

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

Org. Lett. **2017**, *19*, 1454–1457

The benzodiazepine scaffold can be found in many marketed drugs, such as Valium and Klonopin (Figure 1). Importantly, benzodiazepines are finding resurgence in medicinal chemistry with new indications such as anticancer therapeutics. As part of a Merck drug development program, Dr. Patrick Fier and Dr. Aaron Whittaker from Merck & Co. (Rahway, USA) were tasked with developing an efficient synthesis of a benzodiazepine-based molecule.

However, known approaches involve multistep sequences and lead to racemization of the stereocenter at the alpha position. Dr. Fier said: “We considered that a more direct method to access benzodiazepines could be realized by employing *N*-carboxyanhydrides (NCAs) as the amino acid coupling partner. It was proposed that *o*-ketoanilines could react with an NCA first as a nucleophile and then, upon loss of carbon dioxide, a β -amino amide intermediate would be generated which would then be suited to condense with the carbonyl group (Scheme 1). This proposed reaction sequence was appealing since it would generate water and CO₂ as the only stoichiometric byproducts.”

Dr. Fier continued: “We were pleased to find that the *N*-carboxyanhydrides used for this study were readily prepared as crystalline compounds in a single step from unprotected amino acids and COX₂ reagents, such as triphosgene. None of the NCAs used in this study required purification, as the pure compounds precipitated from solution during their preparation.”

The authors investigated the reactivity between 2-amino-benzophenone and an NCA derived from phenylalanine.

However, it was quickly realized that simply heating an equimolar amount of the two reagents led to oligomerization of the NCA. “This side reaction was not surprising since (i) the electrophilicity of the ketone is lower than that of the anhydride carbonyl of the NCA, (ii) the nucleophilicity of the primary amine generated upon NCA opening is greater than that of the aniline, and (iii) the formation of seven-membered rings is slow,” explained Dr. Fier. He continued: “To suppress this oligomerization pathway we decided to perform the reaction in two stages under different pH regimes. The *N*-acylation step would proceed under acidic 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 authors of this study knew that high conversion of the NCA in the *N*-acylation stage would be required prior to buffering the solution for 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 equivalent of *o*-ketoaniline, 1.2 equivalents of NCA, 2.0 equivalents of CF₃CO₂H, in toluene (0.2 M), at 60 °C for 30 minutes. “With high conversion of the NCA, the cyclization step seemed inevitable, but the identity and the stoichiometry of the base were critical,” said Dr. Fier. “Because of the low rate of forma-

