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A Reaction of N-substituted Succinimides with Hydroxylamine as a Novel Approach to the Synthesis of Hydroxamic Acids

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Abstract

We describe a new reaction for the synthesis of compounds with a hydroxylamide group (hydroxamic acids) which are widely known for their biological activity (histone deacetylase inhibitors, matrix metalloproteinases inhibitors and others). The reaction involves the interaction between N-substituted succinimides and hydroxylamine in aqueous solution. A novel two step approach to the synthesis of hydroxamic acids was developed based on the new reaction. The first stage is the synthesis of N-substituted succinimide via the reaction of aromatic amine or carboxylic acid hydrazide with succinic anhydride. The second step involves the imide ring opening reaction in the presence of hydroxylamine. For the both stages, universal synthetic methods have been developed that exclude additional purification stages for the target compounds.

Sixteen hydroxamic acids were synthesized using the developed approach. Most of the compounds were obtained for the first time.

Keywords

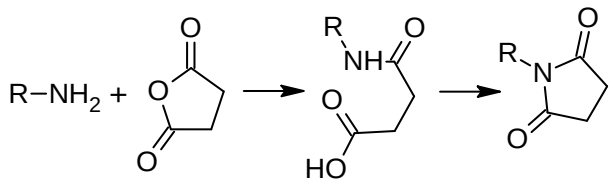
N-substituted succinimides; hydroxylamine; hydroxamic acids; imide ring opening; HDAC inhibitors; MMP inhibitors

Introduction

Hydroxamic acids belong to a very important class of compounds for anti-cancer drug development [1] because of their ability to inhibit metalloenzymes [2] such as Histone Deacetylase (HDAC) [3, 4] or Matrix Metalloproteinase (MMP) [5, 6]. Also, these compounds are great interest for the development of such a modern field of organic chemistry as oxidative coupling reactions [7-9]. There are several well characterized reactions for synthesis of hydroxamic acids that involve carboxylic acids, esters, amides, aldehydes, and alcohols as starting compounds with different reaction activation additives or catalysts [2, 10]. Recently we have found a reaction that expands the possibilities for the synthesis of a broad number of new compounds with hydroxamic acid group [11]: the reaction of N-substituted succinimides with hydroxylamine. Based on the found reaction we developed a novel approach that has such advantages as simplicity and mild conditions. Here we report detailed description of the developed approach which consist of two steps: i. The synthesis of N-substituted succinimides by the reaction of succinic anhydride with amines in chloroform in the presence of polyphosphate ester that can be carried out in one-pot manner; ii. The treatment of N-substituted succinimides by hydroxylamine aquatic solution.

Results and Discussion

For our work, a universal method for synthesis of N-substituted succinimides had to be developed. The simplest way to obtain N-substituted succinimides is the acylation reaction of amine by succinic anhydrite followed by cyclo-dehydration process to a target imide (Scheme 1).



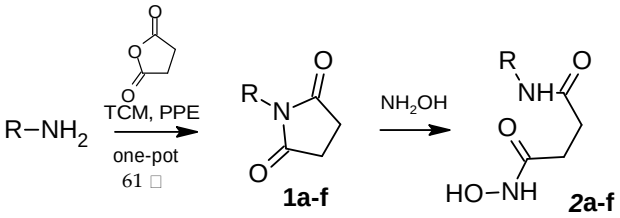
Scheme 1: Synthesis of N-substituted succinimides.

The first step of the reaction depicted in Scheme 1 usually undergoes with high yields under mild conditions in diethyl ether, toluene, 1,2-dimethoxyethane [12], polyethylene glycol [13], etc. The cyclo-dehydration reaction (step 2 in Scheme 1) can be provided by heating (120 ℃) [13-16] or acetic anhydride addition [12, 17, 18]. At first, we synthesized N-phenylsuccinimide by thermal imidization and found some side products formation, which might be caused by partial thermal degradation of the initial amido acid. So, we think that thermal imidization is not universal for N-substituted succinimides synthesis, especially for compounds with less thermal stability than 4-anilino-4-oxobutanoic acid. Using acetic anhydride can result in a side acetylation reaction (e.g., the reaction with phenol groups [19, 20]).

Polyphosphate ester (PPE) is a known mild reagent for cyclo-dehydration reactions [21, 22], and it can be used even without additional protection of the phenol groups [21]. Here we report for the first time the usage of PPE as the dehydration additive for imidization reaction. We have found that addition of 1 – 5 g of PPE per 10 mmol of formed acylation product leads to its conversion into succinimide. This finding provides two step reaction (Scheme 1) in chloroform in one-pot manner (Scheme 2, reaction 1).

