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Selective conversion of *O*-succinimidyl carbamates to *N*-(*O*-carbamoyl)-succinmonoamides and ureas

Natalya I. Vasilevich,[a,*] Navzer D. Sachinvala,[b] Karol Maskos[c] and David H. Coy[a]

[a]*Peptide Research Laboratory, Tulane Health Sciences Center, 1430 Tulane Avenue, SL12, New Orleans, LA 70112, USA*
[b]*Southern Regional Research Center, USDA-ARS, 1100 Robert E. Lee Blvd., New Orleans, LA 70124, USA*
[c]*Coordinated Instrumentation Facility, Tulane University, 605 Lindy Boggs Building, New Orleans, LA 70118, USA*

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Abstract—*N*-Monoalkyl-*O*-succinimidyl carbamates reacted with primary and secondary amines to produce ureas. However, *N*,*N*-dialkyl-*O*-succinimidyl carbamates reacted with primary and secondary amines, via succinimide ring opening, to afford *N*-(*O*-carbamoyl)-succinmonoamide derivatives. This ring-opening trend was also true with hydroxy and alkoxy nucleophiles. Herein, general methods for the synthesis and NMR characterization of *N*-(*O*-carbamoyl)-succinmonoamides are reported.

The reaction between *N*-monosubstituted-*O*-succinimidyl carbamates and primary or secondary amines is a general method for producing symmetrical and unsymmetrical ureas.[1–3,5] While preparing a peptoid combinatorial library, we wanted to obtain unsymmetrical ureas from *N*,*N*-disubstituted-*O*-succinimidyl carbamates (**1**, Fig. 1). Instead, the only products realized from the reaction of **1** with primary or secondary amines were the succinimide ring opening adducts, *N*-(*O*-carbamoyl)-succinmonoamides **2**, and this happened without regard to nitrogen or oxygen nucleophiles (hydroxy, alkoxy, and primary or secondary amines, see structures **2a**–**2k**). In all cases no side reactions were obtained. Therefore, this ring-opening reaction could be a general method for the synthesis of *N*-(*O*-carbamoyl)-succinmonoamide derivatives **2** (Fig. 1), which appear to be analogs of *N*-acyl-*O*-carbamoyl hydroxylamine. To fulfill our original objective, i.e. the synthesis of unsymmetrical urea **3**, we changed the order of events and reacted *O*-succinimidyl carbamates of primary amines with secondary amines (Fig. 1). Herein we will discuss the syntheses of eleven new *N*-acyl-*O*-carbamoyl hydroxylamine analogs **2** and one urea **3** to exemplify our novel discovery.

Syntheses of *N*-(*O*-carbamoyl)-succinmonoamide derivatives **2a**–**2k** were possible under both solid and liquid phase conditions (Fig. 1). Solid-phase syntheses of **2a**–**c**, required the Fmoc-Rink amide resin and TFA cleavage methods.[4] The secondary amines for the synthesis of **2a**–**c** were obtained by method of Heizmann et al.[4] The deprotected Fmoc amide resin was acylated with bromoacetic acid using DCC, and the α-bromo substituent was then displaced with primary amines. Reactions of the resin-bound secondary amines with disuccinimidyl carbonate afforded resin-bound **1**.[5] Compounds **2a** and **2b** were formed by reactions of resin-bound **1** with 4-fold molar excess of 4-phenylbutylamine, and **2c** was formed by reaction with propylamine in DMF. TFA was then used to release compounds **2a**–**c** from the resins.[4] Secondary amines for liquid phase preparations of **2d**, **2g**, **2h**, and **2i** were purchased commercially and those for **2e** and **2f** were prepared by reductive alkylation. Their conversion to **1** was achieved by reacting the amine with excess disuccinimidyl carbonate.[5] *N*-(*O*-Carbamoyl)-succinmonoamides **2d**–**2i** were prepared by equimolar reaction of **1** with amines in the presence of diisopropylethylamine (DIPEA, 2-fold molar excess, 4 h). When **1** was stirred overnight in methanolic sodium hydroxide the C-terminal acid, **2j**, and the methyl ester **2k** were produced in an 8:2 ratio. However, with Na in dry methanol only **2k** was produced. Yields for all products are shown in Fig. 1. While the conversion of the succinimidyl carbamates **1** to hydroxylamine analogs **2** were nearly quantitative, yields reported herein (Fig. 1) are for the overall processes, i.e. starting with amines to

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* Corresponding author. Fax: 504-584-3586; e-mail: nvasile@tulane.edu

