別紙４

報告番号	※　甲　第　　号

主　論　文　の　要　旨

論文題目　N-Alkylation of Amines over Heterogeneous Photocatalysts for Pharmaceutical Synthesis

不均一系光触媒を用いるN-アルキル化反応に基づく医薬品合成法の開発

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論　文　内　容　の　要　旨

N-Alkylamines represent one of the most essential classes of compounds in medicinal sciences. The N-alkylation of amines is one of the best methods for the synthesis of *N*-alkylamines and has been frequently used for building C–N bonds in synthetic pharmaceutical chemistry. Both in industrial and laboratory scale, two classical N-alkylation methods are predominately employed in pharmaceutical synthesis, such as nucleophilic substitution of alkyl halides with amines and reductive amination of carbonyl compounds. Although these methods are reliable and practical, they generally involve harsh reaction conditions, low selectivity, toxic reagents, or the coproduction of stoichiometric waste, which are not desirable in modern pharmaceutical synthesis in view of economical and environmental aspects.

As the green and sustainable chemistry has become a crucial part in the synthesis of pharmaceuticals, the catalytic N-alkylation of amines has been developed. The most popular approach is to employ alcohols or amines as alkylation reagents through the borrowing hydrogen mechanism with water or ammonia as the only byproduct. However, the application foreground of the N-alkylation of amines with alcohols/amines is not so optimistic in synthetic pharmaceutical chemistry, because the reported homogeneous/heterogeneous catalytic methods suffer from harsh reaction conditions, such as high reaction temperature (> 80 °C), and the use of strong base, limiting the scope of amines/alcohols. Thus, to realize pharmaceuticals synthesis by the catalytic N-alkylation reaction in milder conditions, the use of light energy is expected to be effective, since ambient conditions can be frequently used. The goal of this research is to develop heterogeneous photocatalytic processes that allow efficient N-alkylation of functionalized amines towards pharmaceutical synthesis.

There are four parts (General introduction and Chapter 1–3) in this PhD thesis.

General introduction organized the background, objective, and modern photocatalytic methods for N-alkylation of amines with alcohols/amines under ambient conditions.

In Chapter 1, a general method was developed successfully for the photocatalytic N-methylation of amines bearing heterocyclic functionalities using a Pd/TiO_2 photocatalyst under mild reaction conditions. The substrate scope of this Pd/TiO_2 catalyzed reaction was extended to the amines with heteroaromatic structures, which were important to pharmaceuticals yet never demonstrated in previous reports. Several late-stage N-methylation/ethylation leading to pharmaceuticals as well as related deuterated drugs synthesis were also achieved by this photocatalytic system.

In Chapter 2, a further application for Pd/TiO_2 photocatalytic system was achieved for self-condensation of primary amines to secondary amines under mild reaction conditions. This reaction selectively gives secondary amines using amine itself as alkylation reagent. By employing this method, alverine was synthesized directly by one-pot, sequential photocatalytic self-condensation of primary amine and photocatalytic N-ethylation with ethanol.

In Chapter 3, an efficient mixed heterogeneous photocatalyst [achieved by combining a copper-loaded titanium dioxide (Cu/TiO_2) and its gold analogue (Au/TiO_2)] was developed for rapid N-alkylation of amines with several alcohols under mild reaction conditions. Based on the initial discovery of that Cu/TiO_2 was also proved as a good photocatalyst for N-methylation of amines with methanol, and Au/TiO_2 showed highest reactivity as titania-based photocatalyst for the dehydrogenation of primary alcohols to aldehydes. These two photocatalysts were combined to investigate the catalytic ability. As a result, this strategy of mixing two metal-loaded photocatalysts showed in a synergistic increase in reaction rate for the N-alkylation of pharmaceutically relevant molecules. By controlling the polarity of solvent, the mono- or dialkylation of primary amines can also be achieved selectively, in some examples, the amount of alcohols can be reduced to only 2–4 equiv for sufficient reaction.