

Different Reactivity of Hydroxylamine with Carbamoyl Azides and Carbamoyl Cyanides: Synthesis of Hydroxyureas and Carbamoyl Amidoximes

Jairo Paz, Carlos Pérez-Balado, Beatriz Iglesias, and Luis Muñoz*

Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo, Campus Universitario, 36310 Vigo, Spain

lmunoz@uvigo.es

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The carbamoylating agents carbamoyl azides and carbamoyl cyanides (aka cyanoformamides) react with hydroxylamine in different ways, leading in the first case to *N*-hydroxyureas and, in the case of carbamoyl cyanides, to carbamoyl amidoxime derivatives. The synthetic procedure developed for the latter type of compound, which represents an interesting precursor for heterocyclic structures, allowed the highly efficient preparation of a wide selection of examples. The *Z* configuration of the double bond in the amidoxime moiety was proposed on the basis of comparison between experimental and calculated ¹³C and ¹⁵N NMR chemical shift values for the isopropyl and benzyl derivatives.

Introduction

N-Alkyl-*N'*-hydroxyureas are interesting organic compounds with relevant biological activity. The hydroxyurea functional group is capable of interacting with a variety of proteins by making use of its metal-chelating and redox properties.¹ The simple *N*-hydroxyurea is currently in use for the treatment of a variety of cancers and sickle cell disease.² The mechanism of action of this compound, although not fully understood, is believed to be based on the release of nitric oxide.³

N-Hydroxyureas have been traditionally prepared from amines by acylation with phosgene or triphosgene, followed

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by hydroxyamination of the carbamoyl chloride or the isocyanate with hydroxylamine in a basic medium.^{1b,4} The intermediate isocyanate can also be prepared by a Curtius rearrangement from an acyl azide.⁵ Alternatively, hydroxyamination can also be achieved by using benzyloxyamine to yield the corresponding *N*-benzyloxyurea, which can be subsequently reduced.^{1b,6} On the other hand, reaction of an amine with 4-nitrophenyl chloroformate and then with hydroxylamine also gives an *N*-hydroxyurea, albeit in a low yield of 30% for both reaction steps.⁷ More straightforward procedures, which give good results in specific cases, are based on the reaction of an amine with phenyl *N*-hydroxycarbamates,⁸ *N*-benzyloxycarbamates⁹ (in the latter case followed by reduction), or *tert*-butyl *N*-mesitylenesulfonoxycarbamate, followed by acid hydrolysis.¹⁰

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Direct displacement of a benzotriazole group by hydroxylamine has also produced *N*-hydroxyureas, although the isolated yields range from extremely low to only moderate.¹¹ Carbonyldiimidazole and carbonylditriazole have also been used for the transient preparation of hydroxy- or alkoxyureas,¹² and ¹⁵N-labeled hydroxyurea has been prepared in a one-pot procedure in 74% yield from trimethylsilyl isocyanate.¹³ Most of these methods suffer from significant drawbacks, especially when applied to sensitive substrates. Yields are often poor to moderate, and this makes the procedure of little synthetic utility. Some of the reagents are toxic and hazardous, and in addition, intermediates such as carbamoyl chlorides and isocyanates are rather unstable toward nucleophilic attack.

Carbamoyl azides are reported to be good carbamoylating agents toward nitrogen nucheophiles.¹⁴ Similarly, amines have been shown to react with carbamoyl cyanides (aka cyanoformamides) in dichloromethane at room temperature, producing the corresponding ureas in high yields¹⁵ and suggesting that carbamoyl cyanides are also good carbamoylating agents.

Recently, we described the preparation of carbamoyl azides and carbamoyl cyanides through the low temperature reaction of primary amines and carbon dioxide, in acetonitrile, with tetramethylphenylguanidine as a base and either diphenylphosphoryl azide¹⁶ or a cyanophosphonate¹⁷ as the electrophile. When the reactivity of both types of compounds was tested toward nitrogen nucleophiles such as amines and hydrazines, we found that carbamoyl azides were excellent carbamoylating agents but carbamoyl cyanides gave a mixture of compounds in addition to the expected urea.¹⁸ Hydroxylamine provided the most extreme case, producing none of the corresponding urea when reacted with carbamoyl cyanides.¹⁹

In this paper we describe a comparative study on the reaction of hydroxylamine with carbamoyl azides and carbamoyl cyanides. Thus, we report a new and convenient high-yielding method for the preparation of *N*-hydroxyureas by hydroxyamination of carbamoyl azides. On the other hand, we show that the reaction of hydroxylamine with carbamoyl cyanides leads to carbamoyl amidoximes as single products in high yields and short reaction times. Carbamoyl amidoximes are interesting precursors for the synthesis of

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heterocyclic structures.²⁰ However, these compounds have received limited attention, and there are hardly any published methods concerning their preparation. These compounds have only been prepared by the reaction of N(S)-substituted mono-thiooxamides with hydroxylamine in refluxing pyridine²¹ or by aminolysis of nitroisoxazolone in acetonitrile at 50 °C.²²

Results and Discussion

The methodology described here is based on the efficient reaction between carbamoyl azides and nitrogen nucleophiles, specifically amines, which displace the azide group to yield the target ureas.¹⁴ However, the extension of this methodology to the preparation of *N*-hydroxyureas from carbamoyl azides and hydroxylamine has proven to be somewhat challenging, with experimental drawbacks and limitations identified in our initial attempts to develop a synthetic methodology. In an attempt to overcome these limitations, we directed our efforts at the fine-tuning and optimization of all the experimental details, a process that led to the development of several synthetic procedures that allow the transformation of different types of carbamoyl azides into the corresponding *N*-hydroxyureas.

