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Modified Synthesis of Safety Catch Acid-Labile (SCAL) Linker

Marketa Lebl-Rinnova, Hai N. Tran, and Michal Lebl
Spyder Institute, LLC, 3550 General Atomics Ct., San Diego, CA, U.S.A.

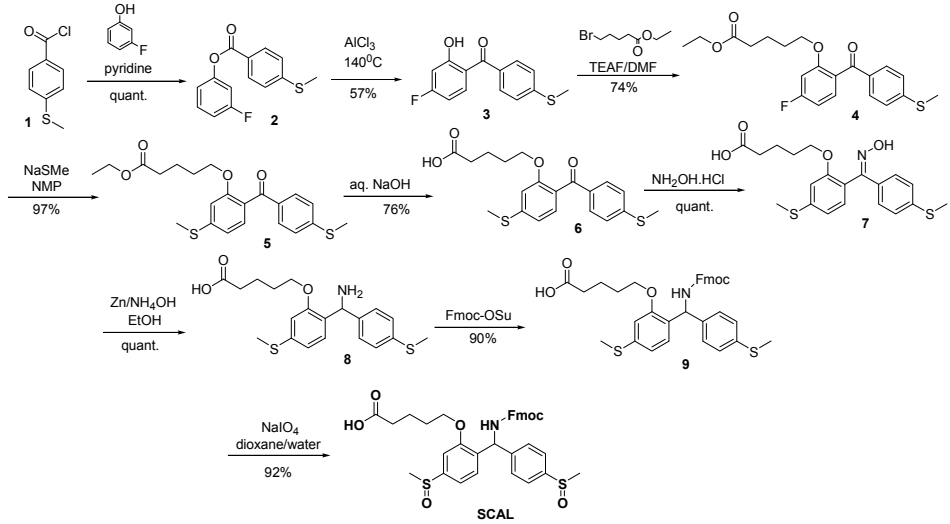
Introduction

SCAL linker (CAS 147046-64-8) was introduced by Patek and Lebl [1,2] twenty years ago in order to increase orthogonality and to enable synthesis of branched or cyclic peptides with C-terminal amide function. The linker in the oxidized form is stable to a wide range of chemical conditions (e.g. strong acids, TFA, HF). It is compatible with Fmoc, Boc and Alloc peptide chemistry protocols. However, when sulfoxides are reduced ($SiCl_4$, PPh_3/Me_3SiCl, Me_3SiBr, HBr/AcOH) to sulfides the transformed linker becomes labile to TFA. The linker has been used, for its stability and versatility, by many research groups for a variety of applications, e.g. chemical ligations [3,4], glycoconjugate- [5] and glycopeptide- [6] syntheses and cyclizations [7,8]. Due to continuous demand and recent unavailability (Sigma-Aldrich Cat. No. 84607) of the linker, we decided to reevaluate the procedure and make this unique precursor available again. The original synthetic protocol consisted of 14 steps. Using our new strategy the linker is built in 9 synthetic steps.

Results and Discussion

A central benzophenone scaffold was originally constructed using Friedel-Crafts acylation in the 8th step of the synthesis. In the new procedure (Scheme 1) we were able to optimize Fries rearrangement of a readily available ester 2. Following O-alkylation of the benzophenone 3, a substitution of aromatic fluoride using NaSMe was trouble-free in NMP (reacts already at room temperature) yielding an intermediate 5. Attempts to introduce SMe group earlier in a presence of free hydroxyl group, directly on benzophenone 3 provided low yields and only after using various high temperatures (90-170°C). Following hydrolysis of an ester group to yield an intermediate 6, an amino group was generated from oxime 7 in aqueous ammonia in a presence of zinc dust. Protection of amine by Fmoc-group using a standard procedure, followed by oxidation of sulfides resulted in the final product, the SCAL linker.

The procedure involves certain limitations and some steps have required substantial optimization. Mainly the Fries rearrangement protocol needed extensive experimentation with reaction conditions and work-up. To some extent the solvent free reaction in $AlCl_3$ causes decomposition of an ester intermediate 2 and the major product 3 of the reaction is hard to quantitatively extract from an aqueous phase in the following work-up. We were able to



Scheme 1. New synthetic procedure.

improve yield (57%) from the originally isolated low 30%, together with purity. This intermediate could be used after optimized work-up without further purification in the next step. The final step, the oxidation of sulfides to sulfoxides, is time consuming (4-5 days) but provides a clean product.

Conclusion

The presented synthesis was developed in order to facilitate the preparation of the SCAL linker on a larger scale that would accommodate demand from the peptide/glycopeptide-synthetic community. We were able to shorten the original 14 steps synthetic protocol to 9 steps and make the synthesis and its scale-up feasible.

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