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One-Pot Synthesis of Aza-Diketopiperazines Enabled by Controlled Reactivity of *N*-Isocyanate Precursors

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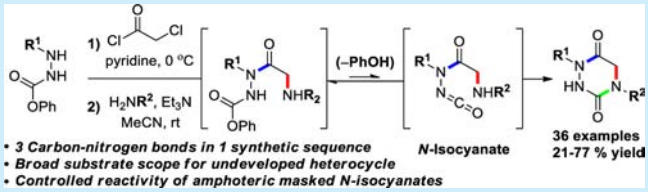
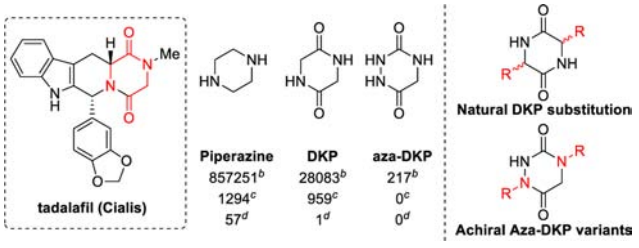
Supporting Information

ABSTRACT: A one-pot sequence for the synthesis of aza-diketopiperazines is reported, involving carbazate acylation with chloroacetyl chloride, S_N2 with a primary amine, *N*-isocyanate formation, and cyclization. Nitrogen-substituted isocyanates (*N*-isocyanates) are a rare class of amphoteric isocyanate with high, but severely underdeveloped synthetic potential. This approach highlights that *β*N-acyl carbazates can act as blocked (masked) *N*-isocyanates, thus allowing a challenging intermolecular S_N2 reaction of a primary amine to proceed while the *N*-isocyanate is "protected", and then cyclization once it is unmasked. Control experiments show that the alternate pathway—*N*-isocyanate substitution and then cyclization by an intramolecular S_N2 reaction—is not operating.



Nitrogen-containing heterocycles comprise nearly 60% of all small-molecule drugs approved by the US Food and Drug Administration.[1] Piperazines are important in heterocyclic chemistry, with over 1,200 natural products and 57 pharmaceuticals[1] incorporating this heterocyclic core in their structures. An important subclass of the piperazine family, 2,5-diketopiperazines (DKPs), account for ca. 75% of piperazine-based natural products, yet there is only a single example of a clinically approved drug: tadalafil (Cialis). Nevertheless, DKPs are bioactive and have affinity for a variety of receptors.[2] Simple DKPs are biosynthetically produced via intramolecular cyclization of hetero- or homodipeptides, and several other synthetic routes have also been developed. In stark contrast, their nitrogen analogues, aza-diketopiperazines (aza-DKPs), have received significantly less synthetic attention. In fact, very few practical syntheses are available for the formation of these rare heterocycles (Scheme 1).[3] Representative examples include a limited scope of disubstituted aza-DKPs synthesized from *N*-(mesyloxy)malonamide reacting with hydrazines,[3g,h] the use of triphosgene and gaseous HCl to form aza-DKPs from *N*-Boc hydrazides and proline aminoesters,[3i] and a recent solution- and solid-phase synthesis affording aza-DKPs from *α*-aminoesters and *N*-Boc hydrazides.[3l,m]

Scheme 1. Prevalence of Aza-DKPs in the Literature[a]



[a]Search generated with Reaxys: see Supporting Information for details. [b]Molecules containing this core. [c]Natural products containing this core. [d]Approved drugs containing this core.

