Pergamon

Tetrahedron Letters 39 (1998) 8031–8034

TETRAHEDRON LETTERS

A Facile and Convenient Solid-Phase Procedure for Synthesizing Nucleoside Hydroxamic Acids

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Received 19 June 1998; revised 5 August 1998; accepted 19 August 1998

Abstract: The solid-phase synthesis of a nucleoside hydroxamic acid is accomplished by the Pd(0) cross-coupling of 5-iodouridine and an O-linked hydroxylamine alkyne bound to 2-chlorotrityl chloride polystyrene resin. © 1998 Elsevier Science Ltd. All rights reserved.

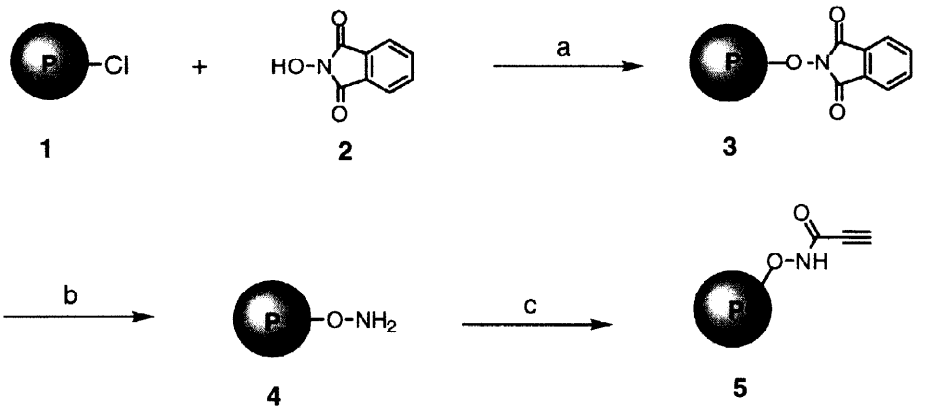
Hydroxamates are know to possess a wide spectrum of biological activities including antibacterial, anticancer, and antifungal.[1-3] The hydroxamic acid functionality is an effective metal ion (e.g., zinc) chelator.[4,5] Consequently, compounds containing this functionality can be potent inhibitors of metalloenzymes such as thermolysin,[6,7] angiotensin-converting enzyme (ACE),[8] and matrix metalloproteases (MMPs)[9-11]. Hydroxamic acids are also observed to inhibit ribonucleoside diphosphate reductase (RDPR),[12-15] a key enzyme involved in the rate-determining step of DNA biosynthesis. For example, hydroxyurea is clinically used and believed to be efficacious by trapping the free tyrosyl radical present in the RDPR active site.[16,17] However, the weak in vivo effectiveness of hydroxyurea has prompted additional synthetic studies towards other RDPR hydroxamic acid inhibitors. Specifically, the hydroxamic acid nucleosides and analogues are of interest for RDPR inhibition, yet the current synthetic procedures to these derivatives are limited.[18,19] Herein, we report a facile strategy for the preparation of a nucleoside hydroxamic acid on solid-support.

A number of requirements must be met to successfully synthesize nucleoside hydroxamic acid derivatives on solid support and demonstrate the utility of this synthetic method. The goals in this initial study are to: 1) identify a suitable linker and reaction conditions for optimal nucleoside modification, 2) capitalize on the obvious advantages of solid-phase synthesis,[20] and 3) design a strategy amenable to combinatorial library synthesis. Presently, nucleoside hydroxamic acids are synthesized by a solution phase method via acylation of hydroxylamine with activated carboxylic acid derivatives, and reports of a solid-phase procedure are not known.[18,19] Solid-phase procedures for synthesizing peptide and peptidomimetic hydroxamic acids using either resin bound N-[21] or O-linked hydroxylamines are described in the literature.[22-27] The O-linked hydroxylamine can be used if subsequent solid-phase reactions do not alter the unprotected amine (pKa ≈10). With these issues in mind, we decided to use the 2-chlorotrityl chloride polystyrene resin as solid support, an O-linked

PII: S0040-4039(98)01794-8

hydroxylamine, and the well-precedented Pd(0) Heck catalyst to construct the nucleoside hydroxamic acid.

