

Shelf-stable amino acid derived diazoketones – perspective reagents for medicinal chemistry



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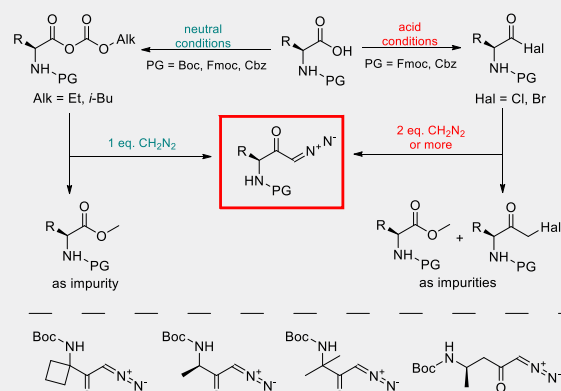
Background and synthetic strategy

Amino acids derived diazoketones (AADDK) are an important class of reagents in organic synthesis. Using natural proteinogenic alpha-amino acids as starting material leads to easy access to chiral AADDK. Therefore, the reagents could be considered as one of the instruments for chiral pool alpha-amino acids synthesis. In this research, we have elaborated the semi-industrial methodology for generating a solution of diazomethane in the organic phase in the flow reactor. An efficient and practical flow procedure for Boc-protected aminodiazoketones was developed. After an investigation of the thermal properties, as well as the shelf-life time of diazoketones, it was found that the compounds are good "shelf-keeping" reagents for medicinal chemists.

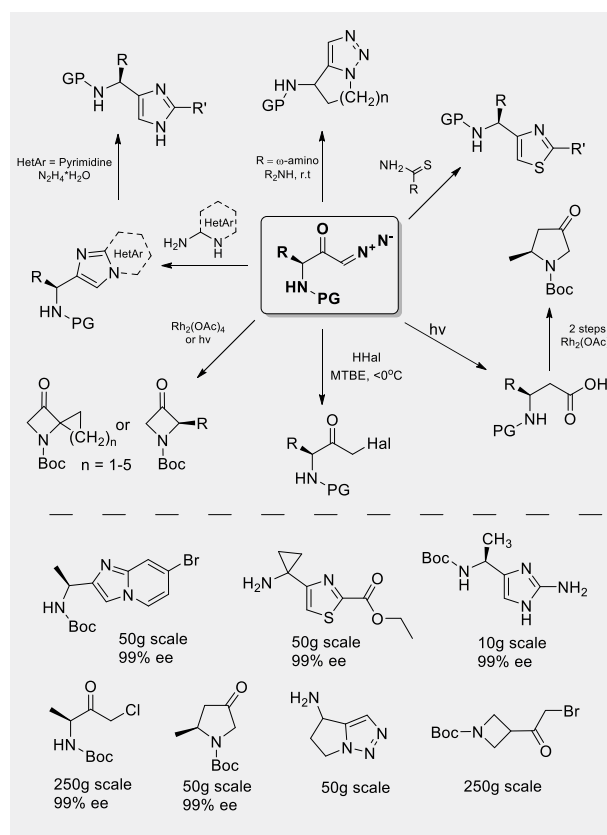
The utility of diazoketones was demonstrated by multi-gram (up to 150 g from a single synthetic run) synthesis of Boc-protected amino acid-derived bromoketones – valuable intermediates for the active pharmaceutical ingredients synthesis. The proposed procedure gives the target compounds a high purity level without any additional purification.

Moreover, the obtained diazoketones were used as haloketone's surrogates in cyclizations. Various heterocyclic compounds, β -amino acids and protected aminoketones were synthesized.

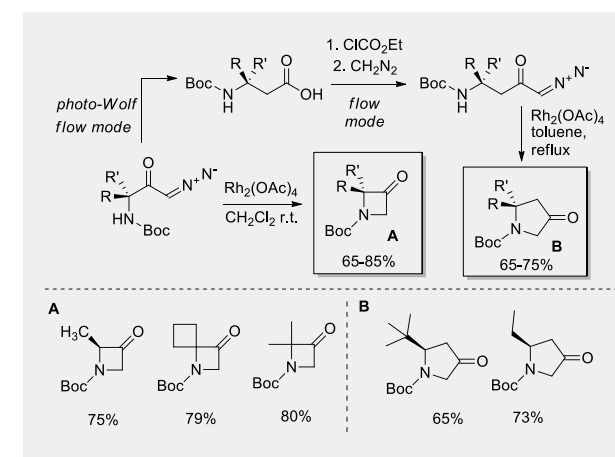
Synthesis of amino acid derived diazoketones



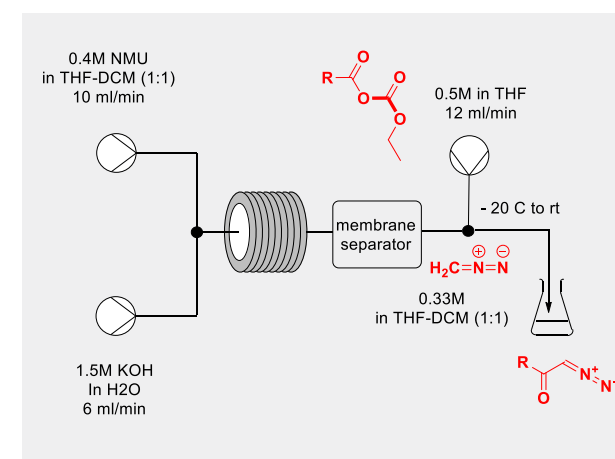
Research results & diversity of the products



Synthesis via NH-insertion



Scheme of the flow reactor



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