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An Atom-Economical Method To Prepare Enantiopure Benzodiazepines with *N*-Carboxyanhydrides

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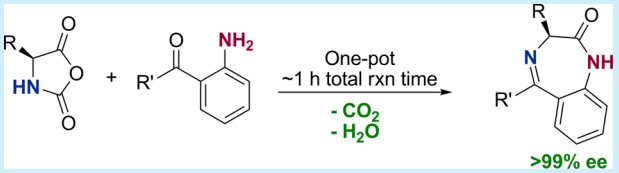
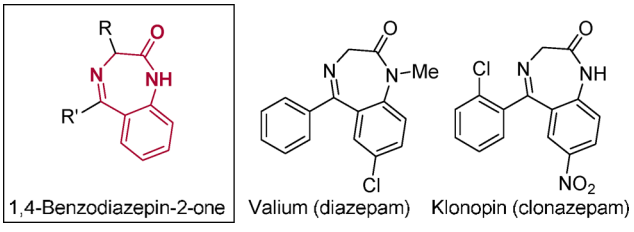
Supporting Information

ABSTRACT: The development of a rapid, one-pot synthesis of diazepinones with simple reagents is described. *N*-Carboxyanhydrides (NCAs) are employed as amino acid building blocks that react with *o*-ketoanilines sequentially as electrophiles and nucleophiles to form diazepinones with water and carbon dioxide as byproducts. Notably, these reactions enable the coupling of stereodefined amino acid derived NCAs without racemization. This method is demonstrated by an improved synthesis of a key intermediate toward a bromodomain and extra-terminal (BET) bromodomain inihibitor.



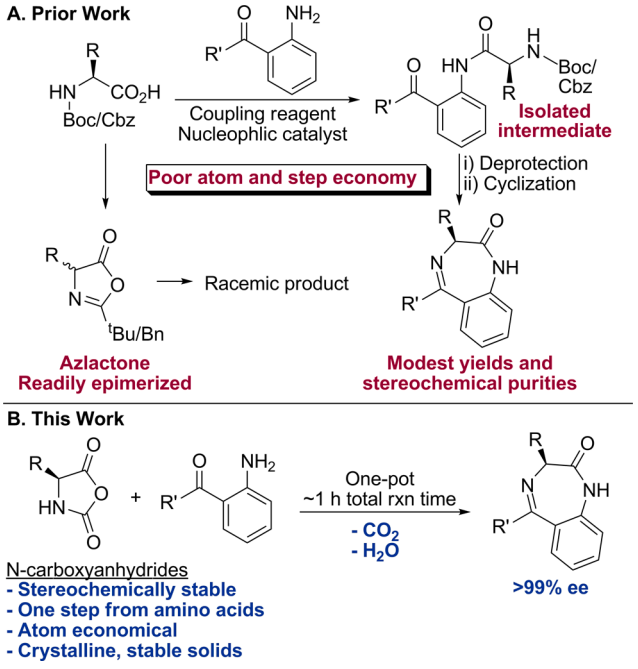
Benzodiazepines and their analogues are considered to be privileged structures in medicinal chemistry.[1] These subunits are prevalent in several marketed drugs, such as Valium, Xanax, and Klonopin, and drug candidates currently under development. Within the benzodiazepine family, 1,4-benzodiazepin-2-ones are the most common structural subtype (Scheme 1). Due to their widespread prevalence in drug discovery, simple and robust methods for their synthesis are highly valued.

Scheme 1. 1,4-Benzodiazepin-2-ones: Structure and Illustrative Examples



The most common approaches to 1,4-benzodiazepin-2-ones involve a multistep sequence of (i) coupling *N*-Boc or *N*-Cbz protected amino acids with an *o*-ketoaniline, (ii) isolation of the amide product, (iii) deprotection, and (iv) cyclization (Scheme 2A).[2] Beyond the long processing times and low atom economy, a major concern revolves around the potential for racemization of the stereogenic center derived from the amino acid.[3] In peptide coupling reactions of *N*-Boc or *N*-Cbz amino acids, facile racemization of the stereogenic center can occur through azlactone formation (Scheme 2A), which leads to low stereochemical purity of the product.[4] The extent of the racemization is highly dependent on the identity of the amino acid and the rate of the coupling reaction; racemization is particularly problematic with poorly nucleophilic amines such as *o*-ketoanilines. To overcome all of these issues, we sought to develop a rapid, one-pot synthesis of stereochemically pure diazepinones without the need for wasteful protecting groups and activating reagents. We proposed that *N*-carboxyanhydrides (NCAs) could react with *o*-ketoanilines with loss of carbon dioxide to form a *β*-amino amide intermediate; the primary amine revealed would then be suited to condense with the carbonyl group (Scheme 2B). Ideally, such reactions would liberate water and CO_2 as the only stoichiometric byproducts.

