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Efficient synthesis of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacids: access to 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers

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ABSTRACT

The preparation of optically pure N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacids in large scale is described via a S_N2 protocol. These compounds were used as starting materials for the synthesis of 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers.

Hydrazinopeptides are a class of peptide analogues for which one (or more) peptidic bond(s) has (have) been replaced by one (or more) hydrazidic bond(s).[1] As recently demonstrated by Seebach and Lelais,[2] the hydrazidic bond is highly resistant to protease, and hydrazinopeptides could be interesting peptidomimetic candidates in drug design. Moreover, the few investigations concerning the structural analysis of foldamers constructed starting from α-hydrazinoacids seem to demonstrate that the presence of supplementary nitrogen atoms in the backbone leads to new forms of intramolecular structuration.[3] A few years ago,[4–6] we demonstrated that enantiomerically pure N^{α}-Z, N^{β}-Boc-protected α-hydrazinoacids **1** (Fig. 1) can be synthesized by using a Mitsunobu protocol as the key reaction, where *N*-alkoxycarbonyl aminophthalimide acts as an acidic partner.

As a result, the reaction of *N*-*tert*-butyloxycarbonyl- and *N*-benzyloxycarbonyl-aminophthalimides with commercially available (*S*)- and (*R*)-α-hydroxyesters led to either N^{α}-protected, N^{β}-bisprotected or orthogonal N^{α}, N^{β}-triprotected, respectively, (*R*)- and (*S*)-α-hydrazinoesters with high optical purity. These procedures represent also an attractive alternative to the methods currently used for the preparation of α-hydrazinoacid derivatives. The use of *N*-alkoxycarbonyl aminophthalimides as acidic partners allowed for the first time to replace an alcohol function by a hydrazine one via a Mitsunobu protocol. In fact, the success of this reaction is related to the presence of the phthalimide group bearing two carbonyl functions and to the presence of a supplementary carbonyl belonging to the alkyloxycarbonyl one, which contributes to decrease the pK_a of the sole hydrogen and allows to use these compounds as acidic partners. As a proof, we demonstrated that the replacement of the alkoxycarbonyl group by an alkyl one did not lead to any substitution. In our works dealing with the synthesis of mixed alpha-hydrazino oligomers, we were confronted to the synthesis of trimers **14** and **15** bearing an alkyl group on the N^{α} of the hydrazinoacid units (Scheme 2). This synthesis necessitated, first, the synthesis of compound **2**, analog to **1** where the *Z* group is replaced by an alkyl one. As stated before, these compounds cannot be synthesized via the Mitsunobu protocol starting from *N*-alkylaminophthalimide.

In our preliminary studies, we tried to obtain compound **2** from compound **3** (Scheme 1). Unfortunately, in spite of considerable efforts, we were not able to introduce the alkyl group (Fig. 1). The method described by Vidal et al. using oxaziridine method[7] was no more suitable for the preparation of **2** in multigram scale due to the high cost of *N*-Boc-3-(4-cyanophenyl)oxaziridine (BPCO).

In this Letter, first we describe a general method for the preparation of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacids **2** in multigram scale (Fig. 1) in good yields and high optical purity[8] using S_N2 reaction as the key step. Second, we describe the use of compound **2** as the starting material for the initial synthesis of 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers.

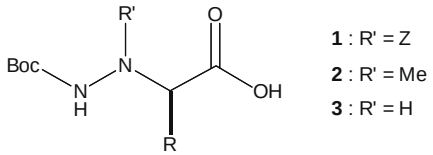

Figure 1. N^{α}-Z and N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacids.

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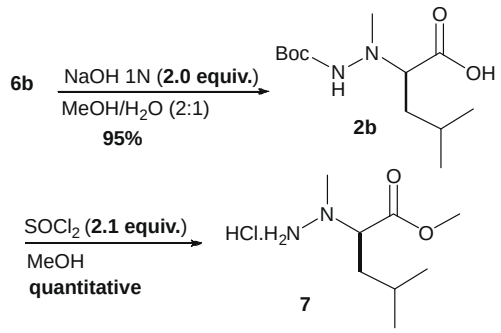


Scheme 1. Synthesis of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacid **2b** and N^{α}-Me α-hydrazinoester **7** stabilized as hydrochloride salt.

In a preliminary study, we decided to use the protocol described by Hoffman and Kim[9] (Method A) for the synthesis of 2-(Boc-hydrazinyl) esters **5**. Starting from 1 mmol of the corresponding hydroxyester **4**, the N^{α}-Me, N^{β}-Boc-protected α-hydrazinoesters **6** were obtained in good yield. Unfortunately, the yield decreased dramatically when performing this reaction on a multigram scale (30 mmol of hydroxyester) (Table 1).

