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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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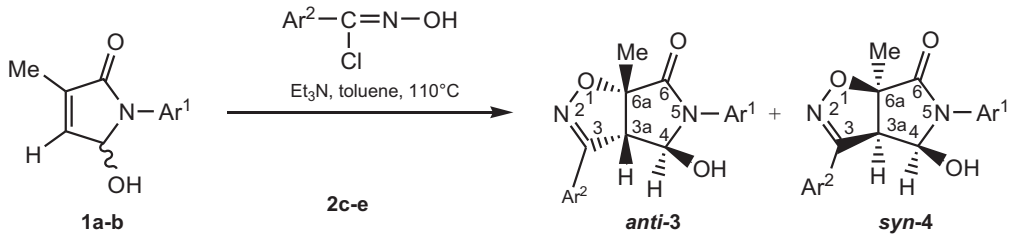


a : Ar^1 = Ph
b : Ar^1 = *p*-C_6H_4-OCH_3

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.

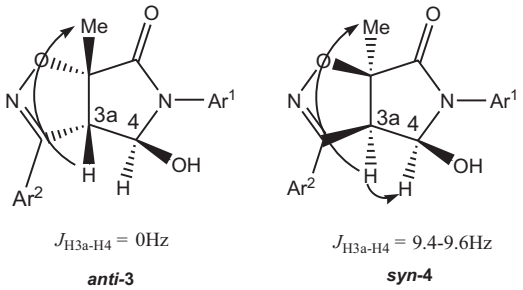
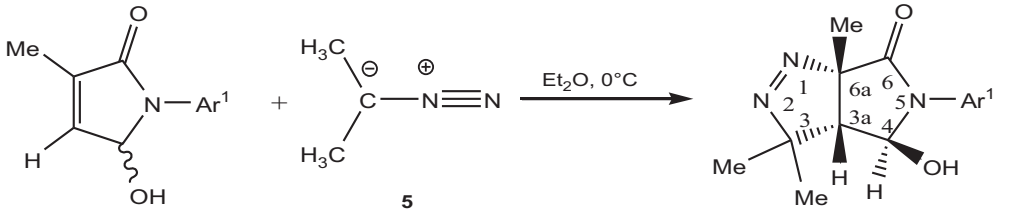


Fig. 1. Coupling constants and major NOE interactions of adduct **3** and **4**.

[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).



Scheme 2. Formation of pyrazolines.

3. Conclusion

We can conclude that the reactions of arylnitrile oxides and 2-diazopropane with racemic 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives are quite interesting in asymmetric synthesis because they evolve in high yields affording bicyclic-isoxazolines and pyrazolines with complete regioselectivity and very high π-facial selectivity. The methyl group increases the dipolarophilic reactivity of the pyrrolidinones, as well as their regioselectivity. Finally, the hydroxyl group was able to completely control the π-facial selectivity of all these reactions.

4. Experimental

IR spectra were recorded on a Perkin-Elmer IR-197 spectrometer. NMR spectra were obtained on a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H and at 75.64 MHz for ^{13}C. Melting points were determined on a Buchi-510 capillary melting point apparatus. All reagents were of commercial quality or purified by standard procedures.

4.1. 1,3-dipolar cycloaddition of nitrile oxides with dipolarophiles

A solution of dipolarophiles **1a-b** (1 mmol) and chloroximes **2c-e** (1.1 mmol) in toluene (10 mL), was stirred at 110 °C. To this solution trimethylamine (0.2 mL), dissolved in toluene (10 mL), was added dropwise. The precipitated triethylammonium chloride was removed by filtration and the filtrate was concentrated in vacuo, and chromatography (SiO_2; ethyl acetate/petroleum ether, 2:1) to afford compounds **3ac-be** and **4ac-be**.

