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The synthesis of 6-trifluoroethyl-L-lysine: a method to introduce functionality at C-6 of L-lysine

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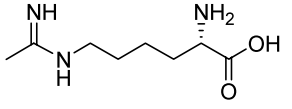
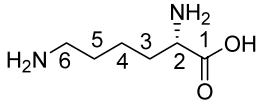
Abstract—Described is a method of introducing trifluoroalkyl groups at C-6 of lysine. This chemistry has the potential to introduce a variety of functionality at C-6 of lysine.

In the course of our research on selective inhibitors of induced nitric oxide synthase (iNOS), iminoethyl-L-lysine (L-NIL, **1**)[1] was identified as a potent selective inhibitor of iNOS.[2] Low levels of NO generated by the constitutive endothelial nitric oxide synthase (eNOS) regulate blood pressure, platelet adhesion, gastrointestinal motility, and bronchomotor tone. Whereas, low levels of NO generated by constitutive neuronal nitric oxide synthase (nNOS) regulate neurotransmission.[3] Elevated levels of nitric oxide (NO) generated by the action of iNOS on L-arginine and the resulting NO derived-metabolites cause cellular cytotoxicity and tissue damage and are thought to contribute to the pathophysiology of a number of human diseases.[4]

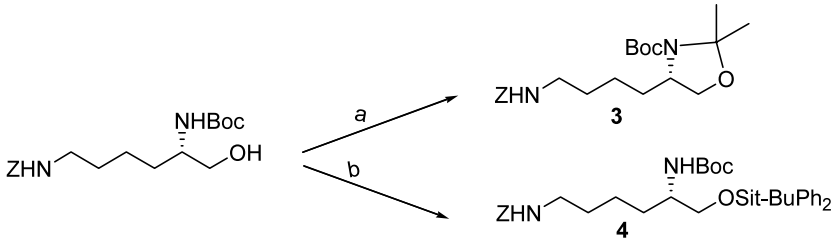
L-NIL is an analog of lysine (Lys, **2**) where the ε-amine has been functionalized as an amidine. The amidine moiety is employed as an isostere for the guanidine group of arginine, which is the endogenous substrate for the NOS enzymes. Enhancing the desirable biological properties of L-NIL by the incorporation of fluorine into L-NIL was investigated.[5] Introduction of fluorine into the lysine side chain was one of our strategies to modulate the lysine framework. A variation on this strategy was incorporation of fluoro-alkyl groups at C-6 to provide novel lysine analogs. The literature is virtually devoid of methodology on alkylation at C-6 of lysine.[6] Our strategy was to exploit commercially available L-lysine derivatives as opposed to de novo assem-



L-NIL (**1**)



L-Lys (**2**)



Scheme 1. Protection of lysinol. *Reagents and conditions*: (a) 2,2-dimethoxypropane, TsOH, 96 h, rt, 100%; (b) *t*-$BuPh_2SiCl$, imidazole, DMF, rt, 96 h, clear oil, 100%.