SCHEME 1



The reaction was initially performed by adding a solution of the carbamoyl azide 1a in dichloromethane to a mixture of hydroxylamine hydrochloride and triethylamine in methanol, with a workup procedure that included a washing step with 10% aqueous HCl (Scheme 1). This approach led to the isolation of the hydroxyurea 2a in very good yield. This method was successfully applied to the synthesis of several *N*-hydroxyureas (Table 1, entries 1-10, procedure A). Although the expected products were isolated in very good yields (84-95%), an unidentified byproduct was also detected in all experiments. Furthermore, extraction from the aqueous phase of some of the compounds proved to be particularly difficult due to the small size of some molecules (e.g., allylamine or isopropylamine derivatives 2d and 2f) or to the presence of polar groups (e.g., glutamic acid or homoveratrylamine derivatives 2g and 2i).

In order to devise a more efficient method for the preparation of *N*-hydroxyureas, we decided to change the experimental conditions. The use of potassium carbonate in acetonitrile led to a cleaner process and the reaction of carbamoyl azide **1a** gave the expected hydroxyurea **2a**, albeit in low yield (30%), together with a new product identified as the *N*-carbamoyloxyurea **3** (61%) (Figure 1). This compound seems to arise from the reaction between the hydroxyurea **2a** and the starting azide **1a**, a hypothesis corroborated by the results shown in Scheme 2.

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TABLE 1. Synthesis of N-Hydroxyureas from Carbamoyl Azides

		O		O ⊥		
		RHN [^] N ₃ Proced.	A, B, C or D	► RHN´ `N	ІНОН	
		1		2		
Entry	1	R	Yield proc. A	Yield proc. B	Yield proc. C	Yield proc. D
1	a	Bn ⊡. MeO₂C	95%	92%		91%
2	b	Ph	94%	84%	73% ^a	31%
3	c		91%		84%	
4	d	>>/	89%		66% ^b	
5	e	\rightarrow	95%			
6	f	\downarrow	85%			
7	g	MeO ₂ C MeO ₂ C	93%		90%	98%
8	h	MeO ₂ C	90%	41%		96%
9	i	MeO MeO	84%			
10	j	Bn	92%		79%	
11	k	MeO ₂ C			81%	93%
12	1	PMB			76%	
13	m	MeO ₂ C			68%	
14	n	tBuO ₂ C			76%	95%
15	0	HN MeO ₂ C				91%
16	р	Ph MeO ₂ C				99%
17	q	EtO ₂ C				97%
18	r	MeO ₂ C				98%
19	s	MeO ₂ C				93%
20	t	EtO ₂ C				93%

^{*a*}Carbamoyloxyurea **6** was isolated in 18% yield. ^{*b*}Carbamoyloxyurea **9** was isolated in 13% yield.

The formation of the *N*-carbamoyloxyurea side product appears to be a consequence of a lack of hydroxylamine in the reaction medium. As a result, a new procedure (procedure B) was devised that involved the portionwise addition of the base to the

mixture of azide **1a** and NH₂OH·HCl in CH₃CN, which led to isolation of urea **2a** in 92% yield (Table 1, entry 1, procedure B).²³ This procedure was applied to the synthesis of N hydroxy.

This procedure was applied to the synthesis of N-hydroxyureas 2b and 2h, but inconsistent results were obtained



(Table 1, entries 2 and 8, procedure B). Compound **2b** was isolated in 84% yield along with a small amount (13%) of the *N*-carbamoyloxyurea **6** (Figure 2). The L-valine methyl ester derivative **2h** could only be isolated in a low yield (41%), accompanied by the carbamoyloxyurea derivative **7** (32% yield) (Figure 2), when the reaction was carried out on a 1.45 mmol scale. However, a larger scale experiment (3.10 mmol) led to the isolation of the *N*-carbamoyl-*N*-hydroxyurea **8** in 78% yield (Figure 2). The formation of this type of byproduct was not observed in subsequent procedures of synthesis of *N*-hydroxyureas.



FIGURE 1



FIGURE 2

In order to minimize the generation of side products that could arise from the reaction between the *N*-hydroxyurea and the carbamoyl azide, the addition procedure was modified again in an effort to guarantee an excess of free hydroxylamine throughout the whole process by allowing the reaction of the base with hydroxylamine hydrochloride before the addition of the substrate.²⁴ The results of the reaction for several carbamoyl azides derived from different amines are shown in Table 1 (entries 2–4, 7 and 10–14, procedure C). *N*-Hydroxyureas were prepared in good yields, although the carbamoyloxyurea derivatives were isolated in several cases (entries 2 and 4). The formation of these byproducts cannot be completely ruled out for the remaining examples, even though they were not detected.

An alternative experimental procedure was finally developed in an attempt to improve the solubility of the hydroxylamine hydrochloride in the reaction medium, and this involved reducing the particle size by grinding.²⁵ The results for several carbamoyl azides are shown in Table 1 (entries 1-2, 7-8, 11 and 14-20, procedure D). Carbamoyl azides derived from α -aminoesters have been efficiently transformed into the corresponding *N*-hydroxyureas, with isolated yields in the range of 91–99% and reaction times between 1 and 3 h (Table 1, entries 1, 7, 8, 11 and 14–20, procedure D). However, under these reaction conditions the carbamoyl azide derived from (*R*)- α -methylbenzylamine, the precursor of **2b**, proved to be fairly unreactive and gave only low conversion rates after 3 h, with most of the starting azide (66%) recovered (Table 1, entry 2, procedure D). Longer reaction times did not seem to improve the results for this particular azide.

