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Unconventional Passerini Reaction toward α-Aminoxy-amides

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Supporting Information

ABSTRACT: The Passerini multicomponent reaction (P-3CR) toward the one-step synthesis of α-aminoxy-amide, by employing for the first time a *N*-hydroxamic acid component, has been reported. The sonication-accelerated, catalyst-free, simple, fast, and highly efficient Passerini reaction is used for the synthesis of diverse α-aminoxy-amides. The reaction is compatible with a vast range of aldehydes, isocyanides, and *N*-hydroxamic acids such as *N*-hydroxysuccinimides and phthalimides. The generated Passerini products can be easily converted into several follow-up products.

Recently, the design and synthesis of peptidomimetics has gained attention in drug discovery, due to the potential structural and functional advantages over natural proteins.[1] Modified structures and functional groups increase the activity, selectivity, and bioavailability and provide structural rigidity and stability.[2] Among the peptidomimetics, α-aminoxy-acids stand out as analogs of β-amino acids. The α-aminoxy-amides can adopt the structure of the secondary eight-membered N–O turn, which confers extra stability toward enzymatic degradation (Figure 1).[3] These peptidomimetic foldamers are used as building blocks to construct anion receptors and channels, e.g. to mimic anion recognition and transport processes.[4]

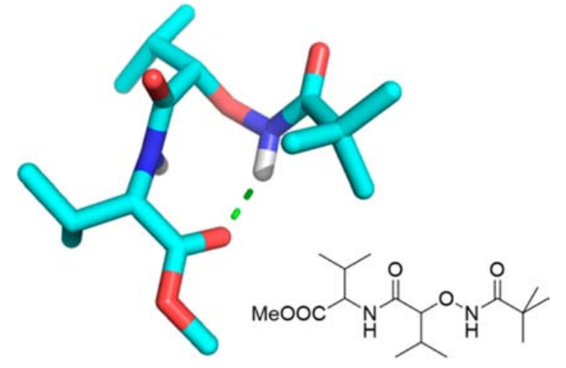
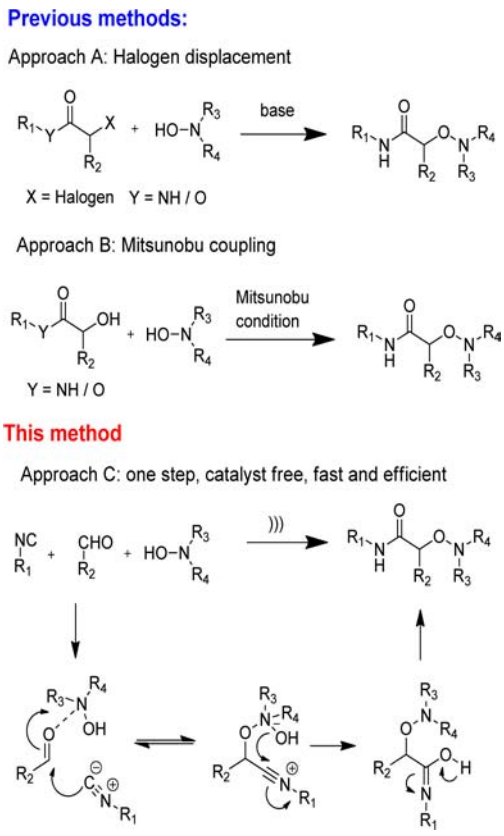


Figure 1. Model of an eight-membered turn involving α-aminoxyamide.

Scheme 1. Previous and New Synthesis of *N*-Aminoxy-amide and Proposed Mechanism for P-3CR



Owing to the importance of α-aminoxy-amides, significant effort has been made toward their design and synthesis. The majority of α-aminoxy-amides synthesis methodologies can be categorized into two general approaches. The first is coupling between an α-halo acid, ester, or amide with *N*-hydroxyphthalimide (NHPI) or *N*-hydroxysuccinimide (NHS)[5] (Scheme 1, Approach A). The second is the Mitsunobu reaction of α-hydroxy acid, ester, or amide with NHPI or NHS[6,7] (Scheme 1, Approach B). These methods suffer from poor availability of starting materials, hence diversity in the products, lengthy multistep preparation, long reaction times, low yields, and also use of coupling reagents which require tedious workup. Currently there is no known method to directly access the α-aminoxy-amides from simple starting materials, with high efficiency and scope. Isocyanide-based multicomponent reactions (IMCRs) have already been proven

