

A Novel Oxidizing Agent Based on the Polymer-Supported Oxoammonium Sulfonate of TEMPO

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Introduction

- Selective oxidation of alcohols to carbonyl compounds is an important objective in organic synthesis
- Aldehydes and ketones participate in many fundamental transformations in organic synthesis as versatile building blocks
- Many reactive aldehydes are unstable to storage
- An expedient method for oxidation of primary alcohols would allow the preparation of fresh activated aldehydes as required for subsequent use in a multi-step synthesis

Polymer-Supported Oxidizing Agents: Alcohol Oxidation

Goal

Develop selective reagent for alcohol oxidation with simple protocol for product purification

- Current methods with bound reagents have drawbacks
 - Chromium reagents often leach
 - Peruthinate resins have low loading
 - Iodine(III) and (V) acetates are difficult to prepare

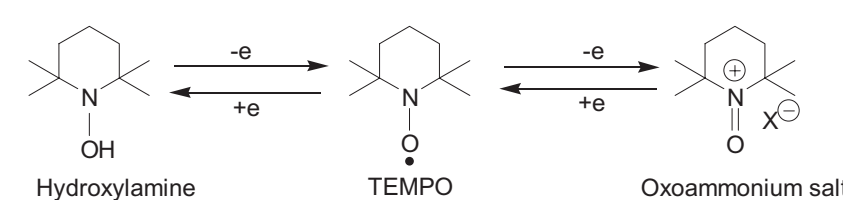
Approach

- Investigate Bound Oxoammonium Salts
 - Mild oxidant generated from TEMPO
 - Review: de Nooy, A.E.J., *et al Synthesis* 1996,1153
 - Shortcomings:
 - Side reactions from secondary oxidant
 - Purification

Investigate stable bound oxoammonium salt

Oxidation of Alcohols with TEMPO

- TEMPO is a remarkably stable radical
- TEMPO and its derivatives used in the oxidation of alcohols both in stoichiometric transformations and as catalysts
- Oxoammonium salt is the active species:
 - Oxidation of TEMPO with a secondary oxidant or byproduct
 - Disproportionation reaction in the presence of a strong protic acid



Oxidation of Alcohols with TEMPO

Advantages

- The oxidation reactions with TEMPO display low over-oxidation to carboxylic acids
- Avoids toxic heavy metals such as chromium, osmium or lead

Shortcomings

- Complex reaction conditions
- Product purification
- Chlorine-based secondary oxidant often generates unwanted side-products with many substrates

Oxoammonium Salt of TEMPO: Rationale for Bound Reagent

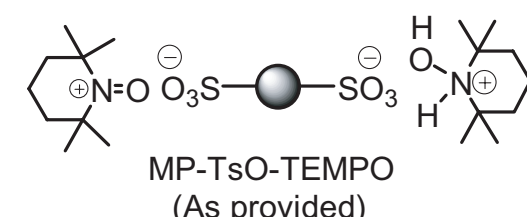
Advantages

- Oxoammonium salt ready for reaction
 - Activation not required
- Selectivity
 - Typically no over-oxidation to carboxylic acids
- Avoids heavy metals such as chromium
- Product isolation by aqueous work-up and chromatography
- Use of a chlorine-based secondary oxidant often generates side-products

Polymer-Supported Oxoammonium salt would provide desired reactivity, selectivity and simplicity

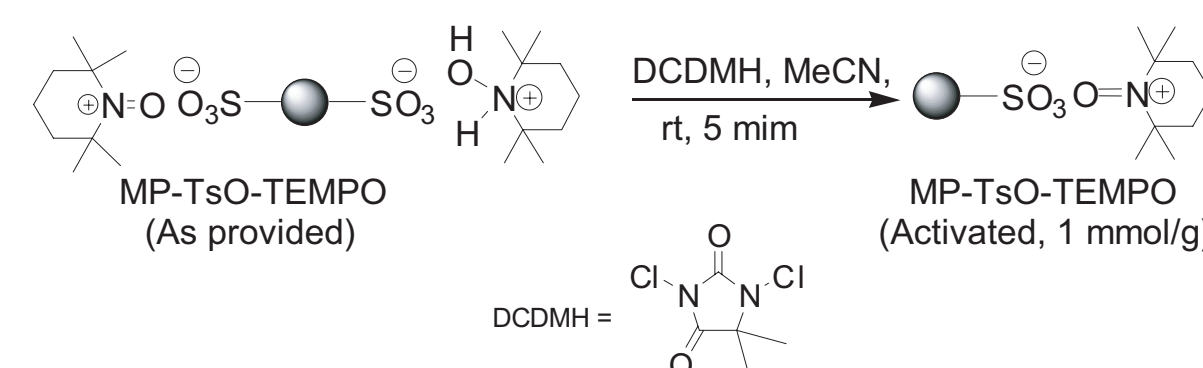
MP-TsO-TEMPO: A Novel Polymer-Bound Oxoammonium Sulfonate

