 Hz, 1H, arom.), 7.61 (m, 7H, arom.), 7.81 (s, 1H, NH), 7.92 ppm (m, 5H, arom.). ^{19}F NMR (D_6-acetone) δ = 6.03 ppm (s, 3F, CF_3). **3c**: ^{1}H NMR (D_6-acetone) δ = 3.06 (s, 3H, Me), 3.42 (s, 3H, OMe), 3.63 (d_{AB}, *J* = 12.3 Hz, 1H, CH_2), 3.65 (d_{AB}, *J* = 12.3 Hz, 1H, CH_2), 7.18 (s, 1H, NH), 7.30 (t, *J* = 3.4 Hz, 1H, arom.), 7.36 (t, *J* = 3.4 Hz,1H, arom.), 7.57 (m, 3H, arom.), 7.64 (m, 1H, arom.), 7.86 (s, 1H, arom.), 8.00 ppm (m, 3H, arom.). ^{19}F NMR (D_6-acetone) δ = 5.61 ppm (s, 3F, CF_3). **3f**: ^{1}H NMR ($CDCl_3$) δ = 2.47 (s, 3H, Me), 3.60 (s, 3H, OMe), 3.47 (d_{AB}, *J* = 15.3 Hz, 1H, CH_2), 4.02 (d_{AB}, *J* = 15.3 Hz, 1H, CH_2), 5.86 (s, 1H, NH), 7.08-7.16 (m, 2H, arom.), 7.33 (d, *J* = 8.2 Hz, 2H, arom.), 7.47-7.59 (m, 3H, arom.), 7.76-7.82 (m, 2H, arom.), 7.92 (d, *J* = 8.2 Hz, 2H, arom.), 7.96-8.00 ppm (m, 2H, arom.). ^{19}F NMR ($CDCl_3$) δ = -41.36 (s, 1F, F), 5.50 ppm (s, 3F, CF_3).

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