SYNLETT
Spotlight 369

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

N-Methylimidazole: Attractive and Valuable Chameleonic Species

Compiled by Graziella Greco

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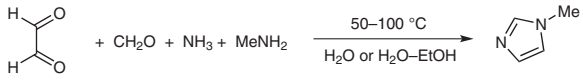
Dedicated to Dr. Raquel P. Herrera for her encouragement and humanity.

Introduction

In the last decades *N*-methylimidazole (*N*-Mim) has attracted the attention of a great number of research groups due to its broad chameleonic behavior, being widely used in organic chemistry as a solvent, as co-catalyst, ligand in metal complexes, Brønsted or Lewis base catalyst. *N*-Mim participates in the active center of several enzymes, as an ionic liquid precursor, as electron acceptor or as key intermediate in synthesis.[1–7] On the other hand, the chemistry of imidazole compounds in general has been also a center of interest due to the presence of its essential functional unit in a large variety of biological important molecules, being the *N*-methylimidazole used to mimic aspects of several of these biomolecules.[8] These derivatives can be helpful in studies to elucidate biological mechanisms, and its importance has led to several international patents. The different roles played by *N*-methylimidazole have been extensively applied for the synthesis of important targets.[8]

Preparation

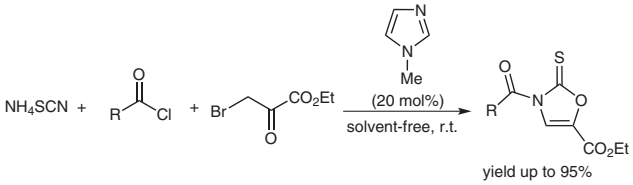
The Radziszewski process is used at industrial scale for the preparation of *N*-methylimidazole. This reaction is performed by using glyoxal, which is condensed with formaldehyde, ammonia and methylamine or in a smaller scale by direct methylation of imidazole.[9] Nevertheless, *N*-methylimidazole is also commercially available as a liquid.



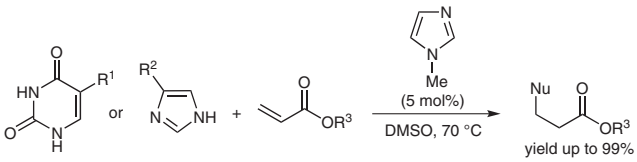
Scheme 1 Industrial synthesis of *N*-methylimidazole

Abstracts

(A) *Lewis Base Catalyst:*
Yavari and co-workers reported an efficient synthesis of functionalized 1,3-oxazoline-2-thiones promoted by a catalytic amount of *N*-methylimidazole. In the invoked mechanism, the role of the *N*-methylimidazole is assumed to be added to the in situ formed isothiocyanate, and released in the last step to generate the final cyclic adduct.[1]

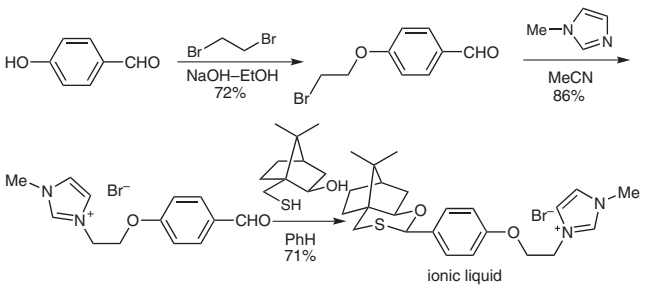


(B) *Brønsted Base Catalyst:*
Lin and co-workers have developed a novel strategy for the aza-Michael addition of N-heterocycles to α,β-unsaturated carbonyl compounds under the catalytic action of *N*-methylimidazole as Brønsted base. The final 1,4-adducts were achieved with very good yields and in short reaction times.[2]

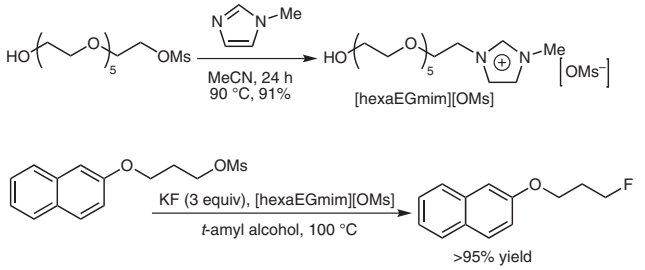


SYNLETT 2011, No. 17, pp 2595–2596
Advanced online publication: 06.10.2011
DOI: 10.1055/s-0031-1289512; Art ID: V37611ST

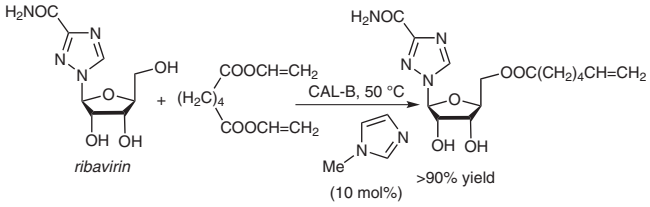
(C) *Chiral Ionic Liquid Precursor:*
Liu, Huang, and co-workers reported the use of *N*-Mim as a key step for the synthesis of a chiral ionic liquid, further efficiently employed as organocatalyst in the epoxidation of aromatic aldehydes in water.[3]



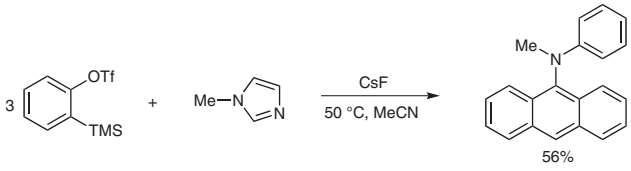
(D) *Synthesis of Ionic Liquids:*
Kim and co-workers developed an hexaethylene glycol substituted imidazolium-based ionic liquid as an efficient catalyst in the nucleophilic fluorination of base-sensitive substrates.[4]



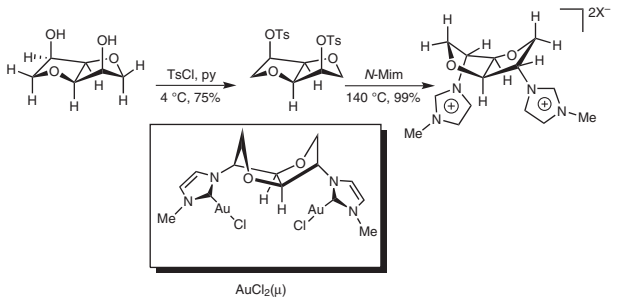
(E) *Hydrogen Bonding Co-Catalyst of Enzymes:*
Lin and co-workers discovered that *N*-methylimidazole enhanced the activity of lipases, by means of hydrogen-bond interactions between the electron pair of the nitrogen in the *N*-Mim and the activated hydroxyl group, all this being favored by the presence of the methyl group in the structure. The result was the remarked increase of the reaction rate in the acylation of ribavirin by adding catalytic amounts of *N*-methylimidazole.[5]



(F) *Useful Synthetic Intermediate:*
Zhang and co-workers provided a pioneering way to prepare aryl amines containing anthracene under mild conditions. They used the in situ generated benzyne and *N*-methylimizadole derivatives. The proposed unusual mechanism is believed to undergo a tandem reaction involving a Diels–Alder reaction and an intermolecular nucleophilic coupling.[6]



(G) *Carbene Ligand in Metal Complexes:*
Fallis, Dervisi, and co-workers reported the synthesis and structural properties of both silver and gold metallamacrocycles with new chiral N-heterocyclic carbenes from *N*-methylimidazole.[7]



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