Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents

Abstract of Thesis

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Abstract

The thesis entitled "**Development of New Synthetic Methodologies for the Synthesis of Secondary Amides, Anilines and Nitriles Using *O*-(sulfonyl)hydroxylamine Reagents**" consists of four chapters. Nitrogen is the most occurred element in nature and also in a major class of biologically active natural and pharmaceutical products. In addition, the key presence of nitrogen in 84% of marketed drugs has a successful impact on the medicinal field and living health. Secondary amides, anilines, and nitriles are important functional groups, and they exist in many natural products and biologically active molecules, and approved drugs. Furthermore, they can be used as versatile building blocks in the synthesis of natural products, Pharmaceuticals, agrochemicals, dyes, and several value-added products. Therefore, the development of efficient synthetic methodologies for the preparation of these groups has attracted intense interest from synthetic chemists. Traditional methods for preparing these compounds generally involve tedious procedures, harsh reaction conditions, metal waste, toxic reagents, or byproducts. In recent decades, many groups have reported modifications of the reaction conditions that allow the transformation to proceed under milder reaction conditions. However, these developed methodologies suffer from limited substrate scope, complicated procedures, multi-step syntheses, elevated temperatures, the requirement of additives, and low functional group tolerance. Additionally, many of the reagents and catalysts used could plausibly take part in side reactions, thus restricting their applications in industries. Therefore the practical and direct synthesis of these nitrogen-containing functional groups from readily available starting materials under mild and environmentally benign conditions with a high scope is still a synthetic challenge. Furthermore, the selection of nitrogen sources is crucial to these transformations.

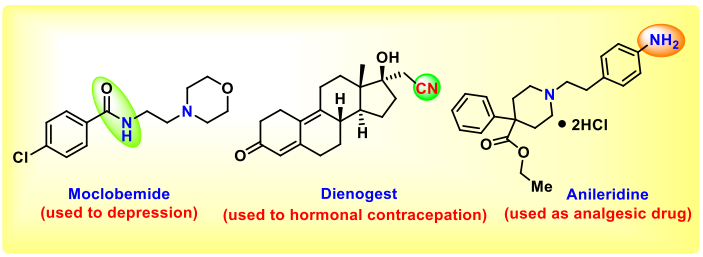
Recently, *O*-(substituted)hydroxylamine reagents have emerged as powerful nitrogen transfer reagents in various synthetic reactions such as amination, amidation, and aziridination etc. These reagents bring in several advantages over the other traditionally used reagents. Some of the special features of these reagents include generation of water-soluble by-products, commercially available reagents or ease of synthesis from cheaper raw materials, non-toxic nature, stability at ambient temperature, and ease of

handling etc made them popular among the scientific community for further applications.

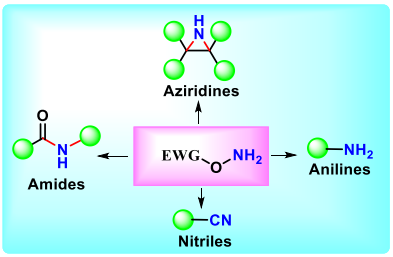
In this context, we have developed highly efficient, one-pot, environmentally benign, mild, and operationally simple methods for the synthesis of secondary amides, anilines, and nitriles from easily available starting materials using *O*-*(*sulfonyl)hydroxylamines as the aminating agents.

Chapter 1: **A General overview of nitrogen-containing compounds and *O*-(substituted)hydroxylamines: Introduction and motivation of present work**

This chapter starts with a brief introduction to nitrogen-containing organic compounds, particularly secondary amides, aryl amines, and nitriles. Their general methods of synthesis, important applications, and transformation have been briefly described. The general overview of *O*-(sulfonyl)hydroxylamine reagents also have been briefly described in this chapter.



