OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Formation of Complex Hydrazine Derivatives via Aza-Lossen Rearrangement

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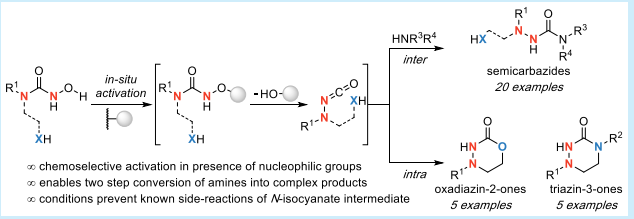
Supporting Information

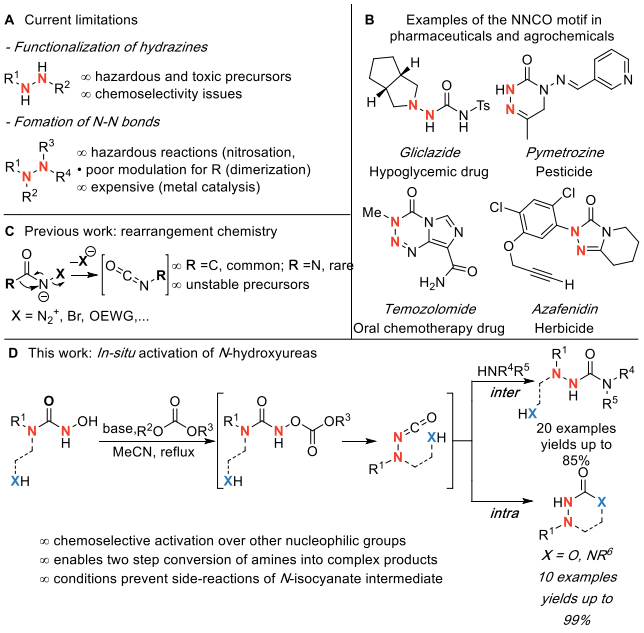
ABSTRACT: The development of a broadly applicable procedure for the aza-Lossen rearrangement is reported. This process converts amines into complex hydrazine derivatives in two steps under safe, mild conditions. This method allows the chemoselective formation of N−N bonds, resulting in the synthesis of cyclic and acyclic products while avoiding side reactions of the amphoteric (ambident) nitrogen-substituted isocyanate intermediate.



Hydrazine derivatives have many uses ranging from rocket propellants, polymers, and agrochemicals to key synthetic intermediates or building blocks for the synthesis of fine chemicals (e.g., heterocycles). While more than 200 natural products and pharmaceuticals contain N−N bonds,[1] the synthesis of complex polysubstituted hydrazine derivatives remains difficult to achieve under mild conditions. Indeed, functionalization of hydrazines is often challenging due to the toxicity, hazardous, and air sensitive character of many reagents. There is also an inherent chemoselectivity issue arising from the two reactive nucleophilic nitrogen atoms.[2a,b] Additionally, the formation of N−N bonds often involves hazardous reactions (e.g., nitrosation[3] or nitration[4]) or a prefunctionalization to perform the cleavage of weak N−X bonds (where X = O, N, or Cl in the Raschig−Olin process).[5] Aza-Favorskii reactions of N-monosubstituted ureas was also reported to form hydrazine derivatives following ring opening of the diaziridone intermediate.[6a,b] Many N−N bonds have been formed via dimerization,[7a,b] but typically, the formation of heterodimers is difficult. Metal-catalyzed N−N bond formation is also used but relies on expensive catalysts (Scheme 1A).[8] Despite all of the previous work, the synthesis of compounds containing N−N bonds, and more specifically hydrazides (the *N*-acyl derivative of hydrazines), remains challenging. Practical, mild approaches are needed to facilitate the synthesis of hydrazides, which are important motifs in pharmaceuticals and agrochemicals (Scheme 1B).[9] In our experience, reactions that can convert simple amines directly into complex hydrazine derivatives have major limitations, which results in synthetic limitations and inefficiencies.

