Trapping of *N*-Acyliminium Ions with Enamides: an Approach to Medium-Sized Diaza-Heterocycles

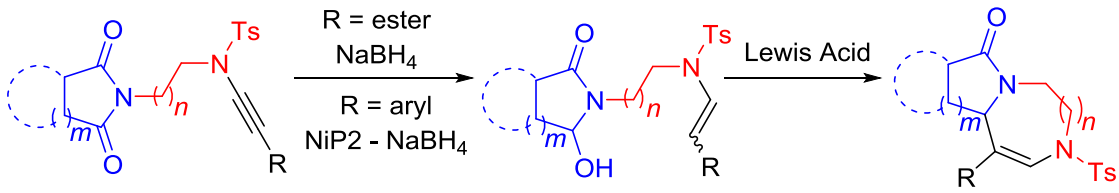
Lucile Andna and Laurence Miesch

Equipe de Synthèse Organique et Phytochimie, Faculté de Chimie, Université de Strasbourg, 4, rue Blaise Pascal, CS 90032, 67081 Strasbourg, France.

Email: lucile.andna@etu.unistra.fr

Despite the exhaustive literature on enamines and enamides, tertiary enamides have only recently proved their enamidic reactivity toward several classes of electrophiles.[1] Moreover, *N*-acyliminium ions (NAIs) are highly reactive electrophiles that have been widely used in intramolecular cyclizations and intermolecular additions for accessing structurally diverse scaffolds of broad biological interest.[2]

In this context, we focused on enamides equipped with *N*-acyliminium ion precursors that were obtained through reduction of ynamides tethered to *N*-imides.[3] Ynamides were reduced to enamides with $NaBH_4$ when bearing an ester group and in a two-step process (NiP2 followed by $NaBH_4$ reduction) when bearing an aryl group. Intramolecular Lewis acid-mediated trapping of *N*-acyliminium ions provided a variety of polyfunctionalized medium-sized diaza-heterocycles of pharmacological interest. The reaction tolerates several *N*-imides skeletons, various substituents on the ynamide function, as well as two- to four-carbon linker chains. In this way, 1,5-diazocanes and 1,5-diazonanes are accessible, allowing an expansion of routes to various diaza-heterocycles attractive in the field of drug design.



References

[1] M.- X. Wang, *Chem. Commun.*, **2015**, *51*, 6039–6049; [2] (a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron*, **2000**, *56*, 3817–3856; (b) P. Wu, T. E. Nielsen, *Chem. Rev.*, **2017**, *117*, 7811–7856; [3] L. Andna, L. Miesch, *Org. Lett*, **2018**, *20*, 3430–3433.