Journal of Pharmacy and Practice

www.pavvjopp.com (e-ISSN 2249 – 5800)

JOPP

# Stereo-Selective Synthesis and Resolution techniques

## (Few pyrrole derivatives)

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**Abstract:** Improved the efficiency of the drug, most of the time depends on its chirality. The two enantiomers of a chiral drug differ significantly in their bioavailability, rate of metabolism, selectivity for enzymes, and toxicity. For example, one enantiomer may be responsible for the therapeutic effects of a drug whereas the other enantiomer is inactive and/or contributes to undesirable effects. The teqniques of resolution and stereo-selective synthesis of 4-membered Spirolactams prepared with extreme enatiomeric purity and yield to support the drug discovery without side effects.

**Key words:** Resolution; β-lactam; CAN; DDQ.

## Introduction

The methoxy benzyl protecting groups (PMB) are used widely. They are very useful in the protecting of amine and hydroxyl groups in multistep synthesis of complex natural products, especially in the synthesis using Heterocyclic compounds and carbohydrates as chiral templates. The p-methoxy benzyl group (PMB) is the most widespread using methoxy benzyl group.

## Methods

Deprotection of methoxy benzyl protecting groups is very studied in the recent time. Oxidizing reagents are very common and useful on the cleavage of methoxy benzyl groups. 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) and cerium ammonium nitrate (CAN) are the most used. Amount of reductive methods are poor. Using acids and especially Lewis acids are often problematically because many protecting groups are cleaved under these conditions.

The most used oxidants are 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) and cerium ammonium nitrate (CAN). Advantages of their use are in cleavage under essentially neutral conditions and in short time which is required on deprotection in excellent yields.

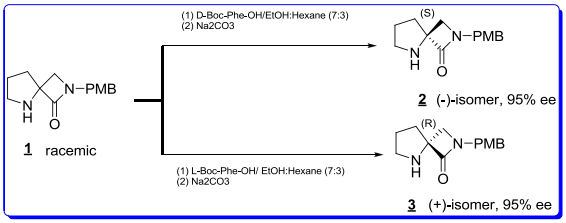
P-methoxy benzyl group cleavage by 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) is performed in 1, 4-dioxane with 10 volumes. 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) is used in small abundance 1.2 eq. The reaction proceeds via initial formation of a charge-transfer complex between an electron-donating aromatic ring of PMB and electron-accepting DDQ. The reaction is completed within 4 hours at reflux temperature.

Cerium ammonium nitrate is very stable compound in aqueous medium and P-methoxy benzyl group cleavage by cerium ammonium nitrate (CAN) is performed in Acetonitrile and water in 2:1 ratio respectively with 10 volumes. Cerium ammonium nitrate (CAN) is used 1.2 eq. The

reaction is completed within 1 hour at ambient temperature.

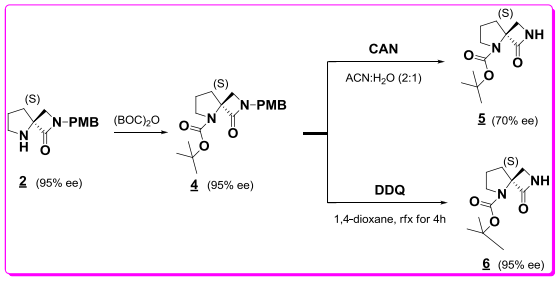
**Results**

**Scheme-I: Resolution via Salt formation**




The resolution ofracemiccompound -1 using chiral acid D-Boc phenyl alanine to afford **compound-2 (-) isomer**with more than 95% enantiomeric purity and 23% yield.The resolution of racemic compound -1 using chiral acid L-Boc phenyl alanine to afford **compound-3 (+) isomer** with more than 95% enantiomeric purity and 23% yield[1].

**Scheme-II: Synthesis of (S) - tert-butyl 1-oxo-2, 5-diazaspiro [3, 4] octane-5-carboxylate:**




Conversion of Compound-2 to compound-4 is protection of NHgroup with di-tertiary butyl dicarbonate to afford compound-4 with more than 95% enantiomeric purity (95% ee) and 98% yield. We observed that during this conversion no disturbance in chirality of compound-4.

