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Synthesis of *N*-Oxyureas by Substitution and Cope-Type Hydroamination Reactions Using *O*-Isocyanate Precursors

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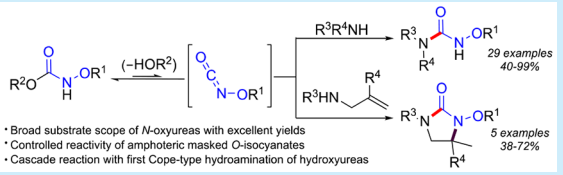
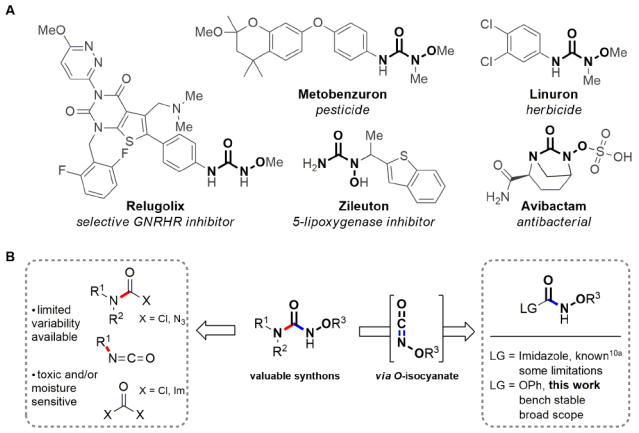
Supporting Information

ABSTRACT: Oxy-carbamate *O*-isocyanate precursors facilitate access to synthetically valuable *N*-oxyureas via substitution with amines. This work exploits the reactivity of suitable *O*-isocyanate precursors, identified by a thorough study highlighting the different reactivity of isocyanate masking groups. This led to bench-stable *O*-isocyanate precursors, offering improved versatility in the synthesis of *N*-oxyureas, and demonstrates the controlled reactivity of masked *O*-isocyanates. Suitable precursors also enabled the first example of Cope-type hydroamination of unsaturated hydroxyureas.



Hydroxamates and hydroxamic acids have many uses as synthetic intermediates,[1] chiral ligands,[2] and directing groups[3] and are also common pharmacophores in enzyme inhibitors.[4] Their nitrogen-substituted analogs, *N*-oxyureas, have garnered interest for similar applications and are also key subunits in agrochemicals and pharmaceuticals (e.g., Scheme 1A).

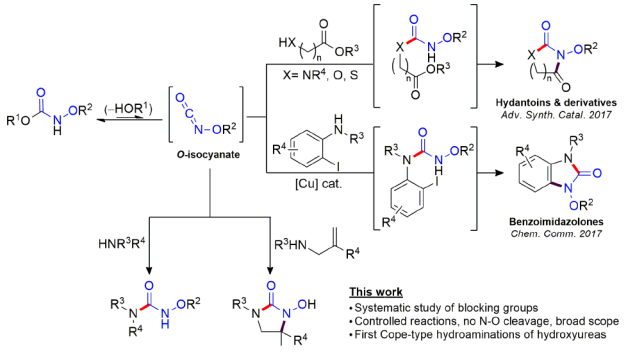
Scheme 1. Synthesis and Applications of *N*-Oxyureas



However, the synthetic methods to produce them are relatively underdeveloped (Scheme 1B). Typically, access to *N*-oxyureas relies on reactive acylating agents (Scheme 1B, left), and a literature survey indicated that approaches based on the use of oxy-carbamates need further development (Scheme 1B, right). Specifically, our work on heteroatom-substituted isocyanates suggested that the use of suitable oxy-carbamates as precursors to oxygen-substituted isocyanates (*O*-isocyanates) could yield a reliable route to form *N*-oxyureas.