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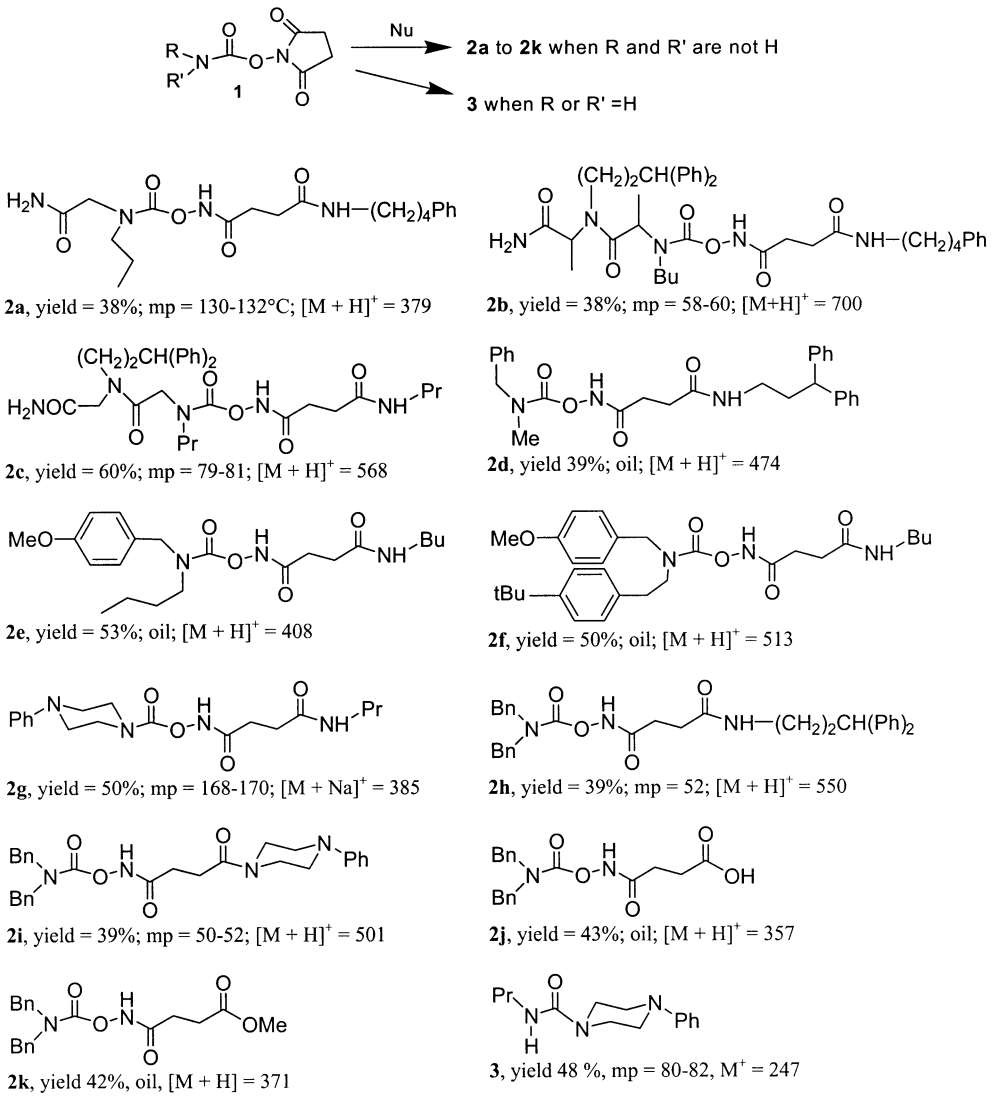


Figure 1. Syntheses of *O*-acyl-hydroxamic acid analogs and an urea.

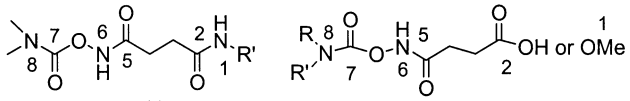
form the carbamates **1**, and then converting them to the *N*-(*O*-carbamoyl)-succinmonoamide derivatives **2**. Urea **3** was obtained by reacting a propyl amine with disuccinimidyl carbonate, followed by nucleophilic displacement of *N*-hydroxysuccinimide with *N*-phenylpiperazine.[5]

General procedure for the preparation of *N*-(*O*-carbamoyl)-succinmonoamides (e.g. **2d**–**2i**): A methylene chloride solution of the secondary amine (0.2 mol in 10 mL) and DIPEA (0.2 mol) was added to *N*,*N*′-disuccinimidyl carbonate in the same solvent (0.4 mol in 50 mL). After 2 h, the solution was washed serially with 10% aqueous HCl, 20% aqueous sodium bicarbonate, and water, then dried over Na_2SO_4, and concentrated in vacuo to give an oil. Excess of *N*,*N*′-disuccinimidyl carbonate was removed by filtration through a short silica gel column (60 angstroms, 2×2 cm) using methylene chloride. The effluent containing crude *O*-succinimidyl carbamate **1**, was concentrated and a solution of the amine (0.2 mol) and DIPEA (800 μL) in DMF (60 mL) was added, and the mixture stirred 4 h. The solvent was evaporated and the product (**2**) was purified by HPLC or crystallization (acetone, acetic acid and water).

