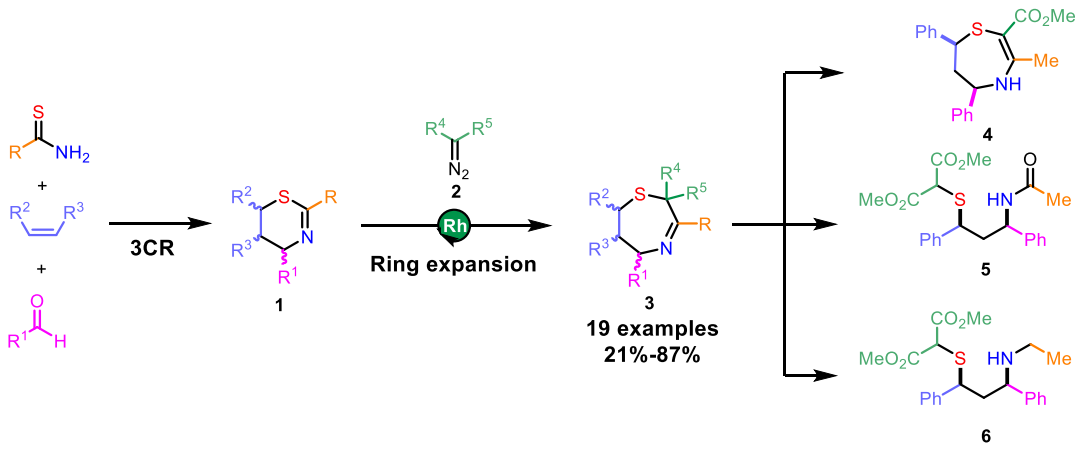
Synthesis of medium-sized *N,S*-heterocycles by rhodium-catalyzed ring expansion

Laurine Tual, Romain Pertschi, Gaëlle Blond and Mihaela Gulea

Laboratoire d'Innovation Thérapeutique – LIT UMR 7200,
Université de Strasbourg, CNRS – 67000 Strasbourg, France
Email : laurine.tual@etu.unistra.fr

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 (e.g. Amoxicillin, Chlorpromazin).[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*)-heterocycles **4**, amidothioethers **5** and aminothioethers **6**.



[1] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem*. **2014**, 57, 5845–5859.

[2] a) A. Martinez, C. Gil, in Drug Discovery (Ed.: S. Bräse), Royal Society of Chemistry, Cambridge, **2015**, pp. 231–261. b) K. A. Scott, J. T. Njardarson, *Top Curr Chem* (Z) **2018**, 376, 5. c) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem*. **2014**, 57, 2832–2842.

[3] F. Peudru, R. Legay, J.-F. Lohier, V. Reboul, M. Gulea, *Tetrahedron* **2012**, 68, 9016–9022.