# N-Hydroxyimide Ugi Reaction toward α-Hydrazino Amides

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S *Supporting Information*

ABSTRACT: The Ugi four-component reaction (U-4CR) with *N*-hydroxyimides as a novel carboxylic acid isostere has been reported. This reaction provides straightforward access to α-hydrazino amides. A broad range of aldehydes, amines, isocyanides and *N*-hydroxyimides were employed to give products in moderate to high yields. This reaction displays N−N bond formation by cyclic imide migration in the Ugi reaction. Thus, *N*-hydroxyimide is added as a new acid component in the Ugi reaction and broadens the scaffold diversity.
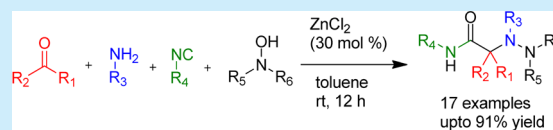
The Ugi reaction (U-4CR) is a widely used multi-component reaction (MCR) for the synthesis of bis-amides and peptidomimetics.[1] This reaction has emerged as a powerful synthetic method for the organic, pharmaceutical, and polymer industries.[2] However, it cannot meet the ever-increasing need for molecular complexity and diversity in organic and medicinal chemistry. An increasing demand for novel scaffolds has led to the interest in U-4CR post-modifications and single-reactant replacement (SRR) by isosteres.[3] U-4CR postmodifications are useful for the synthesis of various heterocycles and peptidic scaffolds.[4] Nevertheless, isostere use in the Ugi reaction is rather limited.[5] An amine component could be replaced by secondary amines, hydroxyl-amines, and hydrazines. As with amines, use of acid isosteres in the Ugi reaction is also limited.

In the Ugi reaction, the carboxylic acid plays several prominent structural roles, including activation of the intermediate imine, the reversible addition to the nitrilium ion, and participation in the irreversible Mumm rearrangement to form the final bis-amide product. Because of carboxylic acid's substantial role in the reaction, isosteric replacement by other agents is difficult to accomplish. In 1962, Ugi reported the first acid isosteric replacements by inorganic acids, such as hydrazoic acids, cyanates, thiocyanates, etc. (Figure 1).[6] To date, only a few acid isosteres have been reported. For example, our group reported the thioacetic acid as an isostere.[7] El Kaïm and co-workers reported the phenol as an acid isostere in the Ugi reaction involving Smiles rearrangement to form an *N*-arylamine.[8] Other Ugi−Smiles and similar strategies have been described by El Kaïm (thiophenol),[9] Charton (squaric acid),[10] and Neo (hydroxycoumarins).[11] Further, Lewis acids and CO_2 were used as acid isosteres in the U-4CR.[5]

As for the related Passerini reaction,[12] organic acid isostere replacement has remained largely unexplored for the Ugi-4CR as there are only a few examples of isostere use in the Ugi-4CR for the synthesis of peptidomimetics.[5] Therefore, finding new isosteres in U-4CR for the synthesis of diverse and complex peptidomimetic derivatives is of high interest.

We hypothesized that *N*-hydroxyimides could be used as a novel acid isostere in the U-4CR reaction, which can directly

Previous acid components in U-4CR
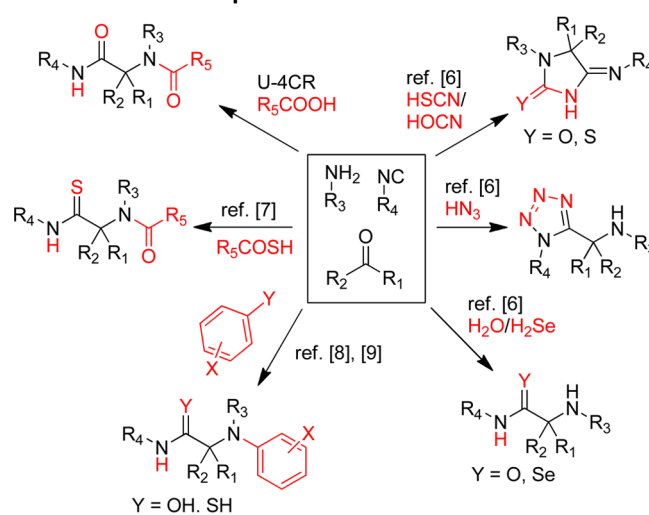
Introduction of *N*-hydroxamic acid in U-4CR
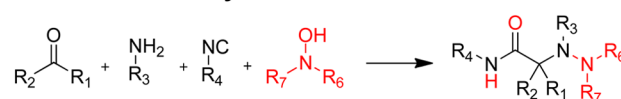
Figure 1. Previously reported and new acid isosteres in U-4CR.

