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Conversion of *O*-succinimidyl carbamates to *N*-(*O*-carbamoyl)-succinmonoamides and ureas: effects of *N*-substituents and reaction conditions on the reaction pathway

Natalya I. Vasilevich* and David H. Coy

Peptide Research Laboratory, Tulane Health Sciences Center, 1430 Tulane Avenue, SL12, New Orleans, LA 70112, USA

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Abstract—Whereas *N*-monoalkyl-*O*-succinimidyl carbamates reacted with primary and secondary amines to produce only ureas, *N*,*N*-dialkyl-*O*-succinimidyl carbamates reacted with primary and secondary amines to produce *N*-(*O*-carbamoyl)-succinmonoamides. *N*-Alkyl-*N*-aryl-*O*-succinimidyl carbamates under the same condition led to mixture of both products. The effects of *N*-substituents and reaction conditions on *O*-succinimidyl carbamates conversion are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

A general method for symmetrical and unsymmetrical urea synthesis utilizes nucleophilic substitution between *N*-monoalkyl-*O*-succinimidyl carbamates and primary or secondary amines.[1–4] Recently, we demonstrated that *N*,*N*-dialkyl-*O*-succinimidyl carbamates under the same conditions afford the succinimide ring opening adducts, *N*-(*O*-carbamoyl)-succinmonoamides or hydroxylamine derivatives.[5] This can potentially cause unexpected synthetic outcomes, particularly in combinatorial studies where intermediates are often poorly characterized, if at all. It was also shown that this unusual reaction pathway does not depend on the type of nucleophile (hydroxy, alkoxy, primary and secondary amines) employed.[5]

In an effort to evaluate whether other reaction conditions affect the reaction pathway, we next focused on two model reactions: the first between *N*,*N*-dibenzyl-*O*-succinimidyl carbamate **1** and 3,3-diphenylpropylamine and the second between *N*-3,3-diphenylpropyl-*O*-succinimidyl carbamate **2** and 3,3-diphenylpropylamine (Table 1). Carbamate **1** selectively produced *N*-(*O*-carbamoyl)-succinmonoamide without regard to solvent and the presence of base. In terms of solvent effects, reaction in methylene chloride, dimethylformamide, benzene, THF and acetonitrile led to the same product and, moreover, yields were very similar. Performing the reaction without base made it much slower and decreased yields to only 30% even after refluxing overnight. As before, *N*-(*O*-carbamoyl)succinmonoamide remained the only product. Carbamate **2** in all cases afforded only the urea and DIPEA base had little influence on the rate and the yield of conversion. Thus, nucleophilic substitutions in *N*-monoalkyl- and *N*,*N*-dialkyl-*O*-succinimidyl carbamates are confirmed to be very selective and appear independent of reaction conditions.

Factors potentially influencing the unexpected reaction pathway include steric, conformational, and electronic considerations. The central carbonyl group in *N*,*N*-dialkyl-*O*-succinimidyl carbamate is more sterically hindered than that in the *N*-monoalkyl-*O*-succinimidyl carbamate and should promote nucleophilic attack on succinimide carbonyl. However, while this is important, it cannot be the determining factor since *N*-alkyl-*N*-nitroso-*O*-succinimidyl carbamates react with amines to produce the corresponding ureas regardless of the degree of steric hindrance.[4,6] Additionally, there is a free hydrogen atom in *N*-monoalkylcarbamates that can form an intramolecular hydrogen bond with the carbonyl or with the nitrogen atom in a succinimide ring thus potentially facilitating succinimide group loss and urea formation. There is no equivalent atom for intramolecular hydrogen bonding in *N*,*N*-dyalkylcarbamates and thus no possibility to facilitate urea formation this way. Again, this factor is not essential, otherwise solvent type and base concentration effects would be far greater than described here. Electronic

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

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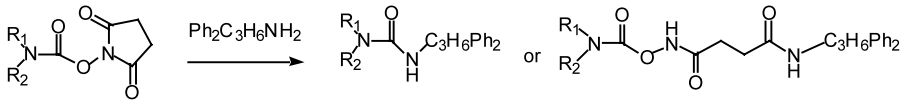
Table 1. Reaction between *O*-succinimidyl carbamates **1** and **2** and 3,3-diphenylpropylamine



