Controlling the Halogen Dance of Bromo(thia)azoles via Flow Microreactors

Baran Ozveren[1,2], Antoine Coeuillas[1], Philippe Jubault[1], Laëtitia Chausset-Boissarie[1], Thomas Poisson[1], and Julien Legros[1]

[1] *CNRS, INSA Rouen Normandie, Univ. Rouen Normandie, Univ. Caen Normandie, ENSICAEN, Institut CARMeN UMR 6064, F-76000 Rouen, France*

[2] *INTEROR, ZI des dunes, rue des Garennes, 62100 Calais, France*

E-mail : baran.ozveren@univ-rouen.fr

Thiazoles, oxazoles, and imidazoles are key five-membered heterocycles with two heteroatoms, prevalent in natural products, drugs, agrochemicals, and functional materials, making them central to organic synthesis.[1]

The Halogen Dance (HD) reaction is a powerful tool for the regioselective functionalization of halogenated heterocycles, but its implementation in batch processes is often limited by the thermal instability of lithiated intermediates. [2,3]

We report here a continuous-flow microreactor approach to control the HD of bromo-azoles. By precisely controlling residence time and temperature, we enabled the reproducible generation and migration of unstable organometallic species toward their thermodynamically favoured isomers.

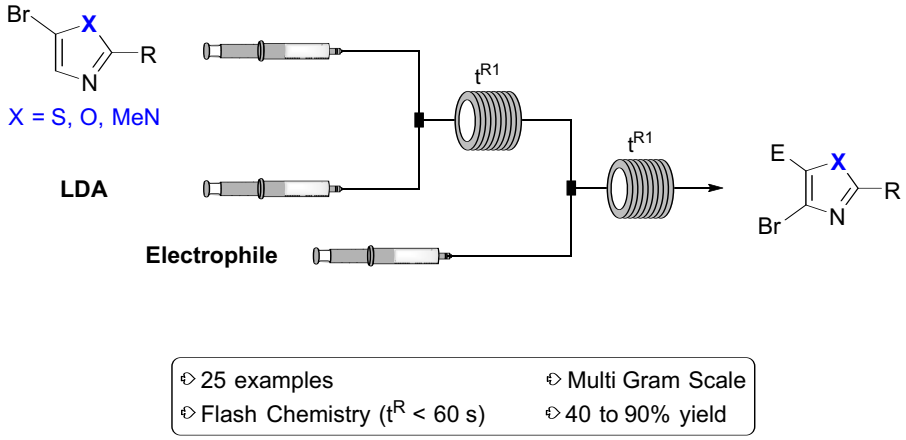

Figure 1: *Schematic depiction of the setup used in continuous flow*

The protocol's robustness was demonstrated by the synthesis of 25 diverse compounds and validated by a gram-scale production. This study shows that flow chemistry provides a safe and versatile platform for optimizing sensitive halogen rearrangements, effectively broadening the scope of heteroaromatic functionalization. We believe that this protocol will be useful and inspiring for the community and will promote the halogen-dance reaction as a truly versatile synthetic tool.[4]

References

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