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

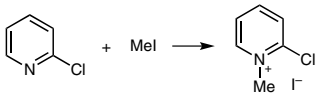
Compiled by Irina Novosjolova

Irina Novosjolova was born in Jēkabpils, Latvia, in 1986. She received her BSc and MSc in Chemical Engineering from Riga Technical University (RTU), Latvia. She is currently pursuing her doctoral degree under the supervision of Professor Maris Turks and Professor Erika Bizdena at RTU. Her research is focused on structure and reactivity studies of bis(triazolyl)purine nucleosides.

Faculty of Material Science and Applied Chemistry, Riga Technical University, Azenes Str. 14/24, LV-1007 Riga, Latvia
E-mail: irina.novosjolova@gmail.com

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]

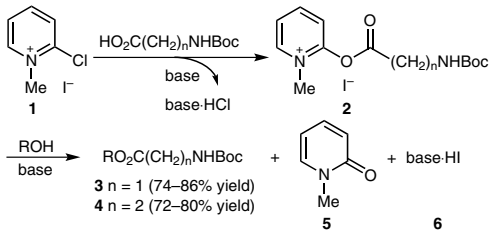


Scheme 1

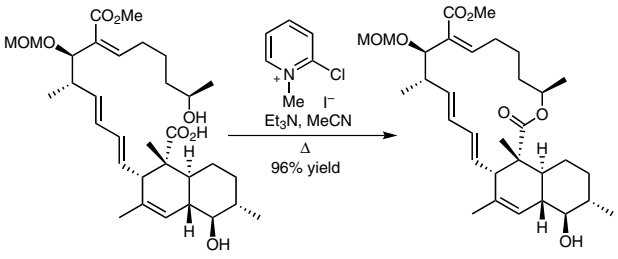
It is widely used for the synthesis of esters,[3] lactones,[4] amides,[5] lactams,[6] and ketenes[7] from the corresponding carboxylic acids, as well for obtaining carbodiimides from thioureas[8] and thiocyanates from alcohols.[9] CMPI was introduced as an useful reagent for the synthesis of carboxylic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

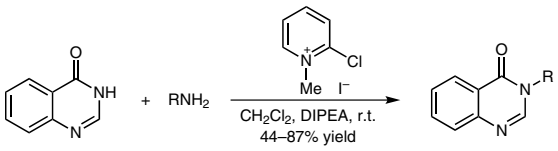
(A) The Mukaiyama reagent is widely used for activation of carboxylic acids in the synthesis of carboxylic esters. A recent example deals with the synthesis of *N*-Boc-glycine and *N*-Boc-β-alanine esters in the presence of various fatty-acid-derived alcohols.[3] Nucleophilic attack of the carboxylate 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.

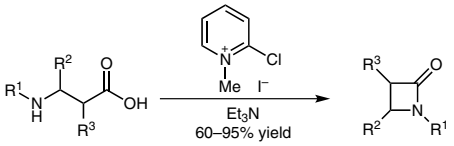


(C) The Mukaiyama reagent can also be used for C–N bond formation, for example for synthesis of 3-alkylquinazolin-4-ones. The latter are valuable molecular scaffolds in medicinal chemistry. Thus, a formal transamidation occurs under very mild reaction conditions.[15]

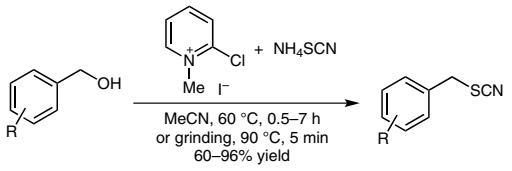


SYNLETT 2013, 24, 0135–0136
Advanced online publication: 04.12.2012
DOI: 10.1055/s-0032-1317530; Art ID: ST-2012-V0424-V

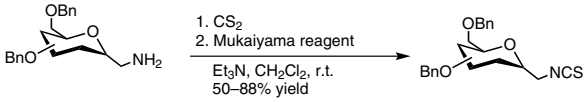
(D) CMPI is applicable for the construction of β-lactams from β-amino acids. When compared with the dicyclohexyl carbodiimid method and the $Ph_3P(PyS)_2$ method of β-lactam synthesis, the Mukaiyama method is often more effective. The reaction proceeds under mild reaction conditions which are compatible 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]



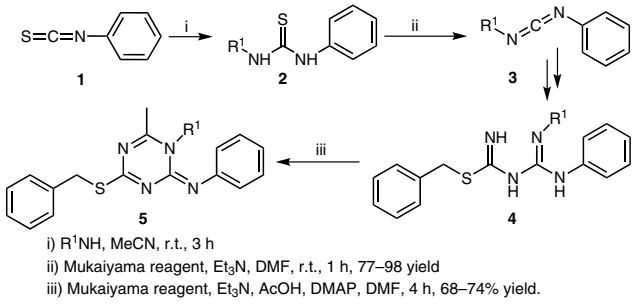
(E) Substituted benzyl alcohols can be converted into alkyl thiocyanates both under solvent and solvent-free conditions using CMPI. The proposed mechanism involves the formation of 1-methyl-2-thiocyanatopyridinium iodide (MTPI) from the reaction of CMPI with NH_4SCN as the first step. Next, the reaction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



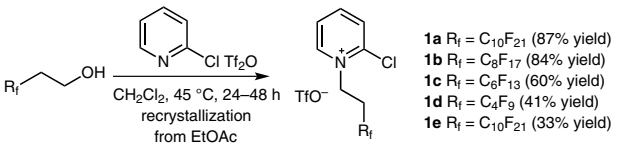
(F) When triethylammonium dithiocarbamate, easily prepared from amine, carbon disulfide, and triethylamine, is treated with 2-chloro-1-methylpyridinium iodide at room temperature, isothiocyanate is produced in a high yield.[17]



(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.