1: R_1=R_2=Bn
2: R_1= $Ph_2C_3H_6$, R_2=H

A **B**

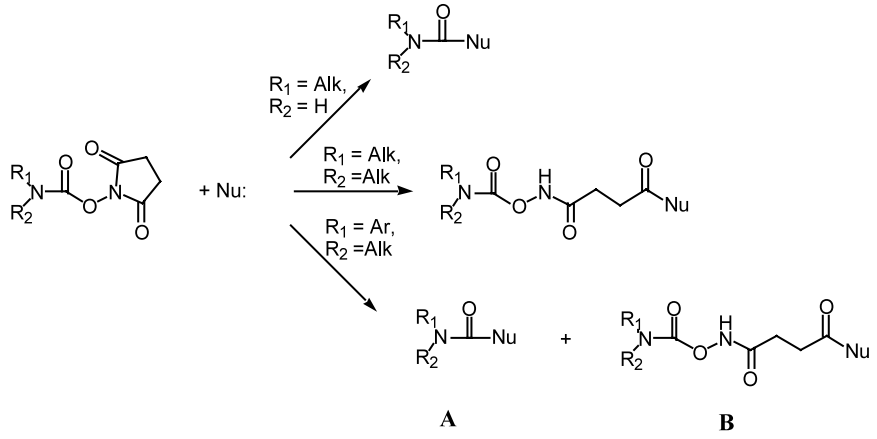
Carbamate	Solvent	Base, DIPEA	Product	Yield, %
1	CH_2Cl_2	1 equiv.	**B**	68
	CH_2Cl_2	2 equiv.	**B**	73
	CH_2Cl_2	0 equiv.	**B**	30[a]
	CH_3CN	2 equiv.	**B**	69
	THF	2 equiv.	**B**	67
	DMF	2 equiv.	**B**	74
	Benzene	2 equiv.	**B**	70
2	CH_2Cl_2	1 equiv.	**A**	83
	CH_2Cl_2	0 equiv.	**A**	69
	CH_2Cl_2	2 equiv.	**A**	85
	CH_2Cl_2	4 equiv.	**A**	88
	DMF	1 equiv.	**A**	90
	CH_3CN	1 equiv.	**A**	85

[a] Refluxing overnight required.

effects could be manifested via the increased electron-donating potential of two *N*-alkyl over monalkyl groups being strong enough to make nucleophilic attack on carbamate carbonyl less preferable than attack on succinimide carbonyl.

Although all three factors favor *N*-monoalkyl carbamates conversion to ureas and *N*,*N*-dialkyl carbamates to the *N*-(*O*-carbamoyl)-succinmonoamides, intuitively the most important seems to be electron properties of the two *N*-alkyl substituents. We theorized that it would be possible to find some *O*-succinimidyl carbamates structures which possess electron properties averaging between *N*-monoalkyl and *N*,*N*-dialkyl carbamates which would be predicted to give mixtures of both urea and hydroxylamine derivative. *N*-Alkyl-*N*-aryl-*O*-succinimidyl carbamates seemed to be possible candidates since, on the one hand, they have two *N*-substituents, so that steric and conformational factors promote ring opening and, on the other hand, although the *N*-alkyl-group contributes electron-donating effects, the *N*-aryl group possesses some σ-electron-withdrawing properties and should facilitate urea synthesis. Regarding a suitable molecular model, some years ago the synthesis of ureas from *N*-indoline-*O*-succinimidyl carbamate, a derivative of a secondary *N*-aryl-*N*-alkyl carbamate, was published.[7,8] Reported yields were poor and the authors used chromatography columns for purification from multiple products. We surmised that this might be due to formation of ring opening products (**B**) as well as the expected ureas (**A**) in the reaction scheme in Fig. 1.

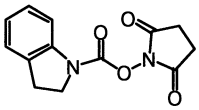
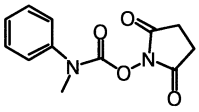
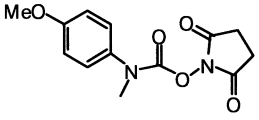
To test this prediction, a number of reactions between *N*-indoline-*O*-succinimidyl carbamates and different nucleophiles were carried out in accordance with reaction conditions described in our previous paper.[5] These are detailed in Tables 2 and 3 and, indeed, in most cases we observed mixtures of products **A** and **B**, which, in contrast to the *N*,*N*-dialkyl-*O*-succinimidyl



A **B**

Figure 1. Effect of *N*-substituent in *O*-succinimidyl carbamates on pathway of the reaction.