Applications of nitrogen containing compounds



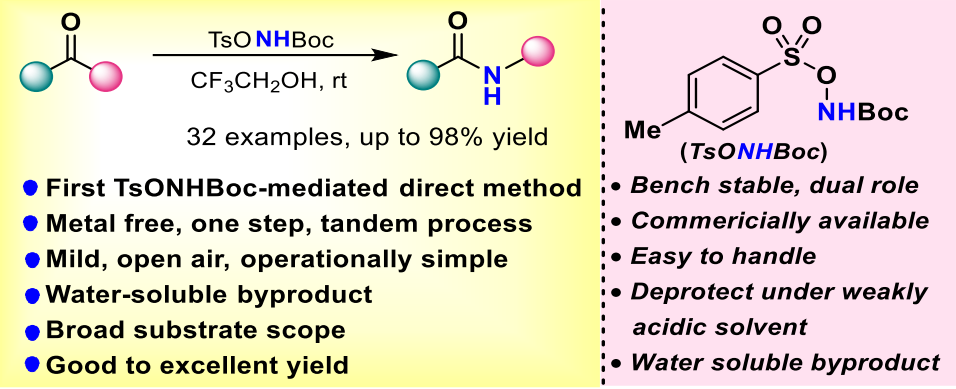
Reactions of *O*-(Substitutedl)hydroxylamine reagents

The experimental investigations and findings are described in the subsequent chapters (Chapters 2-4). Each chapter is individually discussed, and distributed in the introduction, literature review, results and discussions, experimental section, and references.

Chapter 2: Direct and metal-free transformation of ketones into *sec*- amides using TsONH-Boc aminating reagent

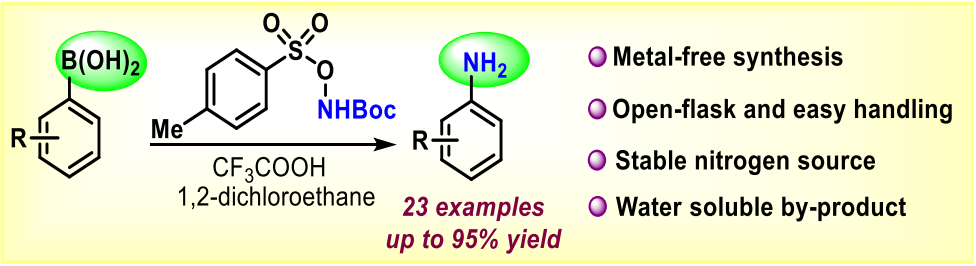
This chapter describes the first methodology for the conversion of ketones directly into the *sec*-amides *via* Beckmann rearrangement using TsONHBoc as the nitrogen source. It is anticipated that this reagent played dual roles: first, it promoted the generation of the activated oxime intermediate, and then the facile formation of amides. The additive

and metal-free direct method works in weakly acidic solvent and generated water soluble byproduct (TsOH).



Chapter 3: **Direct and metal-free transformation of aryl boronic acid into aromatic amines using *N*-Boc-*O*-tosylhydroxylamine reagent**

This chapter describes the direct and metal-free method for the synthesis of aromatic amines from aromatic boronic acids and esters by using the TsONHBoc as an aminating reagent.



This reagent is extremely stable, easy to use, and produces a non-interfering by-product (*i.e.* TsOH) that is easily removed by an aqueous workup. Under acidic conditions, the method applies to boronic acids having electron-withdrawing as well as electron-donating groups to provide corresponding anilines in good to excellent yields. The existing method could be utilized to obtain aromatic primary amines at the gram scale.

Chapter 4: **Metal-free transformation of aldehydes into nitriles using TsONHBoc reagent**

This chapter describes the economical and practical approach of nitriles from readily available aldehydes using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as an aminating agent. This direct and metal-free synthesis of nitriles with high yields tolerates a wide range of substrates such as aromatic, aliphatic, allylic, heteroaryl, and α,β-unsaturated

aldehydes. Shelf stability, low cost, and ease-handling of TsONHBoc introduces an additional advantage.