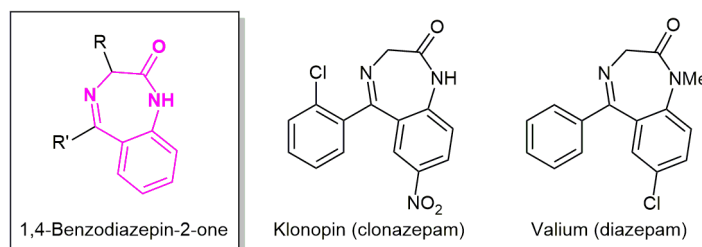
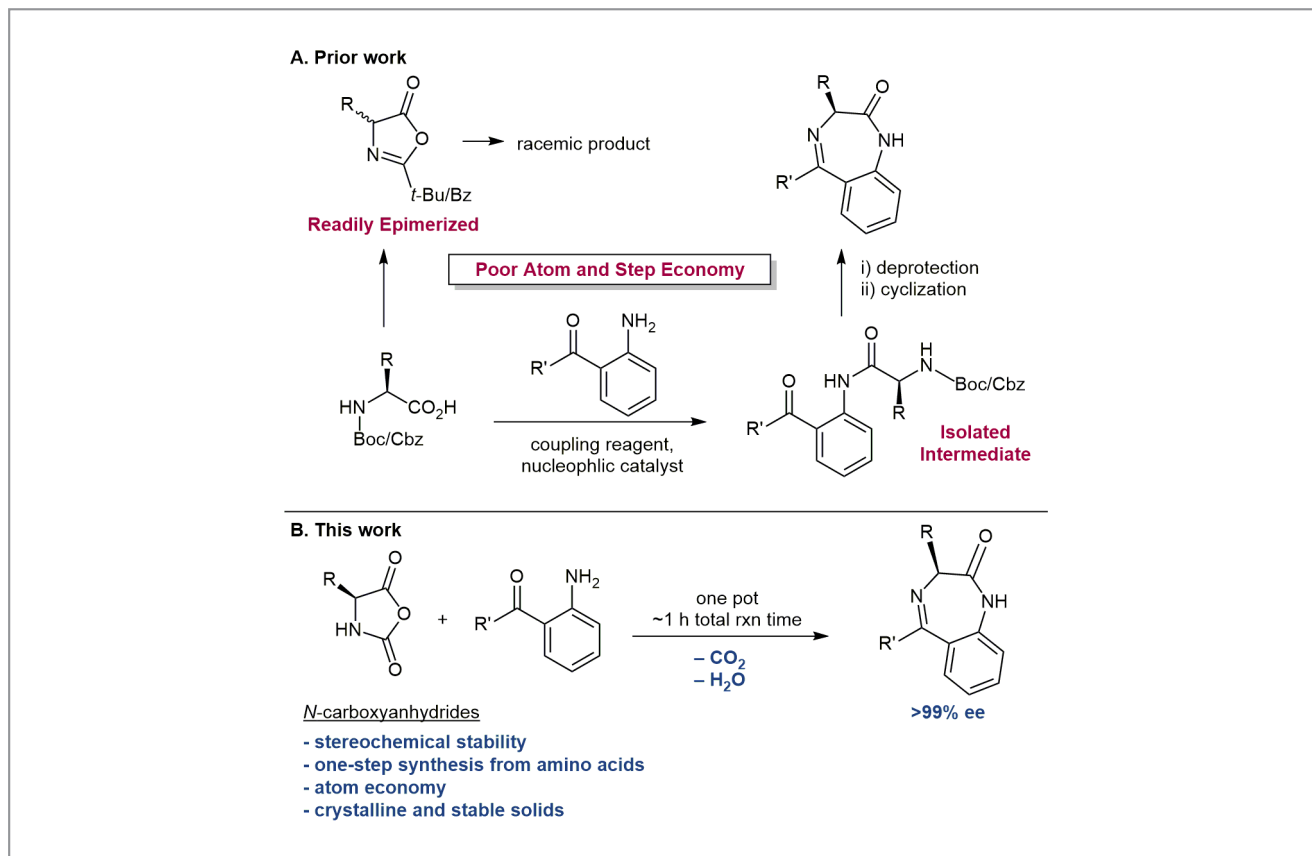


Figure 1



Scheme 1

tion of seven-membered rings, we had to identify conditions that did not lead to racemization of the stereocenter of the β -amino amide intermediates. We eventually settled on 2.0 equivalents of Et_3N followed by heating to 80 °C for 30 minutes."

"We were pleased with the scope of this new reaction sequence," remarked Dr. Whittaker. "Acetophenone- and benzophenone-derived substrates worked equally well, 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, and *N*-carboxyanhydrides derived from glycine, benzyl aspartic acid, *O*-methyl serine, valine and *tert*-leucine, reacted in good yields."

To explore the robustness of their method towards generating highly enantioenriched benzodiazepines, the Merck pair selected a few substrates deemed most likely to racemize under standard coupling conditions. Every substrate tested gave excellent stereo-retention ($\geq 99\%$) including compounds containing a strongly electron-withdrawing *para*-CN, -benzyl,

-methoxymethyl, -indolyl, or -carboxyl groups (Scheme 2). Even a phenylglycine-derived NCA, which is highly susceptible to racemization, gave 99% ee. The phenylglycine substrate was found to slowly racemize (94% ee after 2 h at 80 °C) upon standing in a solution buffered by Et_3N ; therefore, the more hindered base DIPEA was selected.