Table 2. Reaction between *N*-alkyl-*N*-aryl-*O*-succinimidyl carbamates and nucleophiles

	Carbamate	Nucleophile	Solvent	Base	Ratio A:B[a]
3		$BuNH_2$	CH_2Cl_2	DIPEA, 2 eq.	3:1
		$BuNH_2$	CH_2Cl_2	------	3:1
		$BuNH_2$	$BuNH_2$	$BuNH_2$	10:1
4		4-Phenylbutylamine	CH_2Cl_2	DIPEA, 2 eq	1:1.2
5		3-Butoxypropylamine	CH_2Cl_2	DIPEA, 2 eq	1.3:1
		3-Butoxypropylamine	CH_3CN	DIPEA, 2 eq	1.5:1
6		Piperidine	CH_2Cl_2	DIPEA, 2 eq	1.25:1
7		N-Phenylpiperazine	CH_2Cl_2	DIPEA, 2 eq	1:10
8		^-OEt	EtOH	NaOEt	0:1
9		^-OH	MeOH	NaOH	1[b]:2.5
10		$BuNH_2$	CH_2Cl_2	DIPEA, 2 eq	1:3
11		$BuNH_2$	CH_2Cl_2	DIPEA, 2 eq	1:8
12		3-Butoxypropylamine	CH_2Cl_2	DIPEA, 2 eq	1:17

[a] – See ref. 9

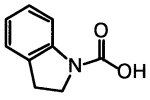
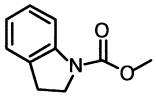
[b] – Instead of  only  was obtained.

Table 3. Physical properties of compounds **3**–**12**

Compound	mp, °C (AcOH)	$(M+H)^+$, or $(M+Na)^+$ (MALDI)	t_R, min[c]	HRMS (FAB)		
				Found m/z	Calcd M^+	Formula
3A	Oil	219[a]	24.6	219.1479	219.1497	$C_{13}H_{19}N_2O$
3B	105–107	334[a]	20.3	334.1782	334.1767	$C_{17}H_{24}N_3O_4$
4A	Oil	295[a]	41.6	295.1788	295.1810	$C_{19}H_{23}N_3O_4$
4B	136–138	432[b]	34.2	410.2100	410.2080	$C_{23}H_{28}N_3O_4$
5A	Oil	278[a]	36.8	277.1916	277.1916	$C_{16}H_{25}N_2O_2$
5B	137–139	415[b]	29.0	392.2188	392.2185	$C_{20}H_{30}N_3O_5$
6A	Unstable oil	231[a]	34.1			
6B	Unstable oil	369[b]	23.7	346.1758	346.1767	$C_{18}H_{24}N_3O_4$
7A	oil	308[a]	24.2	308.1769	308.1763	$C_{19}H_{22}N_3O$
7B	38–40	423[a]	19.7	423.2036	423.2032	$C_{23}H_{27}N_4O_4$
8B	116	307[a]	20.3	307.1295	307.1294	$C_{15}H_{19}N_2O_5$
9A	Oil	178[a]	25.6	178.0879	178.0868	$C_{10}H_{12}NO_2$
9B	153–155	301[b]	11.2	279.0970	279.0981	$C_{13}H_{15}N_2O_5$
10A	Oil	230[b]	24.7	207.1504	207.1497	$C_{12}H_{19}N_2O$
10B	136–139	344[b]	18.8	322.1752	322.1767	$C_{16}H_{24}N_3O_4$
11A	Oil	237[b]	19.4	237.1586	237.1603	$C_{13}H_{21}N_2O_2$
11B	146–148	375[b]	16.7	352.1866	352.1872	$C_{17}H_{26}N_3O_5$
12A	Oil	295[a]	35.3	295.2008	295.2022	$C_{16}H_{27}N_2O_3$
12B	123–125	410[a]	25.7	410.2271	410.2291	$C_{20}H_{32}N_3O_6$

[a] Denotes $(M+H)^+$.
[b] Denotes $(M+Na)^+$.
[c] RP-HPLC on C-18 bonded silica gel column, 20%B to 80%B (20%B to 80%B).

carbamate reactions, essentially depend on the type of nucleophile and the reaction conditions used. *N*-Methyl-*N*-phenyl-*O*-succinimidyl carbamate also leads to a mixture of products but the reduced percentage of urea was probably due to stronger steric hindrance. Comparison of the reaction products from *N*-methyl-*N*-*p*-methoxyphenyl carbamate and *N*-methyl-*N*-phenyl-*O*-succinimidyl carbamate reveals higher yields of the ring opening product presumably because of the electron-donating effect of *p*-methoxy-substituent of the aryl-group.

