

# Diversity synthesis of indolizidine alkaloids from $\alpha,\beta$ -unsaturated diazoketones by the Wolff rearrangement.

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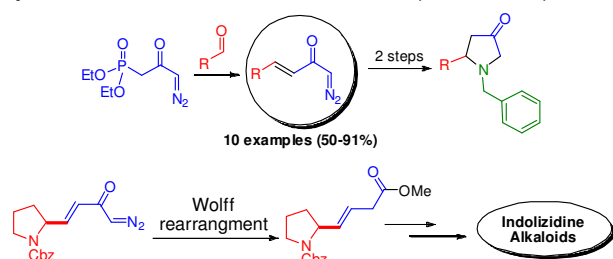
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## INTRODUCTION

Diazocarbonyl compounds are important reagents in organic synthesis.<sup>1</sup> Among these reagents,  $\alpha,\beta$ -unsaturated diazoketones have proven to be very promising as multi-functional intermediates, but they usually are difficult to prepare by common methods. Recently, we reported a general and straightforward methodology to prepare these important synthetic substrates and its application in the synthesis of pyrrolidine alkaloids<sup>2</sup> (scheme1). Herein, we report another utility of these  $\alpha,\beta$ -unsaturated diazoketones applying the Wolff rearrangement in the short synthesis of indolizidines alkaloids (Scheme 1).



**Scheme 1.** Synthesis and application of  $\alpha,\beta$ -unsaturated diazoketones.

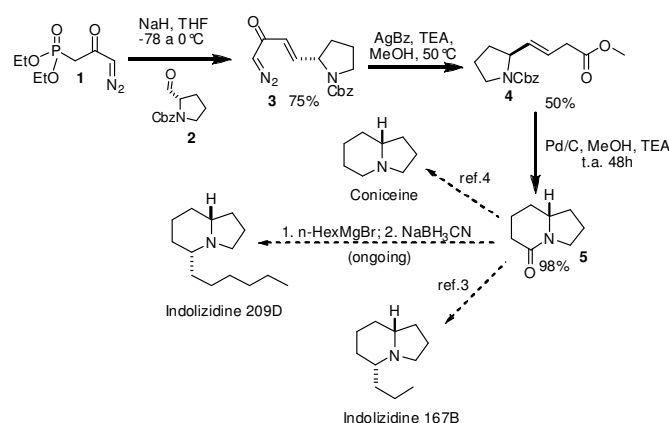
## RESULTS AND DISCUSSION

To begin our investigation,  $\alpha,\beta$ -unsaturated diazoketone **3** (Scheme 2) was prepared in 75% yield employing the protocol described in our recent report<sup>2</sup> (Horner-Wadsworth-Emmons reaction between aldehyde **2** and diazophosphonate **1**). Treatment of diazoketone **3** with silver benzoate as catalyst, in the presence of triethylamine and methanol at 50 °C, furnished the Wolff rearrangement product **4** in 50% yield (not optimized).

**Table 1.** Silver-mediated Wolff rearrangement from **3**.

| entry | catalyst          | solvent  | T (°C) | Yield (%) |
|-------|-------------------|----------|--------|-----------|
| 1     | AgBz              | MeOH/TEA | 25     | 30        |
| 2     | AgBz              | MeOH/TEA | 50     | 50        |
| 3     | Ag <sub>2</sub> O | MeOH     | 25     | -         |
| 4     | Ag <sub>2</sub> O | MeOH     | 50     | 20        |

Next, compound **4** was submitted to hydrogenolysis in the presence of H<sub>2</sub>/Pd and TEA as base, affording lactam **5** in 98% yield and in one step (after deprotection, reduction and cyclization). Lactam **5** is an advanced intermediate in the synthesis of some indolizidine alkaloids such as Indolizidine 167B and Coniceine.<sup>3,4</sup>



**Scheme 2.** Formal syntheses of Indolizidine 167B and coniceine.

## CONCLUSION

As a conclusion, we have demonstrated that  $\alpha,\beta$ -unsaturated diazoketones are powerful bifunctional reagents for the short synthesis of indolizidine alkaloids employing the Wolff rearrangement. At the moment, the use of others silver catalysts to improve the yields of the Wolff rearrangement and the synthesis of other indolizidine alkaloids are being investigated.

## ACKNOWLEDGEMENTS

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