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[A0022]

Asymmetric Synthesis of Functionalized Prolines by Diastereoselective 1,3-Dipolar Cycloaddition Using Chiral Oxazinone Derivatives

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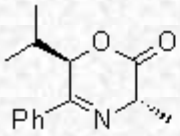
Abstract: The reaction of (5*S*,6*S*)-6-isopropyl-5-phenyl-1,4-oxazin-2-ones from glycine and alanine with formaldehyde in the presence of electron-deficient olefins afforded the corresponding adducts obtained by a diastereoselective 1,3-dipolar cycloaddition of the chiral azomethine ylids. Hydrolysis of these adducts allows the synthesis of enantiomerically enriched functionalized prolines.

Keywords: Amino acids, oxazinones, 1,3-dipolar cycloadditions, prolines

Introduction

The a -amino acids derived from proline, for example the kainic acid derivatives, present an array of interesting biological properties [1]. The most direct strategy for the synthesis of these functionalized prolines is the 1,3-dipolar cycloaddition reaction of azomethine ylids with electron-deficient olefins [2]. The asymmetric synthesis of these amino acids has been developed using unprotected saturated oxazinones, which have been employed as precursors of the corresponding chiral azomethine ylid dipoles upon reaction with aldehydes, mainly formaldehyde [2].

Recently, we have prepared chiral 3,6-dihydro-2*H*-1,4-oxazin-2-ones derived from alanine and glycine, which have been used as templates for the asymmetric synthesis of different a -amino acids [3,4]. We report now the use of these heterocycles for the preparation of chiral saturated oxazinones and their use in diastereoselective 1,3-dipolar cycloaddition reactions for the asymmetric synthesis of functionalized prolines.



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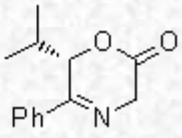
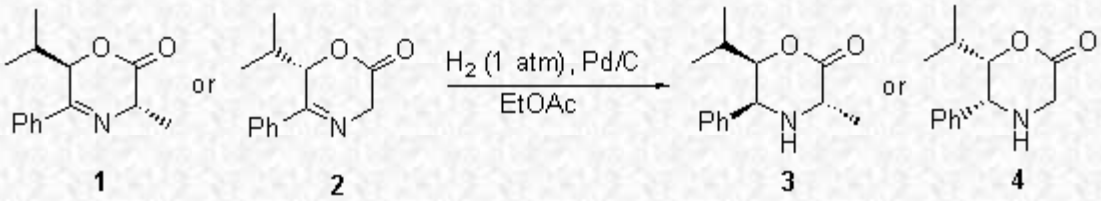


2

Results and Discussion

Oxazinones **1** and **2** were prepared as reported [3,4] and hydrogenated [4b,5] to afford the corresponding saturated oxazinones **3** and **4** in 99 and 70% yield, respectively (Scheme 1).

Scheme 1



Reaction of oxazinones **3** and **4** with mono- and di-substituted olefins or acetylenes with electron-withdrawing groups in the presence of paraformaldehyde afforded the corresponding adducts **6** from a 1,3-dipolar cycloaddition reaction through the intermediate azomethine ylid **5** (see Scheme 2 and Table 1). The pure major adducts were isolated by column chromatography and their configuration determined by NOE experiments, resulting products of an *endo* approach. The reaction took place with good diastereoselectivity relative to the phenyl and isopropyl groups.

Scheme 2

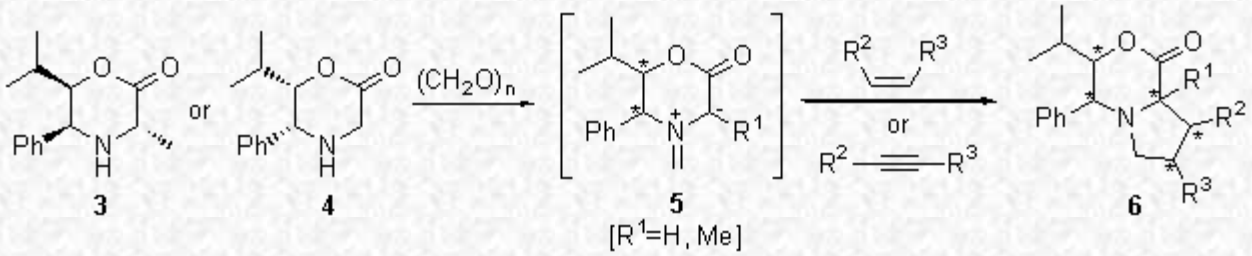
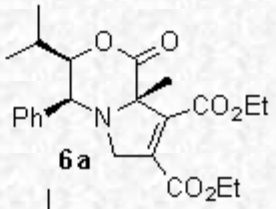
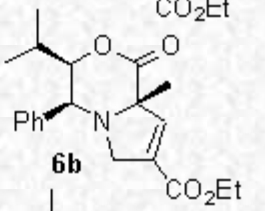
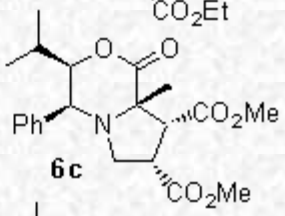
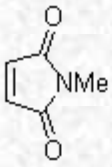
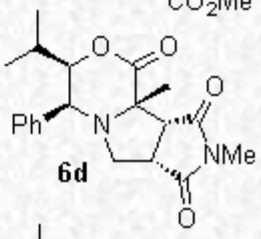
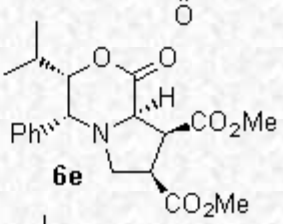
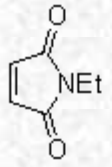
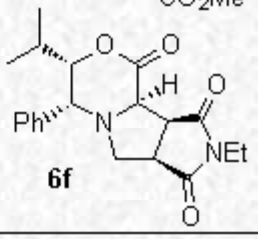