Nitrogen-substituted isocyanates (*N*-isocyanates) are a rare yet powerful class of heterocumulene. Compared to *C*-substituted isocyanates (>100,000 publications and patents in the literature), the synthetic potential of *N*-isocyanates has been largely overlooked (ca. 60 publications to date).[4] This scarcity is likely due to the known propensity of amphotheric *N*-isocyanates to dimerize, even at low temperature (ca. −40 °C).[4h] This issue prevented the ability of *N*-isocyanates to act as simple synthons for nitrogen analogues of bioactive products possessing *α*-amino carbonyl motifs, such as aza-DKPs. However, we have recently shown that *N*-isocyanates can be versatile intermediates for the synthesis of various N−N−C═O containing molecules, using either alkene aminocarbonylation[5] or cascade reactions.[6] This reactivity has been developed using blocked (masked) *N*-isocyanate precursors, which reversibly form the *N*-isocyanate upon heating or in the presence of a base as a catalyst. This blocked *N*-isocyanate approach allows for controlled reactivity and prevents side reactions such as *N*-isocyanate dimerization. The control provided by this strategy allowed for the development of cascade reactions forming saturated nitrogen heterocycles,[6a] amino-hydantoins,[6b] acyl-pyrazoles,[6c] acyl-phthalazinones[6c] and 6-azauracils.[6c] However, in all these approaches the first step of the reaction sequence involved the generation and reaction of the *N*-isocyanates and did not take advantage of the ability of blocked isocyanates to

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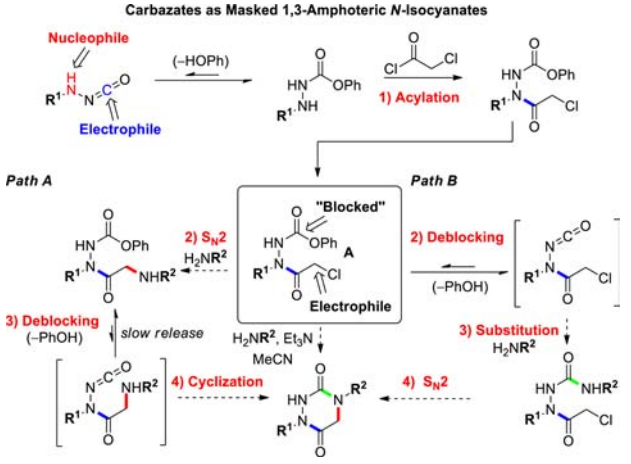
serve as a hemilabile protecting group. Herein, we use this ability to achieve a mild synthesis of aza-DKPs, using a one-pot reaction sequence involving acylation with chloroacetyl chloride, S_N2 with a primary amine, *N*-isocyanate formation, and cyclization (Scheme 2).

Scheme 2. Amphoteric *N*-Isocyanates



At the beginning of our investigations, we believed that several different strategies using *N*-isocyanates could allow the formation of aza-DKPs (Scheme 2). For example, starting with substrate **A** the final cyclization (step 4) could occur either through addition of the amine on the *N*-isocyanate (path A) or through an intramolecular S_N2 reaction (path B) depending on where the amine adds first (step 2/3, path A/B). Having previously established that base catalysis allows *N*-isocyanate generation at room temperature,[5c,6c] we embarked on optimization of a one-pot sequence using *O*-phenyl *β*N-benzyl carbazate (**1a**) as a model starting material. Selected optimization results are shown in Table 1.

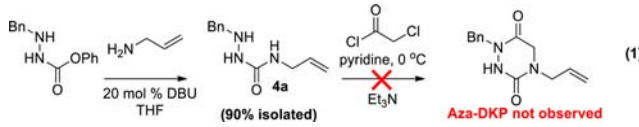
Table 1. Optimization of One-Pot Aza-DKP Formation[a]

entry	solvent	amine equiv	base	yield (%)[b]
1	THF	1.1	Et_3N	44
2	MeCN	1.1	Et_3N	60
3	CH_2Cl_2	1.1	Et_3N	38
4	DMSO	1.1	Et_3N	35
5	DMF	1.1	Et_3N	33
6	MeCN	1.5	Et_3N	68
7	**MeCN**	**2.0**	**Et_3N**	75[c]
8	MeCN	2.0	DMAP	37
9	MeCN	2.0	NMI	46

[a]Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M), then pyridine (1.1 equiv), and then chloroacetyl chloride (1.05 equiv). The solution was warmed to room temp and stirred for 2 h. A solution of amine (1.1–2.0 equiv) and base (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. [b]NMR yield based on trimethoxybenzene. [c]Isolated yield.

