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1,3-dipolar cycloadditions of arylnitrile oxides and 2-diazopropane with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives

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ABSTRACT

The reactions of arylnitrile oxides **2** and 2-diazopropane **5** with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives **1** have been studied. 1,3-dipolar cycloaddition of arylnitrile oxides and 2-diazopropane with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives is taking place regiospecifically. The asymmetric induction expected by the chiral centre of the 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives was very effective, diastereoisomers **3** and **4** were formed in an approximate 90:10 ratio. The stereoselectivity of the 1,3-dipolar cycloaddition of the 2-diazopropane with the 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives are investigated. The attack of the 1,3-dipole occurred from the less hindered face of the dipolarophile, giving the isomer **6**.

1. Introduction

The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of heterocyclic compounds [1]. It has a nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step. 1,3-dipolar reactions of alkenes with nitrile oxides and diazoalkanes have been used to prepare isoxazolines and pyrazolines. Isoxazolines are a class of heterocyclic compounds having a remarkable number of applications and have been demonstrated to be very versatile building blocks in organic synthesis. The wide range of biological activities includes pharmacological properties such as anti-influenza virus activities [2], antifungal properties [3], anti-inflammatory, antibacterial and HIV-inhibitory activity [4]. The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen-oxygen bond which, under certain reaction conditions, particularly in reductive or basic conditions, is a potential site of ring cleavage The ring opening provides difunctionalized compounds, namely γ-amino alcohol, ß-hydroxy ketone, etc., so that isoxazolines can be considered masked forms of these synthetic units [5]. Pyrazolines present an interesting group of compounds, many of them show antibacterial [6], antidepressant [7], anticonvulsant [8], antiparkinsonian [9], and anti-inflammatory activities [10].

Our group has a current interest in the synthesis of pyrazolines derivatives based on 1,3-dipolar cycloaddition of 2-diazopropane (DAP) to C-C double bands [11]. Because of controls exerted by electronic and steric factors [12]. Consequently, pyrazolines have become an important synthetic tool. In this line, an impressive effort has been devoted to the synthetic application of the cycloaddition of arylnitrile oxides and 2-diazopropane to alkenes to give isoxazolines and pyrazolines. In this paper, we present complete regioselectivity and highly stereoselectivity 1,3-dipoar cycloaddition reactions of 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives.

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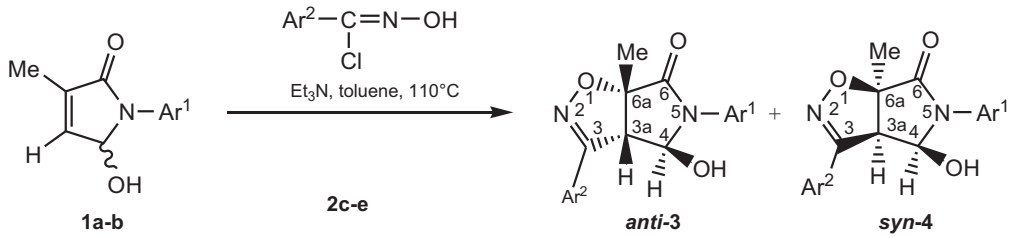

a : Ar^1 = Ph
b : Ar^1 = *p*-C_6H_4-OCH_3

c : Ar^2 = Ph
d : Ar^2 = *p*-C_6H_4-CH_3
e : Ar^2 = *p*-C_6H_4-OCH_3

3ac : Ar^1 = Ph, Ar^2 = Ph
3ad : Ar^1 = Ph, Ar^2 = *p*-C_6H_4-CH_3
3ae : Ar^1 = Ph, Ar^2 = *p*-C_6H_4-OCH_3
3bc : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = Ph
3bd : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = *p*-C_6H_4-CH_3
3be : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = *p*-C_6H_4-OCH_3

4ac : Ar^1 = Ph, Ar^2 = Ph
4ad : Ar^1 = Ph, Ar^2 = *p*-C_6H_4-CH_3
4ae : Ar^1 = Ph, Ar^2 = *p*-C_6H_4-OCH_3
4bc : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = Ph
4bd : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = *p*-C_6H_4-CH_3
4be : Ar^1 = *p*-C_6H_4-OCH_3, Ar^2 = *p*-C_6H_4-OCH_3

Scheme 1. Synthesis of isoxazolines.