(3aR*,4S*,6aS*)-4-exo-hydroxy-6a-methyl-3,5-diphenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3ac)

Yield (0.227 g, 73.6%); colourless solid. M.p = 160 °C, Anal. Calcd. For $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09%; Found: C, 69.98; H, 5.13; N, 9.20%; IR (KBr) $\nu_{cm}{}^{-1}$; 1638 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.60 (s, 3H, CH_3), 4.00 (s, 1H, 3a-H), 5.23 (s, 1H, OH), 5.33 (s, 1H, 4-H), 7.25-7.85 (m, 10H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.10 (CH_3), 60.94 (C-3a), 89.46 (C-4), 91.00 (C-6a), 123.02–138.01 (C_{arom}), 154.06 (C_3), 168.92 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-6a-methyl-3,5-diphenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4ac)

Yield (0.02 g, 6.4%); colourless solid. M.p = 204 °C, Anal. Calcd. For $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09%; Found: C, 70.25; H, 5.40; N, 8.89%; IR (KBr) $\nu_{cm}{}^{-1}$; 1637 (C = N); 1745 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.67 (s, 3H, CH_3), 4.01 (s, 1H, OH), 4.66 (d, 1H, 3a-H, J = 9.6 Hz), 5.57 (d, 1H, 4-H, J = 9.6 Hz), 7.24–7.86 (m, 10H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.08 (CH_3), 60.24 (C-3a), 89.25 (C-4), 92.05 (C-6a), 123.88–136.81 (C_{arom}), 154.46 (C_3), 168.54 (C-6).

(3aR*,4S*,6aS*)-4-exo-hydroxy-6a-methyl-3-(4-methylphenyl)-5-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3ad)

Yield (0.203 g, 63%); colourless solid. M.p = 159 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69%; Found: C, 70.75; H, 5.66; N, 8.74%; IR (KBr) $\nu_{cm}{}^{-1}$; 1640 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, DMSO) δ: 1.56 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.12 (s, 1H, 3a-H), 5.11 (s, 1H, OH), 5.31 (s, 1H, 4-H), 7.29–7.72 (m, 9H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.23 (CH_3), 20.98 (CH_3), 60.06 (C-3a), 89.34 (C-4), 91.03 (C-6a), 123.31–141.09 (C_{arom}), 153.79 (C_3), 168.51 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-6a-methyl-3-(4-methylphenyl)-5-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4ad)

Yield (0.039 g, 12%); colourless solid. M.p = 161 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69%; Found: C, 70.60; H, 5.51; N, 8.50%; IR (KBr) $\nu_{cm}{}^{-1}$; 1640 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.70 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.26 (s, 1H, OH), 4.64 (d, 1H, 3a-H, J = 9.5 Hz), 5.81 (d, 1H, 4-H, J = 9.5 Hz), 7.47–7.95 (m, 9H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.12 (CH_3), 21.93 (CH_3), 60.38 (C-3a), 89.27 (C-4), 91.66 (C-6a), 123.55–141.46 (C_{arom}), 154.30 (C_3), 168.64 (C-6).

(3aR*,4S*,6aS*)-4-exo-hydroxy-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3ae)

Yield (0.265 g, 78.3%); colourless solid. M.p = 232 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28%; Found: C, 67.50; H, 5.41; N, 8.24%; IR (KBr) $\nu_{cm}{}^{-1}$; 1630 (C = N); 1735 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.27 (s, 1H, 3a-H), 5.05 (s, 1H, OH), 5.48 (s, 1H, 4-H), 6.84–8.03 (m, 9H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ:

18.86 (CH_3), 55.52 (OCH_3), 59.86 (C-3a), 89.04 (C-4), 91.69 (C-6a), 114.44–158.46 (C_{arom}), 154.46 (C_3), 167.94 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4ae)

Yield (0.04 g, 11.7%); colourless solid. M.p = 222 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28%; Found: C, 67.55; H, 5.39; N, 8.26%; IR (KBr) $\nu_{cm}{}^{-1}$; 1645 (C = N); 1735 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, C_3D_6O) δ: 1.69 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.52 (s, 1H, OH), 5.12 (d, 1H, 3a-H, J = 9.6 Hz), 5.67 (d, 1H, 4-H, J = 9.6 Hz), 6.99 (d, 2H) and 7.99 (d, 2H): AA'BB' part. J = 9 Hz, 7.21–7.58 (m, 5H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, C_3D_6O) δ: 19.21 (CH_3), 56.01 (OCH_3), 61.98 (C-3a), 85.37 (C-4), 90.45 (C-6a), 115.05–162.06 (C_{arom}), 155.03 (C_3), 167.60 (C-6).