Regardless of the experimental procedure followed in the synthesis of the *N*-hydroxyureas derived from α -aminoesters, these compounds should not be kept in the basic reaction medium for prolonged periods due to the possibility of intramolecular reaction between the hydroxylamino and ester groups. In fact, in some of the experiments aimed at the synthesis of *N*-hydroxyurea **2a**, traces of the *N*-hydroxyhydantoin byproduct **10a** were detected (Figure 3).



FIGURE 3

This type of cyclized product is not unprecedented and has been previously observed in the synthesis of *N*-hydroxyureas derived from aminoesters in which the ester group is located at a distance of four bonds from the hydroxylated nitrogen.²⁶ This situation was further corroborated by our own results, which showed that the reaction of *N*-hydroxyurea **2a** with K_2CO_3 in CH₃CN yields the corresponding hydantoin **10a** quantitatively after 10 h.

Strict control of the reaction time must be maintained during the synthesis of *N*-hydroxyureas from aminoesterderived carbamoyl azides in order to avoid the formation of these unwanted side products.

In order to study this process and to investigate the general tendency of the α -aminoesters derived *N*-hydroxyureas to produce *N*-hydroxyhydantoins in basic media, we reacted several *N*-hydroxyureas with K₂CO₃ (200 mol %) and Cs₂CO₃ (100 and 200 mol %) in CH₃CN. The results are shown in Table 2.

The use of potassium carbonate as the base led to the slow evolution of *N*-hydroxyureas derived from L-Phe-OMe, L-Ala-OMe, and L-Glu-OMe into the corresponding *N*-hydroxyhydantoins. These processes required long reaction times (8-12 h) to achieve high conversion rates (Table 2, entries 2,

⁽²³⁾ Procedure B: see Experimental Section.

⁽²⁴⁾ Procedure C: see Experimental Section.

⁽²⁵⁾ Procedure D: see Experimental Section.

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	R ₂ 0	R ₁ 0 O₂C / N / NHOH - 2	K ₂ CO ₃ or CH ₃	$\begin{array}{ccc} & & & & \\ CS_2CO_3 & & & & \\ CN & & & & \\ \hline CN & & & & \\ \hline \end{array} \begin{array}{c} HO_{N} & & \\ NH \\ O & & \\ R_1 \\ \hline \end{array}$	
Entry	2	R ₁	R ₂	Base, time	Yield
1	р	Ph	Me	K ₂ CO ₃ (200 mol %), 10 h	99%
2	a	Bn	Me	K ₂ CO ₃ (200 mol %), 10 h Cs ₂ CO ₃ (200 mol %), 2 h	98% 97%
3	s	Ме	Ме	K ₂ CO ₃ (200 mol %), 12 h Cs ₂ CO ₃ (100 mol %), 1.5 h	91% 98%
4	g	MeO ₂ C	Me	K ₂ CO ₃ (200 mol %), 8 h Cs ₂ CO ₃ (100 mol %), 1.5 h	39% 96%
5	h	\downarrow	Me	Cs ₂ CO ₃ (200 mol %), 2 h	96%
6	k	\checkmark	Me	Cs ₂ CO ₃ (200 mol %), 1.5 h	98%
7	0	HN	Ме	Cs ₂ CO ₃ (200 mol %), 3 h	93%
8	q	Ph	Et	Cs ₂ CO ₃ (100 mol %), 1.5 h	95%

TABLE 2. Intramolecular Reaction in Basic Conditions of α -Aminoester-Derived N-Hydroxyureas

3, and 4). Compounds **10a** and **10s** were obtained in high yields (98% and 91%, respectively; Table 2, entries 2 and 3), whereas the yield for the glutamic acid derivative was much lower (39%; Table 2, entry 4) and the presence of a new byproduct was detected. The formation of this compound can be attributed to a second cyclization process between the heterocyclic NH group and the remaining methyl ester group of hydantoin **10g**, a process that leads to the pyroglutamic acid derivative **11** (Scheme 3).

SCHEME 3



On the other hand, all of the experiments carried out with cesium carbonate led to the expected *N*-hydroxyhydantoins in high yields and short reaction times (Table 2, entries 2-8). The time factor could be the reason for the high yield obtained in this case of the L-Glu-OMe derivative **10g** (96%; Table 2, entry 4).

Our results show that the standard carbamoyl azides react more slowly than the ones derived from α -aminoesters. The higher reactivity of the latter compounds is a clear advantage in the synthesis of the corresponding *N*-hydroxyureas that minimizes the possible formation of *N*-hydroxyhydantoin byproduct. Steric reasons do not seem to account for this difference in reactivity between the two groups of carbamoyl azides because the least hindered structures are also the least reactive ones. In turn, carbamoyl cyanides were also reacted with hydroxylamine, directly applying the methodology thus far developed. Reaction of carbamoyl cyanide **12a** with a mixture of hydroxylamine hydrochloride and Et₃N in MeOH/CH₂Cl₂ led to isolation of the carbamoyl amidoxime **13a**, resulting from addition of hydroxylamine to the nitrile group, as the only product. This compound was obtained in high yield within a short reaction time (< 5 min) (Scheme 4).

SCHEME 4



An optimized procedure for the preparation of carbamoyl amidoximes that avoids the use of an aqueous workup was therefore developed. The use of an excess of KOH or *t*BuOK as a base, in MeOH, gave the results shown in Table 3. The yields are excellent in all cases and they refer to isolated and purified products.

All of these reactions were complete in approximately 10 min and gave the corresponding carbamoyl amidoxime as the only product.

