Site-selective and multiple deuteration and application to drug discovery

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Abstract

Deuterium (D) is a non-radioactive and stable isotope of hydrogen (H). Deuterium-incorporated compounds have been widely utilized in various scientific application. We continuously developed the deuteration methods of various organic compounds.

The phamacokinetics of pharmaceutical drugs can be improved by replacing C-H bonds with more stable C-D bonds at the α-position of heteroatoms in the drugs, a typical metabolism site by cytochrome P450. However, the applicable deuterium-incorporated synthetic synthons are crucially limited. We recently established the novel concept to provide the breakthrough deuterated reagents, which successfully realized to syntesize the complicated drug skeletons possessing deuterium atom at thier α-positions. d_n-Alkyl diphenylsulfonium salts, prepared from the corresponding hydrogen forms using inexpensive and abundant D_2O as a deuterium source under basic conditions, played as electrophilic alkylating reagents to enable the synthesis of various deuterated drugs.

Furthermore, PPh_3 efficiently underwent the multiple deuteration at all aromatic C-H bonds using Ru/C and Ir/C co-catalysts in 2-PrOH and D_2O. The Raman live-cell imaging of non-radioactive and safe deuterium-incorporated Mito-Q, derived from deuterated PPh_3, was successfully accomplished.

Background & Results

The replacement of C-H bonds with more stable C-D bonds at metabolic sites of drugs can improve their phamacokinetics. The commercially available d_3-methyl sources (e.g., CD_3OD) were frequently utilized for the syntheses of target materials including the approved heavy drugs, deutetrabenazine and deucravacitinib. Therefore, we recently developed the novel concept to prepare breakthrough deuterium-incorporated reagents, i.e., d_n-alkyl sulfonium salts, d_n-alkyl halides and azide, and (d_n-alkyl)amine, to introduce d_n-alkyl groups into drug candidates and such analogs, including the complicated skeletons.

On the other hand, Raman microscopy offers molecular imaging of deuterated compounds in living cells using the specific signals of molecular stretching vibrations of C-D bonds, which are exhibited in the cellular silent region (wavenumber range where Raman scattering of intracellular molecules such as proteins and lipids is not observed). Namely, deuterium is functioned as an efficient tag of target material in Raman imaging analysis. However, numerous C-D bonds in the target molecule are usually required due to the weak Raman intensity of each C-D bond, which indicates the importance to develop the direct and multiple H/D exchange reactions (deuteration) of a wide variety of organic compounds. Platinum group metal on carbon catalysts enabled the multiple deuteration of various organic compounds, including PPh_3.

Significance of the research and Future perspective

Although the utility of deuterated compounds is well recognized, the difficulty in obtaining the desired deuterated substances is a problematic issue. We can synthesize various deuterated substances using our original methods. We will promote their use in various fields in the future.

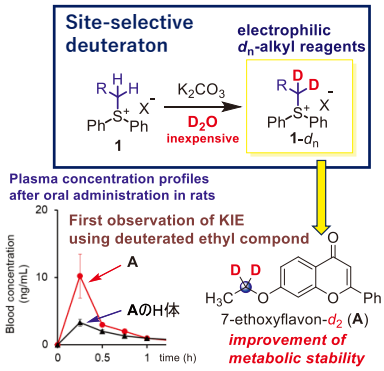

Fig. 1 Development of d_n-alkyl reagents and application to drug discovery

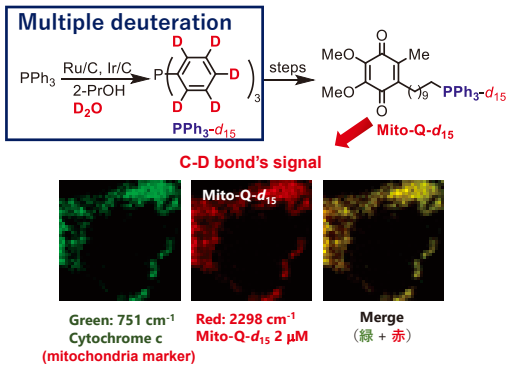

Fig. 2 Live-cell Raman imaging using deuterium-tag drugs

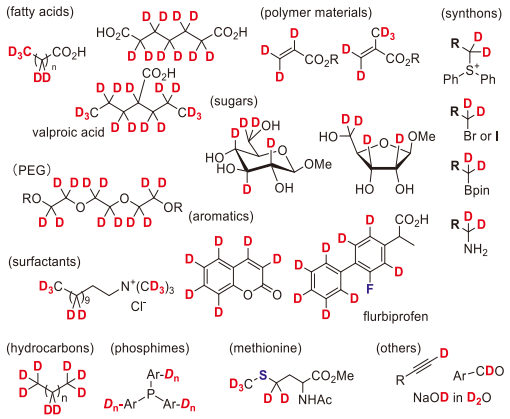

Fig. 3 Synthetic examples of deuterated compounds using our original methods

Patent

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Akai, Shuji; Sawama, Yoshinari et al. Multiple deuteration of triphenylphosphine and live-cell Raman imaging of deuterium-incorporated Mito-Q. Chem. Commun. 2023, 59, 12100–12103. doi: 10.1039/D3CC04410F

URL

Keyword deuterium, heavy drug, organic chemistry, molecular imaging