Encouragingly, we rapidly obtained proof-of-concept results when we first performed the acylation using chloroacetyl chloride, followed by addition of the amine (Table 1). Early studies showed that an intermolecular S_N2 reaction was possible in the presence of a mild base and occurred with minimal *N*-isocyanate formation. Performing a solvent scan then showed that acetonitrile was the optimal solvent for this one-pot sequence, which resulted in an increased yield for the aza-DKP products (entries 1–5). A crucial aspect of this optimization was also to identify suitable bases for each step, to ensure that formation of the *N*-isocyanate intermediate is controlled. Pyridine proved to be an ideal base for the acylation step (see Supporting Information for additional optimization data), and triethylamine emerged as the optimal base to facilitate the second step (entries 7–9). Using an excess of the amine (2 equiv) also proved beneficial to maximize the yield of aza-DKP product **3o** (entries 6–7).

Most importantly, the release of the *N*-isocyanate needed to be carefully controlled in order to follow the preferred reaction sequence (path A) and avoid unproductive pathways. Reaction monitoring indicated that the productive pathway for this one-pot sequence involves: (1) Acylation using chloroacetyl chloride; (2) Intermolecular S_N2 with a primary amine; (3) Base-induced *N*-isocyanate formation; and (4) Cyclization. In contrast, if the *N*-isocyanate was formed too early, addition on its electrophilic carbon led to a semicarbazide that could not perform the desired cyclization at room temperature (path B). This observation was verified in a separate control experiment, where we isolated **4a** and submitted it to the reaction conditions (eq 1).



Overall, this reaction optimization provided a convenient one-pot sequence in which four steps could occur sequentially to form the desired product in 75% isolated yield. We were thus eager to explore the applicability of this procedure to form other aza-DKPs. First, we examined the ability of several primary amines to engage in the one-pot reaction sequence and studied the impact of changes in amine structure on the efficiency of the overall process (Table 2).

A variety of amines could be used in this one-pot sequence to form the desired aza-DKP products, typically in moderate to good yields (Table 2). Various aliphatic amines are tolerated: methylamine and unbranched/branched primary amines all led to formation of the corresponding aza-DKPs. Hindered, branched primary amines such as isopropylamine typically led to lower yields, but the sequence nevertheless proved preparatively useful (**3a–d**). While benzylamine was an excellent reaction partner (72% yield, **3e**), substituted benzylic amines at the *meta*- and *para*-positions typically led to lower isolated yields (37% and 42% yield, **3g** and **3f** respectively). The reaction using *ortho*-aminobenzylamine was chemoselective (50% NMR yield, **3h**) but led to a product that was difficult to isolate. The reaction sequence occurred in the presence of functional groups, including a carbamate (*N*-Boc, **3k**), free hydroxyl groups (**3i** and **3q**), and acetal (**3j**); allylamine (**3o**) and propargylamine (**3n**) could also be used. Heterocycles were also tolerated and notably allowed the formation of pyridyl-, furyl-, indoyl-, and morpholinyl-functionalized aza-DKPs (**3l**, **3m**, **3p**, and **3r**, respectively). Overall, this approach proved versatile to incorporate a variety of substituents at the 4 position

