REACTIVITY OF KETENES USING FLOW CHEMISTRY

I. Marchand, S. Carret, J.-F. Poisson

Département de Chimie Moléculaire (SERCO)
301 Rue de la Chimie, BP 53, 38058 Grenoble Cedex 09

With years of experience working on ketenes[1] and total synthesis of natural products,[2] the SeRCO team recently discovered a formal (3+2) cycloaddition of ketenes with aziridines,[3] affording in very good yields a direct synthetic pathway to γ-lactams, a very common motif in natural products. However, the high reactivity and instability of ketenes, generally generated *in situ*, did not allow for a wide diversification of substituents on the lactams. In this context, the work on generating ketenes by flow chemistry was initiated.[4] Flow chemistry often solves problems of efficiency and safety, offering a more robust and reliable way to synthesise and manipulate reactive species and hazardous or toxic compounds.

Figure 2: Flow device

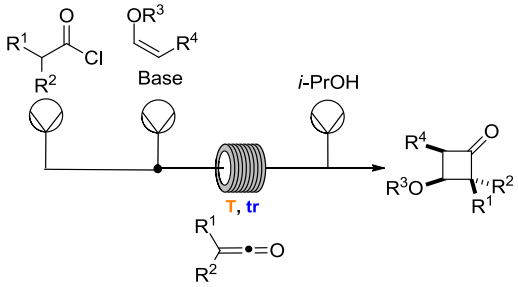

Figure 1: Generation and reactivity of ketenes in flow chemistry

The generation of ketenes by flow has already been described through different processes such as Wolff rearrangement,[5] thermolysis of alkoxyalkynes,[5] dehalogenation of α-haloacyl halides[5] or dehydrohalogenation of acyl halides,[5] however the subsequent reactions of the ketenes are very limited in term of scope, often relying only on nucleophilic addition to the highly reactive species.

In this work, we have studied the [2+2] cycloaddition of enol ethers with ketenes generated by flow, affording crucial information on the overall process (solvent compatibility, kinetic of the cycloaddition, base to be used…).

References

[1] P. Rullière, J. Grisel, C. Poittevin, P. Cividino, S. Carret, J.-F. Poisson *Org. Lett*., **2016**, 18, 2824-2827
[2] J.-P. Deprés, P. Delair; J.-F. Poisson, A. Kanazawa, A. E. Greene *Acc. Chem. Res*., **2016**, 49, 252-261
[3] A. Viceriat, I. Marchand, S. Carret, J-F. Poisson *Org. Lett.*, **2021**, 23, 2449-2454
[4] ANR program KetFlo : ANR-18-CE07-0035-01
[5] (a) S. Fuse, Y. Otake, H. Nakamura *Eur. J. Org. Chem.*, **2017**, 6466-6473. (b) C. Henry, D. Bolien, B. Ibanescu, S. Bloodworth, D. C. Harrowven, X. Zhang, A. Craven, H. F. Sneddon, R. J. Whitby *Eur. J. Org. Chem*., **2015**, 1491-1499. (c) A. Hafner, S. V. Ley *Synlett*, **2015**, 26, 1470-1474 (d) S. Karlsson, R. Bergman, C. Löfberg, P. R. Moore, F. Pontén, J. Tholander, H. Sörensen *Org. Process Res. Dev*., **2015**, 19, 2067-2074