Towards new functionalized 1,4-thiazepines through metallocarbene-mediated ring expansion

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Résumé

The pharmaceutical industry is currently faced with the need for molecular diversity and structural originality to discover new drug candidates. Heterocycles play a key role in the structure of bioactive molecules.(1) Among them, mixed sulfur and nitrogen (N,S)-heterocycles, especially 5- and 6-membered rings, have demonstrated their interest in medicinal chemistry and pharmaceutical industry.(2) Medium-sized rings are however under-represented due to the difficulty of synthesis. In this context, the development of new synthetic routes is crucial to access complex and original (N,S)-heterocyclic structures efficiently and in a minimum of steps.
Here we report a ring expansion of 6-membered (N,S)-rings leading to new diversified 7-membered (N,S)-heterocycles. Starting from 1,3-dihydrothiazine precursors **1** obtained via a three-component reaction developed by our group,(3) the ring expansion proceeds via their reaction with a metallocarbene to yield 1,4-thiazepines **3**. The metallocarbene is generated in situ by decomposition of the diazo compound 2 in the presence of a rhodium(II) complex. After optimisation, the scope of the reaction was investigated by varying both the 1,3-dihydrothiazine **1** and the diazo partner **2**. Finally, the reactivity of the 1,4-thiazepines was explored and allowed to obtain new (N,S)-heterocycle **4**, amidothioether **5** and aminothioether **6**.

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Mots-Clés: methodology, sulfur, diazo, heterocycle, metallocarbene

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