Base-Mediated [3 + 4]-Cycloaddition of Anthranils with Azaoxyallyl Cations: A New Approach to Multisubstituted Benzodiazepines

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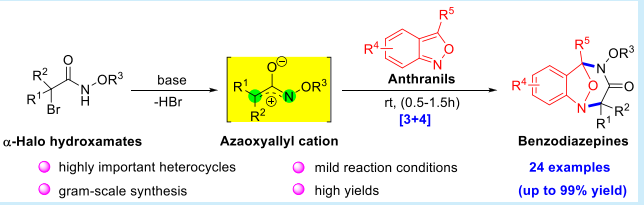
S *Supporting Information*

ABSTRACT: A new [3 + 4] cycloaddition of azaoxyallyl cations and anthranils has been achieved for rapid access to multisubstituted benzodiazepine derivatives. A variety of anthranils and α-halo hydroxamates were both effective substrates with simple operations under transition-metal-free conditions. The intriguing features of this method include its mild nature of the reaction conditions, high efficiency, broad substrate scope, and wide functional group compatibility.



Nitrogen heterocycles are widespread structural motifs in bioactive natural products, therapeutic agents, agrochemicals, and material molecules with significant activities.[1] In particular, benzodiazepines, a member of the family of privileged scaffold, occupy a significant place in pharmaceutical ingredients.[2] As representative examples shown in Figure 1, SB-214857 (lotrafiban), a potent glycoprotein IIb/IIIa receptor antagonist, displays antithrombotic activity.[3] Diazepam, commercially known as Valium, is used to treat anxiety.[2a] Abbemycin, isolated from *Streptomyces sp. AB-999F-52*, is an antibiotic.[4] TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-resistance could be overcome by use of fuligocandin B.[5] Circumdatin D and E are two quinazolinobenzodiazepine alkaloids isolated from the fungus *Aspergillus ochraceus*.[6] Given the rich biological profiles of the seven-membered nitrogen heterocycles in organic synthesis and medical chemistry, the development of a novel method to access benzodiazepine and related scaffolds remains highly desirable.

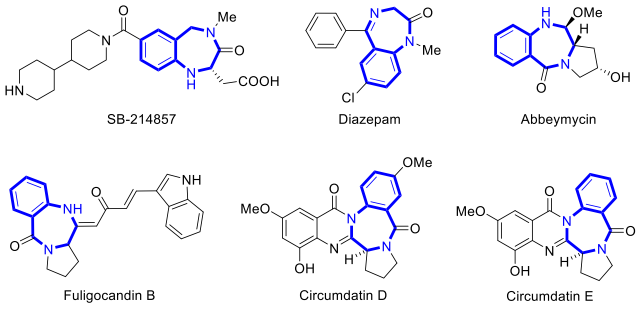
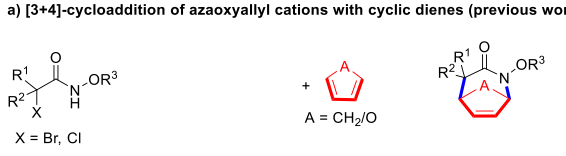


Figure 1. Selected biologically active molecules with the benzodiazepine unit.

Scheme 1. Base Mediated [3 + 4] Cycloadditions with Azaoxyallyl Cations



[3 + 4]-Cycloaddition reaction is an efficient strategy to assemble seven-membered rings.[7] In recent years, azaoxyallyl

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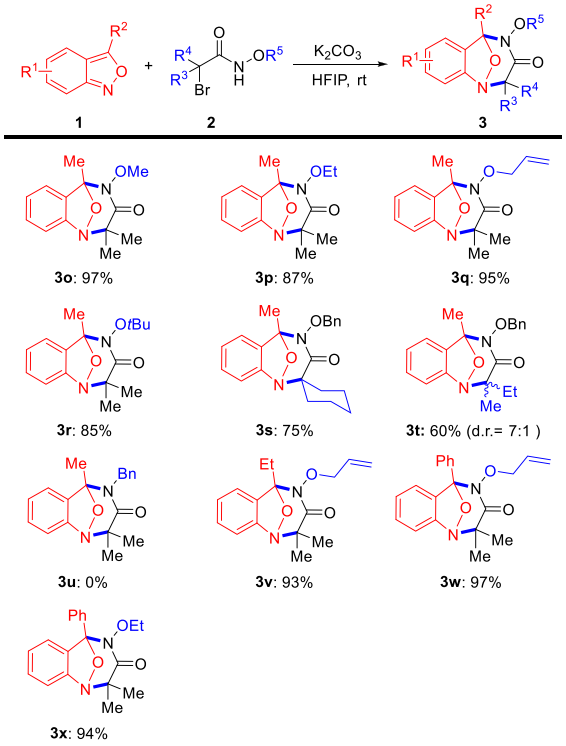
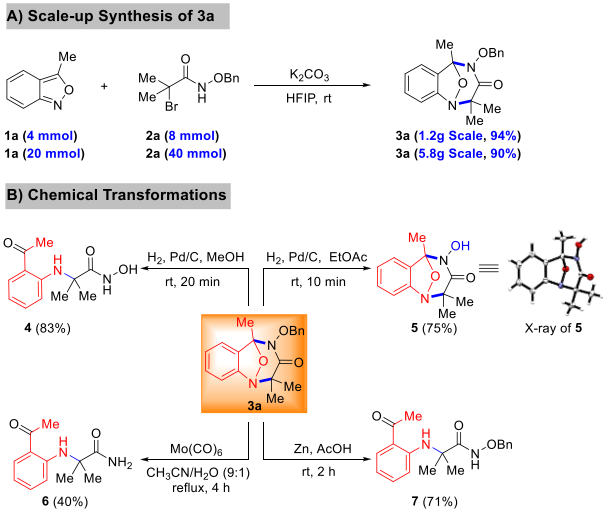
Scheme 3. Substrate Scope of α-Halo Hydroxamates[a,b]



