Development and Applications of Selective Deuteration in Organic Molecules.

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Abstract

Deuterium is a stable, non-radioactive isotope of hydrogen. It contains one additional neutron, making it twice as heavy in atomic mass compared to normal hydrogen. This unique property results in carbon-deuterium bonds that are shorter by 0.005 Å and possess higher activation energy, making them less susceptible to metabolic oxidation. Consequently, the use of deuterium-labeled organic molecules has become increasingly attractive in research chemistry, medicinal chemistry, and the pharmaceutical industry, particularly for drug discovery.

Deuterium labeling allows organic molecules to become heavier without altering key biochemical properties such as chemical shape, size, physical characteristics, or their ability to interact with enzymes, receptors, or ligands, making it a valuable tool in ADME (Absorption, Distribution, Metabolism, and Excretion) studies.

Precision deuteration is crucial for developing deuterium labeling in drug discovery. While H/D exchange methods have been extensively studied for aromatic and aliphatic positions, allylic deuteration remains an underdeveloped area of research, with only a few examples of deuteration at the allylic position.

This research document presents three main projects: first, a novel copper-catalyzed method for selectively installing deuterium at the allylic position using conjugated dienes as starting substrates; second, a new method for accessing a deuterated version of a nitrogen-mustard-based prodrug molecule for ADME studies; and third, the development of selective deuteration of silanes and alcohols that would be applied to selective tritiation, along with their application in copper-catalyzed transfer hydrotritiation of small molecules.

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