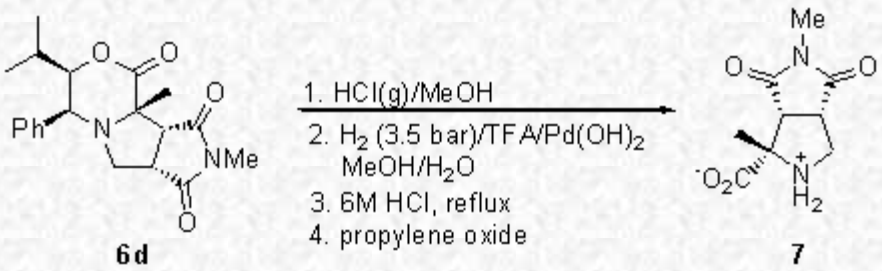
Table 1

Oxazinone	Dipolarophile	t (h)	dr[a]	Adduct **6**[b]	Yield (%)[c]
3	$EtO_2C-\equiv-CO_2Et$	3	99:1	 **6a**	75
3	$\equiv-CO_2Et$	3	96:4	 **6b**	44
3	MeO_2C CO_2Me	24	91:9	 **6c**	33
3		6	77:17:6	 **6d**	32
4	MeO_2C CO_2Me	2.5	85:8:7	 **6e**	81
4		6	55:25:20	 **6f**	30

[a] From the reaction crude (^{1}H NMR, 300 MHz). [b] Major adduct. [c] Isolated yield of the major adduct after column chromatography.

Hydrolysis of adducts **6** allowed the synthesis of functionalized prolines. For example, adduct **6d** was transesterified with HCl (g)/MeOH and hydrogenated at 3.5 bar in the presence of $Pd(OH)_2$ on carbon and TFA [6]. Subsequent hydrolysis with refluxing 6M HCl and treatment with propylene oxide afforded proline derivative **7** (Scheme 3).

Scheme 3



6d **7**

Conclusions

We have prepared chiral saturated oxazinones from alanine and glycine which react with electron-deficient olefins and acetylenes in the presence of paraformaldehyde to give adducts from a diastereoselective 1,3-dipolar cycloaddition reaction. These adducts can be employed for the preparation of functionalized prolines.

Experimental part

General procedure for the cycloaddition reaction: A suspension of the corresponding dipolarophile (5 mmol) and paraformaldehyde (10 mmol, 300 mg) in toluene (25 mL) was heated at 80?C and a solution of the oxazinone **3** or **4** (1 mmol) in toluene (10 mL) was added dropwise. The reaction mixture was stirred at 80?C until completion (GC), cooled at room temperature and filtered through a plug of silica gel (AcOEt). The solvents were evaporated (15 Torr) and the residue was purified by column chromatography (hexane/AcOEt gradients).

Physical and spectroscopical data of adduct **6d** follows:

TLC (Hexane/EtOAc 1:1): Rf 0.37.

$[a]_D^{25}$ +44.0 (*c*, 1; CH_2Cl_2).

M. P. 210-211 ?C.

IR (KBr): 1732 and 1704.

1H-NMR (300 MHz, $CDCl_3$): 0.76 (d, J=6.8Hz, 3H), 1.09 (d, J=6.8Hz,3H), 1.58 (s, 3H), 1.74 (m, 1H), 2.99 (s, 3H), 3.31 (m, 2H), 3.52 (m, 2H), 3.89 (d, J=4.2Hz, 1H), 4.16 (t, J=4.2, 1H), 7.21 (m, 2H) and 7.35 (m, 3H).

13C-NMR (75 MHz, $CDCl_3$): 17.84, 21.11, 25.15, 25.46, 28.30, 43.45, 53.35, 56.27, 63.22, 68.79, 86.71, 128.11, 128.45, 128.97, 136.29, 169.12, 175.84 and 178.30.

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