

SYNLETT Spotlight 417

The Mukaiyama Reagent: An Efficient Condensation Agent

Compiled by Irina Novosjolova



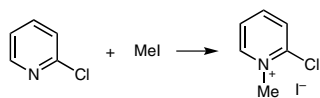
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

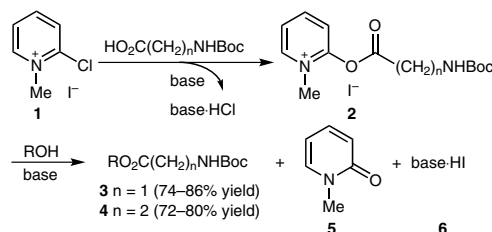
The Mukaiyama reagent (2-chloro-1-methylpyridinium iodide, CMPI) is one of the most valuable reagents for activation of hydroxyl groups of carboxylic acids and alcohols.¹ It is a pale yellow crystalline solid which is stable at room temperature in closed containers under normal storage and handling conditions.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



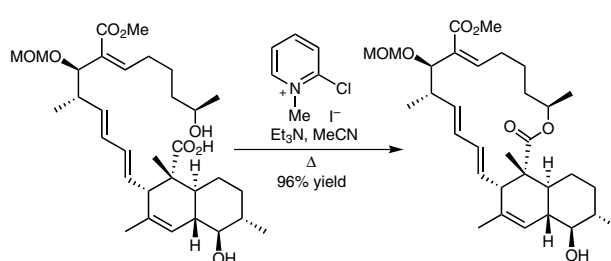
Scheme 1

Abstracts

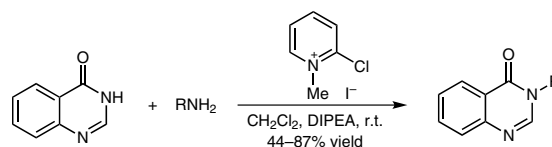
(A) The Mukaiyama reagent is widely used for activation of carboxylic acids in the synthesis of carboxylic esters. A recent example deals with the synthesis of *N*-Boc-glycine and *N*-Boc- β -alanine esters in the presence of various fatty-acid-derived alcohols.³ Nucleophilic attack of the carboxylate 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 ω -hydroxy carboxylic acids ($n = 5, 6, 7, 10, 11, 14$) has been developed under mild conditions in good yields using the Mukaiyama reagent.^{1,4} 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 transamidation occurs under very mild reaction conditions.¹⁵



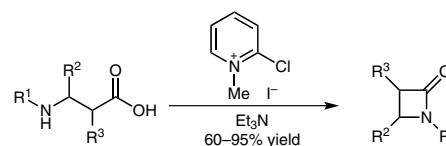
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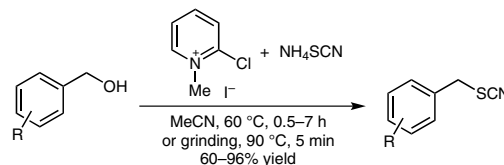
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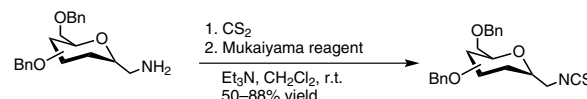
(D) CMPI is applicable for the construction of β -lactams from β -amino acids. When compared with the dicyclohexyl carbodiimide method and the $\text{Ph}_3\text{P}(\text{PyS})_2$ method of β -lactam synthesis, the Mukaiyama method is often more effective. The reaction proceeds under mild reaction conditions which are compatible with the acid- and base-sensitive β -lactam ring.⁶ For example, the use of Mukaiyama salt in the macrobis-lactamization step shortened the synthesis of tetraaromatic tetraamide macrocycles.¹⁶



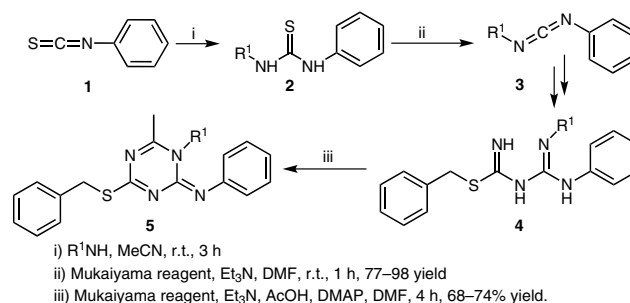
(E) Substituted benzyl alcohols can be converted into alkyl thiocyanates both under solvent and solvent-free conditions using CMPI. The proposed mechanism involves the formation of 1-methyl-2-thiocyanatopyridinium iodide (MTPI) from the reaction of CMPI with NH_4SCN as the first step. Next, the reaction of the alcohol with MTPI produces the desired alkyl thiocyanates.⁹



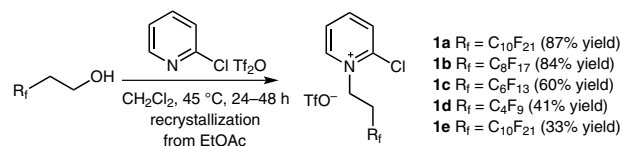
(F) When triethylammonium dithiocarbamate, easily prepared from amine, carbon disulfide, and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide at room temperature, isothiocyanate is produced in a high yield.¹⁷



(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 **5**.⁸



(H) 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 fluorinated tagged reagents have been developed.^{18a–c} They are useful in ester- and amide-forming reactions.



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