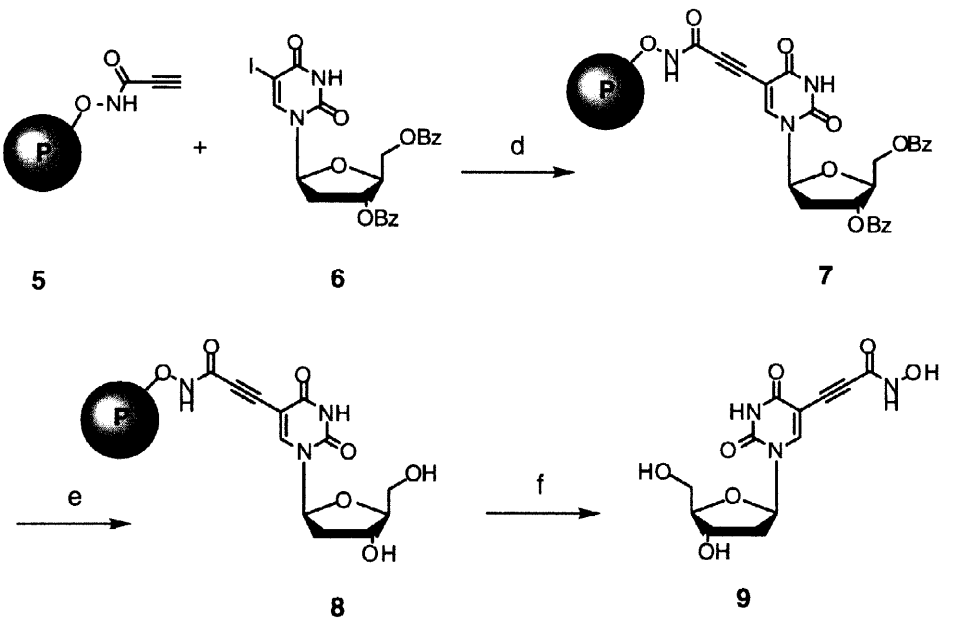
Scheme 1



1 2 3 4 5

Reagents and Conditions: a) TEA, DMF, 25 °C; b) $H_2NNH_2.H_2O$, THF, 25 °C; c) DCC, HOBt, DIPEA, propiolic acid, -10 °C. **P** = 2-chlorotrityl polystyrene resin

Scheme 2



5 6 7 8 9

Reagents and Conditions: d) $Pd(PPh_3)_4$, CuI, DMF, TEA, 25 °C; e) MeOH-NH_3, 25 °C; f) 5% TFA, DCM, 25 °C; 89% yield. **P** = 2-chlorotrityl polystyrene resin

As shown in Scheme 1, the 2-chlorotrityl chloride polystyrene resin, **1**, was reacted with N-hydroxyphthalimide, **2**, in the presence of TEA to afford the N-hydroxyphthalimide derivative **3**. This intermediate was cleanly transformed to the desired hydroxylamine resin, **4**, by treatment with

hydrazine hydrate. Hydrazinolysis of phthalimide to the free amine functionality was confirmed by a positive ninhydrin test.[26,28] Finally, the free amine was efficiently coupled with propiolic acid by the DCC/HOBt method to afford compound **5**, and the disappearance of the starting amine, **4**, was indicated by a negative ninhydrin test.

As shown in Scheme 2, the alkyne terminated hydroxylamine resin was subsequently cross-coupled with 3',5'-dibenzoyloxy-2'-deoxy-5-iodouridine, **6**, using a Heck catalyst.[29,30] Exposure of the resin to iodo-uridine in the presence of Pd(Ph3P)4 and CuI, in DMF and TEA afforded the modified nucleoside, **7**. Next, the resin was treated with methanolic ammonia to remove the benzoyl protecting groups. Finally, the hydroxylamine nucleoside was cleaved from the resin by 5% TFA/DCM to afford the product, **9**, in 89% overall yield.

In summary, a new procedure for the synthesis of a hydroxamic acid nucleoside on solid support is described. Based on the results shown above, we are currently pursuing other halo-nucleosides such as ribo, deoxy, and acyclic nucleosides for selective modification. This synthetic strategy may also serve to facilitate the development of combinatorial libraries containing hydroxamic acid nucleosides and to accelerate the discovery of novel nucleoside structures with biological activities.[31]

Acknowledgments

This work was supported by Duke University.

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