Diversity-Oriented Transformation of Doyle-Kirmse Products in Flow

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Résumé

Diversity-Oriented Synthesis {1} (DOS) and cascade rearrangement reactions represent powerful strategies that, when combined, can significantly accelerate drug discovery by providing a rapid access to a large variety of complex compounds from simple precursors. The Doyle-Kirmse (2,3)-sigmatropic rearrangement represents a good example of such a strategy, yielding complex compounds with various points of diversification starting from readily available thioethers and diazo compounds.{2} However, despite the high interest for this reaction only few post-Doyle-Kirmse reactions have been developed, especially when an allene is obtained as the —2,3) rearrangement product.{3}

In this context, a modular and divergent approach toward thiophene-derived structures has been developed using flow chemistry involving cascade reactions starting from a unique precursor, obtained through a rhodium-catalysed rearrangement. The corresponding allenes were heated at high temperatures in *tert*-amyl alcohol to trigger multiple cascade sequences yielding three different benzothiophene derivatives, depending on the conditions used and substrate structures. Overall, this strategy allowed a swift and direct access to complex molecular structures containing *S*-heterocyclic scaffolds of interest in drug discovery.{4}

References

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Mots-Clés: Flow chemistry, Diazo compounds, Doyle, Kirmse reaction