Molecular Design and Synthesis of Quinolones Activated by Steric Effect

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Citation
高知工科大学 博士論文

Date of issue
2013-09

URL
http://hdl.handle.net/10173/1059

Text version
ETD

Kochi, JAPAN
http://kutarr.lib.kochi-tech.ac.jp/dspace/
The thesis deals with studies on molecular design and synthesis of quinolones activated by steric effect between the 1-methyl and 8-substituent groups. While the 1-methyl-2-quinolone (MeQone) framework is not reactive because of aromatic property in the pyridone ring, 1-methyl-3,6,8-trinitro-2-quinolone (TNQ) exhibits extremely high reactivity. Indeed, TNQ undergoes cine-substitution to afford 4-substituted 6,8-dinitro-1-methyl-2-quinolones upon treatment with versatile nucleophiles. Moreover, TNQ also undergoes cycloaddition reactions at the 3- and the 4-positions under mild conditions leading to polycyclic compounds, which reveals that the pyridone moiety of TNQ shows nitroalkene property rather than aromatic property. It is considered that the high reactivity of TNQ is caused by steric repulsion between the 1-methyl and the 8-nitro groups. In other words, the MeQone framework can be sterically activated even in the absence of electronic activation. In the present work, the molecular design and synthesis of the sterically activated MeQones was studied on the basis of this hypothesis. Firstly, reactivity of several kinds of MeQones having both 1-methyl and the 8-substituent was predicted by DFT calculation, by which the dihedral angles between N1-Me and C8-R8 bonds are estimated. The calculated results suggested 1,6-dimethyl-3,8-dinitro-2-quinolone and 1,8-dimethyl-3,6-dinitro-2-quinolone are considered to surely reveal high reactivity as well as TNQ. As a result of study on the preparation, the latter quinolone was successfully synthesized in addition to 3,5,7-trinitrated and 3,5-dinitrated 1,8-dimethyl-2-quinolones. When nitrated 1,8-methyl-2-quinolones were subjected to the reactions with 2,4-pentanedione in the presence of triethylamine, the peri-substituent (R5) was found to prevent the cine-substitution. Thus, a small nucleophile, potassium cyanide, was employed for estimation of the reactivity of the MeQone framework. The high reactivity was maintained, even when the 6-nitro or 8-nitro groups of TNQ was replaced with a methyl group, to afford corresponding cine-substituted products upon treatment with potassium cyanide. These results strongly support our consideration that the steric repulsion between 1-methyl and 8-methyl groups activated the MeQone by disturbing the coplanarity, which decreases aromaticity of the pyridone moiety. This work affords researchers valuable information for the functionalization of the MeQone framework, which is helpful for finding new biologically active compounds.