Our results show that, under these reaction conditions, carbamoyl cyanides behave as activated nitriles and hydroxylamine selectively reacts with the cyanide group.

The experimental procedure developed for the synthesis of carbamoyl amidoximes was also applied to several carbamoyl azides in order to compare the reactivity of azides and cyanides under the reaction conditions employed. In this

$\begin{array}{c} 0 \\ R_{NH_{2}OH HCI, \text{ base, MeOH}} \\ H \\ 12 \end{array} \xrightarrow{\text{NH}_{2}OH HCI, \text{ base, MeOH}} R_{NH_{2}} \\ R_{NH_{2}} \\ R_{NH_{2}} \\ 13 \end{array}$						
Entry	12	R	Base	Yield		
1	a	Bn ™ MeO₂C	КОН	99%		
2	b	Ph	KOH †BuOK	99% 99%		
3	c	MeO ₂ C	tBuOK	99%		
4	d	Bn	KOH tBuOK	99% 98%		
5	e	MeO ₂ C	КОН	99%		
6	f	HN MeO ₂ C	KOH /BuOK	98% 99%		
7	g	EtO ₂ C	КОН	98%		
8	h	\bigcirc	КОН	99%		
9	i	MeO ₂ C	КОН	99%		
10	j	\downarrow	<i>t</i> BuOK	99%		

TABLE 3. Synthesis of Carbamoyl Amidoximes from Cyanoformamides

context, azides proved to be less reactive than cyanides, and after 2 h, the starting carbamoyl azide was recovered together with the expected *N*-hydroxyurea and the product from the addition of hydroxylamine to the carbonyl group through the hydroxyl oxygen atom (Scheme 5).

Computational Study

The configuration of the amidoxime moiety could not be established from routine experimental data. However, comparison between calculated and experimental NMR chemical shifts has been used in structural analysis to propose the conformation,²⁷ stereochemical features,²⁸ and even the whole

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apply this methodology to our molecules. The conformational space of the carbamoyl amidoxime group was explored in order to find all possible minima. First of all, Z and E isomers around the C=N bond were built, and the following bonds were subsequently considered for rotation (180°): N3-O4, C1-C2, and N6-C1 (see Figure 4 for numbering scheme).



FIGURE 4. Conformational minima of the amidoxime moiety.

The amide bond N6–C1 was found to be much more stable in the *trans* conformation, as the *cis* alternative has to be nonplanar to accommodate all atoms. The *s-cis* and *s-trans* conformations for the C1–C2 bond and the two planar dispositions for the N3–O4 bond were considered, yielding a total of 4 starting conformations for each configuration of the double bond. When all of the starting conformations had been minimized, only two conformers for each configuration of the double bond were found (Figure 4).

In general, the calculations show that the Z conformers are more stable than the E ones. In all cases, Z1 is the most stable conformation and is at least 4 kcal/mol lower in energy than the next minimum.

Compounds 13j and 13d, with isopropyl and benzyl side chains, respectively, were fully modeled in order to calculate their NMR chemical shifts. Rotation around the C_{sp3} -N6 bond in each compound yielded 3 and 2 minima, respectively, for each amidoxime moiety conformer. The 12 structures of compound 13j and the 8 structures of 13d were minimized in DMSO (PCM model) with three different basis sets: 6-31G(d), 6-311+G(d,p), and 6-311+G(2d,p). All of the minimized structures, together with their energies, are included in the Supporting Information section.

Isotropic shieldings were calculated for each minimized structure in DMSO at the same level of theory as the minimization. ¹⁵N and ¹³C NMR chemical shifts were calculated according to the linear regression formulas proposed by Franca et al.³⁰ and van Eikema Hommes et al.,³¹ respectively. Both authors propose two equations, one for isotropic shieldings calculated with the 6-31G(d) basis set and the other for isotropic shieldings calculated at a higher level of theory $[6-311+G(d,p) \text{ for } {}^{13}C \text{ and } 6-311+G(2d,p) \text{ for } {}^{15}N].$ The chemical shifts for the amidoxime moiety conformers are presented in Table 4. Each value was obtained by averaging the individual chemical shifts from all side chain conformers according to their respective free energies by means of a Boltzmann distribution. Two sets of calculated chemical shifts are presented for each compound: one with all the chemical shifts calculated with the smallest basis set (level A) and the other with the ¹³C NMR chemical shifts calculated with the 6-311+G(d,p) basis set (level B) and the 15 N NMR chemical shifts calculated with the 6-311+G(2d,p)

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SCHEME 5



TABLE 4. $^{13}\mathrm{C}$ and $^{15}\mathrm{N}$ NMR Chemical Shift Values for the Amidoxime Moiety Conformers

			C1	C2	N3	N5	N6	R2
$\mathbf{R} = i\mathbf{P}\mathbf{r}$	А	<i>Z</i> 1	157.6	145.4	-96.3	-312.5	-256.6	0.99975
		Z2	159.3	149.8	-73.1	-315.0	-245.9	0.99907
		<i>E</i> 1	156.4	149.3	-88.2	-317.9	-238.0	0.99883
		E2	160.5	145.5	-36.5	-325.1	-242.9	0.98768
	B/C	<i>Z</i> 1	156.4	144.4	-98.6	-318.1	-254.5	0.99974
		Z2	158.1	149.9	-82.6	-318.8	-242.8	0.99925
		<i>E</i> 1	154.8	148.2	-91.5	-320.9	-234.8	0.99794
		<i>E</i> 2	158.9	145.1	-45.7	-327.3	-240.3	0.99049
		Expt	159.8	145.9	-91.7	-320.2	-258.6	
R = Bn	А	<i>Z</i> 1	158.8	145.3	-95.7	-312.2	-266.2	0.99968
		Z2	160.1	149.8	-72.0	-314.9	-253.8	0.99878
		<i>E</i> 1	157.5	149.0	-87.5	-317.4	-248.4	0.99827
		<i>E</i> 2	161.1	145.3	-35.3	-325.2	-251.2	0.98755
	B/C	<i>Z</i> 1	157.1	144.2	-97.8	-317.8	-264.7	0.99950
		Z2	158.9	149.7	-80.8	-318.9	-252.7	0.99872
		<i>E</i> 1	155.1	147.9	-90.7	-320.7	-244.7	0.99706
		<i>E</i> 2	159.4	144.0	-35.6	-329.1	-248.9	0.98620
		Expt	160.9	145.8	-90.6	-320.0	-274.0	