Arguably, intramolecular rearrangements of amine-derived precursors could form N−N bonds more reliably. To our surprise, despite many examples of rearrangements forming N−C bonds [e.g., Curtius, Schmidt, Hofmann and Lossen rearrangements (Scheme 1C)],[10] the corresponding N−N bond forming reactions remain severely underdeveloped. Indeed, there have been a few examples of aza-Curtius rearrangement,[11a−e] and there have even fewer for the aza-Lossen rearrangement.[12a−f] While this work established that efficient N−N bond formation can occur, uses of such rearrangements can suffer from the fast dimerization of the nitrogen-substituted isocyanate (*N*-isocyanate) intermediate.[13] This side reaction can occur at temperatures as low as −40 °C and may account for the scarcity of processes exploiting these rearrangements. Thus, such reactions are typically applicable only in specific systems and relied on unstable starting materials

Scheme 1. Synthesis of Semicarbazide Derivatives



Received: May 17, 2019

DOI: 10.1021/acs.orglett.9b01742
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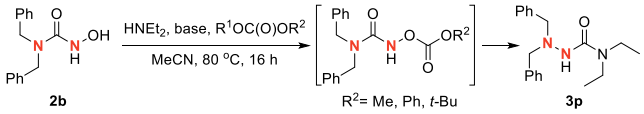
(e.g., carbamoyl azides). Over the past decade, our group has reported various methods for the synthesis of hydrazides and related compounds, through the controlled formation of masked *N*-isocyanates.[14a−d] Unfortunately, several substrate syntheses were relatively inefficient and displayed low functional group tolerance. Herein, the reactivity of *N*-hydroxyureas[15] is exploited to achieve a broadly applicable two-step conversion of simple amines into complex hydrazine derivatives via aza-Lossen rearrangement (Scheme 1D). This procedure addresses two key challenges: (1) chemoselective activation of the N−OH moiety in the presence of an intramolecular nucleophile enabling new heterocyclic syntheses and (2) overcoming the facile dimerization of *N*-isocyanates, which allows intermolecular reactions.

Initial efforts targeted aza-Lossen reactions, followed by intermolecular reactions to form semicarbazides. This subunit is present in drugs (Cloretazine and Goserelin) and in the backbone of azapeptides.[16] Semicarbazide synthesis can be challenging and usually involves the use of hydrazine derivatives.[17] In contrast, the strategy envisioned the *in situ* activation of the bench-stable *N*-hydroxyureas, which are easily prepared in one step from simple amines.[15] However, the first attempts to induce the aza-Lossen rearrangement from tosyl and benzoyl *N*-hydroxyureas lead to only degradation. Gratifyingly, efforts with the use of carbonates as activating agents proved to be more encouraging.[18] Selected optimization data are listed in Table 1.

Table 1. Optimization of Reaction Conditions for Aza-Lossen Rearrangement and/or Semicarbazide Synthesis[a]



