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Novel Chiral Templates for 1,3-Oxazolium-4-olate (Isomünchnone) Cycloadditions: (5*R*)- and (5*S*)-Phenyloxazin-2,3-dione

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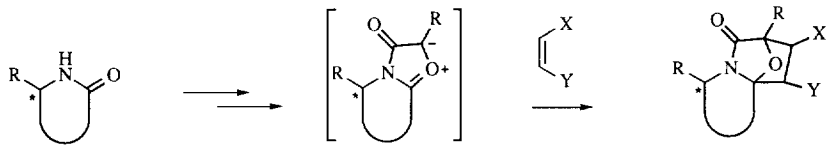
Abstract: Cycloadducts (**4-10**) were synthesised from isomünchnone derivatives of (5*R*)- and (5*S*)-phenyloxazin-2,3-dione by rhodium(II)-catalysed decomposition. High *endo*/*exo*-selectivities for additions to carbon-carbon dipolarophiles were observed.

The cycloaddition chemistry of carbonyl-ylides in organic synthesis has been studied extensively[1] and used for efficient constructions of core skeletons of biologically important molecules and for the synthesis of enantiopure natural products.[2] Since there had been no report on chirally templated isomünchnone dipolar additions at the outset of our work we wanted to investigate the asymmetric induction of such a system. It was necessary to develop a template model that would produce the required starting materials efficiently, leading to chemo-, regio- and stereoselective cycloadditions with a variety of dipolarophiles (**Scheme 1**). Such cycloadducts have the capacity of subsequent transformations with regeneration of the template.



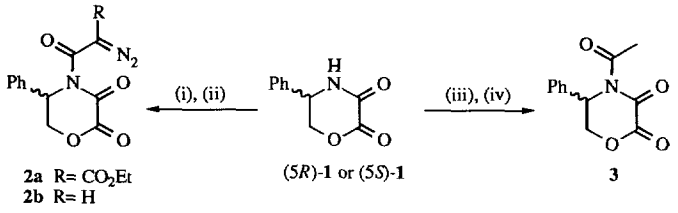
Scheme 1

We had previously described the synthesis of various optically active oxazin-2,3-diones. (5*R*)- or (5*S*)-Phenyloxazin-2,3-dione (**1**) may be prepared from the corresponding antipode of phenylglycinol in two steps in an overall yield of 77 %[3] and so we turned our attention to the use of these substrates in the above process.

Diazoimide **2a** could be prepared in a good yield from (5*R*)-**1** using lithium-hexamethyldisilazane as a base and subsequent addition of ethyl diazomalonylchloride[4] (**Scheme 2**); although the preparation of the parent α-diazocarbonyl compound **2b** (R= H) proved to be problematic. However the use of NaH as base in THF as solvent and succinimidyl diazoacetate[5] as the diazoacetylation reagent led to the product in an isolated yield of 32

%. Several other base/solvent systems were investigated but did not improve the yield and other known standard literature procedures failed to form diazocompound **2b**.

In contrast the formation of the corresponding acetamide **3** occured readily. Analysis of ^{1}H-NMR coupling constants of **2b** and **3**[6] indicated that dihedral angles between the methylene protons on C-6 and the proton on C-5 were close to 90° and X-ray crystallographic data of acetylated derivative **3** (**Figure 1**)[7] confirmed that the molecule exists in a boat-like conformation with the phenyl group in an axial position, in agreement with the observations on similar *N*-acetylated oxazinone systems.[8]



2a R= CO_2Et
2b R= H

(5*R*)-**1** or (5*S*)-**1**

3

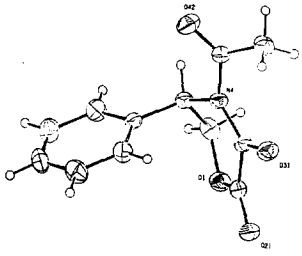
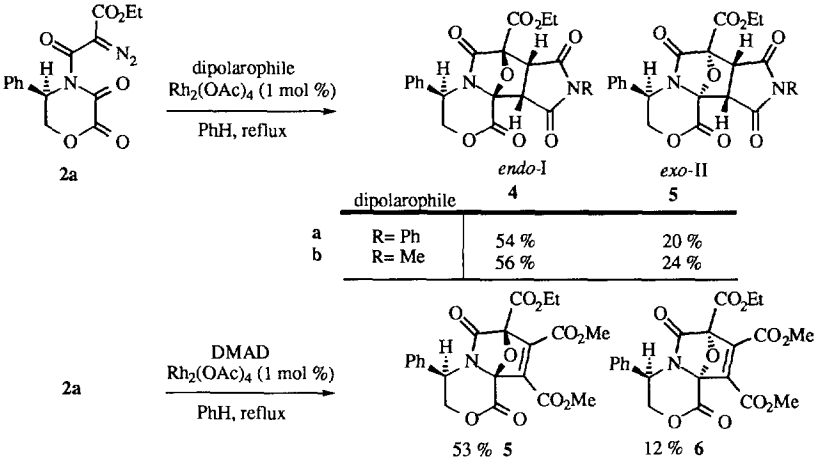


