Synthesis of Piperidines from *Z*-α,β-Unsaturated Diazoketones

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INTRODUCTION

Piperidine systems are highly widespread in many natural products of great pharmaceutical interest.[1] These systems have many interesting biological activities, such as anticancer and anti-HIV.[2] In this work, we describe the stereoselective preparation of *Z*-α,β-unsaturated diazoketones from aldehydes and their conversion to substituted dihydropyridin-3-ones like **3** in just one step after an intramolecular N-H insertion reaction. The application of this chemistry in the direct synthesis of the natural 3,4,5-trihydroxypiperidine **4** is also described (Fig 1).

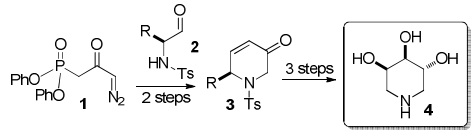


Fig. 1. Direct synthesis of Piperidine systems.

RESULTS AND DISCUSSION

Three new Ando-type phosphonates, containing a diazo group, were synthesized (Fig. 2) and employed in the HWE reaction (Tab 1), aiming the preparation of the *Z*-unsaturated diazoketones.

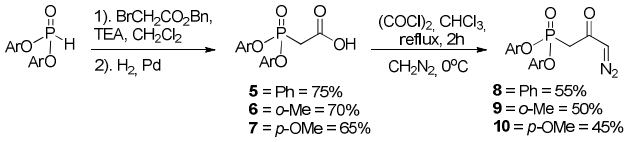
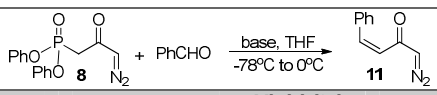


Fig. 2. Synthesis of diazophosphonates.

First, we studied the preparation of the *Z*-α,β-unsaturated diazoketones, using benzaldehyde as a model in the HWE reaction.

Table 1. Optimization of HWE reaction to *Z*-α,β-unsaturated diazoketones synthesis.



Entry	Base	Yield (%)	*Z*:*E* ratio[a]
1	NaH	63	7:3
2[b]	NaH	97	7:3
3	DIPEA	11	1:1
4	BuLi	41	6:4
5	*t*-BuOK	92	9:1
6[c]	*t*-BuOK	80	8:2

[a]Measured by ^{1}H NMR. [b]2 equiv. of the phosphonate anion was employed. [c]3 equiv. of 18-crown-6 ether was used as additive.

Next, to show the scope of the methodology, new *Z*-α,β-unsaturated diazoketones with aliphatic, aryl and amino groups were prepared in good yields and selectivity (Fig. 3).

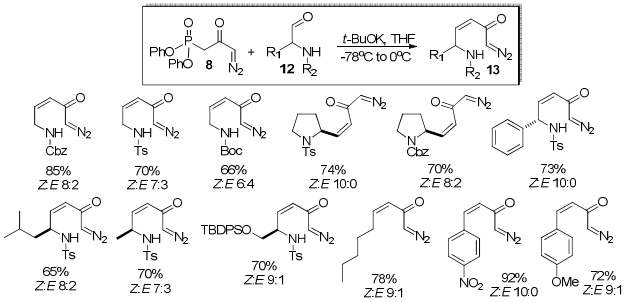


Fig. 3. *Z*-α,β-unsaturated diazoketones from HWE reaction.

These diazoketones were converted to substituted dihydropyridin-3-ones after an intramolecular N-H insertion reaction and applied to the synthesis of (+/-)-(3*R*,5*R*)-piperidine-3,4,5-triol **4**, an α-glycosidase and β-galactosidase inhibitor isolated from *Eupatorium fortunei TURZ*[3] (Fig. 4).

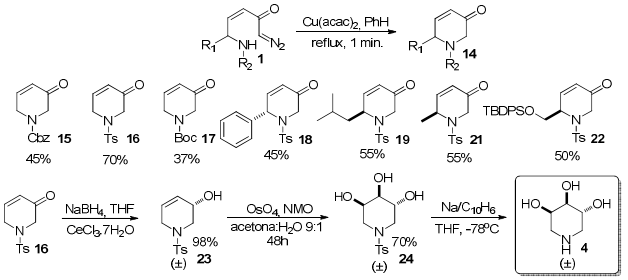


Fig. 4. N-H insertion reaction and synthesis of (+/-)-(3*R*,5*R*)-piperidine-3,4,5-triol.

CONCLUSION

We have developed a two-step method for the easy access to highly functionalized piperidine systems, such as dihydropyridin-3-ones, from aldehydes[4]. The sequence is direct and permits the synthesis of several types of hydroxylated piperidines.

ACKNOWLEDGEMENTS

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