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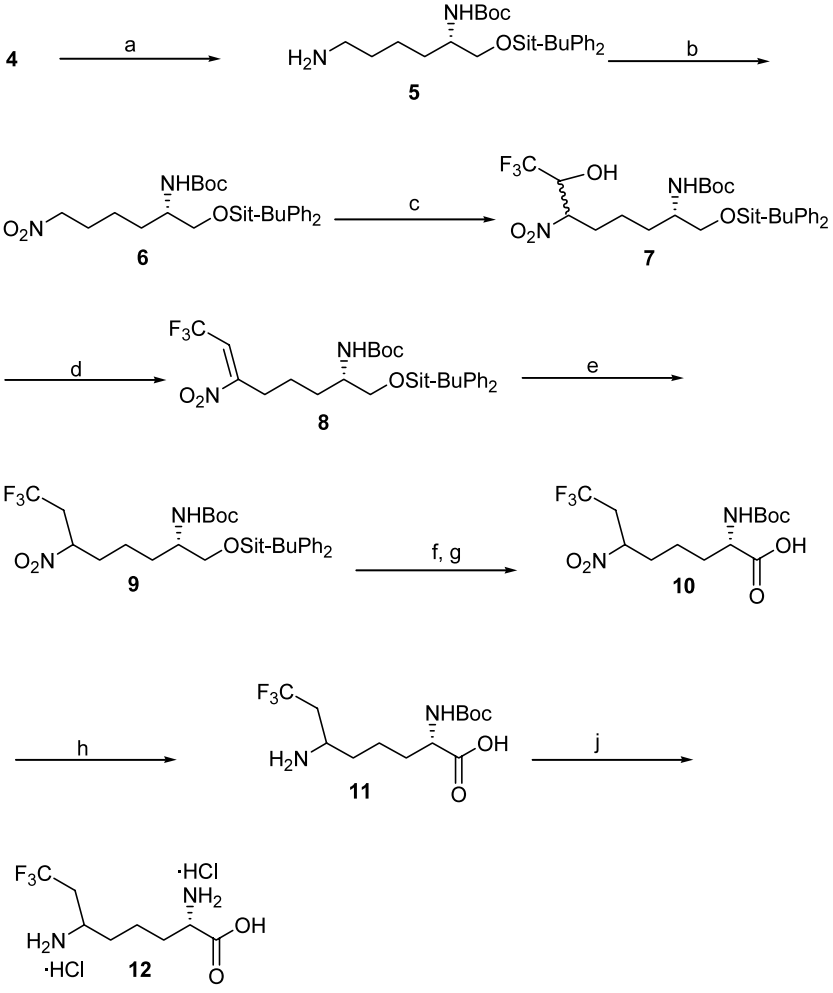
bly of the side chain skeleton. As shown in Scheme 1, initiation of the synthesis of 6-trifluoroethyl-L-lysine began with commercially available protected lysinol.[7] Two protecting group strategies of the alcohol were explored. *N*,*O*-Acetal **3** worked but the yields in subsequent chemistry were low. The alcohol protected as *t*-butyldiphenylsilylether **4** proved more robust under the reaction conditions used to install a trifluoroethyl group at C-6.

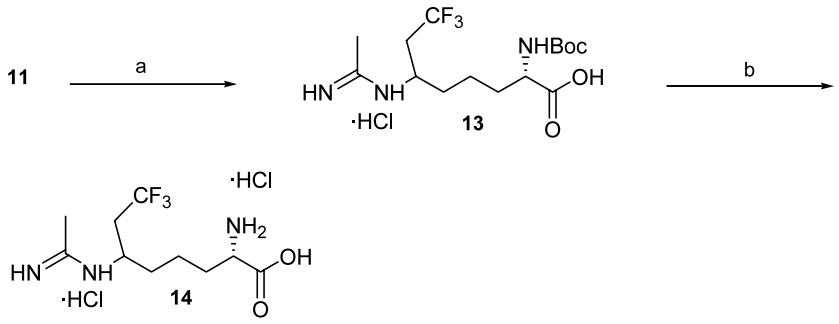
As illustrated in Scheme 2, the benzyloxycarbonyl group was removed under standard catalytic hydrogenation conditions. The ε-amine was successfully oxidized to the nitro group using technical grade *m*-chloroperbenzoic acid. Initially, model studies were performed with 1-nitrohexane, trifluoroacetaldehyde ethyl hemiacetal,[8] and a variety of bases. The most effective base for the Henry reaction was DBU. Thus, with nitro-intermediate **6** in hand, the Henry reaction with DBU and trifluoroacetaldehyde ethyl hemiacetal successfully introduced a trifluoroethyl group yielding **7**. Acetylation of the hydroxy group gave the desired elimination product **8** in a single step. Reduction of the olefin was achieved with sodium borohydride in the presence of water to give **9**.[9] No diastereoselectivity was seen under these reduction conditions. Had **14** showed any biological promise, we would have explored the stereoselective reduction of **8**. The silyl protecting group was removed using tetra-*n*-butylammonium fluoride and the alcohol was successfully oxidized using pyridinium dichromate to give the nitro-amino acid **10**. Catalytic hydrogenation of the nitro group was achieved with the use of Pearlman's catalyst to yield **11**. The 6-trifluoroethyl-L-lysine (**12**)[10] was isolated upon treatment of **11** with anhydrous hydrochloric acid.

