SYNTHETIC APPLICATION OF OXYGEN SUBSTITUTED HYDROXYLAMINE REAGENTS IN BECKMANN REARRANGEMENT

Abstract of Thesis
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Abstract of the thesis

The thesis entitled **“Synthetic Application of Oxygen Substituted Hydroxylamine Reagents in Beckmann Rearrangement”** consists of four chapters. The work of the thesis is based on the preparation of *sec*-amides. Amides are a key component in many life-nurturing biological systems and value-added natural products. In addition, amides serve as monomer units for numerous synthetic aliphatic and aromatic polyamides, such as nylon and kevlar. It is one of the most ubiquitous moieties in pharmacological compounds. 25% of the marketed drugs contain amides and the manufacturing of 66% of drug candidates is based on amide bond formation. Amides are prominent and reliable moiety for many living chemical processes due to their remarkable stability, polarity, and structural diversity. The ease of formation, wide occurrence, and stability under an open atmosphere are some of the salient features of the frequent use of amides in synthetic transformations. Conventionally, amides are prepared by stoichiometric activation of acids followed by coupling with amines. These protocols endure low atom-economy and generation of large amounts of waste. In 1886, Beckmann discovered acid-catalyzed conversion of ketoximes to amides, known as Beckmann rearrangement. However, high temperatures and strong acidic conditions used in this reaction are a question of compatibility for sensitive functional groups. As amide groups have a preponderance in every aspect of chemical science, organic chemists focused on a quest for catalytic and sustainable methods. Despite a myriad of developed procedures, major highlights involved a two-step process for amide synthesis from isolated oximes with transition metals and costly reagents. In this regard, we wish to contribute to the mild and single-step conversion of ketones to amides through in situ-generated oximes with *O*-substituted hydroxylamines. These reagents are recognized as a versatile choice for the selective introduction of nitrogen in organic reactions such as C-H amination, aziridination, hydroamination, and *vic*-functionalization.

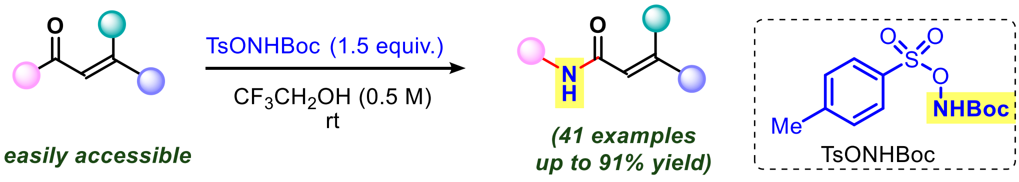
Chapter 1: General overview of *sec*-amides and their synthesis via Beckmann rearrangement

This chapter describes a brief introduction of the structures, properties, and general application of amides. This part of the thesis summarizes the synthetic transformations of amides and their conventional synthesis. A historical overview of the preparation

of *sec*-amides *via* Beckmann rearrangement explains the well-exploration of oximes to *sec*-amides synthesis. Whereas, only a few methods are available for the direct conversion of ketones to *sec*-amides.

Chapter 2: The first direct amidation of *α,β*-unsaturated ketones using *N*-Boc-*O*-tosylhydroxylamine as nitrogen source

The preparation of *α,β*-unsaturated amides are carried out by stoichiometric activation and coupling of carboxylic acids with amines. The general catalytic methods invlove aminocarbonyloation of unsaturated hydrocarbons with transition metal catalyst and carbon monoxide sources. However, the use of metal complexes of Pd, Rh, Ru, and Ti is high in cost and toxic CO gas requires a precise handling. This chapter describes the first direct amidation of widely available *α,β*-unsaturated ketones using *N*-Boc-*O*-tosylhydroxylamine (TsONHBoc) as nitrogen source. TsONHBoc is a bench stable and commercial reagent, which in situ generated highly reactive $TsONH_2$ in weakly acidic 2,2,2-trifluoroethanol (TFE) solvent. Tosylic acid (TsOH), a by-product of this reaction, accelerated the rearrangement of enone oxime intermediates to the desired products. This metal and additive-free process provided chemo-and stereoselective synthesis of *α,β*-unsaturated amides. The present reaction conditions produced the conversion of a variety of mono-, di-, tri-substituted enones and vinyl ketones to their amides in good to excellent yields at room temperature.

