A flexible method for the synthesis of 2-substituted 1,2,5,6-tetrahydropyridines and piperidines from chloro-containing propargylamines

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A flexible method for the synthesis of 2-substituted 1,2,5,6-tetrahydropyridines and piperidines from chloro-containing propargylamines

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Abstract

A general approach for the stereoselective synthesis of 2-substituted 1,2,5,6-tetrahydropyridines and piperidines is described. The addition of 4-chloro-1-butyne to Ellman sulfinimines to produce chloro-containing propargylamines, reduction with Lindlar catalyst, and cyclization using LHMDS provides efficient, stereoselective access to diverse 2-substituted 1,2,5,6-tetrahydropyridines. For substrates incompatible with the LHMDS cyclization reaction conditions removal of the sulfinamide moiety and cyclization with Cs_2CO_3 allows the preparation of the corresponding 2-substituted 1,2,5,6-tetrahydropyridines. This method can be extended to the synthesis of 2-substituted piperidines through reduction of the chloro-containing propargylamine with PtO_2.

Keywords

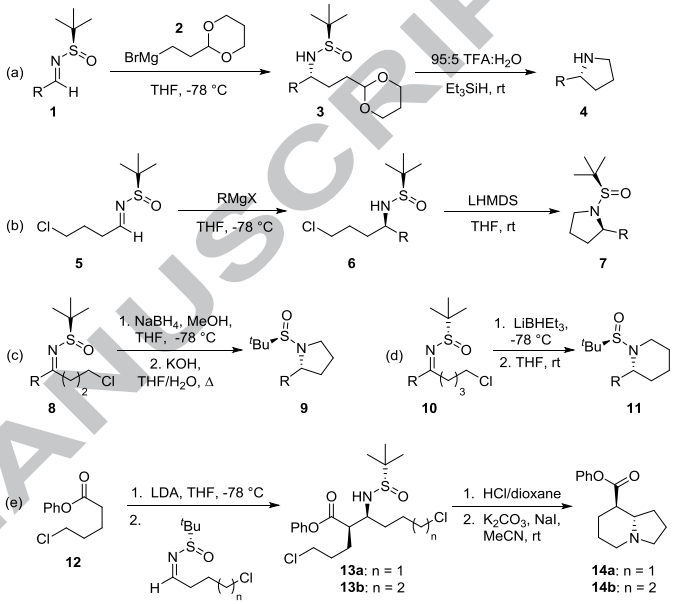
1,2,5,6-Tetrahydropyridine; Piperidine; Stereoselective; Propargylamine; Azaheterocycle

Introduction

The development of new methodologies for the synthesis of chiral 2-substituted pyrrolidines and piperidines has been the subject of extensive investigation due to their prevalence in alkaloid natural products[1] and their importance in medicinal chemistry.[2] With the development of the Ellman *N-tert*-butanesulfinamide auxiliary for the stereoselective synthesis of chiral amines,[3] a robust and versatile strategy for the preparation of chiral 2-substituted azaheterocycles of various ring sizes utilizes the addition of organometallic reagents to Ellman *N-tert*-butanesulfinyl (*N-t*-BS) imines to yield chiral amines capable of cyclization.[4,5a]

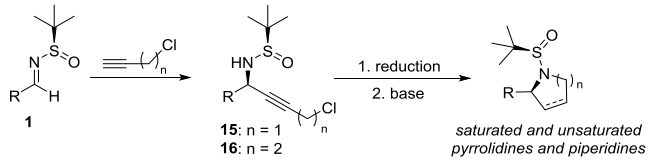
This approach was first demonstrated by Ellman and coworkers (Scheme 1a) in the addition of acetal Grignard reagent **2** to imine **1** to generate pyrrolidine precursor **3** which can undergo reductive amination under acidic conditions to form the pyrrolidine ring **4**.[4a] A complementary approach utilizing γ-chlorinated *N-t*-BS imines **5** was later developed by Reddy and coworkers in which chiral 2-substituted pyrrolidines were accessed via diastereoselective Grignard addition to **5** and base-promoted cyclization (Scheme 1b).[4b] This method was later successfully extended to δ- and ε-chlorinated *N-t*-BS imines to achieve the synthesis of the piperidine and azepane ring systems.[4e,f] In addition to these approaches, the reduction and cyclization of *N-t*-BS γ- and δ-chlorinated ketimines has also been frequently exploited for the synthesis of pyrrolidines and piperidines (Scheme 1c,d).[4c,d,g]

In contrast to these methodologies (Scheme 1a-d), a much less utilized approach for the preparation of chiral azaheterocycles involves the addition of a halogen containing nucleophile to *N-t*-BS imines. Brown and coworkers have demonstrated the successful application of this strategy in the addition of chloro-containing enolates to γ- and δ-chlorinated *N-t*-BS imines (Scheme 1e).[5a] The resulting chloro-containing imino-aldol adducts **13a** and **13b** can readily undergo a double cyclization reaction after removal of the sulfinamide group to achieve the indolizidine (**14a**) and quinolizidine (**14b**) ring systems.



Scheme 1. Strategies for chiral azaheterocycle formation utilizing the *N-tert*-butanesulfinamide auxiliary.

Due to the fact that the majority of existing methodologies for chiral azaheterocycle synthesis employing *N-t*-BS imines incorporate the halogen within the electrophile, we argue that the addition of halogen containing nucleophiles to *N-t*-BS imines remains underutilized. To expand the scope of halogen containing nucleophiles that can be utilized for azaheterocycle synthesis we envisioned employing halogenated acetylide nucleophiles as shown in Scheme 2. Addition of chloro-containing alkynes to *N-t*-BS imines, reduction of the propargylamine intermediates, and cyclization under basic reaction conditions would furnish 2-substituted pyrrolidines and piperidines (Scheme 2). We deemed this strategy attractive as it affords access to multiple ring sizes through variation of the alkyne chain length. Furthermore, it can be easily adapted to the synthesis of saturated or unsaturated 2-substituted azaheterocycles through partial or complete reduction of the acetylenic bond. In particular, we viewed unsaturated azaheterocycles as useful precursors for the synthesis of more highly functionalized pyrrolidine and piperidine ring systems.[1e]



Scheme 2. Chloro-containing propargylamines for the synthesis of saturated and unsaturated pyrrolidines and piperidines.