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Triflates as synthons for the synthesis of lysine analogues

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Abstract

A simple synthesis of various 6-amino-2-substituted hexanoic acids has been developed starting from lysine via the triflate of 6-amino-2-hydroxy hexanoic acid. The same reactions have also been successfully applied starting from the lysyl-proline sequence. The lysine analogues have been introduced in pseudopeptide sequences by the acylfluoride methodology.

Keywords: amino acid derivatives; deamination; hydroxylamine; hydrazine; acylfluoride.

In the course of our studies concerning the tetrapeptide NAcSDKP,[1] it was necessary to obtain analogues of the native tetrapeptide stable to peptidases as it has been shown that the main metabolic pathway was under the control of angiotensin-converting enzyme (ACE) which cleaves the Asp–Lys bond of the molecule.[2] We thought that the replacement of the scissile bond by different surrogates would yield a molecule stable towards ACE hydrolysis.

In order to synthesize such compounds, we envisioned to use a single synthon which would afford a wide range of pseudopeptides.

Such a strategy relies upon the unique properties of the triflate derivative of 2-hydroxy 6-benzyloxycarbonylamino hexanoic acid derivative **2**. Triflate derivatives have been extensively used since the pioneer work of Effenberger demonstrating the much higher reactivity of this class of compounds compared to the corresponding bromo derivatives.[3] Such an enhanced reactivity allows substitution with nucleophiles to take place with negligeable racemization. Consequently, the triflate **2** could be treated by various *N*-nucleophiles to afford 2-substituted derivatives.

Triflate **2** can easily be obtained through a four step sequence starting from lysine. In order to obtain an analogue of the natural amino acid, we had to use D-Lys as the starting material. However, the reactivity of the triflate **2** was first studied with the *S*-enantiomer derived from L-lysine. The same reactions were applied to the *R*-enantiomer using piperidine, methylamine and 2-aminoacetaldehydediethylacetal as nucleophile (Table 1, entries 3, 6, 11).

Nitrous deamination of D-lysine yielded the corresponding alcohol with retention of configuration.[4] Protection of the ε-amine function by the *Z* protecting group followed by esterification of the carboxylic acid gave compound (*R*)-**1b**. The triflate (*R*)-**2** was obtained by treatment with triflic anhydride in presence of lutidine according to known procedures (Scheme 1).[3]

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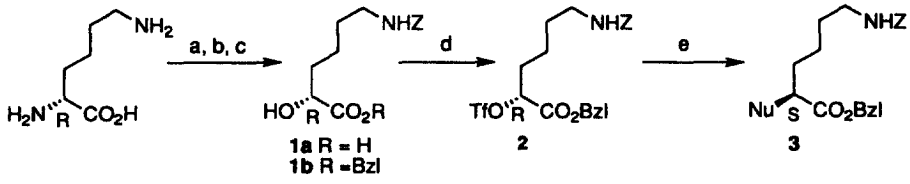
Table 1
2213Nucleophilic substitution of the triflates (*R*)-**2** and (*S*)-**2**

Entry	Triflate	Nucleophile (equiv.)[b]	Reaction conditions	Yield[a] (%)
1	S	Aniline (3)	3 days, R.T.	70
2	S	Piperidine (2.6)	1h, 0°C	90
3	R	Piperidine (3)	1.5h, 0°C-R.T.	91
4	S	Allylamine(4)	3 days, R.T.	74
5	S	Methylamine in MeOH (10)	1h, 0°C	93
6	R	Methylamine in MeOH (10)	1h, 0°C-R.T	86
7	S	tert-Butyl carbazate (3)	2h, 0°C	90
8	S	O-Benzylhydroxylamine (5)[7]	1h, R.T.	64
9	S	(S)-(-)-α-Methylbenzylamine (2.5)	2.5h, R.T.	80
10	S	2-Aminoacetaldehydediethylacetal (3)	6h, R.T.	90
11	R	2-Aminoacetaldehydediethylacetal (5)	6h, R.T.	86

a : Non-optimized yields of isolated and purified compounds; *b* : the nucleophile should be used as the free base.



Scheme 1. Synthesis of L-lysine analogues. a: lit.[4]; b: Z-OSu, NEt_3; c: BzlBr, NEt_3, acetone; d: $(Tf)_2O$, lutidine, CH_2Cl_2; e: nucleophile, NEt_3[9]

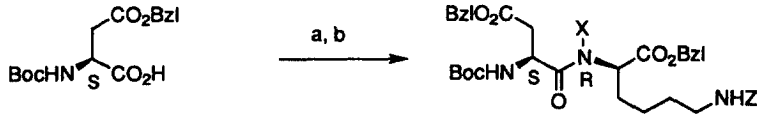
The triflate (*S*)-**2** has been treated with a number of *N*-nucleophiles such as aniline, piperidine, allylamine, *N*-methylamine, (*S*)-(−)-α-methylbenzylamine, 2-amino acetaldehyde diethylacetal, *O*-benzylhydroxylamine, *tert*-butyl carbazate (2 equiv.) in CH_2Cl_2.[9] The results in Table 1 show the efficiency of the substitution whatever the nature of the nucleophile. It is noteworthy that no product resulting from dialkylation had been isolated.[5]

The stereoselectivity of the reaction has been checked in two ways. The reaction of **2** with (*S*)-α-methylbenzylamine yielded two products which were separated by column chromatography in a 1/26 ratio in close agreement with Effenberger's results.[3] We also derivatized the amines resulting from the treatment of (*R*)-**2** with 2-aminoacetaldehydediethylacetal and aniline with (*R*)-2-phenylethyl isocyanate;[6] the diastereoisomeric mixture showed a 1/24 ratio from ^{13}C NMR spectrum analysis in both cases.

