

SYNLETT Spotlight 196

Nitromethane (MeNO₂)

Compiled by Prarthana Devi



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

Nitromethane (NM) is a colorless, oily liquid (mp -28.5 °C; bp 101.1 °C) with a moderately strong disagreeable odor. It is a highly flammable liquid at room temperature and reacts with alkali, strong acids, oxidizers, and metallic oxides.¹ NM is completely miscible with most organic solvents. If not properly handled, stored, or used, it can be dangerous and can detonate. The hazardous decomposition products of NM are toxic fumes of nitrogen oxides.

Kolbe first prepared NM in 1872.² It is synthesized by the reaction of chloroacetic acid with sodium hydroxide followed by the treatment of sodium nitrite.³

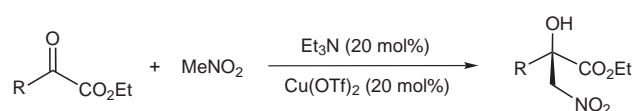
The versatility and synthetic ability of this reagent have been exemplified in its increasing use in organic synthesis (e.g., pharmaceuticals, pesticides, fibers, painting, and ore dressing).⁴ The potential applications of NM in the Syn-

thesis of agricultural soil fumigants and industrial antimicrobials have drawn much more attention. It is widely applied as extraction solvent or reaction medium. To name a few of the many applications, NM is used as solvent in capillary electrophoresis^{5a} and in the synthesis of glucosyl asparagines,^{5b} it also plays a role as scavenger⁶ of acrylonitrile in the deprotection of synthetic oligonucleotides. An enclave inclusion compound is afforded by the recrystallization of 18-crown-6 from NM.⁷ With an iridium pincer complex, NM forms a coordinated ion that acts as a putative active species in metal-catalyzed nitro-aldol reactions.⁸

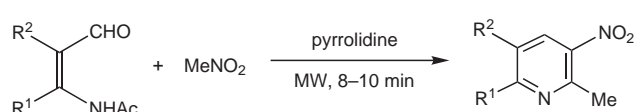
In this Spotlight, current advances using nitromethane in organic syntheses are emphasized with respect to stereoselectivity. The success of this reagent is related to the unique capacity of the nitro group to be selectively converted into various functionalities under mild conditions.

Abstracts

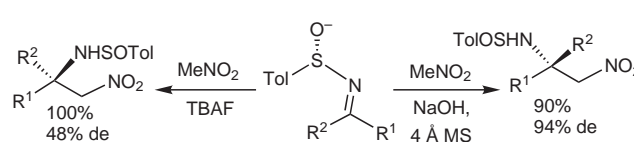
(A) The catalytic enantioselective Henry reaction of α -keto esters with NM affords β -nitro- α -hydroxy esters.⁹ The reaction proceeds via a 1,2-addition reaction and the product can be converted into β -amino acids.



(B) The efficacy of NM has been extended to the base-catalyzed solid-phase condensation of steroidal, alicyclic or aromatic β -formyl enamides under microwave irradiation.¹⁰ Boruah and co-workers found a new application of the Henry reaction and provided a route for facile, one-pot combinatorial synthesis of annelated pyridines.



(C) NM reacts with *N*-sulfinylimines in the presence of NaOH to produce nitroamines in a highly diastereoselective manner.¹¹ In the presence of TBAF, the reaction rates are strongly increased and the stereoselectivity is inverted. This approach offers enantiomerically pure β -nitroamines, which have been hardly accessible by aza-Henry reactions so far.



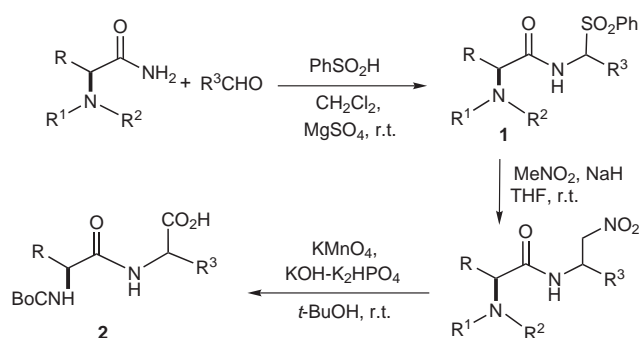
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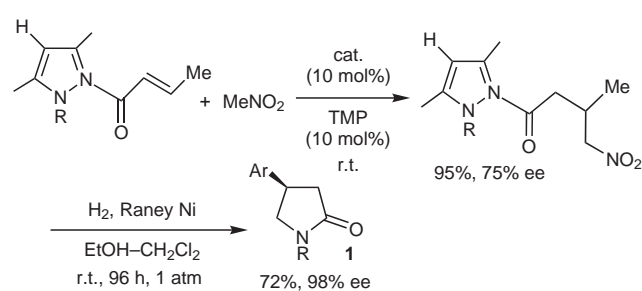
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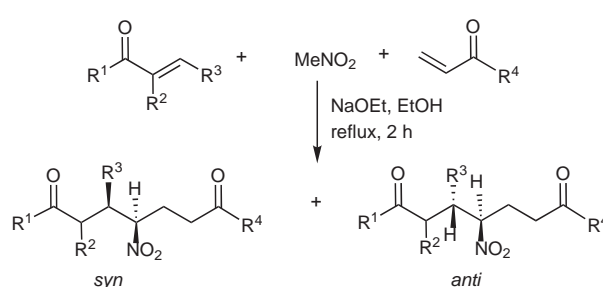
(D) α,α -Dipeptides are valuable synthetic intermediates and biologically active compounds. Recently, Petrini and Seri¹² have utilized NM in a two-step synthesis of α,α -dipeptide from α -amido sulfone. The procedure involves the nitromethylation of **1** followed by Nef conversion of the nitro group to furnish product **2**.



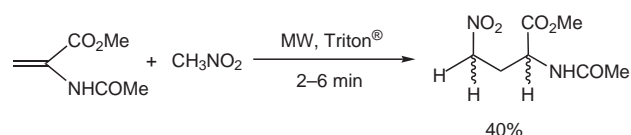
(E) NM undergoes an enantioselective Michael addition with 1-(2-alkenyl)-3,5-dimethyl pyrazoles by a catalytic double activation method using chiral Lewis acid and achiral amine catalyst to give 1-(3-substituted 4-nitrobutanoyl)-3,5-dimethyl pyrazole in high yields.¹³ This method has been successfully employed for the total synthesis of the antidepressant (*R*)-rolipram (**1**).



(F) A three-component Michael addition reaction of NM with two unsymmetrical α,β -unsaturated carbonyl compounds in the presence of base provides a convenient one-pot synthesis of 1,7-dicarbonyl compounds.¹⁴ 1,7-Dicarbonyl compounds are initial starting materials for the synthesis of enantiomerically pure alcohols, which are useful building blocks for natural product synthesis.



(G) Under solvent-free conditions, γ -nitroacetamido ester can be obtained via Michael addition from the commercial acetamido acrylate and NM.¹⁵ The product is a versatile precursor for the preparation of α -amino acids.



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