Scheme 2. Synthetic Routes to Benzodiazepines



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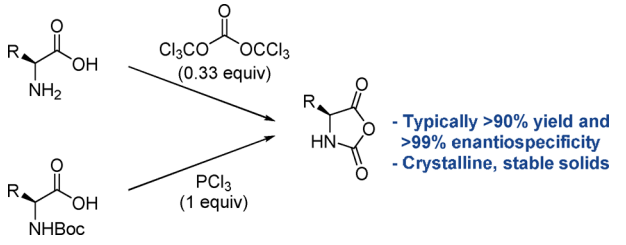
N-Carboxyanhydrides are readily prepared as crystalline compounds in a single step without racemization from unprotected amino acids and COX_2 reagents, such as triphosgene (Scheme 3).[5] Alternatively, NCAs can be prepared

Scheme 3. General Routes To Prepare NCA Reagents

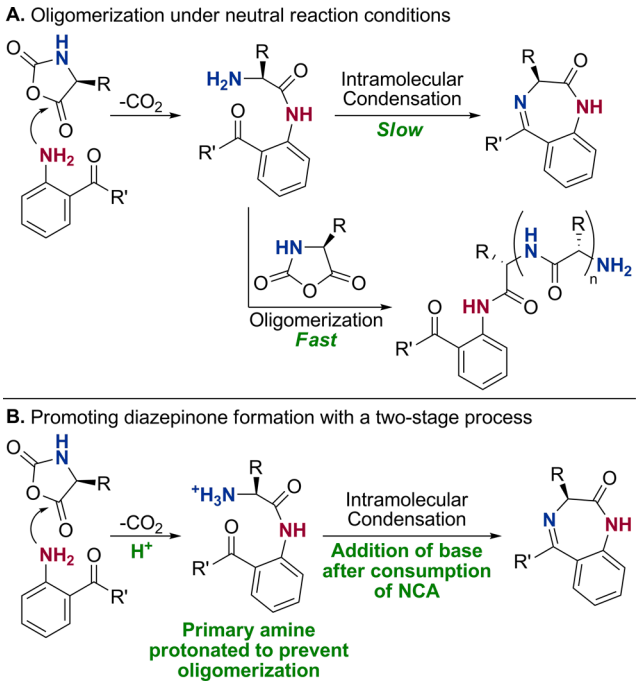


from *N*-Boc amino acids with 1 equiv of PCl_3 at ambient temperature.[6] NCAs are chromatographically stable and bench-stable compounds that have been widely applied to polymerization reactions for the preparation of high molecular weight polypeptides.[7]

At the outset, we investigated the reactivity between various *o*-ketoanilines and NCAs. However, simply heating an equimolar amount of the two reagents together led to the complete consumption of the NCA, only trace conversion of the *o*-ketoaniline, and no formation of the benzodiazepinone. These results are consistent with oligomerization of the NCA taking place after an initiation event. It was concluded that oligomerization pathways were occurring due to the (i) lower electrophilicity of the ketone compared to the anhydride carbonyl of the NCA, (ii) greater nucleophilicity of the primary amine compared to the *o*-ketoaniline, and (iii) relatively slow formation of the seven-membered ring (Scheme 4A).

We considered that the oligomerization pathway could be suppressed, and the desired pathway be favored, by performing the reaction in two stages under different pH regimes (Scheme 4B). The *N*-acylation step would proceed under acidic