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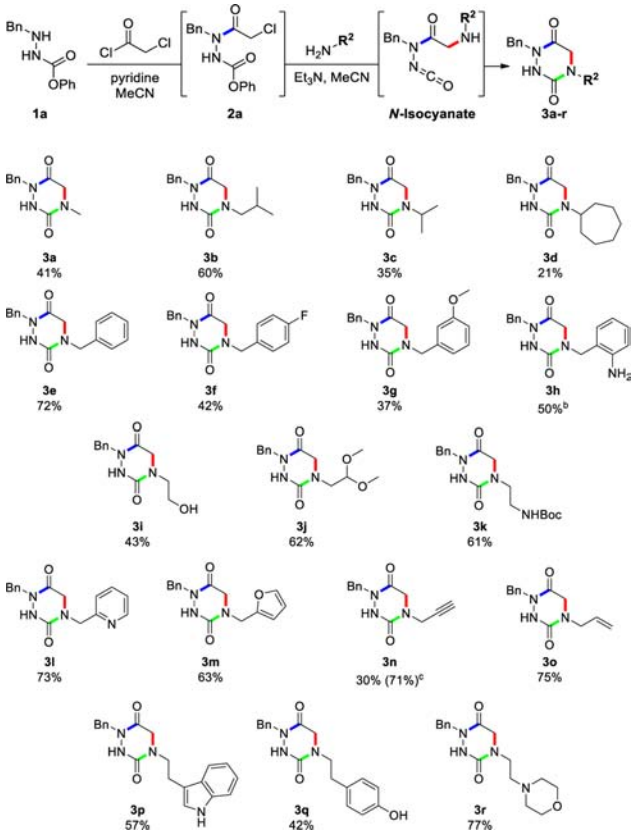
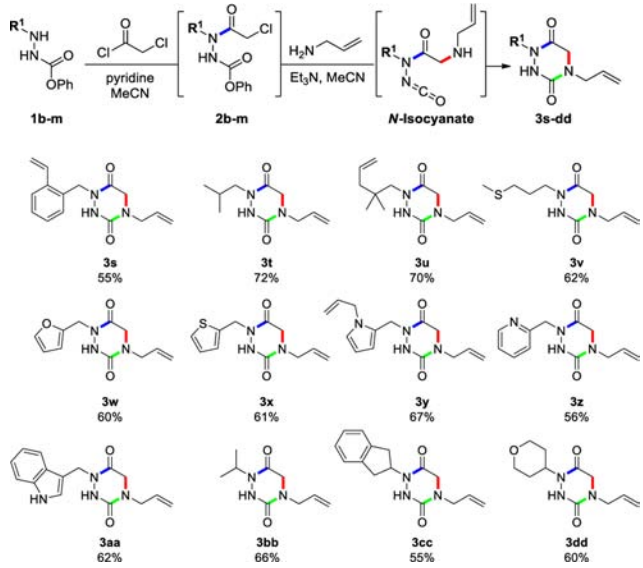
Table 2. One-Pot Aza-DKP Sequence: Amine Scope[a]



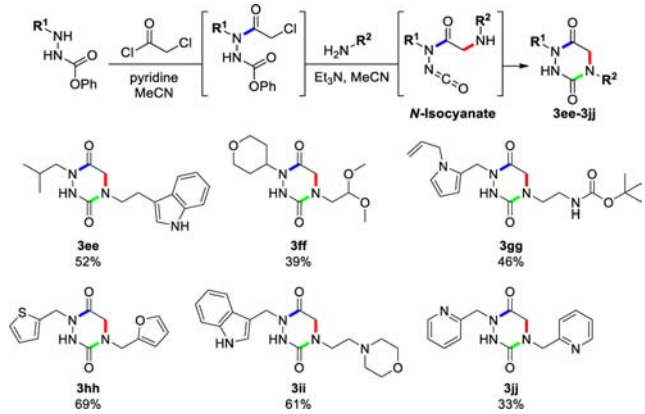
[a]Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M), then pyridine (1.1 equiv), and then chloroacetyl chloride (1.05 equiv). The solution was warmed to room temp and stirred for 2 h. A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. Isolated yields are shown. [b]^{1}H NMR yield based on 1,3,5-trimethoxybenzene as internal standard. [c]Aqueous extraction after acylation and then reflux in THF with amine (1.1 equiv) and Et_3N (1.3 equiv).