- The synthesized resin contains a mixture of active oxoammonium and the reduced hydroxylamine species
- The resin requires activation to its full capacity prior to use
- Activation is rapid requiring only 5 min



Activation of MP-TsO-TEMPO

- A simple and rapid procedure
- Oxidation of the hydroxylamine species by DCDMH



- Contains only the active oxoammonium species
- Capacity: ~1.0 mmol/g

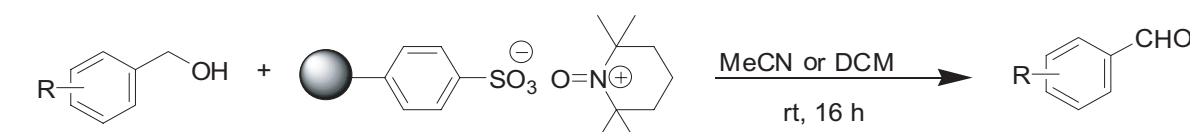
MP-TsO-TEMPO Oxidation Studies

Objective

- Define oxidation protocols
 - Solvent, stoichiometry, time and temperature
- Determine scope and selectivity for these conditions
 - Activated alcohols: benzylic, allylic and acetylenic
 - Cyclic secondary alcohols
 - Acyclic primary and secondary alcohols
- Define an integrated reaction and work-up protocol that facilitates parallel synthesis

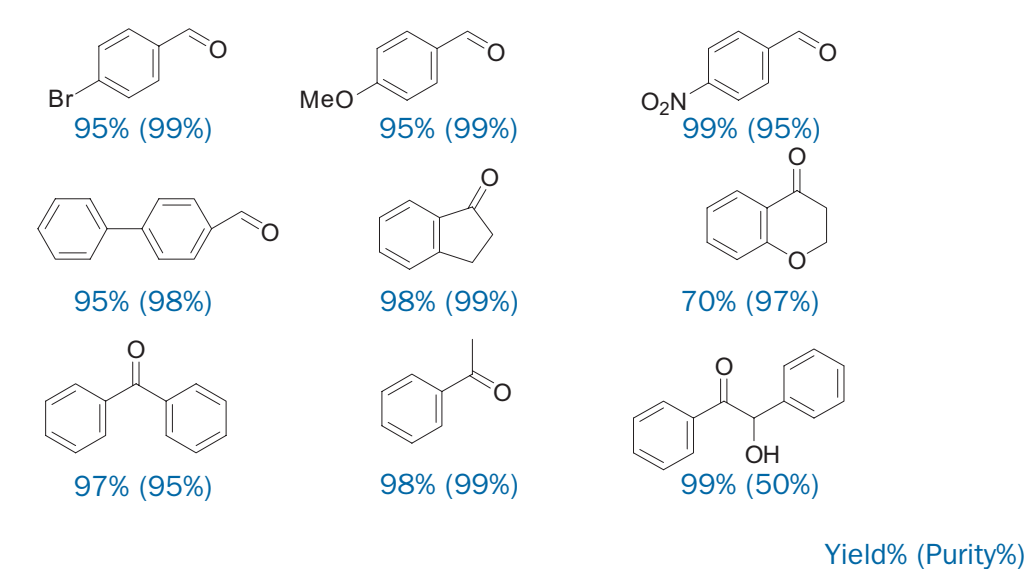
Scope Studies with MP-TsO-TEMPO: Oxidation of Benzylic Alcohols

