Pergamon

Tetrahedron Letters, Vol. 38, No. 3, pp. 321-322, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02336-2

A TFA-Cleavable Linkage for Solid-Phase Synthesis of Hydroxamic Acids

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Abstract: A novel linkage for the solid-phase synthesis of hydroxamic acids is described. The linkage is stable to all reagents commonly used in Fmoc peptide synthsis. Cleavage is induced by treatment with trifluoroacetic acid, providing hydroxamic acids in high purity and good yields.

Over the past several years, hydroxamic acids have been used extensively as an important structural component in mechanism-based metalloprotease inhibitors.[1] For the solid-phase synthesis of combinatorial libraries[2] directed towards metalloproteases, we were interested in the synthesis of a TFA-cleavable hydroxamate linkage. Such a strategy takes advantage of the linkage as a "protecting group" for the desired functionality[3] and circumvents solution-phase synthesis of protected building blocks.

The construction of the desired linkage is summarized in Scheme 1. We were able to synthesize hydroxamic acids on either Rink acid,[4] Sasrin[5] or Wang[6] resin; for cost efficiency, we recommend the use of a Wang linker. Mesylation of **1**,[3] followed by displacement of **2** with N-hydroxyphthalimide (**3**), resulted in formation of the resin-linked hydroximide **4**. Complete deprotection of the phthalimido group was accomplished under very mild conditions, and the ether-linked hydroxylamine **5** can be manipulated using standard procedures for Fmoc peptide[7] or submonomer[8] synthesis. Virtually quantitative cleavage from the solid support is accomplished with 50% TFA / 5% iPr_3SiH / 45% CH_2Cl_2 or 90% TFA / anisole,[9] and the desired hydroxamic acids were obtained in high purity and good yields. (Scheme 1, Figure 1).

Scheme 1

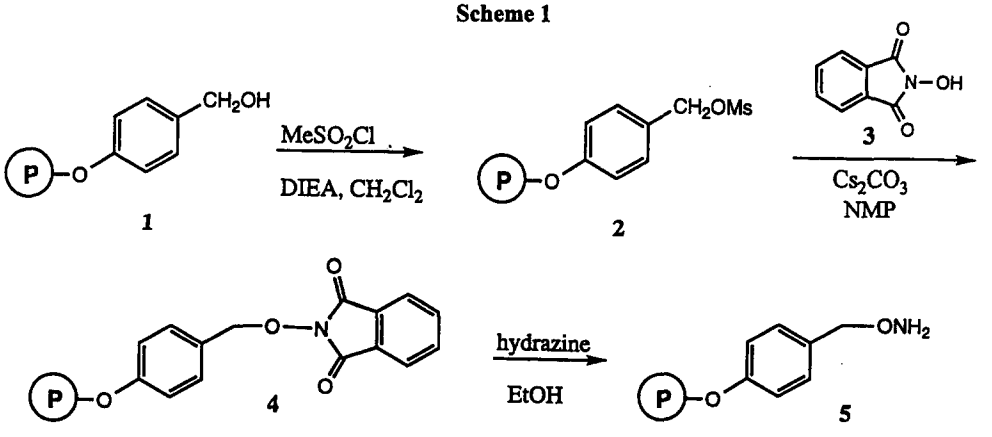
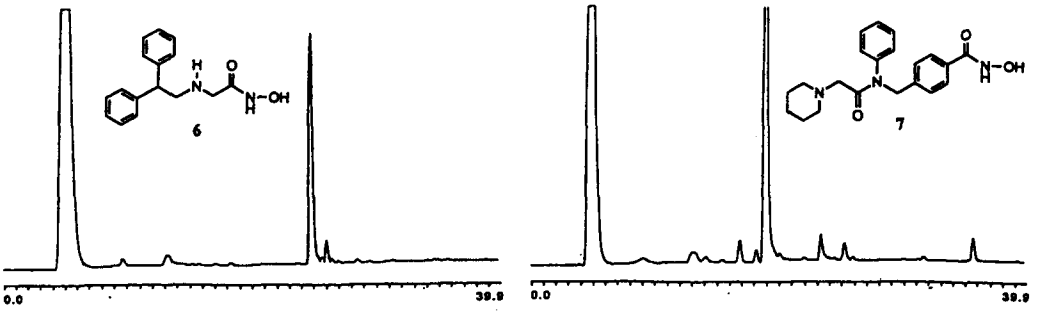


Figure 1



Analytical HPLC chromatograms (λ = 214 nM) of crude peptoids **6** and **7**. Test compounds **6** and **7** were synthesized using the procedures described in ref. 8 and characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

Using the described linkage, we were able to synthesize a wide variety of peptidic and peptidomimetic hydroxamic acids such as **6** and **7**. The stability profile of the linkage **5** under more stringent synthetic conditions is currently being investigated.

Experimental:

Synthesis of the linkage **5**: a) Wang resin (10.0 g, 0.73 mmol/g) was swelled in dichloromethane (40 mL) and diisopropylethylamine (40 mL), and cooled to 0°C. A solution of methanesulfonyl chloride (5.0 mL, 7.40 g, 64.6 mmol) in dichloromethane (20 mL) was added dropwise while stirring under argon, and stirring was continued for 30 min at 0°C and for 45 min at 25°C. Subsequently, the resin was drained and washed with dichloromethane (3 portions of 80 mL) and N-methylpyrrolidinone (NMP; 3 portions of 80 mL). b) In a 500 mL flask equipped with a mechanical stirrer, N-hydroxyphthalimide (23.8 g, 146 mmol) was dissolved in NMP (280 mL), and cesium carbonate (27.7 g, 73 mmol) was added. The mesylated resin **2** was added in small portions at 25°C, and stirring was continued for 30 min at 25°C and for 16 h at 80°C. The chocolate-brown reaction mixture was poured into a Buchner funnel and washed extensively with methanol, water, methanol, dichloromethane, until the resin was colorless. c) The resin **4** was suspended in ethanol (70 mL), anhydrous hydrazine (8 mL) was added, and the mixture was shaken at 25°C for 16 h. The resin was washed extensively with methanol, dichloromethane, methanol and dried; yield 9.50 g (95%) of **5**.

References and Notes:

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9. In order to prevent TFA-induced hydrolysis of acid-sensitive hydroxamates to the corresponding carboxylic acids, we recommend to cleave the resin under anhydrous conditions.

(*Received in USA* 30 *October* 1996; *accepted* 21 *November* 1996)