

Microwave-assisted Green Approach to Dihydrocoumarins and Splitomicin Analogues via Hetero-Diels-Alder Reaction

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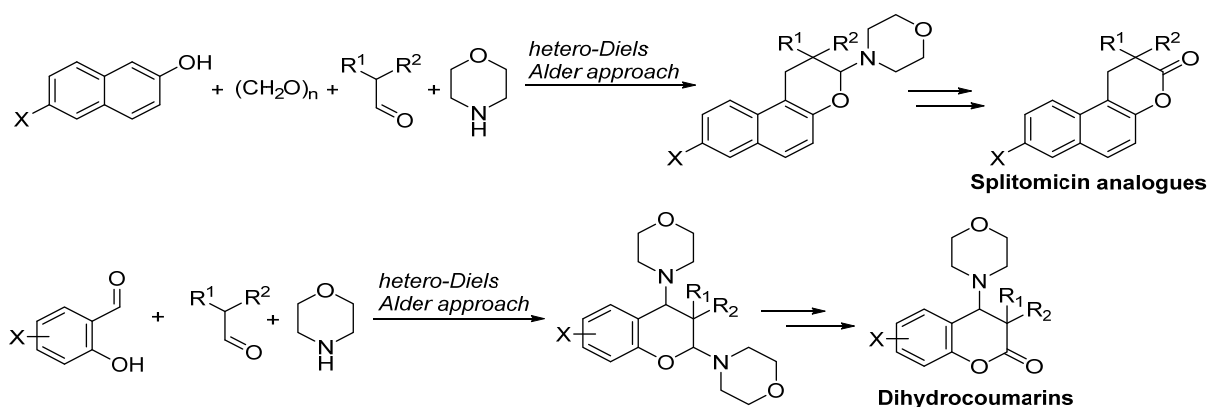
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Abstract—Natural products undoubtedly are rich in chemical diversity, biological specificity and pharmacological properties. They are an inspiration in drug discovery for lead drug candidates. Dihydrocoumarins are widely prevalent in nature and have received considerable attention due to their interesting biological activities.ⁱ Also, splitomicin, bearing dihydrocoumarin moiety is an inhibitor of Silent Information Regulator 2 (SIR2). It inhibits the NAD⁺-dependent deacetylase activity of Sir2 *in vitro*.ⁱⁱ Multi-component cascade processes have emerged as economical and environmentally friendly alternatives to more traditional strategies for generating molecular complexity and for procuring natural product analogues. On the other hand, microwave-assisted chemical reactions are well-established green chemistry practice with reduced reaction time, enhanced yields and purity of the product.

In the present study, synthetic methodology was developed to prepare dihydrocoumarins from substituted salicylaldehydes, morpholine, and isobutyraldehyde.ⁱⁱⁱ It involves amination, deamination, enamine formation, hetero-Diels-Alder reaction achieved in microwave-assisted catalyst-free conditions. Similarly, a green, one-pot synthesis of novel splitomicin analogs from mixture of a phenol, formaldehyde, an enolizable aldehyde and morpholine was devised under microwave irradiation.^{iv} Further, hydrolysis and oxidation steps in both the cases resulted in the desired products.



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