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Title(English)	
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（博士課程）
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論 文 要 旨

THESIS SUMMARY

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申請学位（専攻分野）：Academic Degree Requested 博士 Doctor of （ 工学 ）
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

This thesis, entitled "Installation of a Carbon Chain to Pyridines at Their 4-Position with Organometallic Reagents," describes the development of methods for introduction of a carbon chain to pyridines at their 4-position with organometallic reagents.

Chapter 1. "Introduction".

The pharmaceutical utility of pyridines, the recent research on their syntheses, and the fundamental reactivity of pyridines are described. In addition, the outline and the importance of these studies are discussed from the practical and scientific points of view.

Chapter 2. "Installation of a Carbon Chain to Pyridines at Their 4-Position with Styrenes and Yttrium Reagents".

Alkylation of pyridines in the presence of styrenes and an yttrium reagent consisting of YCl_3, n-C_4H_9Li, and $(i\text{-}C_4H_9)_2AlH$ in THF proceeded selectively at their 4-position, affording 4-(1-arylethyl)pyridines as a single regioisomer. For example, 2-ethylpyridine was treated with styrene and the above yttrium reagent to give 4-(1-phenylethyl)pyridine as a single regioisomer in good yield. However, the similar reaction did not proceed at all with other metal salts such as $TiCl_4$, $ZrCl_4$, and $LaCl_3$ instead of YCl_3. A proposed reaction course was also illustrated. Control experiments revealed that a benzylmetal reagent was formed from a styrene and the yttrium reagent. Thus, the alkylation most likely proceeds through the following steps: (i) the generation of a benzylmetal reagent from styrene and the yttrium reagent via hydrometallation, (ii) the nucleophilic addition of the benzylmetal reagent to pyridines, giving metallo-dihydropyridines, and (iii) aromatization of the intermediate metallo-dihydropyridines affording the observed product via hydride elimination or aerial oxidation. This reaction shows the following characteristics, (i) the synthetic transformation with an yttrium reagent, which is rarely used in organic synthesis and (ii) the highly regioselective addition to pyridines at their 4-position.

Chapter 3. "Installation of a Carbon Chain to Pyridines at Their 4-Position with Grignard Reagents ".

As described in Chapter 2, the benzylmetal reagents generated from styrenes and the yttrium reagent via hydrometallation could be utilized for the selective 4-alkylation of pyridines. Based on this observation, benzyl Grignard reagents, which are more conveniently prepared than the benzylmetal intermediates in Chapter 2, were attested for the same purpose. Treatment of pyridines with benzyl Grignard reagents afforded various 4-(1-arylalkyl)pyridines as a single regioisomer in good yields. For example, the reaction of 2-ethylpyridine and [1-(4-*tert*-butylphenyl)ethyl]magnesium chloride in THF at reflux afforded 4-[1-(4-*tert*-butylphenyl)ethyl]-2-ethylpyridine as a single regioisomer in good yield. Multi-substituted pyridines could be prepared by this method in good yields. For example, [1-(4-*tert*-butylphenyl)ethyl]magnesium chloride and 2,3-dimethylpyridine afforded 4-[1-(4-*tert*-butylphenyl)ethyl]-2,3-dimethylpyridine as a single regioisomer in good yield. The aromatization of the intermediate magnesio-dihydropyridine most likely involves the hydride elimination, as evidenced by the fact that an aldehyde added after the reaction of 2-ethylpyridine and benzylmagnesium chloride was reduced to the corresponding alcohol. This reaction provides a practical method for the facile preparation of diarylmethanes, which are a useful pharmacophore in medicinal chemistry.

Chapter 4. “Installation of a Carbon Chain to Pyridines at Their 4-Position with Benzylzinc Reagents”.

For further extension of the 4-selective addition of benzyl Grignard reagents to pyridines, benzylzinc reagents, which are of higher functional group tolerance than Grignard reagents, were subsequently considered. A reaction of 2-ethylpyridine and [1-(4-*tert*-butylphenyl)ethyl]zinc chloride prepared from 1-(*tert*-butyl)-4-(1-chloroethyl)benzene afforded 4-[1-(4-*tert*-butylphenyl)ethyl]-2-ethylpyridine as a single regioisomer in good yield. Pyridines with an electron-withdrawing or -donating group are good substrates for this reaction to gave 4-alkylated pyridines as a single regioisomer without affected by these functional groups. In addition, pyridines with a side chain carrying a functional group are also utilized in this reaction to give functionalized 4-substituted pyridines. Functionalized benzylzinc reagents also gave functionalized 4-benzylpyridines in good yields. For example, 2-ethylpyridine and a benzylzinc chloride having a butanamide side chain afforded the corresponding 4-benzylated pyridine in good yield. When *tert*-butyl 2-pyridinebutanoate was allowed to react with benzylzinc reagents, bicyclic 4-benzyl-1,4-dihydropyridines were obtained in good yields. This reaction is not only an interception of the reaction intermediate, a metallo-dihydropyridine, but also a new practical synthetic method of bicyclic 1,4-dihydropyridines. In summary, the method described herein is useful for a selective preparation of various 4-alkylated pyridines with functional groups.

Chapter 5. “Summary”.

New synthetic methods for the installation of a carbon chain to pyridines at their 4-position with styrenes and the yttrium reagent, Grignard reagents, or benzylzinc reagents have been established. Utility of the products obtained herein for the preparation of natural products and biologically active compounds was also discussed.