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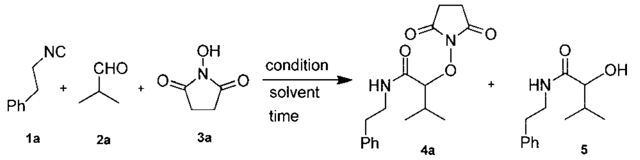
as a promising strategy for the synthesis of peptidomimetics.[8] This highly convergent approach provides pronounced diversity and complexity.[9]

We envisioned the use of *N*-hydroxamic acid as a novel acid isostere in the Passerini reaction, which is potentially suitable for the synthesis of *α*-aminoxy-amides. Surprisingly, the use of carboxylic acid-isosteres in the Passerini reaction is relatively unexplored,[10] with the exception of hydrogene azide,[11] nitrophenol,[12] silanol,[13] and phosphinic acid.[14] In the Passerini reaction, the acyl group of the carboxylic acid acts mechanistically as an electrophile while the OH group works as a nucleophile. Here we hypothesized that, in the Passerini reaction, the OH group of the hydroxamic acid acts as the nucleophile, and the imide-N as the electrophilic species toward the nitrilium intermediate. Weak hydroxamic acids such as NHS or NHPI (pK_a ≈ 7.5) might be able to activate an aldehyde in the Passerini reaction to allow the attack of the isocyanide. Further trapping of the resulting nitrilium intermediate by the hydroxamate affords the final product after the migration of the imide onto the oxygen atom, originating from the aldehyde (Scheme 1).

To test the feasibility of hydroxamic acids, we investigated the reaction between isobutyraldehyde (1.0 equiv), phenylethyl isocyanide (1.0 equiv), and *N*-hydroxysuccinimide (2.0 equiv) with different solvents and conditions (Table 1). When the reaction was performed in DCM, a promising 22% yield of a mixture of the expected product **4a** and the free hydroxyl-amide **5** was obtained (Table 1, entry 1). Use of catalysts such as $ZnCl_2$, PTSA, or $BF_3·OEt_2$ then resulted in only trace product formation (Table 1, entries 2−4). However, CH_3CN and THF solvents gave the desired product in moderate 58% yields, after stirring overnight at room temperature (Table 1, entries 5 and 6).

Table 1. Optimization Conditions[a]



entry	solvent	temp	condition/ catalyst	time (h)	yield (%)[c]
1	DCM	rt		12	22[f]
2[b]	DCM	rt	$ZnCl_2$	12	trace
3[b]	DCM	rt	PTSA	12	trace
4[b]	DCM	rt	$BF_3·OEt_2$	12	trace
5	CH_3CN	rt		12	58
6	THF	rt		12	58
7	MeOH/H_2O (1:1)	rt		12	56[f]
8	H_2O	rt		12	trace
9	MeOH/H_2O (1:1)	60 °C		12	35[f]
10	H_2O	60 °C		12	45[f]
11	THF	60 °C		12	50
12	CH_3CN	60 °C		12	38
13	DCM	60 °C		12	44[f]
14	MeOH/H_2O (1:1)	rt	sonication	2	76[f]
15	H_2O	rt	sonication	2	63[f]
16	THF	rt	sonication	2	97
17[d]	THF	rt	sonication	2	82
18[e]	THF	rt	sonication	2	78

[a] The reaction was carried out with phenylethyl isocyanide (1.0 mmol), isobutyraldehyde (1.0 mmol), and *N*-hydroxysuccinimide (2.0 mmol). [b] 10 mol % catalyst used. [c] Yield of isolated product **4a**. [d] 1 equiv of NHS used. [e] 3 equiv of NHS used. [f] Total yield of **4a** and **5** as a mixture.

Water is a known accelerator of the Passerini reaction.[15] However, use of water or a mixture with methanol in our case led to hydroxyl amide **5** as the major product. The expected product **4a** formed only in a trace amount even after increasing the temperature (Table 1, entries 7−10). Increasing the temperature in THF solvent reduced the yields slightly to 50%, while in acetonitrile a considerable yield decrease to 38% was found (Table 1, entries 11 and 12). Recently we showed that sonication greatly increased the efficiency of the Passerini reaction.[16] Applying sonication to our new reaction led to the *α*-hydroxy amide **5** as the major product in water and a water/methanol mixture (Table 1, entries 14 and 15). Remarkably, use of sonication together with THF as the solvent increased the yield to an almost quantitative 97%, and moreover the reaction required only 2 h for completion. An equivalence study of NHS showed that 2 equiv are necessary to obtain maximum yield. An increase or decrease in the NHS equivalents reduced the yield (Table 1, entries 16−18).