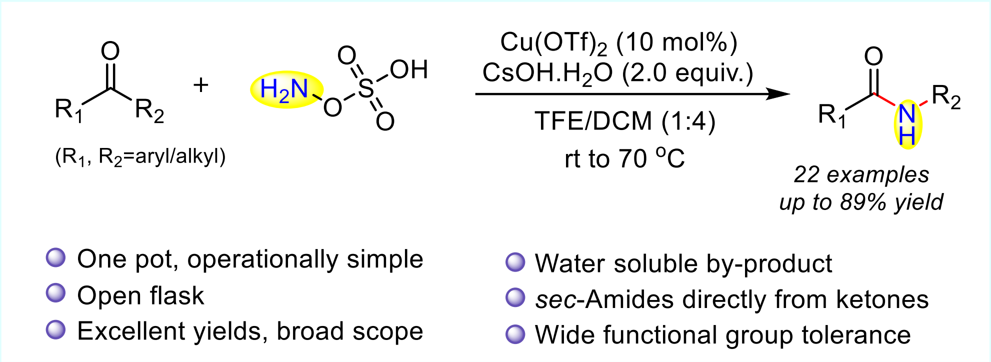


- Bench stable
- Easy to handle
- Commercial
- *N*-Boc deprotection under mild condition

- First direct amidation of *α,β*-unsaturated ketones
- Stereospecific and chemoselective process
- Metal and additive free process
- Three-step tandem process
- Suitable for mono-,di- and tri-substituted enones

Chapter 3: $Cu(OTf)_2$-catalyzed Beckmann rearrangement of ketones using hydroxylamine-*O*-sulfonic acid (HOSA)

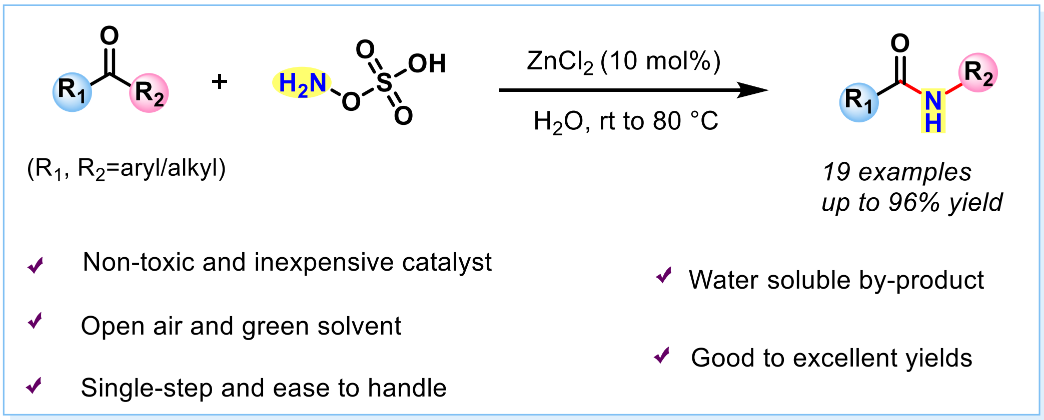
The present work describes $Cu(OTf)_2$-catalyzed synthesis of secondary amides directly from ketones *via* Beckmann rearrangement (BKR). Hydroxylamine-*O*-sulfonic acid (HOSA) is a commercial and user-friendly nitrogen source that produces a water-soluble byproduct. In addition to the tolerance of various aryl ketones containing reactive functional groups, the present method is also compatible with aliphatic cyclic and acyclic ketones, providing good to excellent yields of the amides.



- One pot, operationally simple
- Open flask
- Excellent yields, broad scope
- Water soluble by-product
- *sec*-Amides directly from ketones
- Wide functional group tolerance

Chapter 4: Zinc(II)-catalyzed synthesis of secondary amides from ketones *via* Beckmann rearrangement using hydroxylamine-*O*-sulfonic acid in aqueous media

This work describes a simple zinc(II)-catalyzed direct Beckmann rearrangement of ketones in water under an open atmosphere using hydroxylamine-*O*-sulfonic acid (HOSA) as the aminating agent. The mild condition did not require any harsh or expensive additives. After a basic aqueous workup, this catalytic system afforded the secondary amides in pure form with 62-96% yields.



- ✓ Non-toxic and inexpensive catalyst
- ✓ Open air and green solvent
- ✓ Single-step and ease to handle
- ✓ Water soluble by-product
- ✓ Good to excellent yields