Benzylic Alcohols + MP-TsO-TEMPO



- Acetonitrile proved to be the solvent of choice
- Reactions may also be performed in DCM
- 2.0 equiv of MP-TsO-TEMPO
- 0.5 mmol reaction scale
- Product isolated by simple filtration of the resin

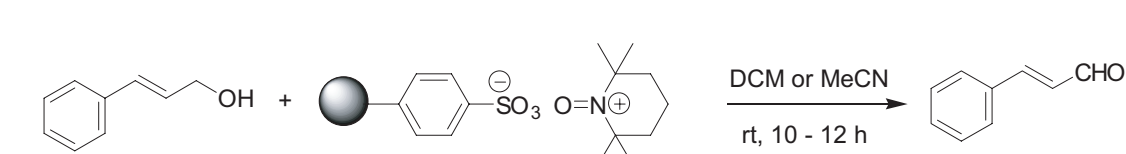
Oxidation of Benzylic Alcohols



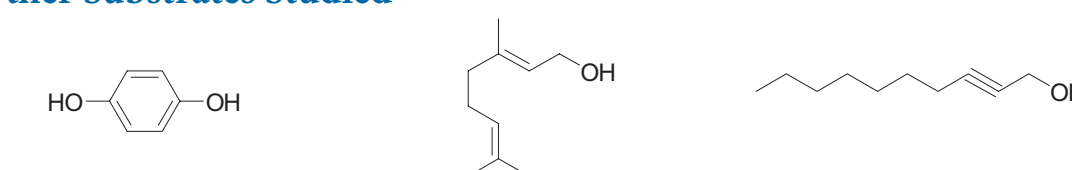
- The diol afforded a 1:1 mixture of diketone and monoketone