Multidimensional NMR, mass spectrometry, and reverse-phase chromatography (Dynamax® 300 A, 5 or 8 μM, 21.4×250 mm, UV detection 280 nm) were used to characterize all new compounds. Chemical shift assignments for compounds **2a**–**2k** were made using ^{1}H, ^{13}C, and ^{15}N spectra. Table 1 shows the ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of the 9-atom region (including oxygen) common to the new hydroxylamine analogs **2a**–**2i**. Derivatives **2j** and **2k** contain oxygen (instead of nitrogen) at position 1, therefore the chemical shift entries for N1 in Table 1 are missing. Proton assignments were made from the 1 and 2D, COSY,[6,7] TOCSY,[8,9] and ROESY[10,11] spectra. Carbon and nitrogen assignments were made using the HSQC[12–14] and HMBC[15,16] methods.

Analogs of hydroxyl amines inhibit nucleic acids synthesis,[17] are mutagenic,[18] and may possess antimalarial

Table 1. ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in the common part of *N*-(*O*-carbamoyl)-succinmonoamides[a]



2a- 2i **2j** and **2k**

Compound	N_1H (C_1–^1H)	N_1 ($^{13}C_1$)	C_2=O	C_3H	C_3	C_4H	C_4	C_5=O	N_6H	N_6	C_7=O	N_8
2a	7.968	116.4	171.59	2.312	31.06	2.312	28.41	170.47	11.551	175.0	155.71	83.5
							28.45	170.40	11.538	174.8	155.29	83.1
2b	7.848	117.0	171.48	2.389	31.01	2.389	28.50	170.6	11.613	175.4	155.60	126.4
2c	7.835	116.8	171.52	2.315	31.10	2.319	28.52	170.25	11.481	174.6	155.76	82.6
								170.32	11.525	174.8	155.71	81.6
											155.65	
											155.46	
2d	7.957	116.5	171.67	2.404	31.18	2.404	28.60	170.70	11.579	174.9	155.90	65.3
											155.34	
2e	7.815	117.1	171.00	2.351	31.04	2.351	28.44	170.42	11.520	174.7	155.67	[b]
2f	7.829	117.1	171.00	2.351	31.04	2.351	28.44	170.52	11.588	175.0	155.57	[b]
2g	7.847	116.9	171.48	2.346	31.07	2.346	28.53	170.57	11.540	174.5	154.34	80.57
2h	7.918	116.5	171.52	2.367	31.00	2.367	28.45	170.73	11.672	175.5	155.81	[b]
2i		113.5	170.35	2.677	28.21	2.433	28.18	170.83	11.713	175.5	155.85	90.1
2j			173.21	2.508	28.49	2.390	26.84	169.37	11.853	176.0	154.78	91.7
												90.9
2k	3.605	51.34	172.27	2.587	28.11	2.428	26.65	169.05	11.722	174.9	154.72	[b]

[a] NMR chemical shifts on δ scale; ^1H shifts relative to δ (DMSO) = 2.500 ppm; ^{13}C shifts relative to δ (DMSO) = 39.51 ppm; ^{15}N shifts relative to δ (liquid NH_3) = 0.00 ppm.

[b] Crosspeaks not seen in the ^1H–^{15}N HMBC spectrum—concentration of the compound too low.

activity.[19] In the clinic they find use as metal chelators.[20–24] Our new preparative methods for their analogs are convenient and may be used in the synthesis of diverse peptoid libraries that contain ureas and *N*-(*O*-carbamoyl)-succinmonoamides. A study involving the ring-opening reactions of substituted succinic, glutaric, and adipic imides under similar conditions is underway. Finally, we propose the following generalization: When *N*-(*O*-carbamoyl)-succinmonoamides via the succinimide ring-opening reaction are required the synthesis should begin with *N*,*N*-dialkyl-*O*-succinimidyl carbamates. When unsymmetrical ureas are required, the synthesis should start with *N*-monoalkyl-*O*-succinimidyl carbamates.

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