2. Results and discussion

The labile arylnitrile oxides generated in situ were allowed to react with pyrrolidinones **1** and **2** in toluene. The reaction of racemic 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives **1** [13] and the arylnitrile oxides **2** proceeded with the formation of diastereoisomers **3** and **4**, in favour of diastereoisomer **3** (Scheme 1). We now have to determine the addition mode of arylnitrile oxides with **1**. Unambiguous proofs for the obtained cycloadducts regiochemistry arised from their spectral data. However, regiochemical assignments of all adduct were deduced from their ^{13}C-NMR spectra. In particular, the chemical shifts of C-6a are in excellent agreement with those usually obtained when this quaternary carbon is attached to oxygen atom [14].

The attack of the 1,3-dipole occurred from the less hindered face of the dipolarophile **1** giving the major isomer **3** (Table 1) [15]. The *syn* or *anti* stereochemistry[1] of the 2-isoxazolines **3** and **4** was deduced from the values observed for $J_{3a,4}$ (0 and 9.4–9.6 Hz, respectively) [16].

The irradiation of H-3a in the minor isomer **4** shows positive NOE for CH_3 and H-4. These observations show that H-3a, CH_3 and H-4 are on the same side of the pyrrolidinone ring. The presence of NOE at CH_3 and its absence at H-4 on irradiating H-3a confirms the *anti* stereochemistry of the major isomer **3** (Fig. 1).

Also, the stereochemistry *syn* or *anti* could be deduced from a NOESY spectrum. The steric interactions between the substituents at nitrile oxide and at C-4 of the pyrrolidinone rings are the main reasons for the observed *syn*-selectivity [17].

The addition of 2-diazopropane **5** with racemic 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-ones as both a regio- and diastereospecific reaction (Scheme 2).

The 1,3-dipolar cycloaddition of DAP is, in each case, regiospecific. ^{1}H-NMR spectra of adduct **6a-b** showed a singulet near 2 ppm assigned to H-3a, in accordance with Δ^1-pyrazolines structure. Their ^{13}C-NMR spectra showed a quaternary carbon signal (C-6a ~90 ppm). This indicated that DAP cycloaddition to proceeded via the "direct" way, [18] e.g. bond formation between the nucleophilic carbon of DAP and the C-3a carbon atom of pyrrolidinone. The stereochemistry of this cycloaddition product was determined from a NOESY spectrum. The *trans* relationship between protons 3a-H and 4-H was deduced from absence of an NOE effect. The complete *anti* selectivity observed in reactions with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-ones, steric interactions should account for the observed results [19].

Table 1
Stereoselectivity of 1,3-dipolar cycloaditions of nitrile oxides with 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives.

Entry	Ar^1	Ar^2	Ratio *anti*-**3**: *syn*-**4**[a]	Rdt %[b]
1	Ph	Ph	92/8	80
2	Ph	*p*-C_6H_4-CH_3	84/16	75
3	Ph	*p*-C_6H_4-OCH_3	87/13	90
4	*p*-C_6H_4-OCH_3	Ph	90/10	85
5	*p*-C_6H_4-OCH_3	*p*-C_6H_4-CH_3	89/11	87
6	*p*-C_6H_4-OCH_3	*p*-C_6H_4-OCH_3	85/15	79

[a]Relative proportion determined by ^{1}H-NMR of the reaction crude.
[b] Combined yield after column chromatography.

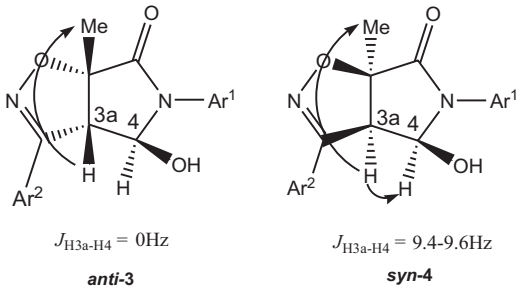

Fig. 1. Coupling constants and major NOE interactions of adduct **3** and **4**.

[1] The terminology *syn*/*anti* indicates the spatial arrangement of the hydroxy group at C-4 and the isoxazoline ring at the pyrrolidinone moiety. It also indicates that the approach of the dipole has taken place either to the face containing the hydroxy group (*syn*-approach) or to the opposite one (*anti*-approach).