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A simple synthesis of 6-hydroxynorleucine based on the rearrangement of an *N*-nitrosodichloroacetamide

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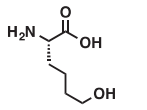
ABSTRACT

6-Hydroxynorleucine is a versatile chemical intermediate that has found broad use in target-oriented syntheses of numerous biologically active molecules. Despite its widespread use, and despite the various strategies that have been reported for its preparation, however, this compound remains an expensive building block, which suggests that the development of new and efficient synthetic strategies for its preparation could substantially impact a wide field of biochemical research. Herein we report a strategy to synthesize 6-hydroxynorleucine from L-lysine in a one-purification sequence that replaces the side chain's nitrogen atom with an oxygen by rearranging an *N*-nitrosodichloroacetamide group into the corresponding ester.

Introduction

6-Hydroxynorleucine (**1**) is non-natural amino acid that is frequently used as a building block in chemical synthesis. The hydroxyl group on the side chain can be converted into numerous other functional groups or serve as a connection point for attaching larger structures. For example, with appropriate protecting groups on the backbone's amine and carboxylic acid, functional group manipulations have been used to convert the side chain's alcohol into iodides,[1–3] chlorides,[4] sulfonates,[5,6] sulfides,[7] thioesters,[8] ethers,[9,10] azides,[8,11] aldehydes,[12,13] nitriles,[14] and hydroxylamines.[15,16] These various intermediates have been used to form cyclic structures[10,13,16–18] and to attach larger chemical moieties including saccharides,[19,20] amino acids,[21] heterocycles,[6] and groups that enable orthogonal chemical ligations via click chemistry.[21]



6-hydroxynorleucine
(1)

The wide range of synthetic chemistry that can be done with hydroxynorleucine has enabled the synthesis and study of a variety of molecular structures with diverse functional properties. Biomimetic structures that have been built from hydroxynorleucine include peptidomimetics,[22–24] crosslink mimics of collagen[3] and elastin,[12] and advanced glycation endproducts.[1,2] Synthetic protein modulators include inhibitors of a variety of enzymes (including lysine-specific demethylase,[25,26] histone deacetylase,[27] inhibitor of apoptosis,[11,13,18,28] calpain,[10] and vasopeptidases[17]) as well as agonists for the histamine H2 receptor[5] and chemical probes to study the enzymes CmaC[29] and p300.[30] Synthetic modulators of the immune system include antibody haptens[6] and glycosaccharide vaccine candidates.[19,20,31] Synthetic metal chelators include antibacterial iron siderophores[16] and technetium ligands for positron emission tomography.[32,33]

The L-hydroxynorleucine structure has been accessed by various synthetic strategies. Enantiomerically pure materials have been isolated from racemic mixtures by enzymatic kinetic resolutions[24] or by chiral chromatography.[18] The stereocenter has been established by using chiral-auxiliary-controlled alkylations,[1,7] asymmetric reductions of enones,[20] or enzyme-mediated transformations.[34] Syntheses from readily available amino acids have utilized derivatives of L-aspartic acid,[5] L-glutamic acid,[6,12] or L-lysine as starting materials. While L-lysine provides cheap access to the full carbon skeleton (50 ¢ per gram), converting it into hydroxynorleucine is not trivial. Reported procedures that use acidified sodium nitrite to convert the side chain's amine into an alcohol or acetate vary substantially in their yields[3,35] (with yields near 15%[30] or yields not reported[26] being common), and in our hands these conditions did not produce satisfying results. Some reports suggest that using sodium nitroprusside may be able to improve

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this transformation.[14,25] Furthermore, before the amine on lysine's side chain can be converted into an alcohol, the amine on the backbone must be selectively protected, which is a synthetic challenge in itself.