basis set (level C). Experimental chemical shifts in DMSO for each compound are included for comparison.

Although all calculated chemical shifts agree rather well with the experimental values, only the square of the Pearson's correlation coefficient of the Z1 conformer is higher than 0.999 for both compounds in the two sets of calculations. Conformation Z2 also shows good correlation coefficients, but for all sets of data they are smaller than the Z1 coefficients.

The agreement between calculated and experimental NMR chemical shifts together with the relative energy values calculated for all conformations suggest a Z configuration for the amidoxime C=N double bond. These results are also consistent with Z1 being the most favored conformation in solution.

Conclusions

In summary, we have shown that carbamoyl azides and carbamoyl cyanides react with hydroxylamine in different ways leading, in the first case, to the expected *N*-hydroxyureas. Several experimental procedures were developed for the efficient preparation of different types of ureas. In the case of carbamoyl cyanides, the reaction with hydroxylamine leads to the carbamoyl amidoxime derivatives. The synthetic procedure developed for this last type of compound allowed the highly efficient preparation of a range of examples. The *Z* configuration of the amidoxime moiety double bond, which could not be established from routine experimental data, was proposed on the basis of comparison between experimental and calculated ¹³C and ¹⁵N NMR chemical shift values for the isopropyl and benzyl derivatives.

Experimental Section

General Procedures for the Synthesis of *N*-Hydroxyureas. Procedure A (Et₃N): Et₃N (900 mol %) was added to a suspension of NH₂OH·HCl (600 mol %) in MeOH (1 mL) and the reaction temperature was maintained with a room temperature water bath. The mixture was diluted with CH₂Cl₂ (10 mL) and stirred for 5-10 min. The carbamoyl azide (100 mol %) was added and the resulting mixture was stirred during the time indicated for each case. The reaction mixture was cooled to 0 °C with a H₂O/ice bath and 10% aqueous HCl saturated with NaCl (10 mL) was added. The two phases were separated and the aqueous solution was extracted with AcOEt $(6-8\times)$. The combined organic layers were dried over Na₂SO₄ and filtered and the solvents removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to give the corresponding *N*-hydroxyurea. **Procedure B** (K₂CO₃): A mixture of the carbamoyl azide (100 mol %), NH₂OH·HCl (400 mol %) and K₂CO₃ (200 mol %) in CH₃CN was stirred for 1 h. K₂CO₃ (100 mol %) was added and stirring was continued for 1 h. A further portion of K₂CO₃ (100 mol %) was added and the mixture was stirred until complete disappearance of the carbamoyl azide (TLC). The mixture was filtered, concentrated and purified by flash chromatography on silica gel to give the corresponding N-hydroxyurea. Procedure C (K₂CO₃): A mixture of NH₂OH · HCl (400 mol %) and K₂CO₃ (300 mol %) in CH₃CN was stirred for 30-40 min. The carbamoyl azide (100 mol %) was added and the resulting mixture was stirred for 1 h. After the addition of a further portion of K_2CO_3 (100 mol %) the mixture was stirred until complete disappearance of the carbamoyl azide (TLC). The mixture was filtered and concentrated and the residue was purified by flash chromatography on silica gel to give the corresponding N-hydroxyurea. Procedure D (K_2CO_3): A suspension of finely ground $NH_2OH \cdot HCl$ (600 mol %) in CH₃CN was stirred for 5-10 min. After this time, K₂CO₃ (300 mol %) was added over 5-10 min, followed by the carbamoyl azide (100 mol %) and a further portion of K_2CO_3 (400 mol %). The mixture was stirred for 1 h and a final portion of K₂CO₃ (100 mol %) was added. The mixture was stirred for the indicated time, diluted with CH₂Cl₂, filtered, and concentrated and the residue was purified by flash chromatography on silica gel to give the corresponding *N*-hydroxyurea.