The importance of isocyanates is exemplified by the greater than 4000 commercially available reagents and the millions of tons produced and used every year. Heteroatom-substituted isocyanates, however; are considerably scarcer, with less than 100 publications relating to nitrogen-substituted isocyanates (*N*-isocyanates)[5] and less than 20 relating to *O*-isocyanates.[6,7] *O*-Isocyanates are particularly difficult to manipulate due to their propensity to trimerize or to undergo Lossen rearrangements through cleavage of the N−O bond.[8,9] Until recently, there was only one reported example of controlled reactivity of an *O*-isocyanate, which was formed *in situ* from precursors containing an imidazole blocking (masking) group.[10,11] This pioneering work by BMS chemists showed that trimerization can be avoided through *in situ* isocyanate formation, likely by controlling the concentration of *O*-isocyanate available. However, only the reactivity of BnO−NCO precursors was studied, and limitations to the reaction scope were present. Recently, we became interested in using different masked *O*-isocyanate precursors (i.e., bench-stable, blocking group: phenol) in cascade reactions yielding hydroxylamine-containing heterocycles (Scheme 2).[12] Given the strict control required to achieve cascade reactions, and the importance of the *N*-oxyureas, a

Scheme 2. Previous and Current Work with *O*-Isocyanates



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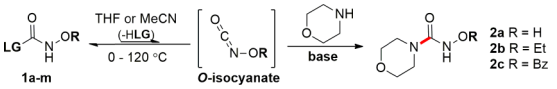
thorough study of the substitution step was needed. Herein, we report the development of broadly applicable substitution reactions to form *N*-oxyureas, document reactivity differences associated with different precursors, and use this reactivity in the first examples of Cope-type hydroamination of *N*-hydroxyureas (Scheme 2).

To explore the reactivity of the *O*-isocyanate precursors, we first examined the ability of several oxy-carbamates and one oxyurea to undergo *O*-isocyanate formation (Table 1), using

Table 1. *O*-Isocyanate Substitution: Leaving Group (LG) Investigation[a]



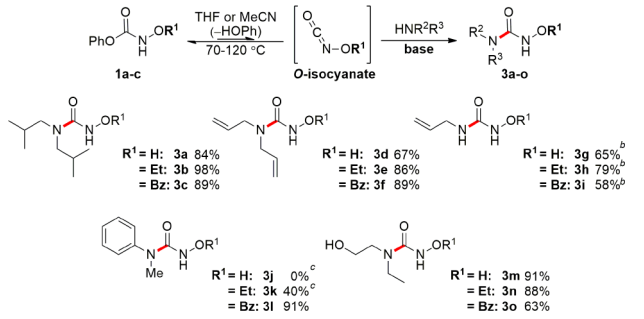
entry	precursor	LG	R	temp (°C)	time (h)	yield (%)[b]
1	**1a**	PhO	H	70	16	71
2	**1b**	PhO	Et	120	0.5	94
3	**1c**	PhO	Bz	120	2	57
4	**1d**	*p*-NO_2PhO[c]	H	rt	16	58
5	**1e**	*p*-NO_2PhO[c]	Et	rt	16	99
6	**1f**	*p*-NO_2PhO[c]	Bz	rt	16	87
7	**1g**	EtO	H	120[d]	16	0[e]
8	**1h**	EtO	Et	120	4	60
9	**1j**	*i*-Pr_2N	H	70	16	74
10	**1k**	BnO	H	120[d]	16	8[e]
11	**1l**	CF_3CH_2O	H	120[d]	16	4[e]
12	**1m**	*t*-BuO	H	120[d]	16	0[e]

[a]Conditions: for R = H, precursor (1.1 equiv), morpholine (1.0 equiv), Et_3N (0.2 equiv) in THF (0.3 M), stir in oil bath overnight. For R = Et, carbamate (1.1 equiv) and morpholine (1.0 equiv) in MeCN (0.2 M), heat in μW to 120 °C. For R = Bz: carbamate (1.0 equiv), morpholine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), heat in μW at 100 °C for 3 h. [b]Isolated yield. [c]Carbamate (1.0 equiv), morpholine (1.0 equiv), Et_3N (1.0 equiv) in CH_2Cl_2 (0.08 M), stir at rt overnight. [d]Reactions at 70 and 100 °C result in no formation of product. [e]^{1}H NMR yield based on 1,3,5-trimethoxybenzene.

