SYNLETT
# Spotlight 417

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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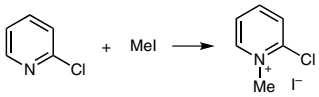
### Introduction

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 methyliodide.[2a–d]

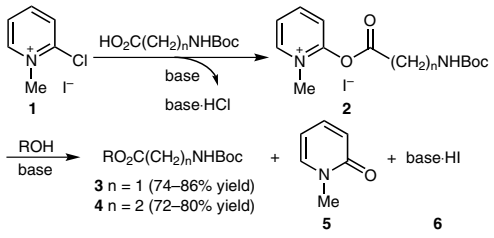



**Scheme 1**

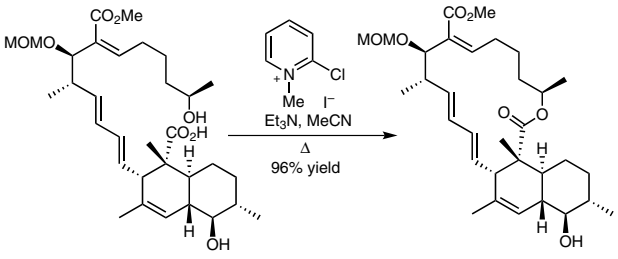
It is widely used for the synthesis of esters,[3] lactones,[4] amides,[5] lactams,[6] and ketenes[7] from the corresponding carboxylic acids, as well for obtaining carbodiimides from thioureas[8] and thiocyanates from alcohols.[9] CMPI was introduced as an useful reagent for the synthesis of carboxylic 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

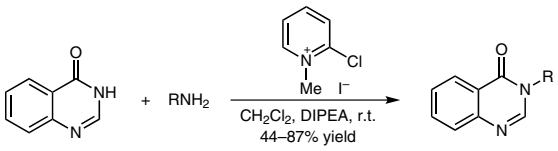
(A) The Mukaiyama reagent is widely used for activation of carboxylic acids in the synthesis of carboxylic esters. A recent example deals with the synthesis of *N*-Boc-glycine and *N*-Boc-β-alanine esters in the presence of various fatty-acid-derived alcohols.[3] Nucleophilic attack of the carboxylate 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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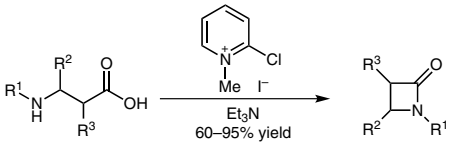
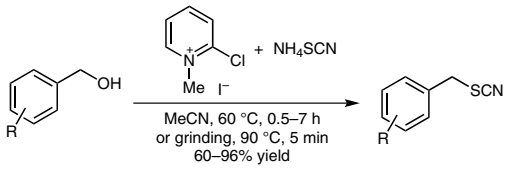
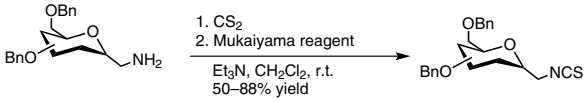
(D) CMPI is applicable for the construction of β-lactams from β-amino acids. When compared with the dicyclohexyl carbodiimid method and the $Ph_3P(PyS)_2$ method of β-lactam synthesis, the Mukaiyama method is often more effective. The reaction proceeds under mild reaction conditions which are compatible with the acid- and base-sensitive β-lactam ring.[6] For example, the use of Mukaiyama salt in the macrobislactamization step shortened the synthesis of tetraaromatic tetraamide macrocycles.[16]



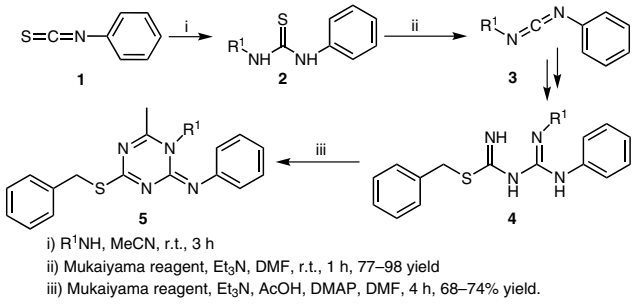

(E) Substituted benzyl alcohols can be converted into alkyl thiocyanates both under solvent and solvent-free conditions using CMPI. The proposed mechanism involves the formation of 1-methyl-2-thiocyanatopyridinium iodide (MTPI) from the reaction of CMPI with $NH_4SCN$ as the first step. Next, the reaction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



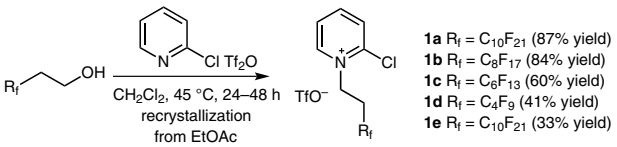

(F) When triethylammonium dithiocarbamate, easily prepared from amine, carbon disulfide, and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide at room temperature, isothiocyanate is produced in a high yield.[17]




(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 fluorous tagged reagents have been developed.[18a–c] They are useful in ester- and amide-forming reactions.




## References


(1) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.
(2) (a) Liveris, M.; Miller, J. *Aust. J. Chem.* **1958**, *11*, 297. (b) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892. (c) Khoroshilov, G.; Demchak, I.; Saraeva, T. *Synthesis* **2008**, 1541. (d) Armstrong, A.; Wang, Y.; Wang, P. *CMPI, e-Eros Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, **2010**.
(3) Yamano, Y.; Tsuboi, K.; Hozaki, Y.; Takahashi, K.; Jin, X.-H.; Ueda, N.; Wada, A. *Bioorg. Med. Chem.* **2012**, *20*, 3658.
(4) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(5) Kulikov, O. V.; Incarvito, C.; Hamilton, A. D. *Tetrahedron Lett.* **2011**, *52*, 3705.
(6) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465.
(7) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36.
(8) Kong, K. H.; Tan, C. K.; Lin, X.; Lam, Y. *Chem. Eur. J.* **2012**, *18*, 1476.
(9) Mokhtari, B.; Azadi, R.; Mardani, E. *Tetrahedron Lett.* **2012**, *53*, 491.
(10) Mukaiyama, T.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.
(11) Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, *6*, 4579.
(12) Li, P.; Xu, J. *Tetrahedron* **2000**, *56*, 8119.
(13) Mazón, A.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1455.
(14) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2265.
(15) Punthasee, P.; Vanitcha, A.; Wacharasindhu, S. *Tetrahedron Lett.* **2010**, *51*, 1713.
(16) Vandromme, L.; Teulade-Fichou, M.-P. *Synlett* **2006**, 3423.
(17) Barghash, R. F.; Massi, A.; Dondoni, A. *Org. Biomol. Chem.* **2009**, *7*, 3319.
(18) (a) Matsugi, M.; Hasegawa, M.; Sadachika, D.; Okamoto, S.; Tomioka, M.; Ikeya, Y.; Masuyama, A.; Mori, Y. *Tetrahedron Lett.* **2007**, *48*, 4147. (b) Matsugi, M.; Suganuma, M.; Yoshida, S.; Kunda, Y.; Hagihara, K. *Tetrahedron Lett.* **2008**, *49*, 6573. (c) Matsugi, M.; Nakamura, S.; Kunda, Y.; Sugiyama, Y.; Shioiri, T. *Tetrahedron Lett.* **2010**, *51*, 133.