provide the α-hydrazino amides as Ugi reaction products. α-Hydrazino amides are aza analogues of β-peptides and are of interest for several reasons.[13] These foldamers exhibit the special hydrazino turn, and the hydrazidic bond is very resistant to protease.[14] Hydrazino amides are found in many natural products such as linatine, a vitamin B6 antagonist;[15a] negamycine, an antibiotic;[15b] and matlystatins, antimicrobial compounds.[15c] They also have broad applications in medicinal chemistry including use as proteasome inhibitors,[16a] anti-microbials,[16b] DNA and RNA interactors,[16c] (S)-(−)-carbidopa
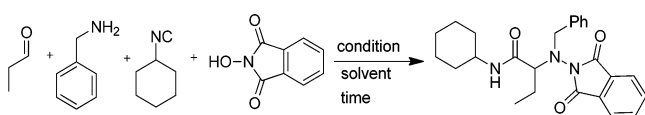
for the treatment of Parkinson's disease,[17] or as human leukocyte elastase (HLE) inhibitors.[18]

Hydrazino peptides are mainly synthesized by two methods: first, by using hydrazine derivatives[19] and, second, by coupling of an amino group with another amine typically employing oxaziridines.[14] The general use of hydrazine and oxaziridine is limited by unavailability of diverse derivatives and their highly toxic and unstable nature. Another drawback is that their synthesis is laborious. Therefore, the development of new methods for the synthesis of this important foldamer is highly desirable.

Herein, we report the successful use of the *N*-hydroxyimides as an acid isostere in the U-4CR for a direct route to the synthesis of α-hydrazino amides. This is the second example of cyclic imide migration to nitrogen (O → N imide transfer) in the Mumm rearrangement to form an N–N bond. This type of N–O bond breaking and N–N bond formation in a Mumm-type rearrangement has been recently reported.[20] This reaction illustrates the use of N-hydroxamic acid for N–N bond formation without phthalimidation.

We started our optimization by using propionaldehyde, benzylamine, cyclohexyl isocyanide, and *N*-hydroxyphthalimides (NHPI) as model reactants. Reaction in methanol did not form any desired product (Table 1, entry 1). In polar aprotic solvents such as THF and CH$_3$CN, only traces of product were formed (see the Supporting Information for details of optimization conditions). In the polar protic solvent

MeOH, the U-3CR product, α-amino amide, was formed as a major product; in contrast, it formed only in trace amounts in solvents such as THF and toluene. This U-3CR product formation might be due to the low acidity of *N*-hydroxyimide (pK_a ∼ 7.5), which functioned only as a catalyst. This observation led us to try a nonpolar solvent and Lewis acid to activate *N*-hydroxyimide for the further optimization. Indeed, nonpolar solvents such as DCE and toluene allowed moderate product formation of 25% and 20%, respectively, at room temperature.

Next, we screened various Lewis acids, (Table S2) such as InCl$_3$, I$_2$, Sc(OTf)$_3$, etc. (10 mol %) in DCE as a solvent. We found that ZnCl$_2$ was the best of the screened Lewis acids (Table 1, entries 7–11). An increase in the temperature failed to improve the product yield (Table 1, entries 11 and 12). In further solvent screening with ZnCl$_2$, (Table S3), we observed that toluene and xylene gave similar yields, 51% and 49%, respectively (Table 1, entries 13 and 14). The nature of the solvent played a critical role in the success of the reaction. Next, we performed a catalyst equivalence study in toluene as solvent. An increase in the catalyst quantity to 30 mol % gave the best yield of 66% (Table 1, entry 18). However, a further increase in the quantity of ZnCl$_2$ to 50 mol % gave a lower yield, 47% (Table 1, entry 19). The use of sonication in this reaction did not have any effect on product yield (Table 1, entries 20 and 21).[12a]

With these optimized conditions in hand, next we examined the generality of this U-4CR by using various aldehydes, amines, isocyanides, and *N*-hydroxyimides (Table 2). Aliphatic aldehydes offered good yields, up to 78% (Table 2, entries 1–3). Aromatic aldehydes are also useful substrates in this reaction (Table 2, entries 6–9).

Electron-withdrawing and -donating groups in aromatic aldehydes at different positions such as ortho and para provided moderate to good yields. Amines with protected functional groups like acetal and halogens were well-tolerated in this reaction, affording moderate to good yields of the products (Table 2, entries 3, 4, and 6). The acid-protected amino acid β-alanine ester gave only 18% yield (Table 2, entry 5). Various aliphatic and aromatic isocyanides like cyclohexyl, phenylethyl, 2-nitrobenzyl, benzyl, 4-methoxyphenyl, and β-cyanoethyl were well-suited within the developed methodology. Among *N*-hydroxyimides, *N*-hydroxysuccinimides (NHS) also proceeded smoothly similarly to NHPI and gave 48–59% yield (Scheme 1, **5n–p**). However, the reaction with hydroxybenzotriazole (HOBt) resulted in only trace product formation (Scheme 1, **5q**).