Figure 1

2a: (i) 1.2 eq. LiHMDS, THF, -78°C (ii) ethyl diazomalonyl chloride[4], 66 % **2b:** (i) 3.0 eq. NaH , THF, 0°C (ii) succinimidyl diazoacetate,[5] 32 % (iii) 1.2 eq. LDA, THF, -78 °C (iv) 1.5 eq. acetyl chloride, 90 %.

Scheme 2

For the transformation of the α-diazocarbonyl compounds into isomünchnones the starting material was treated with rhodium(II) acetate (1 mol %) in the presence of a dipolarophile (**Schemes 2** and **3**).[1]

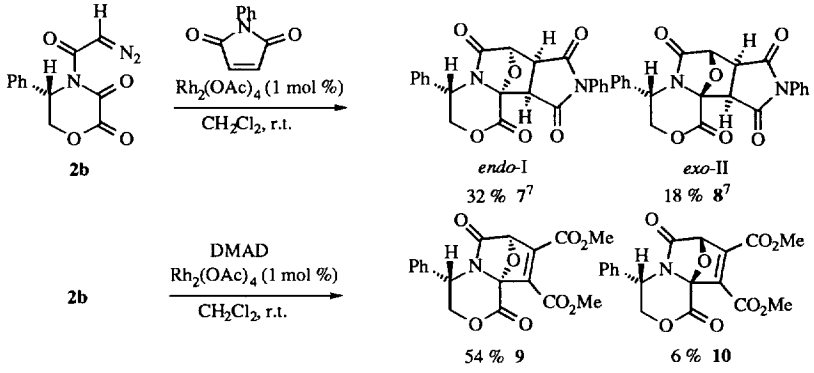


Scheme 3

As shown in **Schemes 3** and **4** the isomünchnones deriving from the diazocompounds **2a** and **2b** were added to maleimide derivatives and DMAD.[9] The best yields were obtained for the additions to maleimide.

All cycloadditions with carbon-carbon dipolarophiles of isomünchnones derived from (5*R*)- or (5*S*)-phenyl-oxazin-2,3-one led to a mixture of two isomers, one as expected by an *endo* attack from the less hindered α-face of the molecule, the other by an *exo* attack on the β-face. The moderate diastereofacial control is not yet fully understood. The observation of *endo*-stereochemistry in the major adduct presumably indicates electronic

control which appears to have been overwhelmed in the minor (*exo*) cycloadducts as a consequence of steric hindrance of the C-5 phenyl-substituent.



Scheme 4

The stereochemistries of the cycloadducts were assigned by evaluation of NOE data and comparison of ^{1}H-NMR data with those of compounds **7** and **8** whose structures were verified by single X-ray crystal structures (**Figure 2**).[7,10]

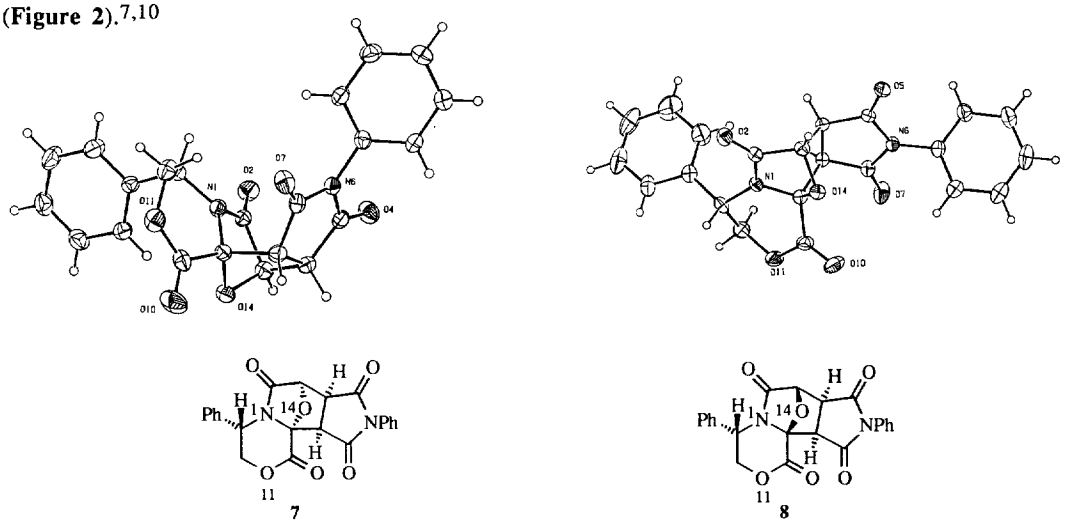


Figure 2

Thus preparation of cycloadducts by a novel templated isomünchnone cycloaddition allows us to study the synthesis of novel enantiopure compounds. Further investigation of the influence of other catalysts than rhodium(II)-acetate on the reaction is in progress.

