Modular Access to Polycyclic N,O-heterocycles Using a Highly Functionalized Allylic Morpholinonate

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Abstract

The morpholine structural motif is prevalent in pharmaceuticals such as viloxazine and chiral ligands such as diphenylylmorpholin. Primarily due to their proneness to ring opening, stereoselective and atom-economical approaches to vicinally functionalized morpholines remain elusive. Here, we present a transitional metal-free, stereo- and regio-divergent approach to polycyclic morpholines starting from commodity chemicals such as amines, enals and diglycolic anhydride. The resipendent outcomes are achieved through a stereocontrolled [4 + 2] cycloaddition between diglycolic anhydride and diversely substituted 1,3-azadienes to arrive at a densely functionalized morpholinonate, which previous work has shown to undergo palladium-mediated etherification to form cyclic enol ethers. We are proposing plans for iron-catalyzed pentannulation to make 6,5-polyheterocycles, as well as haloactonization/elimination to form dihydropyrans. It is anticipated that the divergent nature of the approach endear it to the synthesis and medicinal chemistry communities.

Background

Functionalized piperidines, morpholines and thiomorpholines are abundant structural motifs in natural products, pharmaceuticals, agrochemicals and amino acids (examples in figure 1). The biological application and structural complexity of these heterocycles continue to endear them to the synthesis and medicinal communities, inspiring the development of increasingly more efficient strategies for their construction, functionalization, and evaluation of their structure-activity relationships. Previous approaches to saturated N-heterocycles, include those utilizing by Aggarwal 1-4 (using o-phenylylsulfonium salts), Tiecco5 (using vinyl selenones), and Bode 6-7 (using SnAP reagents). Within these different types of azaheterocycles is a group which bears vicinal stereocenters. However, controlling the installation of vicinal and epimerizable stereocenters on the basic structure of the heterocycles is quite difficult, in part because sequential substitution of a 2- or 3-substituted cyclic amine derivative is rarely allowed in most of the existing C-2 or C-3 functionalization strategies. Furthermore, cyclizing the heterocycles with non-transition metals increases the novelty and applications of the approach.

Overview

Figure 1. Examples of compounds containing morpholine motifs.

Figure 2. Heterocycle alkylate readily with silyl enol ethers to produce Castagnoli-type cyclic aldehydes, but nucleophiles with unsaturated alkenes proceed through a Tamura mechanism. From the Castagnoli product, an oxygenation reaction as well as Pd and Fe catalysed coupling reactions are proposed.

Synthetic Utility: Pentannulation

Figure 3. Anellation of 1,3-azadienes with diglycolic anhydride.

Synthetic Utility: Dihydropyranation

Figure 4. Fe-catalysed dehydroxylation with varying R-groups on the alcohol-bearing carbon. Percentages are recorded below and the high dehydroxylation sites are to be noted.

Figure 5. The mechanism through which the Fe-catalysed dehydroxylation pentannulation goes through.

Synthetic Utility: Epoxidation

Figure 6. Pd-catalysed dehydroxylation using diverse R-groups adjacent to the ether and different protecting groups on the amine motif.

Synthetic Utility: Dihydropyranation

Figure 7. Addition of an allylic-heteroene to diglycolic anhydride with the hopeful Cushman mechanism.

Future Pursuits

Figure 8. An epoxidation of the allylic lactone ester.

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References


Figure 1. Example of compounds containing morpholine motifs.