conditions similar to those used for *N*-isocyanates.[13] As with both carbon and nitrogen-substituted isocyanates,[5,11c] the masking (leaving) group of the isocyanate precursor determines the conditions required for the release of the reactive intermediates. During efforts to determine the ideal conditions for substitution, it became apparent that hydroxy-carbamate precursors (**R** = H, entries 1,4,7) underwent the substitution considerably less efficiently than the alkoxy (**R** = Et, entries 2,5,8) and acyloxy (**R** = Bz, entries 3,6) carbamates. The latter results are noteworthy, given the absence of Lossen rearrangement under the reaction conditions, and the high interest in such OBz hydroxylamine derivatives as amination reagents.[14] Already, the significant differences in reactivity based on oxygen-substitution highlighted the need for further work with hydroxy-, alkoxy-, and acyloxy-substituted carbamates (see below). Susceptibility to oxidation and isolation difficulties likely account for lower yields for hydroxy-carbamates (**R** = H) and, consequently, led to studies with other masking groups (entries 9−12).

Despite this survey, phenol remained the optimal leaving group for the substitution on hydroxy-carbamates (entry 1). Phenol also proved to be the optimal leaving group for the alkyl- and acyl-substituted examples (entries 2, 3). Optimal conditions for the *p*-nitrophenol leaving group were determined to be too mild and required the addition of stoichiometric base, and the corresponding precursors (**1d−1f**) were too unstable for regular use.[7a] In contrast, phenol-derived masked isocyanates proved stable upon storage over prolonged periods of time, and possessed high reactivity under the conditions shown in Table 1.[15] Having determined the optimal leaving groups for a representative array of *O*-isocyanate precursors, we then studied the effect of several amine nucleophiles on the substitution reaction (Scheme 3).

Scheme 3. *O*-Isocyanate Substitution: Amine Scope[a]



[a]Conditions: for R = H, oxy-carbamate (1.1 equiv), amine (1.0 equiv), Et_3N (0.2 equiv) in THF (0.3 M), stir in oil bath at 70 °C overnight. For R = Et, oxy-carbamate (1.1 equiv), amine (1.0 equiv) in MeCN (0.2 M), heat in μW at 120 °C for 30 min. For R = Bz, oxy-carbamate (1.0 equiv), amine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), heat in μW at 100 °C for 3 h. Isolated yields are shown. [b]Five equiv of allylamine used. [c]One equiv of Et_3N used.

Gratifyingly, a variety of oxyureas could be formed using the reaction of blocked *O*-isocyanates with nitrogen nucleophiles (Scheme 3). Secondary aliphatic amines proved competent nucleophiles for all carbamates used (**3a−3f**). Primary amines initially led to lower yields under similar conditions, however, using an excess (5 equiv) of the amine improved the yields substantially (58−79%). The weakly nucleophilic *N*-methylaniline proved a poor reaction partner and led to no substitution under the reaction conditions for the hydroxy-carbamate **1a**. However, the corresponding alkyl and acyl examples underwent substitution well (40%, 91%), though the ethoxyurea **3k** was difficult to isolate. The unprotected secondary ethanolamine underwent a chemoselective substitution reaction with good to excellent yields (**3m−3o**). With the scope of amine nucleophiles explored, we turned our attention to the last variable of the starting materials; the substitution on the oxygen of the carbamate. The results of this study are shown in Scheme 4.