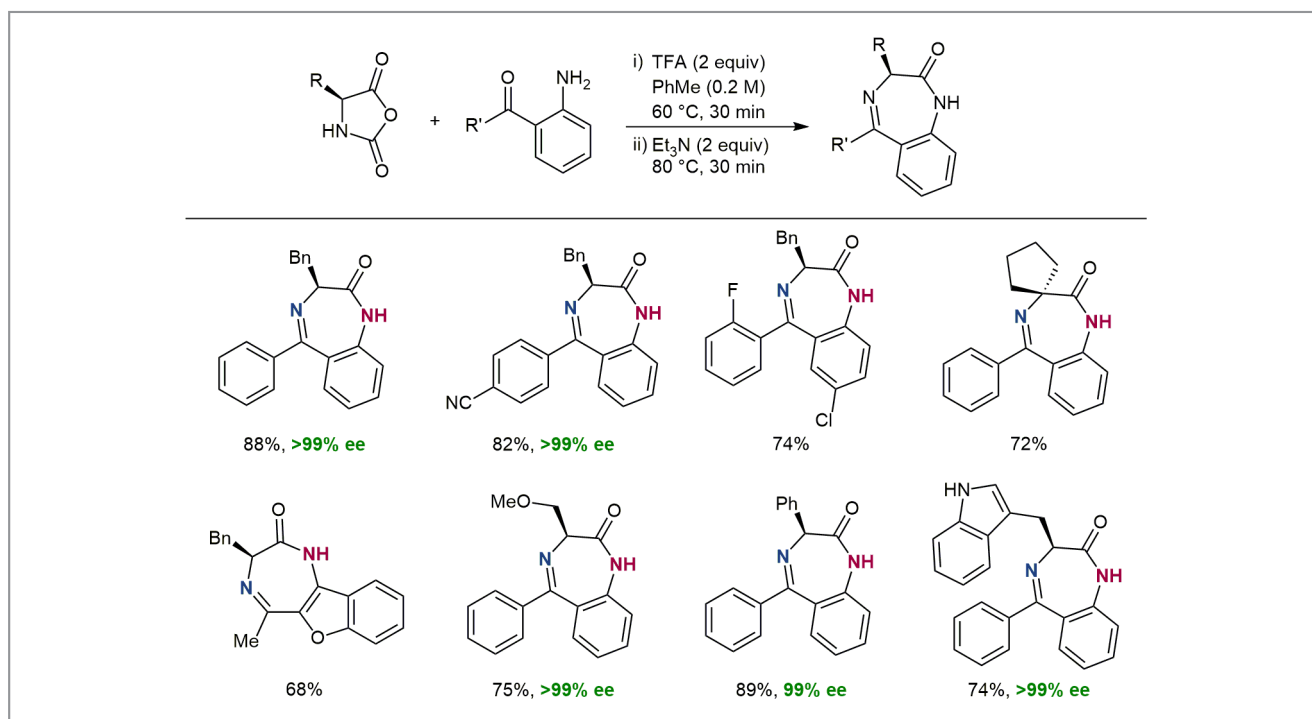
"Our newly developed method was used to target a common intermediate en route to a bromodomain and extra-terminal (BET) bromodomain inhibitor under development for anticancer applications," explained Dr. Whittaker, adding: "The reported routes to this compound rely on a three-step sequence from *N*-protected aspartic acid derivatives. 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 (Scheme 3)."

"By employing the method we developed with an aspartic acid derived NCA, the targeted molecule was formed in just one hour in 85% yield and >99% ee on a 5 g scale, and was isolated without chromatography," said Dr. Fier.