A broad functional group tolerance in this reaction could be of interest for the postmodification condensations. Thus, among the vast number of possible postmodification reactions with this modified U-4CR, we attempted several. Hydrazines are important intermediates for the synthesis of many heterocycles and scaffolds.[19] The U-4CR product (**5d**) treatment with hydrazine hydrate deprotects the NHPI and forms the free hydrazine derivatives **6**.[12a] We obtained free hydrazine in a good yield of 64% after overnight reaction (Scheme 2).

Next, we turned our attention to creating access for pharmaceutically important α-amino amide molecules. We converted the U-4CR product (**5p**) to U-3CR product α-amino amide **7** in good yield (73%). This AlCl$_3$-catalyzed reaction cleaved the N–N bond (Scheme 3) to form the final product.[21]

Table 1. Optimization Conditions[a]

entry	solvent	temp (°C)	catalyst	time (h)	% yield[b]
1	MeOH	rt		12	
2	THF	rt		12	trace
3	CH$_3$CN	rt		12	trace
4	DCE	rt		12	25
5	toluene	rt		12	20
6[c]	DCE	rt	ZnCl$_2$		22
7[c]	DCE	rt	Sc(OTf)$_3$	12	15
8[c]	DCE	rt	I$_2$	12	22
9[c]	DCE	rt	TMSCl	12	19
10[c]	DCE	rt	InCl$_3$	12	10
11[c]	THF	50	I$_2$	12	trace
12[c]	DCE	50	ZnCl$_2$	12	nd
13[c]	toluene	rt	ZnCl$_2$	12	51
14[c]	xylene	rt	ZnCl$_2$	12	49
15[c]	chlorobenzene	rt	ZnCl$_2$	12	31
16[c]	TFE	rt	ZnCl$_2$	12	38
17[d]	DCE	rt	ZnCl$_2$	12	40
18[d]	toluene	rt	ZnCl$_2$	12	66
19[e]	toluene	rt	ZnCl$_2$	12	47
20[f]	toluene	rt	ZnCl$_2$	2	43
21[g]	toluene	rt	ZnCl$_2$	2	50

[a]The reaction was carried out with propionaldehyde (1.0 mmol), benzylamine (1.0 mmol), cyclohexyl isocyanide (1.0 mmol), and *N*-hydroxyphthalimide (1.5 mmol) in 2 mL of solvent. [b]Yield of isolated product **5a**. [c]10 mol % of catalyst used. [d]30 mol % of ZnCl$_2$ used. [e]50 mol % of ZnCl$_2$ used. [f]Reaction performed in sonication with 10 mol % of ZnCl$_2$. [g]Reaction performed in sonication with 30 mol % of ZnCl$_2$. nd = not determined.

Table 2. Substrate Scope[a]

entry	1	2	3	4	% yield[b]
1	CH₃CH₂CH₂CHO	benzylamine NH₂	cyclohexyl NC	NHPI	66 (**5a**)
2	isobutyl CHO	allylamine NH₂	cyclohexyl NC	NHPI	74 (**5b**)
3	isovaleraldehyde CHO	aminoacetaldehyde dimethyl acetal NH₂	phenethyl NC	NHPI	78 (**5c**)
4	Ph CHO	2-fluorobenzylamine NH₂	cyclohexyl NC	NHPI	58 (**5d**)
5[c]	CHO	methyl 3-aminopropanoate·HCl NH₂·HCl	cyclohexyl NC	NHPI	18 (**5e**)
6	PhCHO	4-chlorobenzylamine NH₂	phenethyl NC	NHPI	57 (**5f**)
7	4-Cl-C₆H₄CHO	benzylamine NH₂	cyclohexyl NC	NHPI	51 (**5g**)
8	2-Cl-C₆H₄CHO	benzylamine NH₂	phenethyl NC	NHPI	46 (**5h**)
9	4-OCH₃-C₆H₄CHO	benzylamine NH₂	cyclohexyl NC	NHPI	21 (**5i**)
10	isobutyl CHO	4-chlorobenzylamine NH₂	benzyl NC	NHPI	91 (**5j**)
11	isobutyl CHO	4-chlorobenzylamine NH₂	NC-CH₂CH₂-NC	NHPI	38 (**5k**)
12	isobutyl CHO	4-chlorobenzylamine NH₂	4-methoxyphenyl NC	NHPI	71 (**5l**)
13	isobutyl CHO	4-chlorobenzylamine NH₂	diphenylmethyl NC	NHPI	65 (**5m**)

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and **4** (1.5 mmol), ZnCl₂ (30 mol %) in toluene (2 mL) at rt for overnight. [b] Isolated yield. [c] 1.5 equiv of triethylamine used.

