

Investigation of carbene-based transition-metal-catalyzed cross-coupling and metal-free reactions of N-tosylhydrazones derived from (R)-4-amino Uhle's ketone crucial for the preparation of ergot alkaloids.

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Introduction

Ketones and aldehydes play central roles in organic synthesis. There are numerous broadly used reactions that are related to the carbonyl reactivity, such as Grignard reactions, Wittig reactions, aldol reactions, and so on. In addition, the formation of enol triflates is a classic protocol that enables the ketones to be applied in transition-metal-catalyzed cross-coupling reactions, in which case the ketones are considered as the precursors of alkenyl electrophiles in the C–C bond-forming transformations. In the past decade, a new type of ketone- or aldehyde-based C–C bond-forming transformations has emerged. In this type of reactions, the ketones or aldehydes are first converted to their corresponding stable N-tosylhydrazones, which are employed as reaction partners in various transition-metal-catalyzed and metal free carbene-based cross-coupling reactions.¹ So, the N-tosylhydrazone-based carbene couplings significantly enhance the potential of ketones and aldehydes in modern organic synthesis.

Aim of the project

This proposal project aims to give an overview of carbene coupling reactions with N-tosylhydrazones derived from (R)-4-amino Uhle's ketone, recently reported,² from the viewpoint of exploring new potentials for the preparation of ergot alkaloids. In particular, carbene-based transition-metal-catalyzed and metal-free cross-coupling reactions are a relatively unexplored field and it would be interesting to better investigate this kind of reactions on a versatile and functionalized ketone as (R)-4-amino protected Uhle's ketone. N-tosylhydrazones, which are readily derived from ketones or aldehydes via simple condensation with N-tosylhydrazine, have been used since 1950s in organic chemistry to synthesize functionalized olefins via Shapiro, Bamford–Stevens reactions as well as Caglioti reaction but also, more recently to produce various bioactive heterocycles from transition-metal-catalyzed reactions which proceed through the in situ generated diazo intermediates. So, the N-tosylhydrazones are stable coupling partners in cross-coupling processes. The common features of this type of coupling are the formation of a diazo compound in situ, followed by metal carbene formation and carbene migratory insertion. Along these lines that the project is focused.