We then investigated the coupling step of the secondary amine obtained by reaction of (*R*)-**2** with primary amines with an aspartic acid derivative with proper protection of the α-amino and side chain carboxylic acid groups (Scheme 2). From the different activation methods screened (PyBrOP, PyBOP, mixed anhydride)†, only the acyl fluoride[8] method gave consistently good yields whatever the amino

† Abbreviations. TFFH: tetrafluoroformamidium hexafluorophosphate, *Z*-OSu: benzyloxycarbonyl succinimide ester, $(Tf)_2O$: anhydride triflique, WSC: water-soluble carbodiimide, 1-(3-dimethylaminopropyl)3-ethyl-carbodiimide hydrochloride, HOBT: hydroxybenzotriazole, DIPEA: diisopropylethylamine, PyBOP®: benzotriazoloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate, PyBrOP®: bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate.

component (Table 2). However, PyBrOP gave a satisfactory yield of coupling (50%) with the *N*-methyl derivative.



Scheme 2. Coupling of (2*R*)-lysine analogues **3** with Boc-Asp(OBzl)-OH. a: TFFH, 1.2 equiv., DIPEA, 2 equiv., CH_2Cl_2, 15 min, 0°C; b: **3**, 0.8 equiv., rt

Table 2
Coupling of (2*R*)-lysine analogues with Boc-Asp(OBzl)-OH

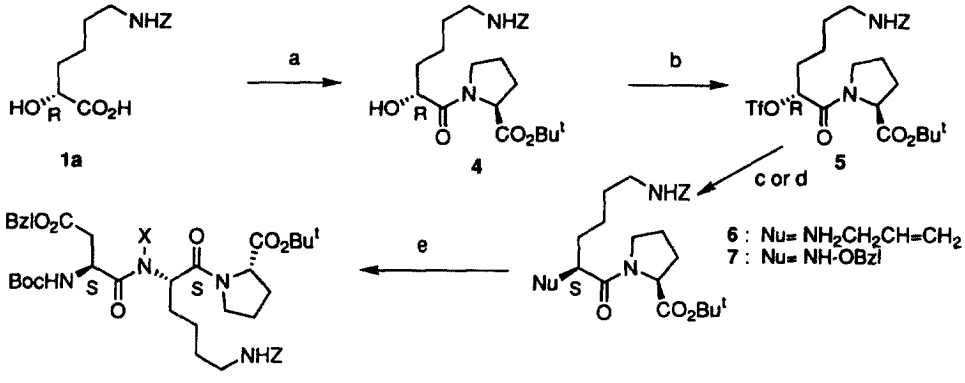
X	Reaction conditions[a]	Yield (%)
-CH_3	2 h, R.T	80
-CH_2-CH=CH_2	5 h, R.T	60
-OBzl	12 h, R.T	93
-$CH_2CH_2(OEt)_2$	18 h, R.T	60
-NHBoc	2.5 h, R.T[b]	66

a : Acylfluoride (2 equiv.), DIPEA (5 equiv.);

b : ultrasound irradiation

We also succeeded in preparing the triflate of the dipeptide **4**. This compound was obtained through coupling of (*R*)-**1a** with (*S*)-*t*-butyl prolinate. The best coupling conditions used WSC (1.5 equiv.) and HOBT (1 equiv.) in THF.

Treatment of **4** with triflic anhydride and lutidine gave **5** with a 70% yield. Substitution of **5** with allylamine or *O*-benzylhydroxylamine gave **6** and **7**, respectively, which have been coupled with Boc-Asp(OBzl)-F as described above in 47 and 49% yields (Scheme 3).



Scheme 3. Preparation of pseudotripeptides from 2-hydroxy 6-(*Z*)-amino hexanoic acid **1a**. a: WSC, 1.5 equiv., DIPEA, 3 equiv., HOBT, 1 equiv., ProOBu^t, 1.2 equiv., 50%; b: $(Tf)_2O$, lutidine, −78°C, 70%; c: H_2NOBzl, 5 equiv., NEt_3, 5 equiv., 64%; d: $NH_2CH_2CH=CH_2$, 4 equiv., NEt_3, 4 equiv., 74%; e: Boc-Asp(OBzl)-F, 1.2 equiv., DIPEA, 2 equiv., 49% and 47%

In conclusion, the triflate derivative **2** derived from lysine was used as a synthon to give access to a number of substituted derivatives of lysine allowing the preparation of various pseudodipeptides. We also demonstrated the preparation of triflates starting from the hydroxy analogue of the dipeptide Lys-Pro **4**. Further work is underway to study the substitution of the triflates **2** and **4** with S- and C-nucleophiles.

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9. General procedure: The triflate **2** had been used after isolation through flash chromatography on silica gel or crude without noticeable differences in the yield of the substitution reaction. In the latter case, it is necessary to use an excess of base (2 equiv.). The nucleophile (3–10 equiv.) was dissolved in dry CH_2Cl_2 (1 ml/mmole). The solution was cooled to 0°C and stirred under Argon at room temperature. The triflate in solution in CH_2Cl_2 (10 ml/mmol) was added dropwise. The progress of the reaction was monitored with TLC. All compounds have spectroscopic properties (^1H NMR, ^{13}C NMR, MS) in agreement with their structures.