(S)-Methyl 2-(3-Hydroxyureido)-3-phenylpropanoate (2a). **Procedure A:** Following the general procedure, the carbamoyl azide 1a (160 mg, 0.64 mmol, 100 mol %) was treated with NH₂OH·HCl (269 mg, 3.87 mmol, 600 mol %) and Et₃N (0.80 mL, 5.76 mmol, 900 mol %) in MeOH/CH₂Cl₂ (1:10, 11 mL) for 8 min to afford, after flash chromatography (silica gel, AcOEt/hexane 1:1 \rightarrow 2:1), the title compound **2a** (145 mg, 95% yield) as a colorless solid. Procedure B: Following the general procedure, the carbamoyl azide 1a (600 mg, 2.42 mmol, 100 mol %), NH₂OH·HCl (673 mg, 9.68 mmol, 400 mol %) and K2CO3 (1.34 g, 9.68 mmol, 400 mol %) in CH3CN (150 mL) afforded, after flash chromatography (silica gel, AcOEt/hexane 1:2 \rightarrow 1:1), the *N*-hydroxyurea **2a** (529 mg, 92%) yield) as a colorless solid. Procedure D: Following the general procedure, the carbamoyl azide **1a** (400 mg, 1.61 mmol, 100 mol %) was treated with NH2OH · HCl (672 mg, 9.67 mmol, 600 mol %) and K₂CO₃ (1.50 g, 10.82 mmol, 700 mol %) in CH₃CN (50 mL) for 2 h to afford, after flash chromatography (silica gel, AcOEt/ hexane 1:1), the N-hydroxyurea 2a (348 mg, 91% yield) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 8.33 (br s, 1H), 7.59 (br s, 1H), 7.3–7.0 (m, 5H), 6.49 (d, J = 8.2 Hz, 1H), 4.72 $(q, J = 3 \times 6.6 \text{ Hz}, 1\text{H}), 3.65 (s, 3\text{H}), 3.11 (dd, J = 13.4, 5.1 \text{ Hz},$ 1H), 3.07 (dd, J = 13.2, 6.2 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 161.3, 135.7, 129.1, 128.4, 126.9, 53.5, 52.3, 37.9 ppm. FT-IR (NaCl): ν 3305, 3066, 3030, 2951, 1723 (C=O ester), 1659 (C=O urea), 1542 cm⁻¹. [α]_D²³ +24° (*c* 4.10, CHCl₃). MS (ESI⁺): m/z (%) 261 ([M + Na]⁺, 100), 258 (13), 239 ([M + H]⁺, 13). HRMS (ESI⁺) calcd for C₁₁H₁₄N₂NaO₄ 261.0846; found 261.0846.

1-(2-Cyclohexenylethyl)-3-hydroxyurea (2c). Procedure A: Following the general procedure, the carbamoyl azide 1c (170 mg, 0.88 mmol, 100 mol %) was treated with NH₂OH·HCl (365 mg, 5.25 mmol, 600 mol %) and Et_3N (1.11 mL, 7.92 mmol, 900 mol %) in MeOH/CH₂Cl₂ (1:10, 11 mL) for 1 h to afford, after flash chromatography (silica gel, AcOEt/hexane 1:1 \rightarrow AcOEt), the title compound **2c** (148 mg, 91% yield) as a colorless solid. Procedure C: Following the general procedure, the carbamoyl azide 1c (200 mg, 1.03 mmol, 100 mol %), NH₂OH·HCl (286 mg, 4.12 mmol, 400 mol %) and K₂CO₃ (569 mg, 4.12 mmol, 400 mol %) in CH₃CN (80 mL) afforded, after flash chromatography (silica gel, AcOEt/hexane 1:2 \rightarrow 1:1), the title compound **2c** (160 mg, 84% yield) as a colorless solid. ¹H NMR (400 MHz, DMSO- d_6): δ 8.51 (d, J = 1.0 Hz, 1H), 8.22 (br s, 1H), 6.50 (t, $J = 2 \times 5.8$ Hz, 1H), 5.38 (m, 1H), 3.11 (m, 2H), 2.04 (t, $J = 2 \times 7.1$ Hz, 2H), 2.0–1.8 (m, 4H), 1.6–1.4 (m, 4H) ppm. ¹H NMR (400 MHz, CD₃OD): δ 8.17 (br s, 0.09 H), 6.62 (m, 0.59 H), 5.48 (m, 1H), 3.27 (m, 2H), $2.15 (t, J = 2 \times 7.0 \text{ Hz}, 2\text{H}), 2.0 - 1.9 (m, 4\text{H}), 1.64 (m, 2\text{H}), 1.57$ (m, 2H) ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.3, 135.1, 121.6, 38.1, 37.2, 27.7, 24.6, 22.4, 21.9 ppm. ¹³C NMR (100 MHz, CD₃OD): δ 164.3, 136.1, 124.1, 39.2, 38.7, 29.0, 26.2, 24.0, 23.5 ppm. FT-IR: v 3420, 3316, 3225, 2914, 2884, 2843, 1635 (C=O), 1551 cm^{-1} . MS (EI⁺): m/z (%) 184 ([M]⁺, 3), 168 (15), 151 (12), 122 (13), 108 (89), 95 (36), 93 (71), 91 (28), 79 (100), 77 (45). HRMS (EI⁺) calcd for $C_9H_{16}N_2O_2$ 184.1212; found 184.1213.

(2S,9R)-Methyl 2-Benzyl-4,7-dioxo-9-phenyl-5-oxa-3,6,8-triazadecan-1-oate (4). K₂CO₃ (79 mg, 0.57 mmol, 100 mol %) was added to a solution of the N-hydroxyurea 2b (102 mg, 0.57 mmol, 100 mol %) and the carbamoyl azide 1a (141 mg, 0.57 mmol, 100 mol %) in CH₃CN (10 mL) and the mixture was stirred for 3 h. The mixture was adsorbed onto silica gel and purified by flash chromatography (silica gel, AcOEt/hexane $1:2 \rightarrow 1:1.5$) to afford the title compound 4 (205 mg, 94% yield) as a colorless oil. 1 H NMR (400 MHz, CDCl₃): δ 8.45 (br s, 1H), 7.4–7.2 (m, 8H), 7.2-7.0 (m, 2H), 6.70 (d, J = 8.2 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.97 (p, $J = 4 \times 7.0$ Hz, 1H), 4.58 (td, $J = 2 \times 7.4$, 5.7 Hz, 1H), 3.66 (s, 3H), 3.13 (dd, J = 13.9, 5.6 Hz, 1H), 3.04 (dd, J =13.9, 7.1 Hz, 1H), 1.43 (d, J = 7.0 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 158.2, 155.0, 142.9, 135.4, 129.0, 128.4, 128.3, 127.0 (2 ×), 125.8, 55.3, 52.3, 49.3, 37.4, 21.9 ppm. FT-IR (NaCl): v 3306, 3086, 3062, 3030, 2977, 2953, 2872, 1740 (C=O), 1681 (C=O), 1604, 1539, 1496 cm⁻¹. $[\alpha]^{27}_{D}$ +15° (*c* 5.80, CHCl₃). MS (ESI⁺): *m*/*z* (%) 408 ([M + Na]⁺, 37), 386 ([M + H]⁺, 100). HRMS (ESI⁺) calcd for $C_{20}H_{24}N_3O_5$ 386.1710; found 386.1700.

