Regiodivergent Ring-Expansion of Oxindoles to Quinolinones

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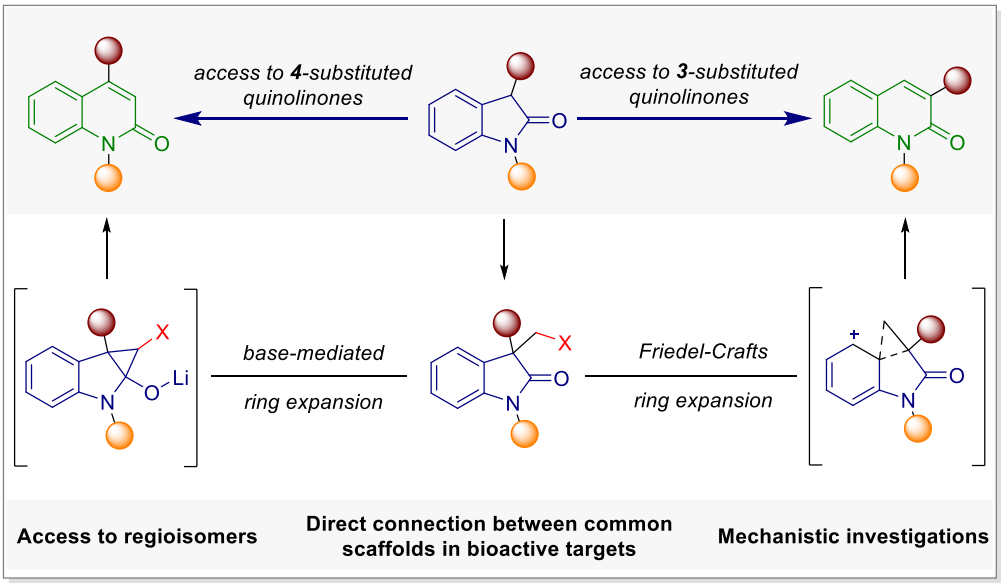
The exploration of diverse molecular structures is pivotal for uncovering innovative pharmaceuticals, pesticides, and other tailor-made compounds. Particularly in studies concerning structure-activity relationships (SAR), the investigation of variations in the core structures of lead compounds holds considerable interest.[1,2] However, to obtain these diverse molecular architectures, usually *de novo* multistep syntheses are required, obstructing access to otherwise desirable analogues. Recently, novel techniques like cut-and-sew and skeletal editing have emerged to directly modify core scaffolds.[1,3] However, these methods often focus on linking two skeletal structures, overlooking the importance of obtaining isomers, which could be particularly valuable in SAR studies.

Here, we present a divergent approach that allows for the interconversion of oxindoles to quinolinone regioisomers.[4] This not only enables the rapid synthetic connection between these two prominent scaffolds, but also offers access to isomers, mitigating the need for *de novo* syntheses in SAR studies.

The initially disclosed method for the conversion of oxindoles to 4-substituted quinolinones comprises a LiHMDS-mediated pathway, allowing for a broad range of functional groups to be tolerated. To investigate mechanistic details of this transformation a variety of experiments are presented, e.g. Hammet-plot analysis and KIE studies. Complementing this initial discovery, we designed a transformation of oxindoles to the isomeric 3-substituted quinolinones, through a Friedel-Crafts type mechanism from the same starting materials. Together, both methods are applied to a variety of oxindole drugs, such as the cognitive enhancer linopiridine, or the epilepsy drug doliracetam. Further, the synthesis of an analogue of the quinolinone drug tipifarnib is achieved, giving access to the drug in the least number of steps as compared to the literature, while also offering a straightforward route to its regioisomer.



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