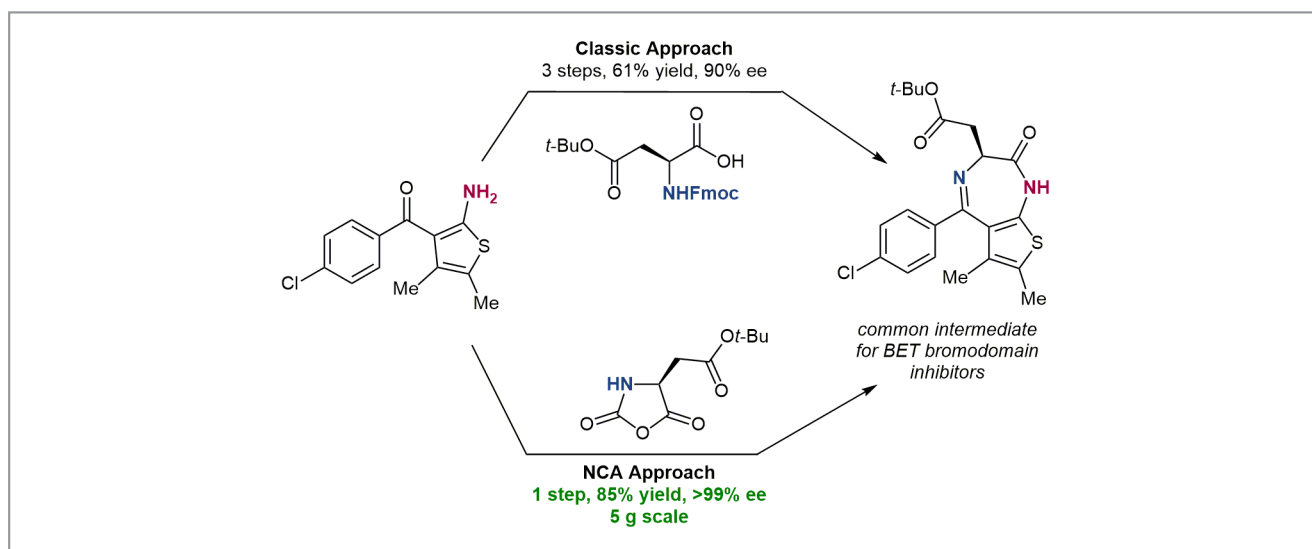
Dr. Fier concluded: "We believe that NCA reagents are under-utilized in synthesis, and our future work will further explore the utility of these reagents. We also anticipate that this method will be rapidly adopted due to the simplicity of

the procedure, wide availability of the reagents, and the value of the products in drug discovery and development."

Matthew Fier

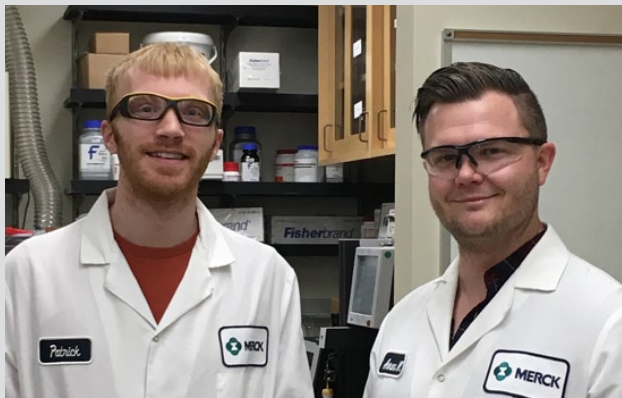


Scheme 2



Scheme 3

About the authors



Dr. P. S. Fier (left), Dr. A. M. Whittaker (right)

Patrick Fier received his Ph.D. at the University of California, Berkeley (USA) from Professor John Hartwig's group. As a graduate student, he developed several methods to incorporate fluorine and fluoroalkyl groups into organic molecules. Since 2015, he has been a process chemist at Merck where he works on the development of scalable, and robust synthetic routes to complex drug molecules.

Aaron Whittaker received his Ph.D. in 2013 at the University of Washington (USA) under the supervision of Professor Gojko Lalic. At the UW, Aaron developed new copper-catalyzed methods for hydroamination, aryl amination, allylic substitution, semi-reduction, and hydrodefluorination. Upon receiving his Ph.D, Aaron moved to the University of California, Irvine (USA) to do postdoctoral research with Professor Vy Dong. At UCI, Aaron developed nickel-catalyzed transfer hydrogenations that enabled the oxidative coupling of alcohols and amines with aldehydes to generate esters and amides. Since 2015, Aaron has been a process chemist at Merck & Co., Inc. where he focuses on developing new methods to enable large-scale synthesis of medicinally relevant molecules.