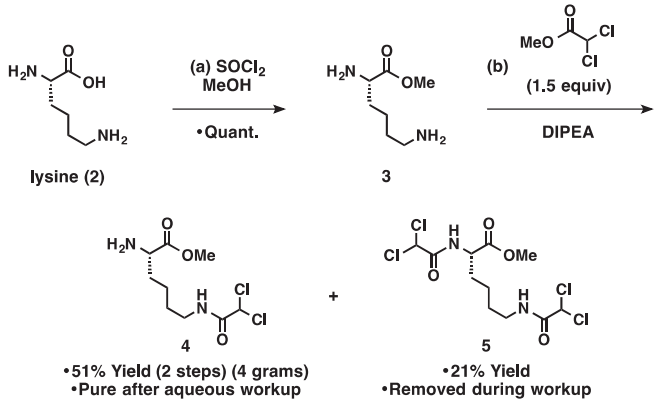
Despite the variety of methods that have been described for synthesizing hydroxynorleucine, this compound remains an expensive building block—for example, Sigma Aldrich sells Boc-protected hydroxynorleucine for $500 per gram[36]—which suggests that there remains a need for new synthetic strategies that can more efficiently access this highly useful core structure. Recently, we have developed a method that utilizes *N*-nitrosodichloroacetamides to convert primary amines into alcohols,[37] and herein we show how this method can be applied to transform L-lysine into 6-hydroxynorleucine using a convenient, 1-purification sequence.

Results and discussion

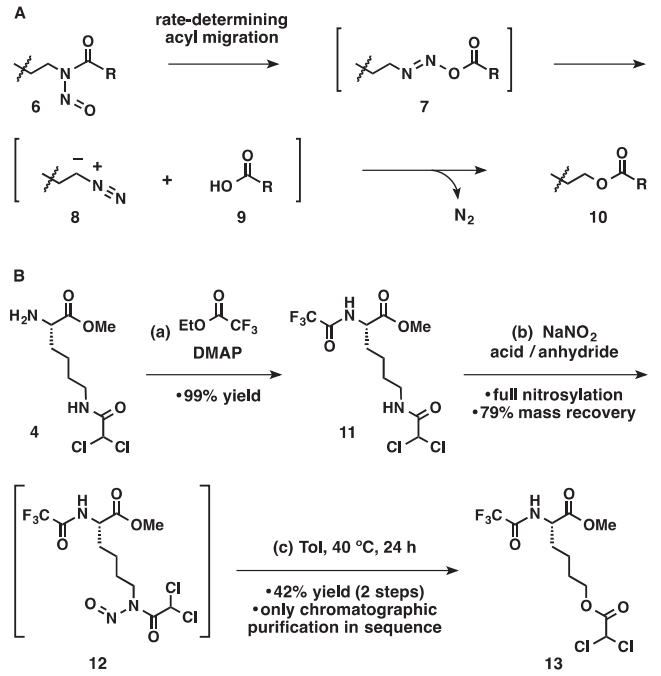
The first challenge of starting a synthesis with lysine (**2**) is to efficiently differentiate the two amino groups. After esterifying lysine's carboxylic acid group, we found that treating diamine **3** with methyl dichloroacetate allows for preferential functionalization of the unhindered amine on the side chain versus the electron-deficient, branched amine on the backbone (Scheme 1). As a result, pure dichloroacetamide **4** can be easily isolated on a multigram scale with only a single aqueous workup required as purification. Some bis(amide) **5** is produced, but this byproduct can be washed or filtered away while product **4** remains dissolved in an acidic aqueous phase. None of the isomer of **4** (in which the backbone is functionalized, but the side chain remains unreacted) was observed, presumably due to a secondary kinetic resolution effect that would readily transform this compound into bis(amide) **5**.

The second challenge of converting lysine into hydroxynorleucine is to convert the side chain's nitrogen-based functional group into an oxygen-based one. Our recent work[37] has shown that *N*-nitrosodicholoroacetamides can be converted into dichloroacetate esters through a thermal rearrangement under mild conditions (40 °C). The mechanism of this transformation (Scheme 2A) begins with migration of the acetate group in **6** onto the nitroso group's oxygen atom to form diazo acetate **7**, which then disassociates into diazoalkene **8** and carboxylic acid **9** and finally recombines into ester **10** with release of nitrogen gas.