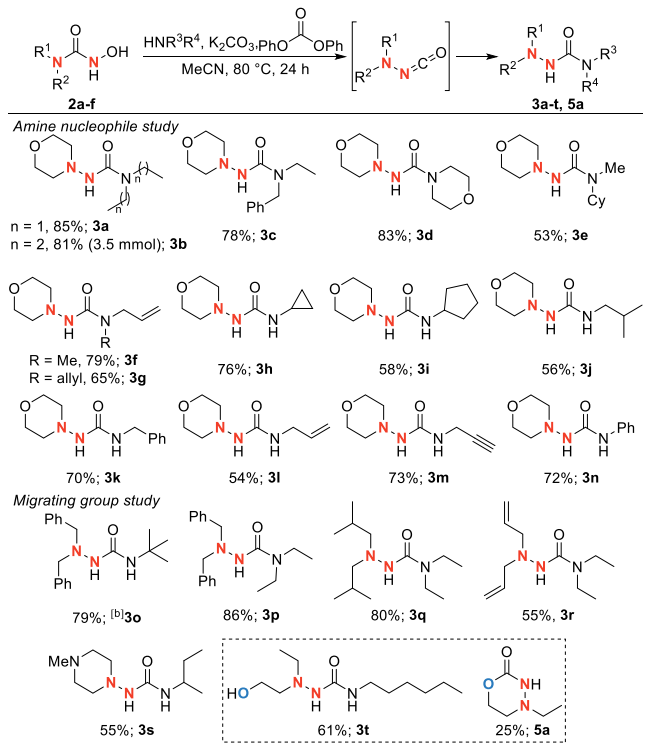
entry	$R^1OC(O)OR^2$ (equiv)	base (equiv)	$HNEt_2$ (equiv)	yield (%)
1	$(MeO)_2CO$ (1.00)	Et_3N (1.00)	5.00	15
2	Boc_2O (1.00)	Et_3N (1.00)	5.00	16
3	$(PhO)_2CO$ (1.00)	Et_3N (1.00)	5.00	9
4	$(PhO)_2CO$ (1.20)	Et_3N (1.00)	5.00	35
5	$(PhO)_2CO$ (1.00)	Et_3N (1.20)	5.00	83
6	$(PhO)_2CO$ (1.00)	*i*-Pr_2NEt (1.00)	5.00	70
7	$(PhO)_2CO$ (1.00)	imidazole (1.00)	5.00	56
8	$(PhO)_2CO$ (1.00)	K_2CO_3 (1.00)	5.00	91
9	–	K_2CO_3 (1.20)	5.00	29
10	$(PhO)_2CO$ (1.00)	–	5.00	23
11	$(PhO)_2CO$ (1.00)	K_2CO_3 (1.20)	1.00	92

[a]Conditions: *N*-hydroxyurea **2b** (0.1 mmol) in MeCN (0.3 M). Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

The initial hit was obtained using dimethylcarbonate and led to the formation of aza-Lossen product **3p** in 15% NMR yield, with no carbamate as a side product from the reaction with the external amine (Table 1, entry 1). The aza-Lossen process was found to be solvent-dependent. Indeed, the synthesis of semicarbazides in high yield was possible in only acetonitrile. Changing the carbonate reagent did not initially increase the conversion to the product (entries 2 and 3). However, diphenylcarbonate was selected for further optimization, because this carbonate generates phenol as a byproduct. Indeed, phenol proved to be a competent blocking (masking) group controlling the reactivity of the transient isocyanate.[14a−d] Increasing the amount of base relative to the carbonate reagent (entry 5) led to an 83% yield of product **3p**. Several different bases were surveyed (entries 6−9), and using potassium carbonate, the desired product was formed in 91% yield (entry 8). The control experiments (entries 9 and 10) indicated that both diphenylcarbonate and potassium carbonate were needed for efficient formation of product **3p**. Finally, these conditions were found to tolerate the use of only a stoichiometric amount of the external amine nucleophile (entry 11).

With optimized conditions in hand, the reaction scope for the external amine could be established (Scheme 2). This aza-

Scheme 2. Scope of Semicarbazides via Aza-Lossen Rearrangement and/or Intermolecular Substitution with the *N*-Isocyanate[a]



[a]Conditions: *N*-hydroxyurea (1 equiv), amine (1 equiv), diphenylcarbonate (1 equiv), K_2CO_3 (1.2 equiv) in MeCN (0.3 M) heated in a sealed vial (oil bath, 80 °C, 24 h). Isolated yields are shown. [b]Using 5 equiv of *t*-$BuNH_2$.

