Solvent-Controlled Chemoselectivity in the Photolytic Release of Hydroxamic Acids and Carboxamides from Solid Support

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Hydroxamic acids have been the source of much biochemical interest in recent years. Therefore, the use of solid-phase combinatorial chemistry for high-throughput generation of structurally diverse hydroxamic acids is highly relevant. Although hydroxamic acids may be obtained by direct cleavage of resin-bound esters with hydroxylamine derivatives, this strategy requires an excess of hydroxylamine and/or addition of base which complicates postcleavage workup. Several approaches involving resin-bound hydroxylamine linkers have been reported. However, these hydroxamate linkages suffer from only being cleavable under acidic conditions, which limits the range of chemical transformations applicable to the solid-phase synthesis of structurally diverse hydroxamic acids. Therefore, other cleavage principles are necessary in order to provide complex molecules assembled through a diverse range of chemical reactivity. A linker system that can be cleaved under photolytic conditions may be considered truly orthogonal in this context. Furthermore, photolytic cleavage offers a mild method of cleavage which is particularly attractive for the direct release of screening compounds into biological screens without contamination by cleavage reagents.

We now wish to report a complete study on a photolabile linker based on the o-nitroveratryl group capable of releasing hydroxamates upon UV irradiation. Uniquely, this linker unit may function as a "bidetachable" system. By simply varying the reaction solvent, the photolysis can be controlled to provide the hydroxamate or carboxamide, respectively (Figure 1). This strategy may introduce further diversity into target molecules and compound libraries. Linker 4 was readily prepared in a few high-yielding steps (Scheme 1) before being explored as a hydroxamate-releasing linker. A N-[[1H-benzo[4,5]imidazol-1-yl](dimethylamino)-methylene]-N-methylmethanaminium tetrafluoroborate N-oxide (TBTU)-mediated coupling of 4 to a Rink linker attached to the commercially available amino-functionalized support (PEGA400) afforded the hydroxylamine-functionalized photolabile support. Using standard TBTU-mediated peptide coupling reactions, derivative 5a was synthesized as a simple and easily monitorable model system. Photolytic cleavage was carried out on resin suspended in H₂O/MeOH (4:1) by irradiating for 30 min at rt with 365 nm light using an LED UV-lamp. Analysis of the released material via RP-UPLC, however, showed release of two products: the hydroxamate 7a and the carboxamide 8a resulting from C-O and N-O cleavage, respectively, in a 3:4 ratio.

The nature of the solvent and the acidity of the solution have been demonstrated to have pronounced effects on the kinetics and equilibrium position of aci-nitro compounds (Figure 2). We first explored the solvent effects in the

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photolysis of 6a on the level of final product formation. The photoreaction was studied by photolyzing aliquots of the resin in various solvents and determining the product distribution via HPLC analysis. Because the solvent also influences the swelling and solvation properties of the support, the obtained results are merely qualitative. While this technique did not allow us to quantify the amount of products formed, it did provide an expedient method to determine the relative photoproduct formation. Selected product yield profiles are listed in Table 1 (for a comprehensive list consult the Supporting Information (SI)). It is evident that the solvent has a strong influence on the product ratio of the reaction and some general conclusions may be drawn. Polar solvents favor formation of the hydroxamic acid product 7a, while apolar solvents mainly give the carboxamide product 8a. In particular, the polar fluorinated alcohol, hexafluoropropionanolate (HFIP), with a high hydrogen-bond-donating ability led to hydroxamic acid product 7a with high selectivity. Apolar solvents favor formation of the carboxamide product 8a over hydroxamate product 7a. Notably, when using mesitylene, carboxamide product 8a was formed exclusively.

Figure 2. Proposed mechanism for the photolytic degradation of hydroxamate-functionalized o-nitroveratryl derivatives. For simplicity, only the E-isomers with regard to the ==C−OR group are shown.
Table 2. Synthesis and Photolytic Release of Hydroxamates 7a−h and Carboxamides 8a−h

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<th>Entry</th>
<th>Substrate</th>
<th>Purity (%)</th>
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"Photolytic cleavage was carried out for 2 h with an LED UV-lamp (360 nm). Purity was determined by RP-HPLC."
In summary, we have developed a photolabile hydroxylamine linker for the synthesis of hydroxamic acids on solid support. The synthesis strategy shows excellent compatibility with a range of structurally diverse compounds. The linker is compatible with most commonly used protecting groups for SPPS and remains intact throughout the multistep synthesis. Products are ultimately released from the solid support in high purity using light. In addition, this linker unit may also function in a bidetachable mode, enabling the release of the corresponding carboxamides when photolysis is performed in an aprotic solvent. Based on results from density functional theory calculations, the present paper provides evidence of the mechanism allowing for the control and selection between these two competing reaction pathways. Finally, we have demonstrated the use of the linker for the generation of a pharmacologically relevant hydroxamate-functionalized natural product-like DKP derivative in high purity.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01386.

Experimental details; RP-HPLC, RP-UPLC, MS, 1H and 13C NMR data; computational details (PDF)

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Notes
The authors declare no competing financial interest.

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206 conditions generated the corresponding aldehyde, and subsequent TFA treatment mediated the N-acyliminium cyclization. Rewardingly, photolytic release gave the hydroxamate-functionalized DKP-derivative 25 in high purity (Scheme 2).

Scheme 2. Synthesis of a Hydroxamate-Functionalized Fused Natural Product-like DKP Derivative (25)

In summary, we have developed a photolabile hydroxylamine linker for the synthesis of hydroxamic acids on solid support. The synthesis strategy shows excellent compatibility with a range of structurally diverse compounds. The linker is compatible with most commonly used protecting groups for SPPS and remains intact throughout the multistep synthesis. Products are ultimately released from the solid support in high purity using light. In addition, this linker unit may also function in a bidetachable mode, enabling the release of the corresponding carboxamides when photolysis is performed in an aprotic solvent. Based on results from density functional theory calculations, the present paper provides evidence of the mechanism allowing for the control and selection between these two competing reaction pathways. Finally, we have demonstrated the use of the linker for the generation of a pharmacologically relevant hydroxamate-functionalized natural product-like DKP derivative in high purity.

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