General Procedure for the Synthesis of *N*-Hydroxyhydantoins. K_2CO_3 or Cs_2CO_3 (100–200 mol %) was added to a solution of the *N*-hydroxyurea in CH₃CN and the mixture was stirred for the indicated time. The reaction mixture was diluted with MeOH (5 mL), adsorbed onto silica gel and purified by flash chromatography on silica gel to give the corresponding *N*-hydroxyhydantoin.

(S)-5-Benzyl-3-hydroxyimidazolidine-2,4-dione (10a). Reaction with K_2CO_3 : Following the general procedure, the *N*-hydroxyurea 2a (100 mg, 0.42 mmol, 100 mol %) was treated with K_2CO_3 (116 mg, 0.84 mmol, 200 mol %) in CH₃CN (10 mL) for 10 h to afford, after flash chromatography (silica gel, MeOH/CH₂Cl₂ 1:10 \rightarrow 1:1), the title compound 10a (85 mg, 98% yield) as a colorless solid. Reaction with Cs₂CO₃: Following the general procedure, the *N*-hydroxyurea 2a (142 mg, 0.60 mmol, 100 mol %) was treated with Cs₂CO₃ (194 mg, 0.60 mmol, 100 mol %) in CH₃CN (10 mL) for 2 h to afford, after flash chromatography (silica gel, MeOH/CH₂Cl₂ 1:8 \rightarrow 1:1), the title compound 10a (120 mg, 97% yield) as a colorless solid. ¹H NMR (400 MHz, CD₃OD): δ 7.3–7.2 (m, 5H), 4.32 (dd, J = 6.0, 4.6 Hz, 1H), 3.13 (dd, J = 14.1, 4.5 Hz, 1H), 3.01 (dd, J = 14.1, 6.0 Hz, 1H) ppm.¹H NMR (400 MHz, DMSO- d_6): δ 10.74 (br s, 0.58H), 8.15 (br s, 1H), 7.3–7.1 (m, 5H), 4.32 (m, 1H), 2.98 (dd, J = 14.1, 4.8 Hz, 1H), 2.91 (dd, J = 14.1, 5.7 Hz, 1H) ppm. ¹³C NMR (100 MHz, CD₃OD): *δ* 170.9, 157.0, 136.3, 130.8, 129.5, 128.1, 57.2, 37.8 ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.5, 154.7, 135.5, 129.7, 128.2, 126.7, 54.8, 36.3 ppm. FT-IR: v 3265, 3033, 2929, 2806, 1761 (C=O), 1707 (C=O), 1495 cm⁻¹. $[\alpha]^{25}_{D} - 106^{\circ} (c 2.10, \alpha)$ MeOH). MS (ESI⁺): m/z (%) 229 ([M + Na]⁺, 81), 207 ([M + H]⁺, 100). HRMS (ESI⁺) calcd for C₁₀H₁₁N₂O₃ 207.0764; found 207.0757.

General Procedure for the Synthesis of Carbamoyl Amidoximes. KOH or *t*BuOK (200 mol %) was added to a solution of NH₂OH·HCl (250 mol %) in MeOH and the mixture was stirred for 5–10 min. The carbamoyl cyanide was added and the final mixture was stirred for 10 min. The mixture was filtered and the solvents removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to give the corresponding amidoxime.

(R,Z)-2-Amino-2-(hydroxyimino)-N-(1-phenylethyl)acetamide (13b). Reaction with KOH: Following the general procedure, the reaction of NH₂OH · HCl (249 mg, 3.59 mmol, 250 mol %), KOH (162 mg, 2.88 mmol, 200 mol %) and carbamoyl cyanide 12b (250 mg, 1.44 mmol, 100 mol %) in MeOH (10 mL) afforded, after flash chromatography (silica gel, AcOEt/hexane 1:4 \rightarrow 1:2), the title compound 13b (295 mg, 99% yield) as a colorless oil. Reaction with tBuOK: Following the general procedure, the reaction of NH₂OH·HCl (249 mg, 3.59 mmol, 250 mol %), tBuOK (323 mg, 2.88 mmol, 200 mol %) and carbamoyl cyanide 12b (250 mg, 1.44 mmol, 100 mol %) in MeOH (10 mL) afforded, after flash chromatography (silica gel, AcOEt/hexane 1:4 \rightarrow 1:2), the title compound 13b (296 mg, 99% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (br s, 1H), 7.4–7.1 (m, 6H), 5.29 (br s, 2H), $5.12 (p, J = 4 \times 7.0 \text{ Hz}, 1\text{H})$, 1.44 (d, J = 6.9 Hz, 3H)ppm. ¹H NMR (600 MHz, DMSO- d_6): δ 9.84 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.4-7.3 (m, 4H), 7.22 (m, 1H), 5.64 (br s, 2H), 5.00 $(p, J = 4 \times 7.2 \text{ Hz}, 1\text{H}), 1.43 (d, J = 7.0 \text{ Hz}, 3\text{H}) \text{ ppm}.$ ¹³C NMR (100 MHz, CDCl₃): δ 159.4, 146.4, 142.2, 128.5, 127.4, 126.0, 48.9, 21.5 ppm. ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.1, 145.9, 144.2, 128.2, 126.7, 126.0, 48.1, 21.8 ppm. FT-IR (NaCl): v 3480, 3348, 3065, 3032, 2979, 2931, 2874, 1646 (C=O amide + C=N oxime), 1532, 1450 cm⁻¹. $[\alpha]^{24}_{D}$ –1° (*c* 2.38, CHCl₃). MS (ESI⁺): m/z (%) 230 ([M + Na]⁺, 25), 208 ([M + H]⁺, 100). HRMS (ESI^+) calcd for $C_{10}H_{14}N_3O_2$ 208.1080; found 208.1082