(3aR*,4S*,6aS*)-4-exo-hydroxy-5-(4-methoxyphenyl)-6a-methyl-3-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3bc)

Yield (0.259 g, 76.5%); colourless solid. M.p = 139 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28%; Found: C, 67.37; H, 5.25; N, 8.20%; IR (KBr) $\nu_{cm}{}^{-1}$; 1640 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.74 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.98 (s, 1H, 3a-H), 5.10 (s, 1H, OH), 5.46 (s, 1H, 4-H), 6.75 (d, 2H) and 7.16 (d, 2H): AA'BB' part. J = 8.7 Hz, 7.43–7.74 (m, 5H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 20.31 (CH_3), 55.47 (OCH_3), 60.18 (C-3a), 85.43 (C-4), 89.24 (C-6a), 114.48–158.68 (C_{arom}), 156.00 (C_3), 171.24 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-5-(4-methoxyphenyl)-6a-methyl-3-phenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4bc)

Yield (0.046 g, 13.5%); colourless solid. M.p = 189 °C, Anal. Calcd. For $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28%; Found: C, 67.60; H, 5.45; N, 8.19%; IR (KBr) $\nu_{cm}{}^{-1}$; 1638 (C = N); 1735 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, C_3D_6O) δ: 1.55 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.53 (s, 1H, OH), 5.69 (d, 1H, 3a-H, J = 9.4 Hz), 6.03 (d, 1H, 4-H, J = 9.4 Hz), 6.98 (d, 2H) and 7.94 (d, 2H): AA'BB' part. J = 8.7 Hz, 7.20–7.63 (m, 5H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, C_3D_6O) δ: 19.24 (CH_3), 55.58 (OCH_3), 60.41 (C-3a), 86.07 (C-4), 90.95 (C-6a), 114.65–160.85 (C_{arom}), 154.77 (C_3), 168.10 (C-6).

(3aR*,4S*,6aS*)-4-exo-hydroxy-5-(4-methoxyphenyl)-6a-methyl-3-(4-methylphenyl)-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3bd)

Yield (0.273 g, 77.4%); colourless solid. M.p = 151 °C, Anal. Calcd. For $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%; Found: C, 68.00; H, 5.80; N, 8.00%; IR (KBr) $\nu_{cm}{}^{-1}$; 1635 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, DMSO) δ: 1.55 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.17 (s, 1H, 3a-H), 5.63 (s, 1H, 4-H), 6.25 (s, 1H, OH), 6.89 (d, 2H) and 7.40 (d, 2H): AA'BB' part. J = 8.7 Hz, 7.30 (d, 2H) and 7.66 (d, 2H): AA'BB' part. J = 7.8 Hz; ^{13}C{^{1}H}NMR (75 MHz, DMSO) δ: 19.17 (CH_3), 20.86 (CH_3), 55.58 (OCH_3), 60.10 (C-3a), 86.05 (C-4), 89.34 (C-6a), 114.17–156.04 (C_{arom}), 155.88 (C_3), 170.19 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-5-(4-methoxyphenyl)-6a-methyl-3-(4-methylphenyl)-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4bd)

Yield (0.034 g, 9.6%); colourless solid. M.p = 215 °C, Anal. Calcd. For $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%; Found: C, 68.40; H, 5.60; N, 7.70%; IR (KBr) $\nu_{cm}{}^{-1}$; 1640 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.83 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.30 (s, 1H, OH), 4.54 (d, 1H, 3a-H, J = 9.6 Hz), 5.73 (d, 1H, 4-H, J = 9.6 Hz), 6.99–7.75 (m, 8H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.17 (CH_3), 21.84 (CH_3), 55.69 (OCH_3), 60.31 (C-3a), 86.17 (C-4), 91.00 (C-6a), 117.81–159.75 (C_{arom}), 153.97 (C_3), 168.15 (C-6).