In conclusion, we have shown that *N*-substituents in *O*-succinimidyl carbamates have a profound affect on reaction pathways due primarily to their electronic effect. While the reactions between *N*-monoalkyl and *N*,*N*-dialkyl carbamates and nucleophiles are very selective, *N*-aryl-*N*-alkyl carbamates fall in between and seem to usually afford a mixture of urea and hydroxylamine derivative. Although from a synthetic standpoint it is sometimes possible to use *N*-aryl-*N*-alkyl carbamates for urea synthesis,[7,8] caution should be exercised regarding the unavoidable production of significant amounts of the ring opening contaminants.

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9. ^{1}H NMR spectra (DMSO) for *N*-[*O*-(*N*′-alkyl-*N*′-arylcarbamoyl)]-succinmonoamides: **3B**: δ 11.79 (br s, 1H); 7.87 (br s, 1H); 7.64 (br s, 1H); 6.82–7.28 (m, 3H); 4.05 (t, 2H); 3.03–3.19 (m, 4H); 2.27–2.41 (m, 4H); 1.24–1.39 (m, 4H); 0.89 (t, 3H); **4B**: δ 11.77 (br s, 1H); 7.87 (t, 1H); 7.64 (br s, 1H); 7.15–7.29 (m, 7H); 7.02 (t, 1H); 4.05 (t, 2H); 3.17 (t, 2H); 3.05–3.09 (m, 2H); 2.575 (t, 2H); 2.34–2.40 (m, 4H); 1.57–1.60 (m, 2H); 1.38–1.44 (m, 2H); **5B**: δ 11.68 (br s, 1H); 7.86 (t, 1H); 7.65 (br s, 1H); 7.01–7.29 (m, 3H); 4.05 (t, 1H); 3.33–3.67 (m, 4H); 3.18 (t, 2H); 3.01–3.11 (q, 2H); 2.36–2.39 (m, 4H); 1.29–1.63 (m, 6H); 0.89 (t, 3H); **6B**: δ 11.80 (br s, 1H); 7.62 (br d, 1H); 6.81–7.34 (m, 8H); 4.05 (t, 2H); 3.61–3.63 (m, 4H); 3.10–3.25 (m, 6H); 2.67 (t, 2H); 2.44 (t, 2H); **7B**: δ 11.77 (br s, 1H); 7.65 (br s, 1H); 4.05 (t, 2H); 3.39–3.43 (m, 4H); 3.17 (t, 2H); 2.59 (t, 2H); 2.40 (t, 2H); 1.42–1.60 (m, 6H); **8B**: δ 11.84 (br s, 1H); 7.65 (br s, 1H); 7.01–7.29 (m, 3H); 4.05–4.09 (m, 4H); 3.17 (t, 2H); 2.43–2.58 (m, 4H); 1.20 (t, 3H); **9B**: δ 11.07 (br s, 1H); 7.01 (d, 1H); 6.48–6.90 (m, 3H); 5.43 (br s, 1H); 3.39 (t, 2H); 2.89 (t, 2H); 2.34–2.42 (m, 4H); **10B**: δ 11.56 (br s, 1H); 7.83 (t, 1H); 7.26–7.43 (m, 4H); 3.28 (s, 3H); 3.01–3.04 (q, 2H); 2.32 (s, 4H); 1.26–1.39 (m, 4H); 0.87 (t, 3H); **11B**: δ 11.49 (br s, 1H); 7.82 (t, 1H); 7.29 (d, 2H); 6.95 (d, 2H); 3.77 (s, 3H); 3.22 (s, 3H); 3.00–3.07 (q, 2H); 2,31 (s, 4H); 1.23–1.39 (m, 4H); 0.87 (t, 3H); **12B**: δ 11.51 (br s, 1H); 7.84 (t, 1H); 7.29 (d, 2H); 6.95 (d, 2H); 3.77 (s, 3H); 3.32–3.36 (m, 4H); 3.22 (s, 3H); 3.05–3.09 (q, 2H); 2.31 (s, 4H); 1.28–1.63 (m, 6H); 0.88 (t, 3H).