With this optimized conditions in hand, we then investigated the scope of this novel P-3CR by probing different hydroxamic acids, aldehydes, and isocyanides (Scheme 2). NHS gave excellent yields with benzyl and phenylethyl isocyanides when used with different aldehydes **4a**−**4c**. Furthermore, we screened the NHPI. An 81% isolated yield resulted from 2 equiv of NHPI with phenylethyl isocyanide and isobutylaldehyde; however, 1.5 equiv of NHPI provided the best yield, 89% **4r**. NHPI in 1 and 3 equiv led to 74% and 63% yields, respectively. NHPI works well with aliphatic aldehydes such as isobutylaldehyde, cyclohexylcarbaldehyde, or even bulky *tert*-butylaldehyde **4e**, **4f**, **4i**. Aliphatic aromatic aldehydes such as phenylacetaldehyde or phenylethylaldehydes gave good yields. Aromatic aldehydes also performed well in this reaction giving moderate to good yields **4k**−**m**. Aromatic aldehydes having electron-donating groups such as a trimethoxy moiety demonstrated very low reactivity, and their reactions did not produce any of the desired product **4n**. Different isocyanides were tested and found to be good substrates for this reaction. Protected isocyanides such as valine ester isocyanide or 1,1-diethoxy-2-isocyanoethane isocyanide **4g**, **4o**, **4p** also provide moderate to good yields, which potentially allows for further modifications for synthesis of the diverse scaffolds and more complex peptide mimetics (Figure 1). Products **4g** and **4p** are formed as an ∼1:1 mixture of diastereomers.

Halogen functionality on an isocyanide could also provide scope for further coupling reactions in the case of **4i**. In the reaction with HOBt it was found that the product (as confirmed by mass spectroscopy) is relatively unstable during silica or neutral alumina column chromatography and converts to *α*-hydroxy amides **4s**. To further investigate the scope of hydroxamic acids, we also tested the free NH hydroxamic acids, but disappointingly they did not form the desired products **4t**−**4v**. These results show that the nitrogen of the hydroxamic acids should not be acidic to give the product.

Next we used our P-3CR toward the preparation of the oxyamines, which are important intermediates for the synthesis of peptidomimetics as well as different scaffolds such as oxime ethers and benzofurans.[17] When 2-((1,3-dioxoisoindolin-2-

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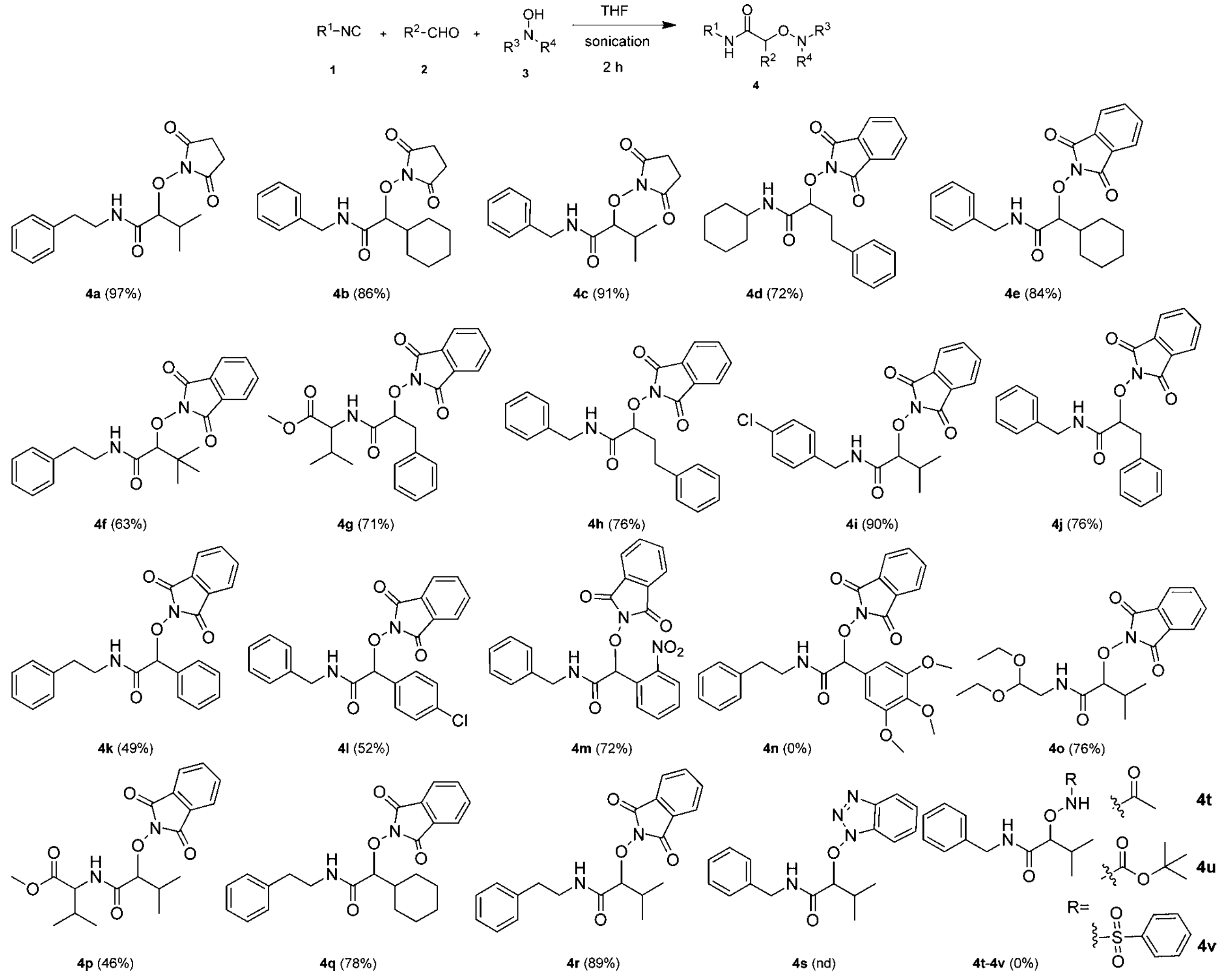
Scheme 2. Substrate Scope of the Synthesis of α-Aminoxy-amides from Isocyanide, Aldehyde, and *N*-Hydroxamic Acid[a]