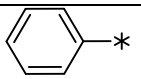
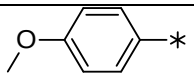
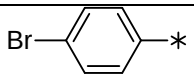
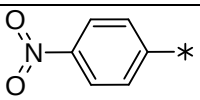
The first step in Scheme 2 can be controlled by visual observing the reaction mixture: the acylation product precipitates from chloroform following by dissolving after PPE addition. It should be noted that using pure amine R-NH_2 is an absolute prerequisite for the one-pot approach. This limitation can be circumvented by separating of the intermediate amido acid precipitate from impurities dissolved in chloroform, hence the subsequent imidization stage can be carried out in pure solvent.

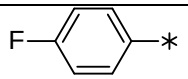
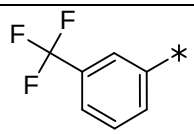
Using this approach, we have synthesized succinimides from different aniline derivatives (Table 1). The main feature of the proposed method is the simplicity of product separation (no additional purification procedures are required, the product is only washed by methanol).



Scheme 2: Synthetic way to hydroxamic acids synthesis based on aniline derivatives.

Table 1: Compounds synthesized according to Scheme 2.

	R	**Yield of 1, %**	**Yield of 2, %**
a		68	73
b		54	66
c		65	53
d		44	64

e		64	38
f		48	34

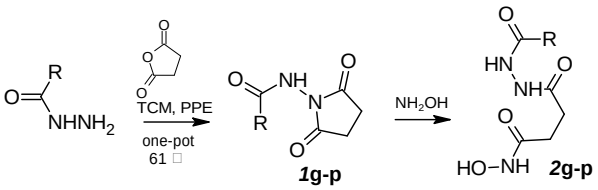
The experimental conditions for the second step in scheme 2 were optimized using **1a**. We found that if the reaction of N-phenyl succinimide with hydroxylamine was carried out in absolute methanol, it was difficult to isolate and purify the target compound **2a** from impurities. Using hydroxylamine water solution (see Experimental section) proved to be more suitable approach. Despite poor water solubility of the succinimides **1a-f**, the imide ring opening reaction can be carried out directly in hydroxylamine water solution, and the reaction proceeds with visible change in the appearance of the precipitate. Addition of some amount of methanol into the reaction mixture can increase the reaction rate, which is probably related to slight increase of the imide solubility.

Using water-based reaction medium simplifies separation and purification process, and all impurities can be removed easily by washing of the filtered precipitate with water and chloroform. The yield primarily depends on solubility of the product in the reaction medium and can be changed by varying the amount of methanol in the reaction mixture.

A necessary condition for imide ring opening in the presence of hydroxylamine is the basicity of initial R-NH_2 (Scheme 2) that must be less than that for hydroxylamine. For example, the calculated value pK_a for anisidine used for **2b** synthesis (5.21 [23]) is close to pK_a of hydroxylamine (5.97 [23]), and the synthesis of **2b** proceeded much slower than other compounds and had to be carried out at a higher temperature for longer time. The additional confirmation of the found effect of initial amine basicity is

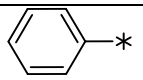
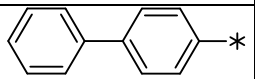
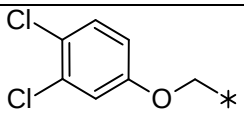
the fact that reaction between hydroxylamine and pyrrolidine-2,5-dione does not take place.

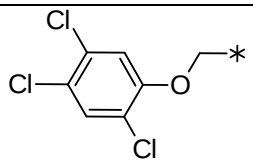
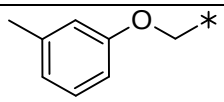
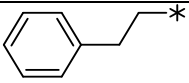
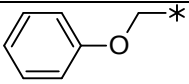
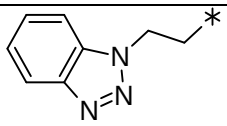
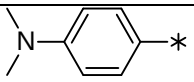
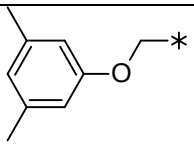
To exemplify the potential of the proposed reaction, hydrazides of carboxylic acids were used (Scheme 3). Their basicity is noticeably lower than that of hydroxylamine and does not depend substantially on the nearest substituents. The calculated pK_a values for hydrazides of acetic, benzoic and p-methoxybenzoic acids are 3.25, 3.06 and 3.26, respectively [23]. The reaction conditions used for aniline derivatives described above proved to be suitable for the synthesis based on hydrazides. Table 2 shows the resulting structures obtained using various carboxylic acid hydrazides.