We did not carry out detailed mechanistic studies but envision the following mechanism (Scheme 4). ZnCl₂ activates an imine **A** to allow the nucleophilic addition of isocyanide **3** to form the nitrilium intermediate **C**. The hydroxamate

Scheme 1. N-Hydroxyimide Scope
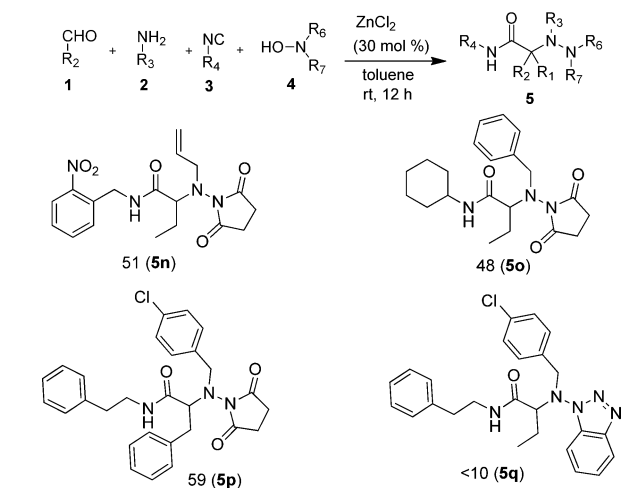
Scheme 2. Deprotection toward Hydrazine Formation
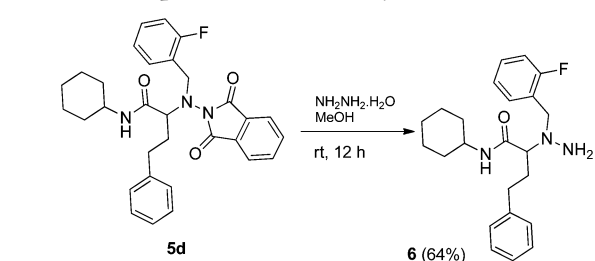
Scheme 3. Deprotection toward α-Amino Amide
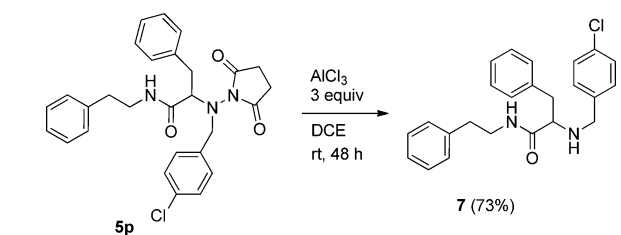
Scheme 4. Anticipated Mechanism for the Ugi−N-Hydroxyimide Reaction
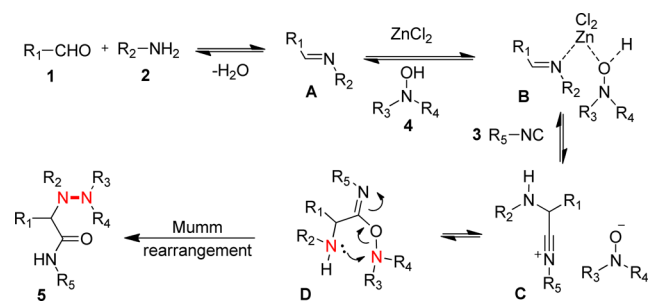
nucleophilicly traps the nitrilium intermediate **C**. Finally, this intermediate **D** undergoes an irreversible Mumm-like N → N migration to form the α-hydrazino amide **5**.

In conclusion, we have reported N-hydroxyimides as novel acid isosteres in the U-4CR toward the one-step synthesis of α-hydrazino amides via N−N bond formation. This mild and general reaction requires catalytic amounts of ZnCl₂. This protocol uses readily available N-hydroxy imides, which replace

the toxic and unstable hydrazines/oxaziridine use for the synthesis of α-hydrazino amides. The method is applicable for a wide range of aldehydes and amines and has the potential for multiple postmodifications. Such scaffolds will be useful to fill the screening decks of the European Lead Factory (ELF).[22] Moreover, as this reaction has significant potential in peptidomimetics synthesis, studies on postmodification reactions are now in progress.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00205.

> General experimental procedures; compound characterization data; ^{1}H and ^{13}C spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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