General procedure for dipolar isomünchnone cycloadditions

Method A : A mixture of diazoimide, dipolarophile and catalytic amount of rhodium(II) acetate (1 mol %) was heated under reflux in benzene until t.l.c. analysis revealed the absence of starting material. The solvent was removed under reduced pressure, the residue redissolved in dichloromethane and the mixture filtered through a pad of Celite® to remove any rhodium residues. Gradient column chromatography permitted isolation of the product(s).

Method B: The starting materials were stirred at r.t. in dichloromethane in the presence of $Rh_2(OAc)_4$. Work-up follows that of Method A.

Acknowledgements

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References and Notes

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6. Selected spectroscopic data **3**: m.p. 185-187°C; $C_{12}H_{11}NO_4$ requires C, 61.88; H, 4.75; N, 6.00; found C, 61.63; H, 5.05; N 6.03. υ_{max} (KBr disc) 2984, 2147, 1774, 1724, 1666, 1072, 984, 934, 746, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42-7.18 (5H, m, Ph), 5.88 (1H, bs, 5-H), 4.88 (1H, dd, *J* 12.1, *J* 2.9 Hz, 6α-H), 4.70 (1H, dd, *J* 12.1, *J* 1.8 Hz, 6β-H), 2.71 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 171.0, 156.0, 154.6, 134.9,, 129.4, 128.9, 125.8, 70.2, 54.2, 27.3; $[\alpha]_D^{19}$ -19.1 (c 0.54, $CHCl_3$). ^{1}H-NMR data of **2b**: δ_H (400 MHz, $CDCl_3$) 7.55-7.20 (5H, m, Ph), 6.96 (1H, s, C(N_2)H), 6.01 (1H, bs, 5-H), 4.89 (1H, dd, *J* 12.1, *J* 2.8 Hz, 6α-H), 4.73 (1H, dd, *J* 12.1,*J* 2.0 Hz, 6β-H).
7. Crystal data (5-*R*-**3**), C_{12} H_{11} N O_4, M = 233.22, monoclinic, $P2_1$, Z = 2, a = 9.964(9), b = 5.905(5), c = 9.423(10) Å, b = 92.35(1)°, U = 554.0 Å; 1026 independent reflections were obtained from 95 2° frames, each collected for 2 minutes on the marresearch Image Plate system. Data analysis was carried out with the XDS program. The structure wasdeterminedby direct methods using Shelx86 and refined (non-heavy atoms anisotropic, hydrogen atoms in calculated positions, isotropic by full matrix least squares on F^2 using Shelxl to R 0.0489.
Crystal data, (**7**), C_{22} H_{16} N_2 O_6, 0.5 CH_2Cl_2, M = 446.82, orthorhombic, $P2_12_12_1$, a = 25.43 (2), b = 10.064 (12), c = 7.944 (9) Å, U = 2033 Å, z = 4, dm = 1.46 gcm^{-3}, F(000) = 294.2385 independent reflections [R(int) = 0.028] were collected on a Marresearch Image Plate. The structure was solved by direct methods and refined by full-matrix least squares (non-hydrogen atoms anisotropic and hydrogen atoms isotropic in calculated positions) to an R of 0.0470 for 2158 data with I>2σ (I).
Crystal data, (**8**), C_{22} H_{16} N_2 O_6, M = 404.37, orthorhombic, $P2_12_12_1$, a = 7.031 (9), b = 12.737 (13), c = 21.03 (2) Å, U = 1883 Å, z = 4, dm = 1.43 gcm^{-3}, F(000) = 840.3197 independent reflections [R(int) = 0,016] were collected on a Marresearch Image Plate. The structure was solved by direct methods and refined by full-matrix least squares (non-hydrogen atoms anisotropic and hydrogen atoms isotropic in calculated positions) to an R of 0.0325 for 2955 data with I>2σ(I). Crystal Data for all structures have been deposited at the Cambridge Crystallographic Data Centre.
8. Dellaria, J., F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916.
9. All novel compounds described had structures in accordance with their spectroscopic data.
10. According to the ^{1}H-NMR of the crude material the cycloadducts **7** and **8** were obtained in a ratio of 53 : 47; the isomers **9** and **10** in a ratio of 76 : 24.

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