Scheme 3: Synthetic way to hydroxamic acids synthesis based on hydrazides.

Table 1: Compounds synthesized according to Scheme 2.

	R	**Yield of 1, %**	**Yield of 2, %**
g		45	75
h		43	69
i		76	72

j		44	63
k		69	35
l		45	43
m		80	46
n		60	85.2
o		70	86
p		88	80

Conclusion

A novel approach for hydroxamic acids synthesis has been proposed based on the reaction between N-substituted succinimides and hydroxylamine. The reaction occurs through imide ring opening and results in formation of N-hydroxybutaneamide derivatives (the imide ring opening is possible only when pK_a (RNH_2) ≤ pK_a (NH_2OH), where RNH_2 is initial amine used for imide synthesis). To obtain N-substituted succinimides of different structures, a new method based on the reaction of amines or hydrazides with succinic anhydride in the presence of polyphosphate ester has been

proposed. The developed approach provides a simple tool to get a broad spectrum of new hydroxamic acids that can be used in medicinal chemistry research or for free radical C-O coupling reactions.

Experimental

Mass spectra were recorded on a Finnigan MAT INCOS 50 mass spectrometer with direct sample injection (EI ionization, 70 eV). IR spectra were acquired on a Bruker Alpha FT-IR spectrometer (all samples were analyzed directly without dilution in KBr). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-500 (and DRX-600) in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. Polyphosphate ester (PPE) was synthesized according to the described method [24]. Hydrazides were synthesized using general approach described in [25].

Synthesis of compounds **1**. General method (one-pot approach). 10 mmol of amine (or hydrazide) R-NH_2 (or R-C(O)-$NHNH_2$) was added to refluxing solution of 10 mmol succinic anhydride in 50 mL of chloroform. Resulted mixture was being refluxed for 6 h, then the PPE (1 g for **1a**; 2 g for **1b-f**; 3 g for **1h-p**; 5 g for **1g**) was added, and reaction continued for 6 h at the same temperature. General method (two-step approach). 10 mmol of amine (or hydrazide) R-NH_2 (or R-C(O)-$NHNH_2$) was added to refluxing solution of 10 mmol succinic anhydride in 50 mL of chloroform. Resulted mixture was being refluxed for 6 h. Formed precipitate was filtered, washed by 30 mL of chloroform, and suspended in 50 mL of chloroform in 100 mL flask. To the resulted suspension the PPE (1.5 g for **1a-f**; 2.5 g for **1h-p**; 5 g for **1g**) was added, and reaction mixture was refluxed for 6 h. For the both approaches the reaction can be controlled by TLC (chloroform as eluent for **1a-f** and chloroform with isopropanol (90 : 10) for **1g-p**). At the completion of the imidization reaction, the reaction mixture turned

homogenous (except for **1g** that precipitates out of the reaction mixture). Isolation of **1a-f** and **1h-p**. Reaction mixture was treated with 35 mL of $NaHCO_3$ hot saturated solution, then organic fraction was separated and dried with Na_2SO_4. Chloroform was removed on rotary evaporator and resulted precipitate was washed by 30 mL of hot methanol. Isolation of **1g**. The precipitate was filtered off and washed by chloroform (3 × 30 mL).

Synthesis of compounds **2** (general method). 1.11 g (16 mmol) of hydroxylamine hydrochloride was dissolved in 6.8 mL of 20% ammonia water solution. The excess of ammonia was removed under vacuum followed by argon bubbling within 3 h. The hydroxylamine water solution was added to a suspension **1** (4 mmol) in 1 mL of methanol. Resulted reaction mixture was stirred at 30 ℃ for 1 h (except for **2b** that was stirred at 40 ℃ for 8 h), the precipitate structure changing (from crystalline to amorphous) was observed during the reaction. Resulted precipitate was filtered, washed by water (3 × 30 mL) and chloroform (3 × 30 mL), and dried under P_2O_5.

Compounds **2b-p** were synthesized for the fist time. Compound **2a** also described in [26]. All spectral data are available in Supporting material. Most of the ^1H NMR spectra of the synthesized hydroxamic acids **2** (see supp. mat.) has additional signals or broad peaks related to cis-trans isomerization [27].

Supporting Information

All the spectra are presented in Supporting materials (Figures S1–S92).

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Science and Higher Education of the Russian Federation (state registration No. AAAA-A19- 119071 890015-6).

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