



Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: [www.elsevier.com/locate/tetlet](http://www.elsevier.com/locate/tetlet)

## Iridium catalyzed three component cycloaddition cascades to fused ring heterocycles

Jamie Hunter, Christopher M. Pask, Visuvanathar Sridharan \*

School of Chemistry, University of Leeds, LS2 9JT, UK

### ARTICLE INFO

#### Article history:

Received 14 April 2016

Revised 27 April 2016

Accepted 9 May 2016

Available online xxxxx

#### Keywords:

Iridium

Dehydrogenation

1,3-Dipolar cycloaddition

Azomethine ylide

Multicomponent reaction

### ABSTRACT

A three component iridium-catalyzed 1,3-dipolar cycloaddition reaction has been used for the synthesis of fused ring heterocycles as *endo/exo* isomers, in good yields with the formation of three new bonds and four stereo centers.

Crown Copyright © 2016 Published by Elsevier Ltd. All rights reserved.

Bicyclic pyrrolidines are important heterocycles and form the structural skeletons of a wide range of compounds which exhibit bioactivities for a variety of medical conditions. Some of these medicinal properties include HIV inhibitors,<sup>1</sup> as well as antifungal, antibacterial,<sup>2</sup> and antithrombotic activities<sup>3</sup> (Fig. 1).

It has become increasingly more important in the drug discovery process that new facile methods are developed in which more complex variants of these heterocyclic scaffolds may be produced in 'greener' ways. This can be achieved by using more selective methods where the number of steps involved and the amount of solvents used and waste produced are reduced, allowing the process to be more efficient and environmentally friendly.

Nonstabilized azomethine ylides are highly reactive intermediates. Classical methods to generate nonstabilized azomethine ylides include desilylation of the methyl iminium ion,<sup>4</sup> reaction of *N*-oxides with strong base,<sup>5</sup> and condensation of  $\alpha$ -amino acids with carbonyl compounds.<sup>6</sup>

Our group and others have been involved in generating stabilized and non-stabilized azomethine ylides and subsequent 1,3-dipolar cycloaddition reactions either via a metal catalyzed route or a thermal decarboxylation pathway.<sup>6,7</sup>

Indirect functionalization of alcohols using catalytic amounts of a metal complex and base which generates only water as a by-product is an attractive green alternative to standard C–C and C–N bond forming reactions. These cascades are termed as redox–neutral,

hydrogen auto transfer or hydrogen borrowing processes. Our group and others have been involved in the alkylation of amines and active methylene compounds using alcohols catalyzed by iridium, rhodium, and ruthenium complexes, to form new C–N and C–C bonds.<sup>8</sup>

In this communication we report a novel one-pot three component iridium catalyzed dehydrogenation/1,3-dipolar cycloaddition cascade utilizing alcohols to generate fused-ring heterocycles with the formation of three new bonds and four stereo centers (Scheme 1, path A).

The initial reaction was performed using 3,4-dimethoxybenzylalcohol (1 mmol), *L*-proline (1.5 mmol), *N*-methylmaleimide (2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.2 mmol), and [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (0.05 mmol) in

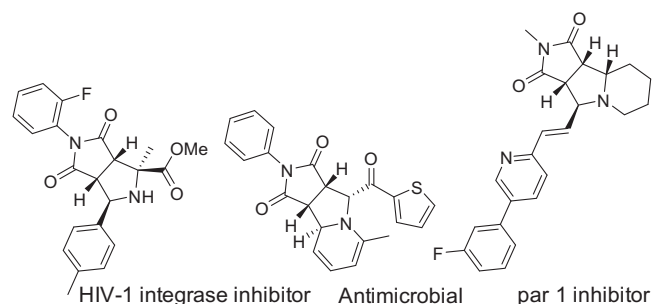
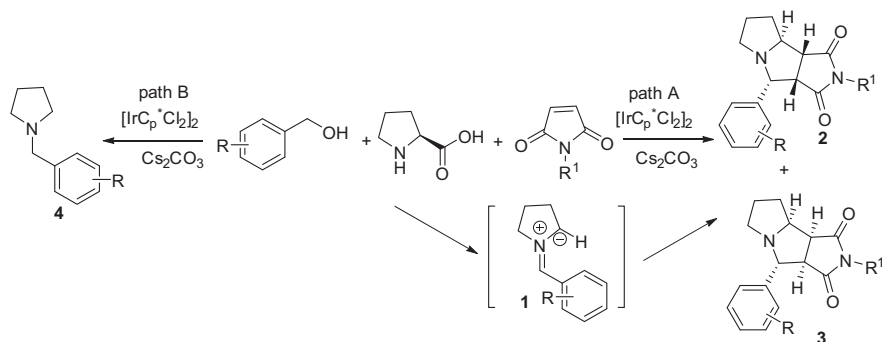


Figure 1. Bioactive bicyclic pyrrolidines.

\* Corresponding author. Tel.: +44 1133436520.

E-mail address: [V.Sridharan@leeds.ac.uk](mailto:V.Sridharan@leeds.ac.uk) (V. Sridharan).



Scheme 1. Ir-catalyzed three component cycloaddition cascade.

**Table 1**  
Iridium catalyzed three component cycloaddition reaction<sup>a</sup>

Entry	Alcohol	Product	Yield <sup>b</sup> (%)
1			73
2			60
3			52
4			60
5			38
6			51 <sup>c</sup>

<sup>a</sup> Dipolarophile (2 mmol), L-proline (1.2 mmol), an alcohol (1 mmol), Cs<sub>2</sub>CO<sub>3</sub>, (20 mol %), and [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (5 mol %) toluene (10 mL) were stirred under reflux (110 °C 24 h).

<sup>b</sup> Isomers were separated and isolated total yield.

<sup>c</sup> Only major isomer was isolated.

Download English Version:

<https://daneshyari.com/en/article/5266702>

Download Persian Version:

<https://daneshyari.com/article/5266702>

[Daneshyari.com](https://daneshyari.com)