**SYNLETT Spotlight 447**

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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**N-Methylmorpholine N-Oxide**

Compiled by Tanya Pieterse

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**Introduction**

N-Methylmorpholine N-oxide [NMMO (2)] is a light yellow powder with a melting point of 180–184 °C. It is commercially available in both the monohydrate (C₆H₁₄NO₂·H₂O) and anhydrous forms, and is stable under normal conditions.

Apart from being a powerful environmentally friendly solvent for dissolving cellulose,²,³ NMMO (2) acts as a strong oxidizing agent and is generally utilized as a stoichiometric oxidant together with TPAP and OsO₄ for hydroxy group oxidation⁴ and dihydroxylation of olefins.⁵,⁶ The oxidative dehydrogenation of amines utilizing gold as the catalyst is also carried out in the presence of NMMO (2), where it acts as a base to afford imines in good yield.⁷ Moreover, NMMO (2) can react as a nucleophile, as is displayed during the reductive work-up of ozonolysis intermediates to afford aldehyde products.⁸,⁹ One of the advantages of using NMMO versus oxidants like hydrogen peroxide is found in the fact that the byproduct after oxidation [NMM (1)] is very low in basicity.

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**Preparation**

Generally amine N-oxides can be prepared via the oxidation of the pyridine analogue or tertiary amine [e.g., (1)] with H₂O₂, Caro’s acid, or peracids like MCPBA.¹⁰ Schwartz and co-workers¹¹ also proposed that NMM (1) can be converted into NMMO (2) in the presence of ozone as the oxidizing agent.

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**Abstracts**

(A) Cellulose is the most abundant renewable polymer source currently available. It is converted into fibers and films utilizing high environmental impact solvent systems such as those applied during the xanthate (ROCS₂⁻⁻⁻⁻⁻ M⁺, M⁺ = Na⁺, K⁺) or cuprammonia processes. However, NMMO (2), has proven to be a powerful solvent, and the use of NMMO constitutes an environmentally friendly process for cellulose dissolution under microwave heating (105–490 W, 2450 MHz).³
(B) NMMO was utilized as a co-oxidant by Mehta and Pan\(^1\) to oxidize the hydroxyl function of the epoxyquinone intermediate 4 during the total synthesis of the novel antifungal agent (±)-jesterone. NMMO, tetrapropylammonium perruthenate (TPAP), and molecular sieves in CH\(_2\)Cl\(_2\) at room temperature afforded the desired product in 92% yield. While TPAP is required in catalytic amounts, a stoichiometric quantity of NMMO maintains the catalytic cycle by regenerating TPAP.

(C) Krishna and Reddy\(^5\) utilized NMMO and OsO\(_4\) during the oxidation of the exocyclic double bond in 6 during the total synthesis of (+)-valienamine with the simultaneous removal of the intermediate protecting groups to obtain the final desired product in 42% yield.

(D) The combination of NMMO and OsO\(_4\) in aqueous tetrahydrofuran led to the dihydroxylation of alkene 8 in 82% yield during the development of a route for the synthesis of the alkaloid (+)-clavizepine by de la Fuente et al.\(^6\)

(E) Klobukowski, Angelici, and Woo\(^7\) examined the use of amine N-oxides (NMMO, trimethylamine N-oxide and pyridine N-oxide) during the oxidative dehydrogenation of Bn\(_2\)NH. They found NMMO to be the most effective base: It afforded N-benzylidene benzylamine in 96% yield and 100% conversion within 24 hours.

(F) Schwartz et al.\(^8\) described a ‘reductive ozonolysis’ protocol where the zwitterion intermediate 13 is captured by NMMO to generate aldehyde 15 as the final product. This methodology was applied to the ozonolysis of a series of allylbenzenes (16) to provide a synthetic route to phenylacetaldehydes, which are important moieties in the environmentally benign synthesis of isoflavonoids.\(^9\)

References