氏　　名	梅　振武
授与した学位	博　士
専攻分野の名称	工　学
学位授与番号	博甲第４６３８号
学位授与の日付	平成２４年　９月２７日
学位授与の要件	自然科学研究科　機能分子化学専攻 （学位規則第５条第１項該当）
学位論文の題目	Studies on Development of Benign Technologies for Some Organic Transformations with Organic Catalysts and Synthesis of the Substituted Neocryptolepines as Drug Candidates of Antimalarial Agents （有機触媒による分子変換のための環境技術および抗マラリア活性を持つ医薬候補としての置換ネオクリプトレピンの合成と活性評価に関する研究）
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学位論文内容の要旨

In this thesis, the author engaged with three research topics focusing on the environmentally friendly technologies for organic transformations with organic catalysts and design and synthesis of neocryptolepine derivatives for antimalarial drug. The author's contributions during these work were summarized as below:

1. High performance and selective oxidation method for secondary alcohols by use of organic catalyst.

A high performance oxidation method of alcohols with organic catalyst TEMPO substituted with an electron-withdrawing group (EWG) at the C4 position, which is useful for oxidation of the electron-deficient secondary alcohols such as $ArCH(OH)CFCl_2$, has been developed by using $Py{\bullet}HBr_3$ as a co-oxidant. Reactivity of $Py{\bullet}HBr_3$ was discussed in terms of efficiency and selectivity in comparison with similar bromine compounds such as Bu_4NBr_3, and the method was easily extended to the polymer supported bromine reagents as a co-oxidant. Inductive activation of TEMPO by the appendage of EWG at the C4 position was shown to facilitate the reaction rate, which was rationalized by measuring the cyclic voltammetry of the 4-substituted TEMPOs.

2. Green procedure for preparation of carboxylic acids by TEMPO oxidation of primary alcohols.

The author developed an efficient primary alcohol-carboxylic acid conversion by employing TEMPO oxidation. A biphasic system composed of ethereal solvent THP and aqueous layer instead of often used harmful solvents like CH_2Cl_2–aqueous layer was proposed. During the TEMPO oxidation of primary alcohols, many easily available oxidants, such as $Py{\bullet}HBr_3$, Bu_4NBr_3 and electrooxidation, were successfully applied as co-oxidants. And this method could easily be applied to various primary alcohols including aromatic, aliphatic, and carbohydrate derivatives, some of which are of significant synthetic value.

3. Synthesis and evaluation of novel neocryptolepine derivatives for developing antimalarial agents.

In order to obtain a high antimalarial activity, modifying and changing the side chains at the C11 position of the neocryptolepine derivatives were executed. At the same time, varying the substituents of an electron-withdrawing or electron-donating nature at the C2 position was examined for a SAR study. As the strategic scaffold of this study, improved synthesis of the 11-chloroneocrytolepines was developed in three steps using *N*-methylanilines and indole-3-carboxylate as the counterpart. Installation of alkylamino and ω-aminoalkylamino groups at the C11 position of the neocrytolepine core was achieved by the reaction of the 11-chloroneocryptolepines and the appropriate amines. For further variation, the aminoalkylamino subsituents were transformed into the corresponding acyclic or cyclic carbamides or thiocarbamides. These side-chain modified neocryptolepine derivatives were tested for antimalarial activity against CQR (K1) and CQS (NF54) of *Plasmodium falciparum* in vitro. The evaluation also included cytotoxicity toward mammalian L6 cells. All tested compounds showed potent antiplasmodial activities against CQR (K1) and CQS (NF54) in vitro and some compounds showed much greater potency than CQ.

論文審査結果の要旨

The development of efficient metal-free oxidation method is currently pursued in organic reaction processes from environmentally point of view. Meanwhile, how to explore new drugs to meet the demand for drug-resistant diseases is still a hot topic in the medicinal chemistry. Especially, malaria remains the most devastating disease in the tropical and subtropical regions, led to 216 million infected cases and 0.7 million died in 2010. This is due to appearance of chloroquine (CQ)-resistant Plasmodium. In this thesis, the author has engaged in three research topics toward the environmentally friendly technologies for organic transformations with organic catalysts and design and synthesis of neocryptolepine derivatives for antimalarial drug.

1) A high performance method for oxidation has been developed using organic catalyst TEMPO in combination with $Py{\bullet}HBr_3$ as a co-oxidant. Oxidation power of TEMPO was increased by the appendages of electron-withdrawing group at the C-4 position, and enhanced reactivity was rationalized by measuring the cyclic voltammetry. The oxidation system comprised by the EWG-substituted TEMPO and $Py{\bullet}HBr_3$ was applied to the secondary alcohols of the electron-deficient structures.

2) The author developed an efficient primary alcohol-carboxylic acid conversion by employing TEMPO oxidation in a biphasic system composed of THP and aqueous layer instead of often used harmful solvents like a CH_2Cl_2-aqueous layer system. And this method was applied to various primary alcohols including aromatic, aliphatic, and carbohydrate derivatives, some of which are of significant synthetic value.

3) The author developed antimalarial agents by designing and synthesizing neocryptolepine derivatives with various substituents at the C2 position and aminoalkylamino substituents at the C11 position. For further variation, the aminoalkylamino substituents were transformed into the corresponding acyclic or cyclic carbamides or thiocarbamides. These side-chain modified neocryptolepine derivatives were tested for antimalarial activity against CQR (K1) and CQS (NF54) of *Plasmodium falciparum* in vitro and cytotoxicity toward mammalian L6 cells. All tested compounds showed potent antiplasmodial activities against CQR (K1) and CQS (NF54) in vitro and some compounds showed much greater potency than chloroquine (CQ). Some derivatives with high antimalarial activities and selective index were tested in vivo and showed moderate biological activity.

Based on the aforementioned results we concluded that the thesis contains new, scientifically valuable results and represents an original contribution to the field. Therefore, we strongly recommend for the award of PhD degree in the present form.