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ORIGINAL PAPER

Synthesis of novel multi-functionalized pyrrolidines by [3 + 2] dipolar cycloaddition of azomethine ylides and vinyl ketones

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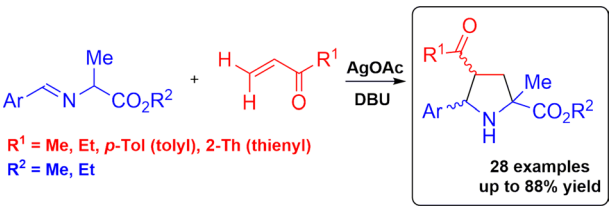
Abstract

An efficient and easy synthetic route to substituted pyrrolidine derivatives has been established through [3 + 2] dipolar cycloaddition of vinyl ketones and azomethine ylides. The reactions proceed smoothly, under mild conditions, affording moderate to high isolated yields (up to 88%) of the products, within a short reaction time (15–45 min), providing a series of novel potentially bioactive compounds. Mechanistic considerations revealed that this cycloaddition exclusively proceeds following *endo*-pathway which enables access to the *cis*-derivatives. The products that contain acetyl group at C4 easily undergo isomerization, as it was confirmed by monitoring of the reaction kinetics and DFT calculations.

Graphical abstract



Keywords Cycloadditions · Enones · Ylides · Heterocycles

Introduction

Pyrrolidine, as frequent structural motif in natural products, occupies significant place in organic, medicinal, and pharmaceutical chemistry [1–4]. It is widely present in biologically active molecules and pharmaceutical drug candidates, classifying pyrrolidine derivatives as a group of attractive synthetic targets. Consequently, these five-membered heterocycles are useful building blocks in the organic synthesis [5–13]. Pyrrolidine's ring is a key structural fragment of L-proline and other organocatalysts derived from it [14–17]. Pyrrolidine-containing compounds also exert the broad spectrum of potential therapeutic properties like analgesic [18], antibacterial [19–21], antitumor [22], anti-inflammatory [23, 24], and enzyme inhibiting [25].

Over the past 3 decades, several synthetic routes toward pyrrolidine core were developed [26–30], and pathways based on [3 + 2] dipolar cycloadditions prevail as the most suitable and used [31]. The leading species employed for this purpose are azomethine ylides acting as dipoles. Wide range of dipolarophiles like α,β-unsaturated carboxylic derivatives [32–50], nitroalkenes [51–57], alkenylsulfones [58–66], enones [67–70], and allenes [71–73] were examined,

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