Ring-Opening Chlorination and Bromination of Pyrazolopyridines and Isoxazoles

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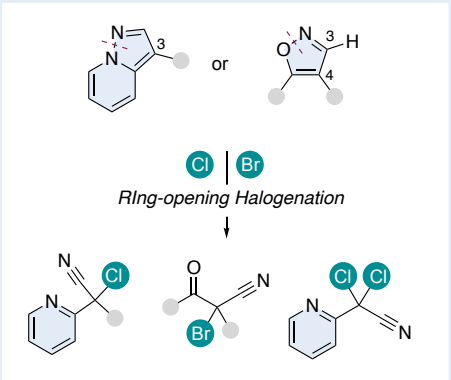
Skeletal editing has emerged as a powerful framework for expanding synthetic methodologies, particularly by enabling the strategic introduction of functional groups while reshaping molecular frameworks. Such transformations provide access to complex structural motifs that are otherwise difficult to synthesize using conventional approaches. In this context, we recently developed ring-opening fluorination reactions of pyrazolo[1,5-*a*]azines and isoxazoles using the electrophilic fluorinating agent Selectfluor®. These reactions proceed through initial electrophilic fluorination followed by deprotonation-triggered heteroatom–heteroatom bond cleavage, ultimately affording structurally unique tertiary fluorinated compounds. Because the resulting products contain heteroaromatic fragments, polar functional groups, and tertiary carbon centers frequently found in pharmaceuticals, this reaction platform offers high value in medicinal chemistry and molecular design.

Building upon this foundation, we further expanded the scope of skeletal editing by establishing ring-opening halogenation reactions of pyrazolo[1,5-*a*]azines, including chlorination, bromination, and dihalogenation processes. These studies, recently published in *Chemistry – A European Journal*, demonstrate that although the overall reaction design is conceptually analogous to our earlier ring-opening fluorination, the methodology can be generalized to accommodate a broad range of halogen electrophiles. This unified strategy allows modular incorporation of chlorine, bromine, or even two distinct halogens, thereby significantly broadening the synthetic utility of the transformation. Moreover, the platform proved versatile for downstream functionalizations. For example, we developed pyrazomixed dihalogenation reactions that introduce two distinct halogens in a single ring-opening event, creating new opportunities for selective diversification based on the differential reactivity of each halogen substituent. Additional ring-opening functionalization pathways were also developed, underscoring the versatility of this skeletal editing approach.



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