Scheme 4. NCAs in Benzodiazepine Synthesis

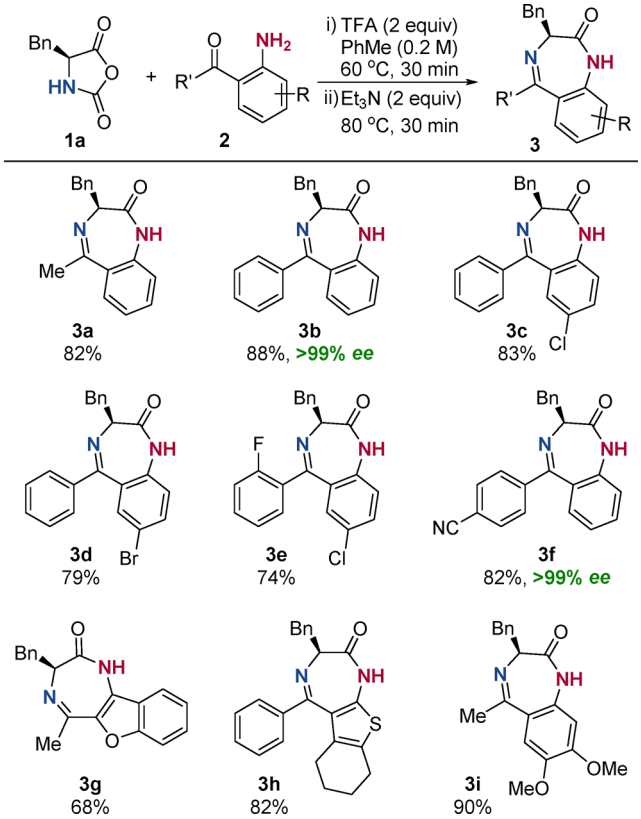


conditions such that the liberated primary amino group would exist as the ammonium salt, suppressing further reactions with the NCA, while the less basic aniline would exist largely as the free base and be suitably reactive toward the NCA. After complete consumption of the NCA, the intramolecular condensation step would occur by buffering the reaction medium to permit the primary amino group to react with the carbonyl group.

The success of the *N*-acylation step would depend largely on the choice of acid and solvent. To prevent bis-amide formation and related oligimerization products from forming, high conversion of the NCA in the *N*-acylation stage would be required prior to adding a base during the condensation stage. With these considerations in mind, a survey of different acids, stoichiometry, solvents, concentrations, and bases was conducted. The most general and mild conditions were identified as 1.0 equiv of *o*-ketoaniline, 1.2 equiv of NCA, 2.0 equiv of CF_3CO_2H, in toluene (0.2 M), at 60 °C for 30 min. After the NCA is consumed, Et_3N (2.0 equiv) is added, and the reaction mixture is heated at 80 °C for 30 min.

First, the scope of this new reaction sequence was investigated with respect to the *o*-ketoaniline (Scheme 5)

Scheme 5. Substrate Scope of *o*-Ketoaniline Substrate[a]



[a]Isolated yields are shown for reactions performed on 1.0 mmol scale. Reactions were performed with 1.2 equiv of **1a**.

with phenylalanine-derived NCA (**1a**). The reaction sequence occurred in good yield with both acetophenone and benzophenone substrates, and the conditions were tolerant of aryl halides, nitriles, esters, *ortho*-substituents, and various heterocycles. Substrates with electron-donating or -withdrawing groups reacted in good yields. Notably, substrate **2f**, a compound containing a strongly electron-withdrawing *p*-CN

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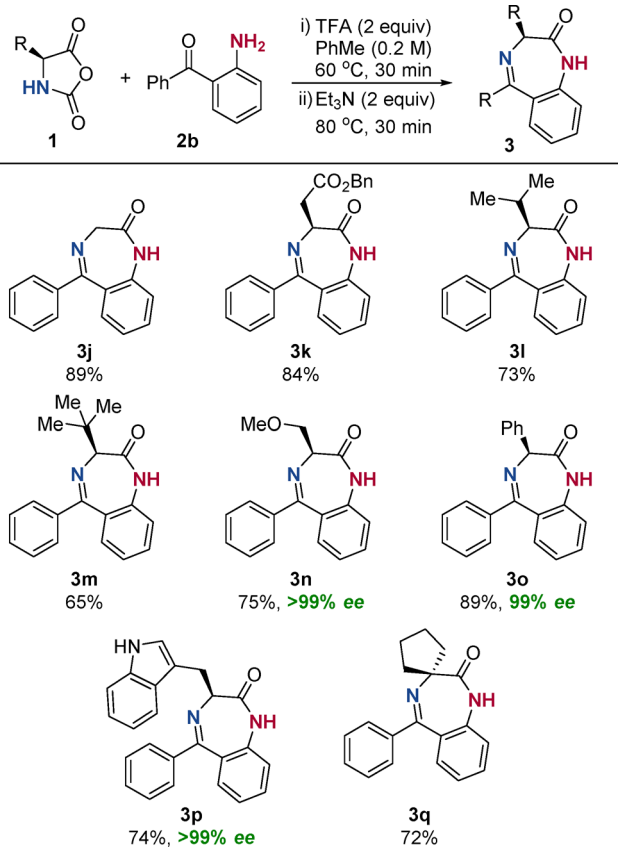
group, reacted under the standard conditions to form **3f** in >99% *ee*.

