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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

The Mukaiyama Reagent: An Efficient Condensation Agent

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Introduction

The Mukaiyama reagent (2-chloro-1-methylpyridinium iodide, CMPI) is one of the most valuable reagents for activation of hydroxyl groups of carboxylic acids and alcohols.\(^1\) It is a pale yellow crystalline solid which is stable at room temperature in closed containers under normal storage and handling conditions. CMPI is commercially available, but can be easily synthesized from 2-chloropyridine and methyl iodide.\(^2a–d\)

It is widely used for the synthesis of esters,\(^3\) lactones,\(^4\) amides,\(^5\) lactams,\(^6\) and ketenes\(^7\) from the corresponding carboxylic acids, as well for obtaining carbodiimides from thioureas\(^8\) and thiocyanates from alcohols.\(^9\) CMPI was introduced as an useful reagent for the synthesis of carboxylic esters by Teruaki Mukaiyama in 1975,\(^10\) after that the miscellaneous \(N\)-alkyl-2-halopyridinium salts had been developed as activating agents.\(^1\) Nowadays, several polymer-supported CMPI analogues have been used for the synthesis of esters and amides due to user-friendly purification procedures.\(^11\) The reagent analogues are also valuable for peptide synthesis.\(^12\)

Abstracts

(A) The Mukaiyama reagent is widely used for activation of carboxylic acids in the synthesis of carboxylic esters. A recent example deals with the synthesis of \(N\)-Boc-glycine and \(N\)-Boc-\(\beta\)-alanine esters in the presence of various fatty-acid-derived alcohols.\(^3\) Nucleophilic attack of the carboxylate anion on CMPI (1) produces pyridinium salt 2. Further reaction between 2 and an alcohol produces esters 3, 4 and 1-methyl-2-pyridone 5. The reagent is also useful for the kinetic resolution of racemic carboxylic acids and alcohols with enantiomerically pure alcohols or carboxylic acids, respectively.\(^13\)

(B) Macrolactonization is very important for the total synthesis of macrolide antibiotics. Macrolactonization is possible in the presence of CMPI.\(^14\) Synthesis of lactones from \(\omega\)-hydroxy carboxylic acids \((n = 5, 6, 7, 10, 11, 14)\) has been developed under mild conditions in good yields using the Mukaiyama reagent.\(^14\) Both small and large macrocycles can be obtained.

(C) The Mukaiyama reagent can also be used for \(C–N\) bond formation, for example for synthesis of 3-alkylquinazolin-4-ones. The latter are valuable molecular scaffolds in medicinal chemistry. Thus, a formal transamination occurs under very mild reaction conditions.\(^15\)
CMPI is applicable for the construction of β-lactams from β-amino acids. When compared with the dicyclohexyl carbodiimide method and the Ph₃P(PyS)₂ method of β-lactam synthesis, the Mukaiyama method is often more effective. The reaction proceeds under mild reaction conditions which are compatible with the acid- and base-sensitive β-lactam ring. For example, the use of Mukaiyama salt in the macrobislactamization step shortened the synthesis of tetraaromatic tetraamide macrocycles.¹⁶

Substituted benzyl alcohols can be converted into alkyl thiocyanates both under solvent and solvent-free conditions using CMPI. The proposed mechanism involves the formation of 1-methyl-2-thiocyanatopyridinium iodide (MTPI) from the reaction of CMPI and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide at room temperature, isothiocyanate is produced in a high yield.¹⁷

When triethylammonium dithiocarbamate, easily prepared from amine, carbon disulfide, and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide, thiocyanatopyridinium iodide (MTPI) from the reaction of CMPI produces the desired alkyl thiocyanates.⁹

After the discovery of the Mukaiyama reagent, various N-alkyl-2-halopyridinium salts were developed, with the purpose to achieve better yields in the condensation reactions. Recently, a number of fluorous tagged reagents have been developed.¹⁸a–c They are useful in ester- and amide-forming reactions.

References

(b) Arnett, E. M.; Reich, R. J. Am. Chem. Soc. 1980, 102, 5892.
(c) Khoshoshilov, G.; Demchak, I.; Saraeva, T. Synthesis 2008, 1541.