Diels-Alder cascades for the synthesis of fused *N*-heterocycles

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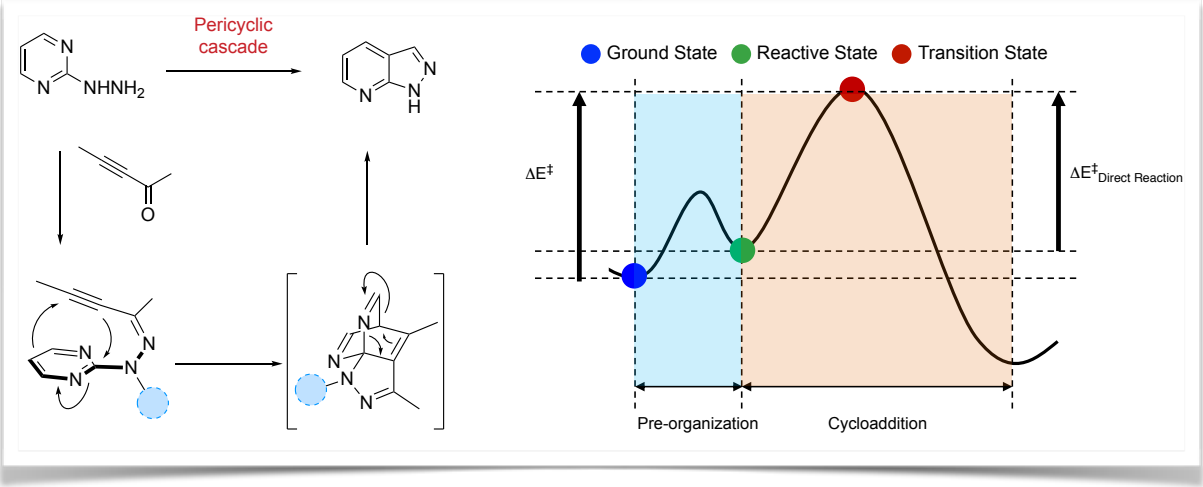
Pyrimidines are almost unreactive partners in Diels–Alder cycloadditions with alkenes and alkynes, and only reactions under drastic conditions have previously been reported. We will discuss how 2-hydrazonylpyrimidines, easily obtained in two steps from commercially available 2-halopyrimidines, can be exceptionally activated by trifluoroacetylation. This allows a Diels–Alder cycloaddition under very mild reaction conditions, leading to a large diversity of *aza*-indazoles, a ubiquitous scaffold in medicinal chemistry.



This reaction is general and scalable and has an excellent functional group tolerance. A straightforward synthesis of a key intermediate of Bayer's Vericiguat illustrates the potential of this cycloaddition strategy. Quantum mechanical calculations show how the simple N-trifluoroacetylation of 2-hydrazonylpyrimidines distorts the substrate into a transition-state-like geometry that readily undergoes the intramolecular Diels–Alder cycloaddition.[1-6]

References

1. Le Fouler, V.; Chen, Y.; Gandon, V.; Bizet, V.; Salome, C.; Fessard, T.; Liu, F.; Houk, K. N.; Blanchard, N. *J. Am. Chem. Soc.* **2019**, *141*, 15901.
2. Brach, N.; Le Fouler, V.; Bizet, V.; Lanz, M.; Gallou, F.; Bailly, C.; Hoehn, P.; Parmentier, M.; Blanchard, N. *Org. Proc. Res. Dev.* **2020**, *24*, 776-786.
3. Le Fouler, V.; Duret, G.; Bisseret, P.; Blanchard, N. *Tetrahedron Lett.* **2018**, *59*, 3349.
4. Duret, G.; Quinlan, R.; Yin, B.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. *J. Org. Chem.* **2017**, *82*, 1726
5. Duret, G.; Quinlan, R.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. *Org. Lett*. **2016**, *18*, 1610.
6. For a review : Duret, G.; Le Fouler, V.; Bisseret, P.; Bizet, V.; Blanchard, N. *Eur. J. Org. Chem.* **2017**, 6816.