Magnesium catalyzed (3+2) cycloaddition of donor-acceptor cyclopropanes and (N,S)-heterodienes to access functionalized thiolanes

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Résumé

Heterocycles are widely present in both therapeutics and natural products, representing more than 85% of bioactive compounds.(1) Even though nitrogen is still the most common heteroatom, other heteroatoms-especially sulfur-are increasingly gaining prominence. Thanks to its rich chemistry and valuable biophysical properties, such as enhanced bioavailability and lipophilicity, sulfur is becoming more prevalent in modern drug design.(2) Nowadays, sulfur can be found in diverse cyclic or acyclic structures and with various oxidation states. Saturated cyclic scaffolds, such as thiolane, are present in natural bioactive compounds (or their synthetic analogs) such as biotin, tetronothiodin, Nuphar sesquiterpene thioalkaloids, or salacinol.(3) However, the rapid and efficient synthesis of such functionalized compounds remains a challenging task, and the development of new synthetic routes is necessary.

Here, we report the synthesis of a large variety of highly functionalized thiolanes **4** (up to 84 % yield) through a (3+2) cycloaddition involving donor–acceptor cyclopropanes (DACs) **2** and (*N,S*)-heterodienes **3.** DACs **2** were generated through a Rh(II)-catalyzed cyclopropanation of a diazo compound **1** with an alkene, while (*N,S*)-heterodienes **3** were obtained after condensation of an acetal derived from dimethylformamide on a thioamide. DACs are known to be more reactive than classical cyclopropane and are activated in our case by a magnesium-catalyst, to act as 1,3-dipoles. After optimization of the reaction conditions, the reaction scope was extended to various DACs and heterodienes, and we successfully synthesized a family of 13 polysubstituted thiolanes with good diastereoselectivity (ranging from 80/20 to 100/0). The chemical stability and reactivity of the amidine moiety is still ongoing.

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Mots-Clés: Thiolanes, (3+2), cycloaddition, Diazo compounds, Magnesium, Scope

*Intervenant