Advancement in Synthesis and Functionalization of Biologically Relevant Heterocyclic Scaffolds

The research involves development of synthetic route to create efficient, sustainable, and economically alternative routes for synthesis and functionalization of various biologically relevant heterocyclic scaffolds, such as diindolylmethanes (DIMs), imidazopyridines, coumarins, and quinazoline based vasicine.

Diindolylmethanes (DIMs) are a significant class of indole alkaloids known for their therapeutic potential, including anticancer and antimicrobial properties. We have explored the synthesis of DIMs via two primary pathways: the coupling of alcohols with indoles and arylacetic acids with indoles. Potassium persulfate ($K_2S_2O_8$) as an oxidant in both methods. In the first pathway, $K_2S_2O_8$ activated by glucose facilitates the conversion of alcohols to aldehydes, which then couple with indoles to form DIMs. This method is metal-free, eco-friendly, and yields high outputs with a broad substrate scope, including various benzyl and aliphatic alcohols. Moreover, the methodology shows robustness due to its gram scale transition, producing the desired product in decent yields. The second pathway involves the coupling of arylacetic acids with indoles, again mediated by $K_2S_2O_8$ in the presence of glucose in water. This green synthesis method offers high yields and tolerates a variety of substituted arylacetic acids and indoles, making it suitable for the scalable production of biologically active DIMs.

Imidazo[1,2-*a*]pyridines (IMP) are crucial pharmacophores found in sedative and anxiolytic drugs. C-3 formylated IMP is a key intermediate in synthesis of alpiderm and zolpiderm. Traditional approach for formylation of IMP often involve harsh conditions and low yields. We have developed a method for the C-3 formylation of IMP using glyoxylic acid and $K_2S_2O_8$. The optimized methods results in high yield and regioselective formylation. This approach is scalable for gram-scale synthesis, confirming its practical application in producing key intermediate in synthesis of alpiderm and zolpiderm.

Coumarins are an important class of natural product scaffolds with diverse therapeutic applications. The research introduces a transition-metal-free C–N cross-coupling method using a multifunctional reagent for coumarin derivatives. This approach addresses the limitations of conventional methods, such as the necessity for transition metals and harsh reaction conditions, by offering a more sustainable and efficient pathway for synthesizing coumarin-based compounds. Further, we have shown the applicability of our method in synthesis of coumarin based fluorescent molecules in gram scale.

Next, we have performed *tert*-butyl nitrite (TBN) mediated conversion of alcohols to amides and showed its application in synthesizing anti-Alzheimer compounds. The transformation of alcohols to amides requires variety of metal based catalyst. This TBN-mediated method provides a straightforward and efficient synthesis route. We have shown the application of our developed method in synthesis of vasicine analogues reported for anti-Alzheimer activitiy. Also we have performed gram scale synthesis of bioactive compounds using our optimized method.

In conclusion, the research has successfully developed several green and efficient synthetic methodologies for the functionalization and synthesis of biologically relevant scaffolds. By utilizing environmentally benign oxidants like potassium persulfate and *tert*-butyl nitrite, the research achieves versatile and scalable synthesis routes. These methods not only deliver high yields and broad substrate scopes but also emphasize sustainability and practicality for large-scale applications. The adoption of green chemistry principles and metal-free synthetic methods exemplifies the potential to transform the field of medicinal chemistry, offering pathways that are both environmentally-friendly and economically viable. This research contributes valuable insights and practical techniques, paving the way for more sustainable pharmaceutical development practices.

References

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