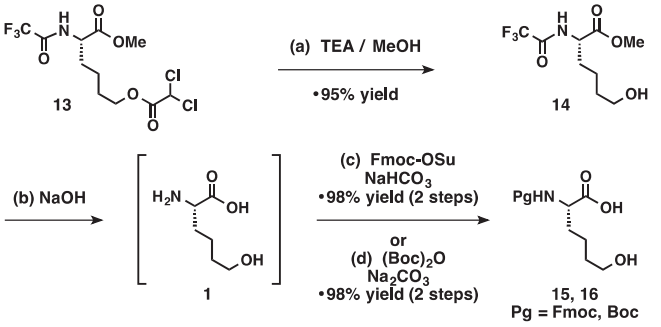
Here we show that the rearrangement of *N*-nitrosodichloroacetamides can be used to install the oxygen-based functionality required for hydroxynorleucine's side chain (Scheme 2B). Starting with amine **4**, the backbone amino group can be simply protected



Scheme 1. Differentiation of lysine's amino groups. Conditions: (a) MeOH (0.9 M), $SOCl_2$ (1.3 equiv), reflux 17 h, quantitative mass recovery; (b) MeOH (0.3 M), diisopropylethylamine (3 equiv), ice bath, methyl dichloroacetate (1.5 equiv), to ambient temperature, 24 h, 51% yield (2 steps).



Scheme 2. Amide-to-ester conversion. (A) General mechanism; (B) conversion of lysine's side chain. Conditions: (a) DCM (0.1 M), 4-dimethylaminopyridine (1 equiv), ethyl trifluoroacetate (2 equiv), 30 °C bath, 23 h, 99% yield; (b) 1:1 dichloroacetic acid/trifluoroacetic anhydride (0.3 M), ice bath, sodium nitrite (2 equiv), 2 h, sodium nitrite (additional 2 equiv), additional 4 h, 79% mass recovery, use directly for rearrangement; (c) toluene (0.1 M), 40 °C bath, 24 h, 42% yield.



Scheme 3. Endgame. Conditions: (a) MeOH (0.2 M), triethylamine (2 equiv), 2 h, 95% yield; (b) 1:1 THF/water (0.2 M), NaOH (3 equiv), 23 h, use directly for next step; (c) add sodium bicarbonate (5 equiv), acetone, Fmoc-OSu (1.05 equiv), 24 h, 98% yield; (d) add sodium bicarbonate (4 equiv), di-*tert*-butyl dicarbonate (1.5 equiv), THF, sodium carbonate (excess), 22 h, 98% yield.

as a trifluoroacetamide. Although dichloroacetamides and trifluoroacetamides are structurally similar, the electron-deficiency of the trifluoroacetamide in molecule **11** causes that group to be much less reactive in the subsequent nitrosylation reaction. Acidified sodium nitrite in the presence of an anhydride cosolvent enables the nitrosylation of amide **11**. A mixture of dichloroacetic acid and trifluoroacetic anhydride enables full nitrosylation of the side chain's dichloroacetamide group (as measured by ^{1}H NMR) with only minimal (approximately 10%) reaction of the backbone's trifluoroacetamide group. Crude *N*-nitrosoamide **12** is directly dissolved in toluene and warmed to 40 °C for 24 h to complete the rearrangement. Dichloroacetate ester **13** is isolated by silica-gel chromatography, which is the only chromatographic purification required in the entire synthetic sequence.

The final steps to complete the synthesis are efficient and straightforward (Scheme 3). First, mild conditions—2 equiv of

triethylamine in methanol—remove the dichloroacetate group from the side chain of ester **13** to yield pure alcohol **14**. This intermediate could be a versatile place to functionalize or protect the side chain's hydroxyl group if that was desired for a specific application. Next, a two-step, one-pot sequence removes both the methyl ester and trifluoroacetamide protecting groups, and then protects hydroxynorleucine (**1**) as either the Fmoc- (**15**) or Boc- (**16**) derivative, either of which can be isolated in pure form by a simple aqueous extraction. We chose to highlight these two target structures because both are useful building-blocks that have found substantial use in target-oriented syntheses.[9–11,26,38,39]

Conclusion

In summary, we report a strategy to convert L-lysine into Fmoc- and Boc-protected 6-hydroxynorleucine, which are versatile building blocks that have been used in the target-oriented syntheses of numerous biologically-active compounds. The two key transformations in this sequence both utilize a dichloroacetamide group, first to differentially functionalize lysine's two amino groups, and then to rearrange the side chain into an oxygen-based functionality. Overall the sequence is operationally simple and only requires one column purification, which we hope will make it a practical and useful synthetic strategy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.070.

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