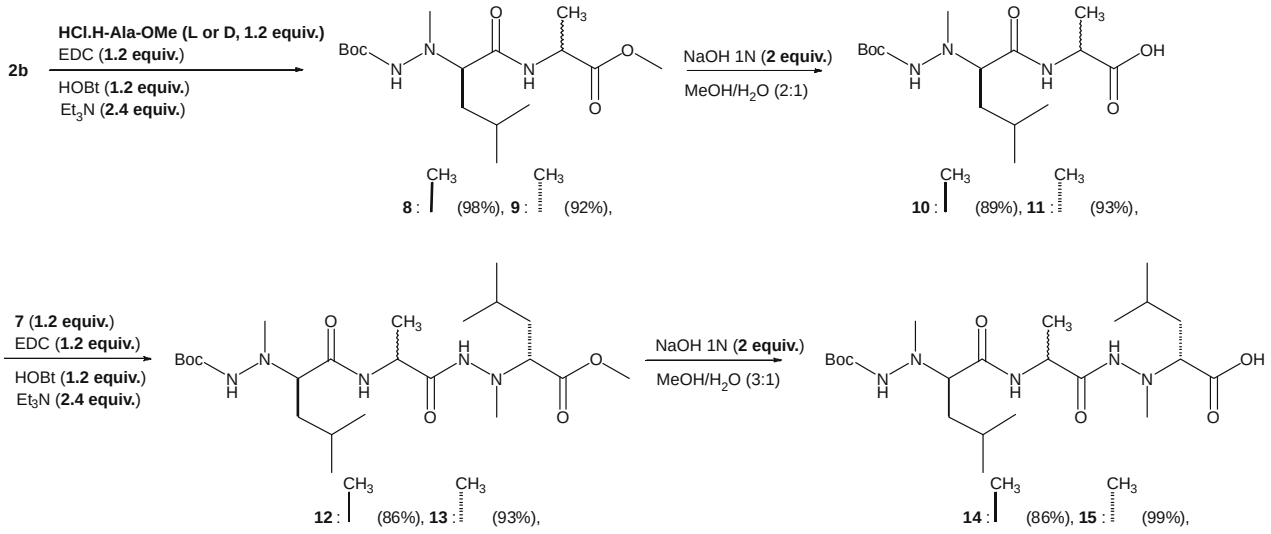
A systematic study[10] demonstrated that the yield can be considerably increased by using 2 equiv of 2,6-lutidine. Moreover, we demonstrated that only 1 equiv. of BocNHNHR′ was necessary to obtain good results (Method B) (Table 1).

As a result, we established the following general procedure (Method B) for the multigram synthesis of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoesters **6a–c**:

'A solution of hydroxyester (1.0 equiv) and 2,6-lutidine (2.3 equiv) in CH_2Cl_2 at 0 °C was treated with triflic anhydride (1.1 equiv). After 15 min, a solution of BocNHNHMe in CH_2Cl_2 was added dropwise for 30 min and the mixture was stirred for 4 h at 0 °C. After evaporation of the solvent, Et_2O was added and 2,6-lutidinium triflate was precipitated by storing the reaction mixture overnight in the refrigerator. The 2,6-lutidinium triflate was filtered and the filtrate was diluted with Et_2O and washed with water, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography.'

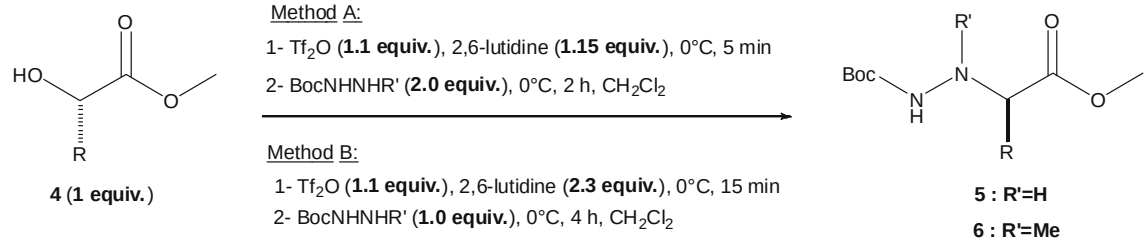
This methodology allowed us to obtain large quantities of compound **6** which can be involved in the preparation of 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers.

The second part of this Letter deals with the use of **6b** as the starting material for the synthesis of two 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino] trimers **14** and **15** (Scheme 2).



Scheme 2. Synthesis of 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers **14** and **15**.

Table 1
Synthesis of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoesters **6**



Compounds	R	Method A		Method B
		Yield (%) (starting from 1 mmol of **4**)	Yield (%) (starting from 30 mmol of **4**)	Yield (%) (starting from 30 mmol of **4**)
5	See Ref. 9	80–100		
6a	CH_3	87	**48**	**82**
6b	$CH_2CH(CH_3)_2$	81	**45**	**80**
6c	CH_2Ph	80	**45**	**78**

After performing the saponification of the ester group of **6b,** we were able to obtain the corresponding free C-terminal compound **2b**. The use of thionyl chloride in methanol[11] led to the deprotection of hydrazine group and to the esterification of carboxylic one giving in one pot compound **7** in quantitative yield (Scheme 1).

A first coupling reaction of the methyl ester of (D or L) alanine and **2b** under classical conditions[12] led to the corresponding pseudodipeptides **8** or **9**. Saponification of **8** and **9** gave in good yields, respectively, **10** and **11** which can be involved in a second coupling reaction with **7,** and led to the formation of the desired trimers **14** and **15** after an ultimate step of saponification.

In summary, we have developed a general method for the preparation of N^{α}-Me, N^{β}-Boc-protected α-hydrazinoacids **2** using the S_N2 reaction as the key step. Starting from **2b** we were able to obtain for the first time the synthesis of 1:1:1 [N^{α}-Me α-hydrazino/α/N^{α}-Me α-hydrazino]trimers **14** and **15** in good yield. The conformational analysis of these oligomers is under active investigation in order to determine their ability to fold in solution.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.095.

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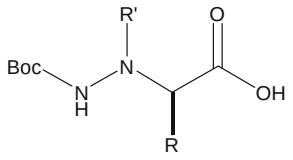
10. A paper concerning the SN_2 methodology to afford N^{α}-R′, N^{β}-Boc-protected α-hydrazinoacids (R,R′ = Ala, Val, Leu and Phe) is still in progress and will be published as soon as possible. The high optical purity will be verified by comparison of $[\alpha]_D$ of N^{α}-CH_2Ph, N^{β}-Boc-protected α-hydrazinoacids already obtained using oxaziridine method.



(R,R'=Ala, Val, Leu and Phe)

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