A variety of carbamates could be used for the substitution, mostly with excellent yields, using di-*n*-propylamine as the nucleophile (Scheme 4). As demonstrated during the leaving group optimization, there was some variability in the yields based on the oxygen substitution. The yield for hydroxy-carbamate **1a** was consistent with previous results (85%). The yields for all alkoxy carbamates (**4b−4e**) were excellent (91 to 96%), as expected. Lower yields were obtained when using acyloxy carbamates with alkyl substituents (**4f**, **4g**); however, when using electron-rich, aromatic acyloxy carbamates (**4h**, **4i**), the substitution yield remained excellent. In contrast, carbamates with better leaving groups (**1j−k**) underwent uncontrolled Lossen rearrangements and did not form the desired products (**4j**, **4k**).[9,16] This clearly indicates that strong electron-withdrawing groups are required for N−O bond cleavage to occur, even at 120 °C in the presence of an amine base. Overall, the results in Schemes 3 and 4 show that variation of each reaction partner was generally well tolerated. With an adequate understanding of the substitution

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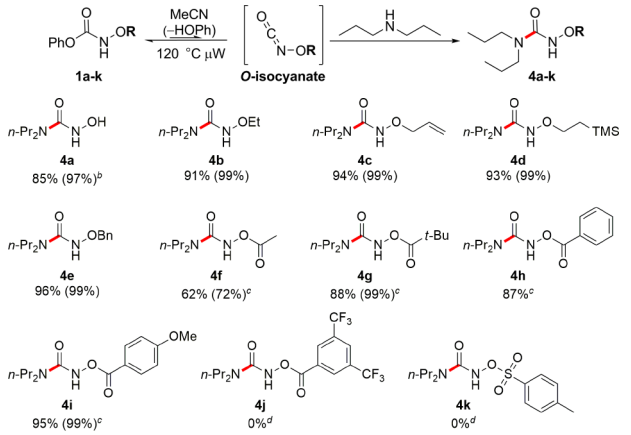
Scheme 4. *O*-Isocyanate Substitution: Oxy-Carbamate Scope[a]

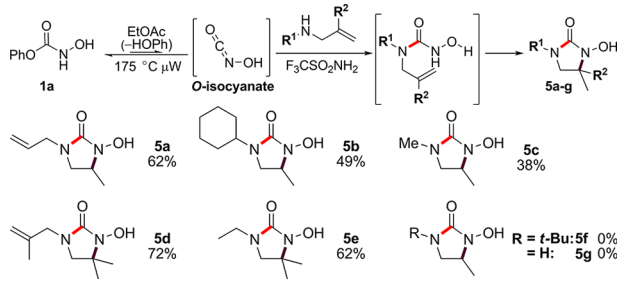


[a]Conditions: oxy-carbamate (1.05 equiv), *n*-Pr_2NH (1.0 equiv) in MeCN (0.2 M), heat to 120 °C in μW for 30 min. Isolated yields are shown (^{1}H NMR yield based on 1,3,5-trimethoxybenzene shown in parentheses). [b]Hydroxy-carbamate (1.1 equiv), Et_3N (0.2 equiv) added, stirred at 70 °C in oil bath overnight. [c]Acyloxy-carbamate (1.0 equiv), amine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), heat to 100 °C in μW for 1–3 h. [d]Uncontrolled formation of products derived from a Lossen rearrangement was observed.

of *O*-isocyanates, we turned our attention to the reactivity of the *N*-oxyurea products.

Given our interest in metal-free, Cope-type hydroaminations using hydroxylamines,[17,18] we recognized the possibility to develop a substitution and hydroamination cascade with hydroxy-carbamate *O*-isocyanate precursor **1a**. Knowing the relatively sluggish reactivity for the substitution on these precursors, we were pleased to obtain some of the unprecedented hydroamination product (Scheme 5). Efforts to improve the

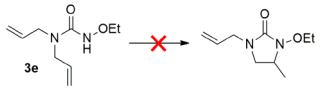
Scheme 5. Cascade *O*-Isocyanate Substitution and Cope-Type Hydroamination of Hydroxy-Carbamates[a]