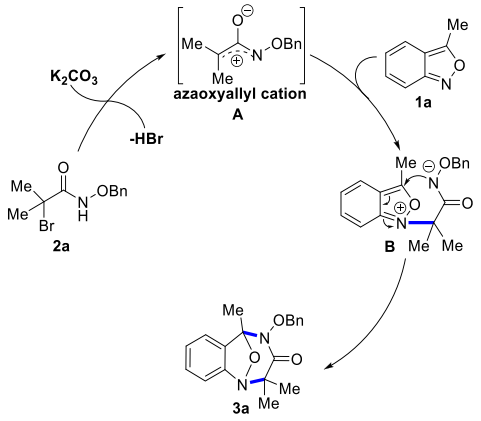
[a]All reactions were performed with anthranil **1** (1.0 equiv) with α-halo hydroxamate **2** (2.0 equiv) and K_2CO_3 (2.0 equiv) dissolved in HFIP (7.5 M) at rt for 0.5−1.5h. [b]Isolated yield.

Scheme 4. Synthetic Applications



Under the optimal conditions, the generality of anthranils **1** were examined (Scheme 2). The cycloaddition reactions could endure anthranils (**1b**−**1c**, **1e**−**1f**) bearing various halide substituents (5-Cl, 5-Br, 6-Cl, 6-F), affording products in high yields (96−99%). In addition, electron-donating methyl group substituted substrate **1d** reacted smoothly to give **3d** in 91% yield. Anthranils with an ethyl group (**1g** and **1h**) and a bromomethyl group (**1i**) at the C-3 position afforded [3 + 4]-cycloadducts (**3g**, **3h** and **3i**) in excellent yields. Moreover, the R_2 substituent could be replaced by various aryl rings. For substrate **3j** bearing a phenyl group, the desired product was obtained in 95% yield. The X-ray diffraction analysis firmly

Scheme 5. Proposed Reaction Mechanism



confirmed the chemical structure of **3j** (CCDC 1923225). Some other anthranils possessing trifluoromethyl or cyanide aryl substituents have showed comparable efficiency. We found that 3-(naphthalen-2-yl)benzo[*c*]isoxazole also behaved well, providing benzodiazepine derivative **3m** in 60% yield. When the R_2-substituent was a pyrimidine group, this reaction also smoothly proceeded to provide the desired product with a relatively lower yield. However, when the anthranil bearing a H atom at the C-3 position was tested, no desired product was obtained (structures not shown).[12a]

We then moved toward investigating the reactivity of an α-halo hydroxamates partner. As depicted in Scheme 3, substrates (**2b**−**2e**) with variation of protecting groups on the nitrogen atom tend to provide benzodiazepine derivatives in 85−97% yields (**3o**−**3r**). Additionally, cyclohexyl-substituted hydroxamate afforded **3s** in 75% yield. When the R^3 and R^4 groups were different alkyl chains, the *N*-benzyloxy α-bromoamides **2g** yielded product **3t** with a diastereomeric ratio (d.r. = 7:1) in 60% combined yield. However, the cycloaddition reaction did not take place with *N*-benzyl-2-bromo-2-methylpropanamide as the substrate, which might arise from the low stability of the azaoxyallyl cation.[10f,11a,13] Moreover, some other combinations of anthranils and α-halohydroxamates were also compatible, providing functionalized benzodiazepine derivatives (**3v**−**3x**) in excellent yields.

In order to address the viability and potential synthetic application of this [3 + 4] cycloaddition, gram-scale reactions and several chemical transformations of product **3a** were carried out. The product was obtained in 94% (1.2 g scale) and 90% (5.8 g scale) yields, respectively (Scheme 4A). This result indicates that there is no loss of efficiency during the scale-up operation of the present methodology.

We found that both the N−O bond and the benzyl group of **3a** were readily transformed through hydrogenation with Pd/C in methanol solvent (Scheme 4B). Hydrogenation in ethyl acetate could be completed to provide **5** without cleavage of the N−O bond. X-ray analysis of product **5** determined its chemical structure (CCDC 1923226). Under more strenuous conditions, when **3a** was treated with $Mo(CO)_6$, N-unprotected **6** could be achieved through deprotection of the benzyl group and cleavage of the N−O bond. In addition, the N−O bond could also be cleaved by zinc under acidic conditions, providing **7** in 71% yield.

A plausible mechanism of the above transformation is proposed in Scheme 5. First, azaoxyallyl cation intermediate **A** was formed from α-halohydroxamate **2a** in the presence of

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K_2CO_3. Next, anthranil **1a** reacted with intermediate **A** generating zwitterionic intermediate **B**. Finally, the [3 + 4]-cycloadduct **3a** was observed through intramolecular nucleophilic addition of **B**.

In summary, aza-oxyallyl cations generated *in situ* and anthranils undergo a [3 + 4] cycloaddition to provide synthetically useful benzodiazepine derivatives in average good yields. The new method was both concise and mild, which exhibited good functional group tolerance. More importantly, the process was performed without addition of a transition-metal catalyst, which further rendered the approach attractive and valuable. The application of the cycloaddition reaction in the synthesis of biological benzodiazepine molecules is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02118.

Procedures, NMR spectra, and X-ray crystallographic structures of **3a**, **3j**, and **5** (PDF)

Accession Codes

CCDC 1923224−1923226 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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