4a (97%) **4b** (86%) **4c** (91%) **4d** (72%) **4e** (84%)

4f (63%) **4g** (71%) **4h** (76%) **4i** (90%) **4j** (76%)

4k (49%) **4l** (52%) **4m** (72%) **4n** (0%) **4o** (76%)

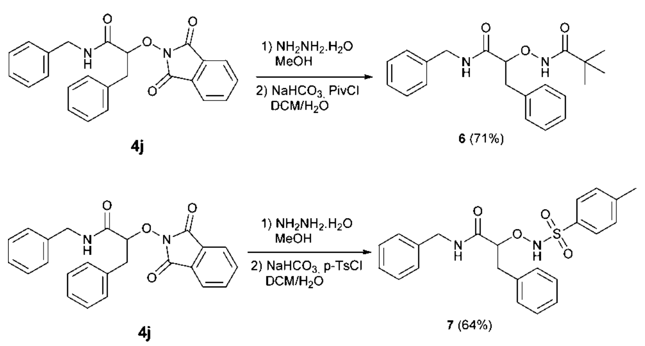
4p (46%) **4q** (78%) **4r** (89%) **4s** (nd) **4t-4v** (0%)

[a]Reaction conditions: 1.0 mmol of **1**, 1.0 mmol of **2**, 2.0 mmol of NHS, HOBT *N*-hydroxamic acids, 1.5 mmol of NHPI **3**, and 1 mL of THF. nd = not determined.

yl)oxy)-3-methyl-*N*-phenethylbutanamide **4j** was treated with hydrazine for 5 h at room temperature, it forms the oxy-amine which was further used for the synthesis of an amide and sulphonamide (Scheme 3). We received 71% product with pivaloyl chloride coupling for **6** and 64% for *p*-TsCl **7**.[18]

In conclusion, we have introduced for the first time hydroxamic acids in the Passerini three-component reaction.

Scheme 3. Deprotection towards *O*-Hydroxylamines and Acylation/Sulfonylation



4j **6** (71%)

4j **7** (64%)

We developed a novel, catalyst-free, mild, workup-free, efficient, and general hydroxamic acid based Passerini reaction to gain access to α-aminoxy-amides. This methodology is applicable for a wide range of isocyanides and aldehydes. Functional group compatibility in this methodology provides easy access for further modifications. This modified Passerini reaction has the ability to expand the scope of substrates for investigation in peptidomimetic design and has the potential to become a preferred method for the synthesis of complex α-aminoxy-amides. Libraries based on these scaffolds will be useful to enrich the screening decks, for example in the European Lead Factory.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03293.

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

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Notes

The authors declare no competing financial interest.

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