MP-TsO-TEMPO: Oxidation of Allylic and Acetylenic Alcohols

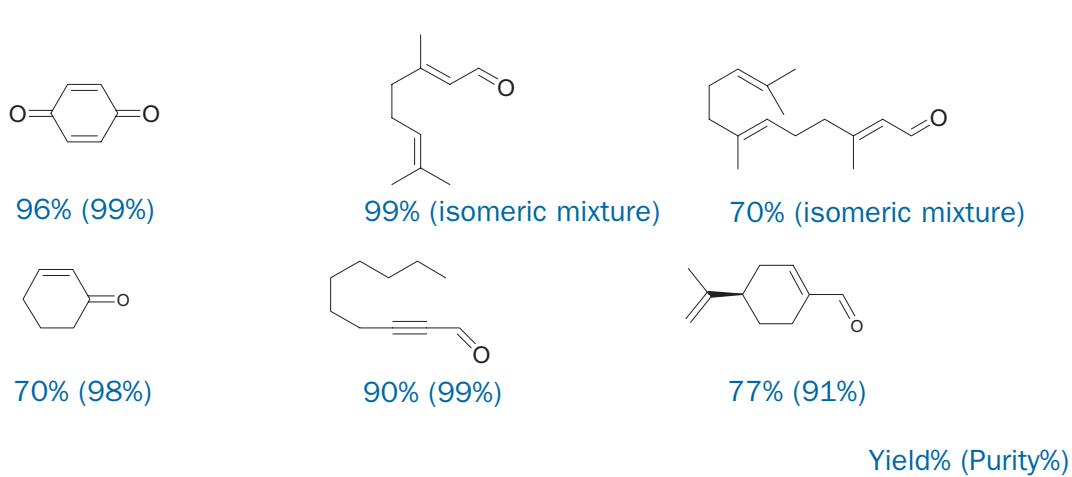
Allylic alcohol + MP-TEMPO



Other Substrates Studied



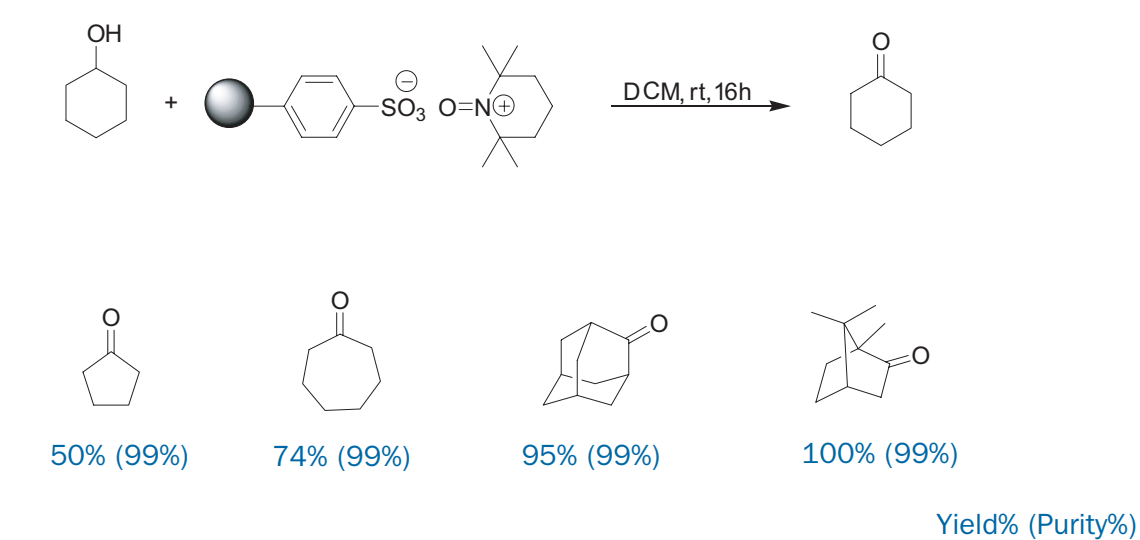
Oxidation of Allylic and Acetylenic Alcohols



Reaction Conditions and Results

- Solvent - DCM or MeCN, MP-TEMPO: 2.0 equiv (4.0 equiv for hydroquinone), 10-12 h, reaction scale - 0.5 mmol
- Products were isolated in excellent yield and > 97% purity

Oxidation of Cyclic Secondary Alcohols

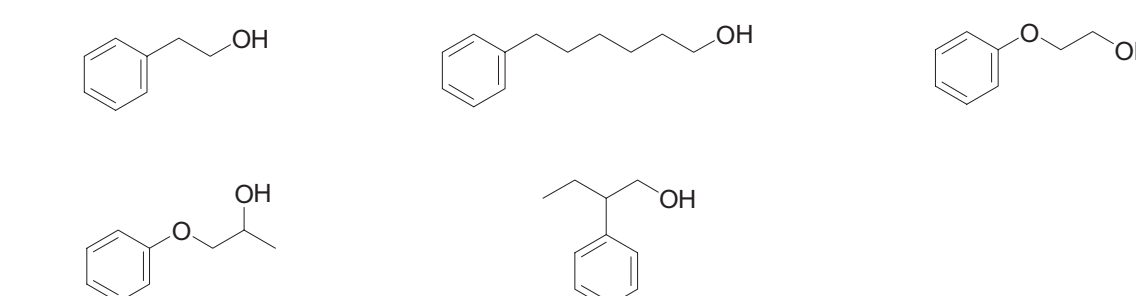


- Complete oxidation with 2.0 equiv of MP-TsO-TEMPO

Scope Studies with MP-TsO-TEMPO: Oxidation of Acyclic 1° and 2° Alcohols

Acyclic 1° or 2° Alcohols + MP-TsO-TEMPO

Substrates Studied



Reaction Conditions and Results

- Solvent: DCM or MeCN, MP-TsO-TEMPO: 2.5 equiv, reaction scale: 0.5 mmol
- In all cases, starting alcohols were recovered

Conclusion

- Clean oxidation of benzylic, allylic, acetylenic and cyclic secondary alcohols to aldehydes and ketones in excellent yield and purity
- Selective oxidation of activated alcohols in the presence of acyclic primary and secondary alcohol may be possible
- Both the active species and the reduced hydroxylamine byproduct remain resin bound
- Acetonitrile proved to be the solvent of choice, however, DCM should be used for reactions generating volatile products
- Reactions are performed at ambient temperature
- Reactions with new substrates easily monitored by performing reaction in H NMR tube (CDCl₃)
- Simple isolation of pure products, no workup or column chromatography required

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