Next, the scope with respect to the NCA reagent was investigated with 2-aminobenzophenone as the substrate (Scheme 6). A range of amino acids could be used to prepare

Scheme 6. Scope of the Amino Acid NCA[a]

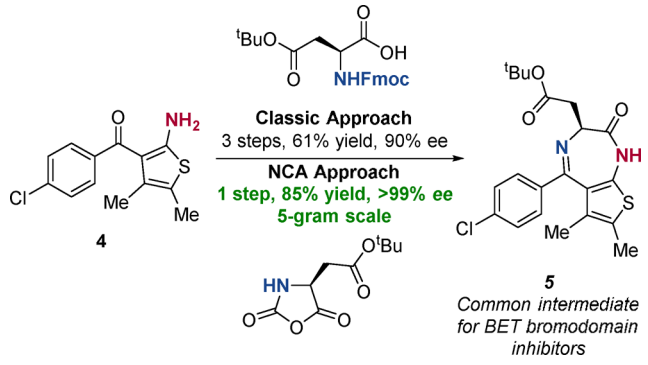


[a]Isolated yields for reactions performed on a 1.0 mmol scale. Reactions were performed with 1.2 equiv of **1**.

a diverse library of substituted benzodiazepines. Glycine NCA coupled in high yield to form the unsubstituted benzodiazepine product, a motif found in many commercial drugs. NCA reagents prepared from benzyl aspartic acid, *O*-methyl serine, phenylglycine, and tryptophan coupled in good overall yield. Hindered NCAs, such as those derived from valine and *tert*-leucine, reacted in good yields. Finally, α,α-disubstituted 1-aminocyclopentane carboxylic acid NCA reacted to form the spirocyclic diazepinone **3q** in 72% isolated yield. Notably, products containing electron-withdrawing benzyl (**3b**), methoxymethyl (**3n**), indolyl (**3p**), and carboxyl groups (**5**, vide infra) were formed in >99% *ee*. Furthermore, in spite of phenylglycine amino acids being highly susceptible to racemization, the method reported here enabled the synthesis of phenylglycine derived benzodiazepine **3o** in 99% *ee*, a testiment to the utility of NCA reagents for stereocontrolled synthesis.

To demonstrate the utility of this method for the synthesis of medicinally relevant molecules, we targeted a common intermediate en route to bromodomain and extra-terminal (BET) bromodomain inhibitors, a class of compounds under development for anticancer and anti-inflammatory applications (Scheme 7). The reported routes to compound **5** rely on a three-step sequence from *N*-protected aspartic acid derivatives.[8]

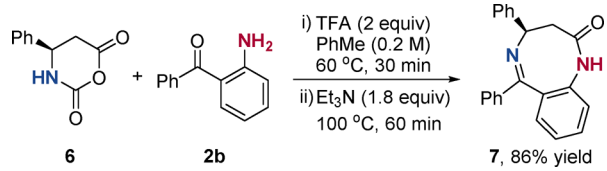
Scheme 7. Application to the Improved Synthesis of BET Bromodomain Inhibitors



The highest yielding route reported occurs in only 61% yield over three steps and provides the product in 90% ee from an enantiopure aspartic acid building block.[8b] By employing the method reported here with an aspartic acid derived NCA, the targeted molecule was formed in just 1 h in 85% yield and >99% *ee* on a 5 g scale without chromatography. This short synthesis highlights the synthetic utility of the NCA approach to access enantiopure benzodiazepine targets rapidly.

The synthesis of eight-membered rings was also investigated using NCAs derived from β-amino acids (Scheme 8). Previous

Scheme 8. Application of an NCA to the Synthesis of an Eight-Membered Ring



attempts to prepare this class of compounds from amino acids resulted in amino acid dimerization.[9] Thus, approaches to 1,5-benzodiazecines typically rely on multistep sequences from β-lactams, dihydroquinazoline, or benzyne.[10] Six-membered NCA reagent **6** was prepared in gram quantities from the reaction of *N*-Boc β-phenylalanine with PCl_3. Compound **6** cleanly reacted with 2-aminobenzophenone (**2b**) under acidic conditions to form the β-amino amide intermediate. In our approach, the reactive primary amine generated upon opening the NCA is deactivated by protonation, therefore eliminating the potential for dimerization. After promoting the cyclization step by the addition of triethylamine, compound **7** was formed in 86% isolated yield.

In summary, we have developed a practical and atom-economical approach to the synthesis of benzodiazepines with readily available *N*-carboxyanhydrides. The method reported here allows the synthesis of a diverse array of enantiopure diazepinones in high yields in approximately 1 h of total reaction time. Notably, our reaction conditions form products in >99% *ee* even with substrates prone to racemization. The synthetic utility has been demonstrated by an improved route to a common intermediate for BET bromodomain inhibitors. We have also demonstrated the potential to use NCAs as convenient precursors to the synthesis of eight-membered rings. We anticipate that the mild reaction conditions, broad generality, and experimental simplicity will make this the

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method of choice for the synthesis of enantiopure benzodiazepines.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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