Methodology and description of the research in the three-year period

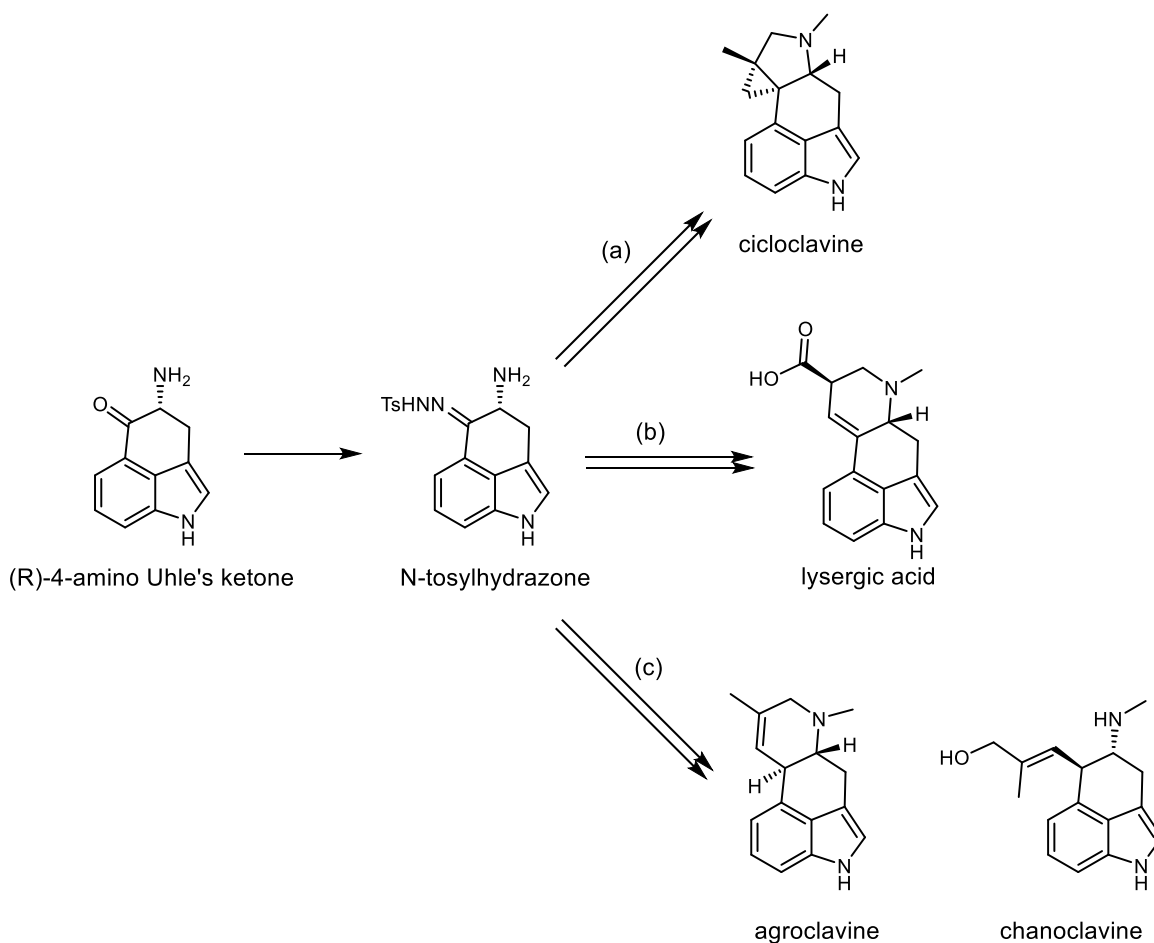
After generation of a N-tosylhydrazone, derived from (R)-4-amino Uhle's ketone and N-tosylhydrazine, with the aim of functionalize the (R)-4-amino Uhle's ketone and obtain various compounds such as ergot alkaloids, I would like to set up different kinds of transition-metal-catalyzed cross-coupling reactions of N-tosylhydrazone.

N-tosylhydrazone, as a species of carbene, could undergo to reactions of cyclopropanation, insertion into a C-H, N-H, O-H bonds, combination with a nucleophile, rearrangements, etc. Furthermore, recent publications show how chemistry of these compounds has expanded greatly, making many different reactions possible starting from N-tosylhydrazones.¹

I would like to exploit the chemistry of N-tosylhydrazones to gain various ergot alkaloids. For example, setting up a cyclopropanation (in presence of double bonds and a metal as catalyst) we could obtain intermediates crucial for preparation of natural products such as cicloclavine (a). With olefinations we could gain intermediates useful for the synthesis of molecules such as lysergic acid (b). NH-Boc intramolecular insertion could lead to a N-Boc aziridine which could react with carbon nucleophiles to give regioselective intermediates for the preparation of ergot alkaloids such as chanoclavine and agroclavine (c).

I'd like to investigate the use of different metals as catalysts (for example Rhodium or cheaper metals such as Copper) in the reactions previously mentioned.

It would be also interesting to focus on N-tosylhydrazone mediated transition-metal-free reactions. Barluenga and co-workers³ developed an efficient metal-free carbon-carbon bond-forming coupling between tosylhydrazones and boronic acids. They show a reaction with a good tolerance for different functional groups; I'd like to extend this reaction to the N-tosylhydrazone derived from (R)-4-amino Uhle's ketone.



Expected results

Finding good transition-metal-catalyzed or metal free reactions of N-tosylhydrazones derived from (R)-4-amino Uhle's ketone would be useful to gain crucial intermediates for the preparation of various ergot alkaloids and other compounds.

It could be considered as a "green" synthetic strategy compared to the other existing procedures as N-tosylhydrazones have very good properties; they are non-toxic, non-hazardous and vary easily produced.

References

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