Since our strategy was to identify L-NIL analogs, the amidine of 6-trifluoroethyl-L-lysine was synthesized as shown in Scheme 3. The amidine was formed as described previously using methyl acetimidate hydrochloride.[11] The *t*-butyloxycarbonyl group was removed with anhydrous hydrogen chloride as illustrated in Scheme 2 yielding **14**.[12]

Interestingly, the amidine **14** had virtually no activity against the NOS enzymes where the amino acid **12** showed modest nNOS activity and selectivity as shown in Table 1.



Scheme 2. Synthesis of 6-(2,2,2-trifluoroethyl)-L-lysine (**12**). *Reagents and conditions*: (a) H_2, Pd/C, EtOH, 5 psi, quantitative; (b) ~77% mcpba, 1,2-$C_2H_6Cl_2$, D, 3 h, 62%; (c) $CF_3CH(OH)OEt$, CH_3CN, DBU, rt, 18 h, 75%; (d) acetic anhydride, pyridine, rt, 48 h, 66%; (e) $NaBH_4$, THF/H_2O, rt, 3 h, 91%; (f) *n*-Bu4N+F^-, THF, 17 h, 95%; (g) pyridinium dichromate, DMF, 20 h, rt, 65%; (h) 20% $Pd(OH)_2$, EtOH, 60 psi, 40°C, 16 h, 90%; (j) HCl/dioxane, HOAc, 1 h, rt, quantitative.



Scheme 3. Amidine synthesis. *Reagents and conditions*: (a) methyl acetimidate hydrochloride, TEA, DMF, 44%; (b) HCl/dioxane, HOAc, 1 h, rt, quantitative.

Table 1. NOS Inhibition (IC_{50}, μM)[13]

Compound no.	i-NOS (μM)	e-NOS (μM)	n-NOS (μM)	Selectivity e-NOS/i-NOS	Selectivity n-NOS/i-NOS
L-NIL (**1**)	4.9	128	47.1	26	10
12	136	88.8	15.6	0.65	0.11
14	>4000	3121	2317	Na	Na

In this paper we have described a method for functionalizing C-6 of lysine starting with a commercially available protected lysine derivative. Nitro intermediate **6** allows for the possibility of a variety of interesting compounds.

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9. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.98 (s, 9H), 1.22–1.42 (m, 4H), 1.46 (s, 9H), 1.50–1.61 (m, 2H), 2.40–2.55 (m, 1H), 2.98–3.14 (m, 1H), 3.54–3.75 (m, 3H), 4.63–4.78 (m, 2H), 7.37–7.40 (m, 6H), 7.62–7.68 (m, 4H). IR 1588, 1350 cm^{-1}. Anal. calcd for $C_{28}H_{41}N_2O_5F_3Si$ (582.72): C, 59.77; H, 7.08; N, 4.60. Found: C, 59.59; H, 7.18; N, 4.60.
10. ^{1}H NMR (400 MHz, D_2O, TSP) δ 1.45–1.62 (m, 2H), 1.70–1.89 (m, 2H), 1.91–1.95 (m, 2H), 2.58–2.79 (m, 2H), 3.69–3.78 (m, 1H), 3.82 (t, J=6.0 Hz, 1H). ^{19}F (376 MHz, D_2O, $CFCl_3$) δ −63.0 (q, J=6.7 Hz). Anal. calcd for $C_8H_{15}N_2O_2F_3 \cdot 2.2\ HCl \cdot 1.2\ H_2O$ (330.05): C, 29.11; H, 5.99; N, 8.49. Found: C, 29.49; H, 5.65; N, 8.19.
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12. ^{1}H NMR (400 MHz, D_2O, TSP) δ 1.30–1.62 (m, 2H), 1.63–1.85 (m, 2H), 1.91 (br q, 2H), 2.24 (s, 3H), 2.44–2.59 (m, 2H), 3.93–4.02 (m, 1H), 4.03–4.30 (m, 1H). Anal. calcd for $C_{10}H_{18}N_3O_2F_3 \cdot 2\ HCl \cdot 1\ H_2O$ (360.20): C, 33.35; H, 6.16; N, 11.67. Found: C, 33.46; H, 5.99; N, 11.33.
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