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. 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.

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-β-alanine esters in the presence of various fatty-acid-derived alcohols. 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.

(B) Macrolactonization is very important for the total synthesis of macrolide antibiotics. Macrolactonization is possible in the presence of CMPI. Synthesis of lactones from ω-hydroxy carboxylic acids (n = 5, 6, 7, 10, 11, 14) has been developed under mild conditions in good yields using the Mukaiyama reagent. 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.
(D) CMPI is applicable for the construction of β-lactams from β-amino acids. When compared with the dicyclohexyl carbodiimid 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

(E) 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-thiocyanatopryridinium iodide (MTPI) from the reaction of CMPI with NH₄SCN as the first step. Next, the reaction of the alcohol with MTPI produces the desired alkyl thiocyanates.⁹

(F) When triethylammonium dithiocarbamate, easily prepared from amine, carbon disulfide, and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide at room temperature, isothiocyanate is produced in a high yield.¹⁷

(G) 2-Chloro-1-methylpyridinium iodide is used in the synthesis of carbodiimides 3 from N,N'-disubstituted thioureas 2. The former can be transformed into derivatives 4 which upon treatment with CMPI and acetic acid provides 1,3,5-triazines.⁸

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

References