Lossen rearrangement protocol can be performed with different secondary amines as nucleophiles, such as symmetrical (**3a**, **3b**, and **3d**) and unsymmetrical dialkylamines (**3c** and **3e**), and allylamines (**3f** and **3g**) in moderate to good yields. Gratifyingly, the reaction also worked with primary amines, and moderate to good yields were obtained with cyclopropylamine (**3h**), benzylamine (**3k**), and even aniline (**3n**). Semicarbazides were also obtained efficiently using diethylamine with *N*-hydroxyureas derived from several different amines: dibenzylamine (**3o** and **3p**), diallylamine (**3r**), and *N*-methylpiperazine (**3s**). To our delight, when the *N*-hydroxyurea possessed an internal alcohol nucleophile, chemoselective formation of semicarbazide **3t** was achieved, albeit in a moderate yield due to competitive formation of the oxadiazin-2-one **5a**. However, this competing reaction suggested that the *N*-isocyanate could also react with an

DOI: 10.1021/acs.orglett.9b01742
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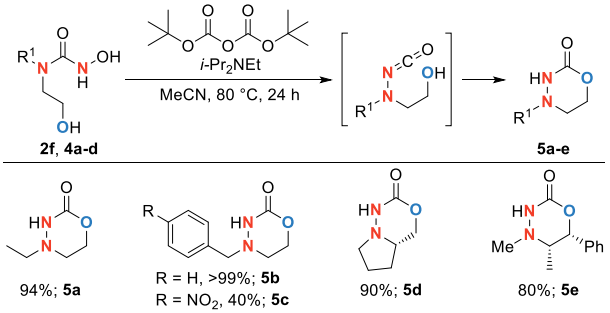
internal nucleophilic group; examination of a variant allowing the synthesis of different heterocycles was started.

The first heterocyclic target chosen was the oxadiazin-2-one core, which has been studied for its activity on the central nervous system,[19] and as a chiral auxiliary.[20] The diversity of oxadiazin-2-ones accessible with current methodologies is very limited. Most of the known examples form the N−N bond by nitrosation of ephedrine derivatives,[19] and only a few examples through ring expansion[21] or by functionalization of hydrazines.[22] Using the same semicarbazide strategy, optimization of the reaction to selectively activate the hydroxyl group of the *N*-hydroxyurea over the required alcohol group on one of the alkyl chains was performed. After optimization (see Table S2), it was pleasing to find that with a change in the carbonate reagent to di-*tert*-butyl dicarbonate and the base for *i*-Pr_2NEt, the formation of the oxadiazin-2-one was achieved with high selectivity.

The first isolated oxadiazin-2-one (Scheme 3, **5a**) was obtained in high yield, and the benzyl derivative (**5b**) was

Scheme 3. Scope of Oxadiazin-2-ones via Aza-Lossen Rearrangement and/or Cyclization with the *N*-Isocyanate[a]

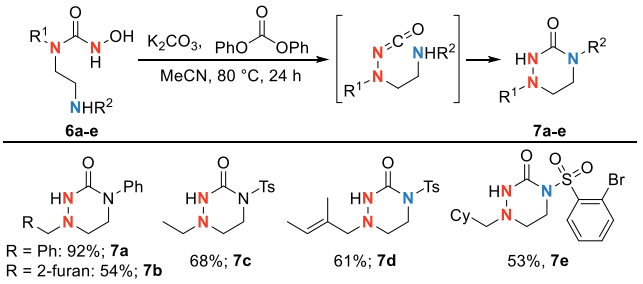


[a]Conditions: *N*-hydroxyurea (1 equiv), di-*tert*-butyl dicarbonate (1 equiv), *i*-Pr_2NEt (1.2 equiv) in MeCN (0.3 M) heated in a sealed vial (oil bath, 80 °C, 24 h). Isolated yields are shown.

obtained in quantitative yield. In contrast, the *p*-nitrobenzyl analogue derivative (**5c**) was obtained in a lower yield likely due to the poor solubility of the starting material. A bicyclic oxadiazin-2-one (**5d**) was also obtained in good yield with retention of stereochemical information. Lastly, this method was compared to other syntheses of ephedrine derivative **5e**: the synthesis was one step shorter than previous reports, and the use of sodium nitrite and lithium aluminum hydride could be avoided.[19] Another difference in the synthetic strategy reported herein is that it could form other heterocyclic systems provided that the internal nucleophile or side chain was changed. To illustrate this, attention was turned toward the synthesis of a triazin-3-ones from simple diamine precursors (Scheme 4).