Table 3. One-Pot Aza-DKP Sequence: Carbazate Scope[a]



[a]Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M), then pyridine (1.1 equiv), and then chloroacetyl chloride (1.05 equiv). The solution was warmed to room temp and stirred for 2 h (or 16 h entries **3cc**, **3dd**). A solution of allylamine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. Isolated yields are shown.

Table 4. Mixed Aza-DKP Synthesis[a]



[a]Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M); then pyridine (1.1 equiv), and then chloroacetyl chloride (1.05 equiv). The solution was warmed to room temp and stirred for 2 h. A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. Isolated yields are shown.

of the aza-DKP. Naturally, we were also interested in determining the impact of carbazate substitution on the efficiency of this reaction sequence. The results of this study are shown in Table 3.

A variety of carbazates could be used as starting materials for the one-pot reaction sequence using allylamine as the reaction partner (Table 3). As expected, the yields proved consistent for several structural variations on the carbazate reagent (55 to 72% yield). *N*-Alkyl carbazates with linear, α-branched, and β-branched carbon chains could be used to form the desired aza-DKPs. However, for sterically hindered βN-substituents, longer reaction times are required for the acylation step (16 h rather than 2 h). The reaction sequence again tolerated the presence of various functional groups, including alkenes (**3s**, **3u**, **3y**), ethers (**3dd**), thioethers (**3v**), and a free N−H group (**3aa**). The reaction also tolerated the presence of heterocycles on $\mathbf{R^1}$, thus forming products including furan (**3w**), thiophene (**3x**), pyrrole (**3y**), pyridine (**3z**), and indole (**3aa**) heterocycles. Overall, the results presented in Tables 2 and 3 showed that variation on each reaction partner was well tolerated. Thus, we decided to vary each reaction partner simultaneously in order to form structurally diverse aza-DKPs (Table 4).

First, we combined a simple aliphatic carbazate and tryptamine to yield a leucine-tryptophan aza-DKP (**3ee**). We could also incorporate functional groups and heterocycles that are not typically present on diketopiperazine analogues. For example, aza-DKP **3ff** combined a saturated cyclic ether with a protected aldehyde; similarly, **3gg** possessed an *N*-allyl pyrrole with a protected amine. Aza-DKPs possessing heterocycles on each side chain were also formed, such as thiophene-furan (**3hh**), indole-morpholine (**3ii**), and pyridine-pyridine (**3jj**) combinations. Overall, the aza-DKPs formed are highly functionalized. It is also important to note the high heteroatom density in the products' backbone (up to 2:3 heteroatom/carbon atoms in the skeleton for entries in Table 4). Finally, as shown below, this one-pot sequence is also scalable (eq 2).

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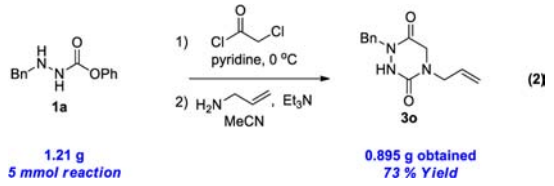

In conclusion, we have developed a mild, operationally simple, one-pot sequence for the synthesis of aza-DKPs. This sequence uses readily available, bench-stable carbazates as *N*-isocyanate precursors, chloroacetyl chloride, and primary amines thus allowing for the rapid assembly of structurally diverse DKP analogues. Optimization of the reaction conditions was required to ensure an efficient acylation reaction with hindered substrates and to slowly form the *N*-isocyanate. These conditions allowed for typical yields in the 50−70% range for this four-step sequence involving acylation, S_N2 reaction with a primary amine, *N*-isocyanate formation, and cyclization. Strategically, this sequence exploits the ability of carbazates to serve as blocked (masked) *N*-isocyanate precursors, and the controlled reactivity results in an S_N2 reaction occurring first, in the presence of a protected *N*-isocyanate. Biological testing of the aza-DKP products and development of other reaction sequences involving *N*-isocyanates is ongoing 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.5b02464.

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

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Author Contributions

§R.A.I. and J.-F.V.-R. contributed equally.

Notes

The authors declare no competing financial interest.

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