Procedure for the Synthesis of Carbamoyl Amidoximes Applied to Carbamoyl Azide 1a. (S)-Methyl 2-(3-Hydroxyureido)-3-phenylpropanoate (2a) and (S)-Methyl 2-(Aminooxycarbonylamino)-3-phenylpropanoate (14). Reaction with KOH: Following the general procedure, the reaction of carbamoyl azide 1a (190 mg, 0.77 mmol, 100 mol %), NH₂OH·HCl (266 mg, 3.83 mmol, 500 mol %) and KOH (184 mg, 3.28 mmol, 429 mol %) in MeOH (10 mL) for 2 h afforded, after flash chromatography (silica gel, AcOEt/hexane 1:2 \rightarrow 2:1), the *N*-hydroxyurea **2a** (99 mg, 54%) yield) as a colorless solid and compound 14 (46 mg, 25% yield) as a colorless oil. A proportion of the carbamoyl azide 1a was recovered (38 mg, 19%). Reaction with tBuOK: Following the general procedure, the reaction of carbamoyl azide 1a (200 mg, 0.81 mmol, 100 mol %), NH2OH+HCl (140 mg, 2.01 mmol, 250 mol %) and tBuOK (182 mg, 1.62 mmol, 200 mol %) in MeOH (10 mL) for 5 h afforded, after flash chromatography (silica gel, AcOEt/hexane 1:2 \rightarrow 2:1), the N-hydroxyurea 2a (99 mg, 52%) vield) as a colorless solid and compound 14 (52 mg, 27% vield) as a colorless oil. A proportion of the carbamoyl azide 1a was

recovered (37 mg, 18%). (*S*)-Methyl 2-(aminooxycarbonylamino)-3-phenylpropanoate (14). ¹H NMR (400 MHz, CDCl₃): δ 7.3–7.2 (m, 3H), 7.2–7.18 (m, 2H), 6.12 (d, J = 7.3 Hz, 0.90H), 5.46 (br s, 2H), 4.65 (dt, $J = 8.3, 2 \times 5.9$ Hz, 1H), 3.72 (s, 3H), 3.15 (dd, J = 13.9, 5.6 Hz, 1H), 3.08 (dd, J = 13.9, 6.4 Hz, 1H) ppm. ¹H NMR (400 MHz, DMSO- d_6): δ 7.78 (d, J = 8.2 Hz, 1H), 7.3–7.2 (m, 5H), 6.83 (br s, 2H), 4.31 (ddd, J = 9.7, 8.2, 5.0 Hz, 1H), 3.63 (s, 3H), 3.07 (dd, J = 13.8, 5.0 Hz, 1H), 2.93 (dd, J = 13.7, 9.7 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 171.6, 157.2, 135.5, 129.1, 128.6, 127.2, 54.9, 52.4, 38.0 ppm. ¹³C NMR (100 MHz, DMSO- d_6): δ 172.1, 157.7, 137.2, 129.0, 128.3, 126.5, 55.3, 52.0, 36.4 ppm. MS (ESI⁺): m/z (%) 180 (100), 181 (16), 195 (9), 235 (26), 279 (10), 297 (6).

Computational Methods. All calculations were performed using the hybrid Becke three-parameter Lee–Yang–Parr DFT B3LYP functional,³² the reliability of which in calculations on ground state geometries has been widely assessed.³³ Geometries were fully optimized with the following three basis sets: 6-31G(d), 6-311+G(d,p)and 6-311+G(2d,p). The absence of imaginary frequencies in the vibrational analysis verified that all structures corresponded to true energy minima. Solvent effects in DMSO were studied in terms of SCFR formalism by employing the PCM solvation model.³⁴ NMR shieldings were calculated for each optimized geometry at the same level of theory at which the structure was optimized. All the calculations were computed by using the Gaussian 09 program.³⁵ ¹³C and ¹⁵N chemical shifts were calculated using the linear regression equations of Franca³⁰ and van Eikema Hommes,³¹ respectively.

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Two chemical shift values at two different levels of theory were obtained for each nucleus. Comparison of calculated and experimental values was performed by computing the square of the Pearson correlation coefficient (R2).

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Supporting Information Available: Experimental procedures and characterization data for those compounds not included in the Experimental Section and copies of ¹H NMR, ¹³C NMR, and HMBC-NH spectra, calculation details, energies, calculated NMR isotropic shieldings and chemical shifts, Cartesian coordinates and structure plots for conformers of compounds **13j** and **13d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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