(3aR*,4S*,6aS*)-4-exo-hydroxy-3,5-di(4-methoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (3be)

Yield (0.247 g, 67.15%); colourless solid. M.p = 229 °C, Anal. Calcd. For $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60%; Found: C, 65.11; H, 5.39; N, 7.46%; IR (KBr) $\nu_{cm}{}^{-1}$; 1640 (C = N); 1740 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 3H, CH_3), 3,76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.09 (s, 1H, 3a-H), 4.67 (s, 1H, OH), 5.44 (s, 1H, 4-H), 6.82 (d, 2H) and 7.47 (d, 2H): AA'BB' part. J = 9 Hz, 6.89 (d, 2H) and 7.80 (d, 2H): AA'BB' part. J = 8.7 Hz; ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 19.20 (CH_3), 55.78 (OCH_3), 55.83 (OCH_3), 60.41 (C-3a), 89.37 (C-4), 91.75 (C-6a), 114.49–161.80 (C_{arom}), 154.18 (C_3), 168.37 (C-6).

(3aS*,4S*,6aR*)-4-endo-hydroxy-3,5-di(4-methoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-6-one (4be)

Yield (0.044 g, 11.85%); colourless solid. M.p = 191 °C, Anal. Calcd. For $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60%; Found: C, 65.32; H, 5.65; N, 7.73%; IR (KBr) $\nu_{cm}{}^{-1}$; 1635 (C = N); 1735 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, DMSO) δ: 1.53 (s, 3H, CH_3), 3,75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.56 (s, 1H, OH), 5.41 (d, 1H, 3a-H, J = 9.6 Hz), 6.36 (d, 1H, 4-H, J = 9.6 Hz), 6.93 (d, 2H) and 7.30 (d, 2H): AA'BB' part. J = 9 Hz, 7.02 (d, 2H) and 7.86 (d, 2H): AA'BB' part. J = 8.7 Hz; ^{13}C{^{1}H}NMR (75 MHz, DMSO) δ: 21.58 (CH_3), 55.60 (OCH_3), 55.67 (OCH_3), 60.33 (C-3a), 87.89 (C-4), 88.56 (C-6a), 114.11–161.06 (C_{arom}), 154.14 (C_3), 166.57 (C-6).

4.2. 1,3-dipolar cycloaddition of 2-diazopropane with dipolarophiles

To a solution of dipolarophiles **1a-b** (1.0 mmol) in diethyl ether, cooled at 0 °C, was added portionwise 2.6 M ethereal solution of 2-diazopropane. The reaction was kept at the same temperature during 1 h. The solvent was removed and chromatography (SiO_2; ethyl acetate/petroleum ether, 2:1) to afford compounds **6a-b**.

(3aR*,4S*,6aS*)-4-endo-hydroxy-5-phenyl-3,3,6a-trimethyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]pyrazole-6-one (6a)

Yield (0.194 g, 75%); colourless solid. M.p = 139 °C, Anal. Calcd. For $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20%; Found: C, 64.88; H, 6.54; N, 16.17%; IR (KBr) $\nu_{cm}{}^{-1}$; 1540 (N = N); 1730 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.94 (s, 1H, 3a-H), 4.03 (s, 1H, OH), 5.34 (s, 1H, 4-H), 7.13–7.33 (m, 5H, H_{arom}); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ: 22.19 (CH_3), 22.48 (CH_3), 29.30 (CH_3), 54.12 (C-3a), 83.90 (C-4), 93.97 (C-6a), 101.38 (C_3), 124.33–136.62 (C_{arom}), 170.17 (C-6).

(3aR*,4S*,6aS*)-4-endo-hydroxy-5-(4-methoxyphenyl)-3,3,6a-trimethyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]pyrazole-6-one (6b)

Yield (0.231 g, 80%); colourless solid. M.p = 129 °C, Anal. Calcd. For $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52%; Found: C, 62.23; H, 6.69; N, 14.59%; IR (KBr) $\nu_{cm}{}^{-1}$; 1545 (N = N); 1730 (C = O); 3300 (OH), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.04 (s, 1H, 3a-H), 3.82 (s, 3H, OCH_3), 4.13 (s, 1H, OH), 5.31 (s, 1H, 4-H), 6.77 (d, 2H) and 7.18 (d, 2H): AA'BB' part. J = 8.7 Hz; $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ: 22.17 (CH_3), 22.39 (CH_3), 29.33 (CH_3), 54.12 (C-3a), 56.02 (OCH_3), 83.89 (C-4), 93.89 (C-6a), 100.96 (C_3), 114.23–160.52 (C_{arom}), 171.07 (C-6).

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