[a]Conditions: carbamate (1.0 equiv), allylamine (1.0 equiv), $TfNH_2$ (0.5 equiv) in EtOAc (0.2 M), heat in μW to 175 °C for 20 min to 2.5 h. Isolated yields are shown.

overall yield of the cyclic products (**5a–g**) by isolating the hydroxyurea intermediates and submitting them to the hydroamination reaction conditions did not improve this reactivity [see Supporting Information (SI) for details]. Given the importance of additives and of hydrogen-bonding for difficult Cope-type hydroaminations,[19] we screened several additives in hopes that the cascade could be improved. Gratifyingly, $TfNH_2$ proved effective for most substrates. The cascade reaction with symmetrical and bulky secondary allylamines proceeded with reliable, albeit somewhat modest yields (**5a**, **5b**). Using allylamine homologues furnishes the six-membered ring in lower yields,[20] in agreement with established reactivity trends in the Cope-type hydroamination literature.[18,21] Reducing the steric bulk of the second substituent on the allylamine results in a similar yield, but necessitates an increased reaction time (**5c**). The hydroamination reaction also formed the cyclic *N*-oxyurea (**5d**, **5e**) with substituted allylamines with good yields.

Several limitations of this reactivity became apparent during the scope of allylamines. Sterically bulky amines, such as *N*-*tert*-butyl allylamine, did not undergo the necessary substitution to furnish the cyclic hydroxamic acid product (**5f**). In contrast, allylamine underwent substitution, but its adduct did not undergo hydroamination under the optimized reaction conditions (**5g**): this result suggests that only substrates derived from secondary allylamines can access the urea rotamer required for cyclization (i.e., with NHOH and allyl groups *s-cis*). To support the likelihood of a concerted, Cope-type hydroamination pathway, the ethoxyurea product (**3e**) was subjected to the hydroamination conditions (eq 1). No product was observed, supporting the



Eq 1

Cope-type pathway since **3e** lacks the hydrogen atom required for the planar, five-membered transition state.[17,18] To our knowledge, this reaction sequence therefore includes the first example of Cope-type hydroaminations of hydroxyureas or hydroxamic acid derivatives. Not surprisingly, the electron-withdrawing nature of the carbonyl group and rotamer issues result in the need to use significantly higher reaction temperatures (see SI for details).

In conclusion, we have optimized the substitution reaction of *O*-isocyanates to form *N*-oxyureas using bench-stable oxy-carbamates as masked *O*-isocyanates. These conditions allowed for high yields for alkyloxy or acyloxy-substituted products and somewhat lower yields for the *N*-hydroxyureas. Nucleophilic primary and secondary amines are well-tolerated under the optimized conditions. Notably, many oxygen-substituents were well-tolerated and N–O bond cleavage was only observed for the most electron-withdrawing substituents. A cascade reaction involving the substitution of an *O*-isocyanate and subsequent Cope-type hydroamination was established: cyclic *N*-hydroxyureas could be obtained from allyl amines. Overall, this work provides an improved method to form *N*-oxyureas and demonstrates the controlled reactivity possible when using masked *O*-isocyanates. Given the amphoteric nature of the under-utilized *O*-isocyanate intermediate and the broad uses of hydroxylamines, we anticipate further applications exploiting this versatile building block.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03288.

Additional optimization data (Tables S1–S3), complete experimental procedures, characterization data, studies securing the structural assignment of products in Scheme 5, and NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(16) Complex mixtures were obtained in attempting to form **4j** and **4k**. While common with hydroxamic acid derivatives, to our knowledge, Lossen rearrangements from oxyureas or oxycarbamate substrates are rare and difficult to control given the formation of *N*-isocyanates or *O*-isocyanates as intermediates. For selected examples, see: (a) Tserng, K.-Y.; Bauer, L. *J. Org. Chem.* **1973**, *38*, 3498. (b) Tamura, Y.; Minamikawa, J.; Haruki, S.; Ikeda, M. *Synthesis* **1974**, *1974*, 361.

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