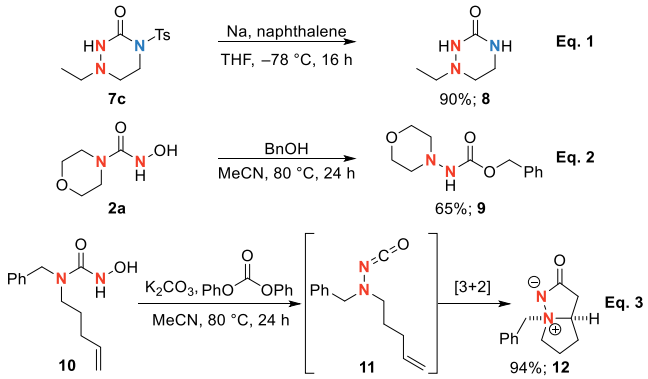
Triazin-3-ones are often used as rigid aza-tripeptides[23] and are selective 5-lipoxygenase inhibitors.[24] Like those of other hydrazide derivatives, their current syntheses involve the use of hydrazines[25] or isocyanates.[24] After facile preparation of *N*-hydroxyureas **6a−e** from the vicinal diamines, it was found that triazin-3-ones were obtained in moderate to excellent yields using the optimized conditions for the semicarbazide synthesis (see Table S3). Five different triazin-3-ones (Scheme 4) were formed using this approach. Two different aniline derivatives afforded the desired products (**7a** and **7b**). Tosyl-substituted diamine was also compatible as a nucleophile (**7c** and **7d**). Finally, a more sterically hindered tosyl group was tolerated giving the triazine-3-one (**7e**).

Scheme 4. Scope of Triazin-3-ones via Aza-Lossen Rearrangement and/or Cyclization with the *N*-Isocyanate[a]



[a]Conditions: *N*-hydroxyurea (1 equiv), diphenylcarbonate (1 equiv), K_2CO_3 (1.2 equiv) in MeCN (0.3 M) heated in a sealed vial (oil bath, 80 °C, 24 h). Isolated yields are shown.

Gratifyingly, the tosyl group can be easily cleaved using sodium naphthalenide reduction conditions (eq 1). When the external nucleophile is changed to an alcohol derivative, the Cbz-protected hydrazine was obtained using non-optimized conditions (eq 2). Finally, as evidence for the *N*-isocyanate intermediate, an aza-Lossen/alkene aminocarbonylation cascade was performed.[14a,26] Using *N*-hydroxyurea **10**, aminimide **12** was obtained in 94% isolated yield (eq 3), via intramolecular [3+2] cycloaddition of the *N*-isocyanate intermediate **11**.



In summary, using this new protocol, *N*-hydroxyureas derived from simple amines undergo the aza-Lossen rearrangement as efficiently as hydroxamic acids. Importantly, the unwanted amphoteric/ambident reactivity of *N*-isocyanates (e.g., facile dimerization) is avoided. Conditions are compatible with external and internal nucleophiles allowing the chemoselective formation of the N−N bonds of semicarbazides and different heterocyclic derivatives. This strategy can also be used in other cascade reactions, with the aza-Lossen rearrangement/aminocarbonylation sequence as an example. The syntheses of other heterocycles and complex hydrazines are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01742.

Additional optimization data, complete experimental procedures, characterization data, and NMR spectra (PDF)

Raw NMR data (ZIP)

DOI: 10.1021/acs.orglett.9b01742
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the University of Ottawa and NSERC for generous financial support. A Yu scholarship to D.E.P. is also gratefully acknowledged. The authors thank Sébastien Roy (University of Ottawa) for exploratory work on aza-Lossen rearrangement involving tosyl and benzoyl derivatives of *N*-hydroxyureas.

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DOI: 10.1021/acs.orglett.9b01742
Org. Lett. XXXX, XXX, XXX−XXX