Conversion of compound-4 to compound-5 is deprotection of p-methoxy benzyl group using cerium ammonium nitrate (CAN) as a reagent, Acetonitrile and water (2:1 ratio) as a solvent at ambient temperature, the reaction is completed within 1 hour. But observedthat during this conversion the chirality is disturbed and obtained only 70% enantiomeric purity (70: 30 ee).Hence this condition for deprotection of p-methoxy benzyl group is not suitable.

Conversion of compound-4 to compound-6 is deprotection of p-methoxy benzyl group using 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) as a reagent, 1, 4-dioxane as a solvent at reflux temperature, the reaction is completed within 4 hour. But observed that during this conversion no disturbance in chirality of compound-6. And obtained more than 95% enantiomeric purity (95% ee) with good yields.Hence this condition for deprotection of p-methoxy benzyl group is suitable.

**Scheme-III: Synthesis of (R) - tert-butyl 1-oxo-2, 5-diazaspiro [3, 4] octane-5-carboxylate:**

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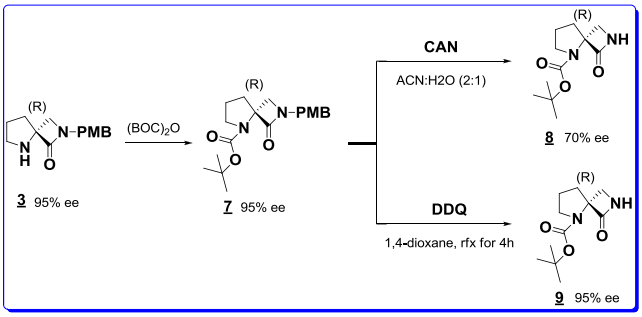


Conversion of Compound-3 to compound-7 is protection of NH group with di-tertiary butyl dicarbonate to afford compound-7 with more than 95% enantiomeric purity (95% ee) and 98% yield. We observed that during this conversion no disturbance in chirality of compound-7.

Conversion of compound-7 to compound-8 is deprotection of p-methoxy benzyl group using cerium ammonium nitrate (CAN) as a reagent, Acetonitrile and water (2:1 ratio) as a solvent at ambient temperature, the reaction is completed within 1 hour. But observed that during this conversion the chirality is disturbed and obtained only 70% enantiomeric purity (70: 30 ee).Hence this condition for deprotection of p-methoxy benzyl group is not suitable.

Conversion of compound-7 to compound-9 is deprotection of p-methoxy benzyl group using 2, 3-dichloro-5, 6-cyano-1, 4-benzoquinone (DDQ) as a reagent, 1, 4-dioxane as a solvent at reflux temperature, the reaction is completed within 4 hour. But observed that during this conversion no disturbance in chirality of compound-9. And obtained more than 95% enantiomeric purity (95% ee) with good yields.Hence this condition for deprotection of p-methoxy benzyl group is suitable.

## Discussion

The introduction of a [5.4]-Spiro lactam, which was validated using as a novel β-turn amidic.[2, 3]

Approximately 50% of marketed drugs are chiral, and of these approximately 50% are mixtures of enantiomers rather than single enantiomers.[4]

In these cases, it is critical to distinguish the single enantiomer from the racemic form because they may differ in their dosages, efficacies, side effect profiles, or even indicated use.

The two enantiomers of a chiral drug may differ significantly in their bioavailability, rate of metabolism, metabolites, excretion, potency and selectivity for receptors, transporters and/or enzymes, and toxicity. The use of single-enantiomer drugs can potentially lead to simpler and more selective pharmacologic profiles, improved therapeutic indices, simpler pharmacokinetics due to different rates of metabolism of the different enantiomers, and decreased drug interactions.

For example, one enantiomer may be responsible for the therapeutic effects of a drug whereas the other enantiomer is inactive and/or contributes to undesirable effects. Currently, there is no regulatory mandate in the United States or Europe to develop new drugs exclusively as single enantiomers. The U.S. Food and Drug Administration (FDA) policy regarding single enantiomers was published in 1992.[5] The FDA leaves the decision to

pursue a racemic or a single-enantiomer formulation of a new drug to its developers, but the choice of a racemic versus a single-enantiomer formulation must be justified. Although both racemic and single-enantiomer drugs will continue to be developed, a higher proportion of single enantiomers are being submitted for new drug approval.[6] Our strategy is to develop enatiomeric pure [5.4]-β-lactam.

**Acknowledgements**

I thank Mr. V. Surendar for the generous gift of the starting material and fruitful discussion and also thanks to Dr Jaya Chandra Reddy for advice and guidance during the course of this study.

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