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Remarkable electronic effect on the total stereoselectivity of the cycloaddition reaction of arylnitrile oxides with pyrrol-2-one derivatives

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Abstract: The regiospecific 1,3-dipolar cycloaddition of 1,5-dihydropyrrol-2-one and arylnitrile oxides derivatives have been investigated. The asymmetric induction expected by the chiral centre of the 5-hydroxy-3-methyl-1,5-dihydropyrrol-2-one derivatives was very effective, single diastereoisomers *anti*-3 was formed. The diastereoselectivity was linked to the destabilization of the *syn* transition state as a result of the electrostatic repulsion between the hydroxy group of the dihydropyrrol-2-one derivatives and the atom oxygen of the dipole.

Keywords: Cycloaddition 1,3-dipolar, 1,5-dihydropyrrol-2-one, arylnitrile oxides, regiospecifically, diastereoisomers.

Introduction

1,3-Dipolar cycloaddition of nitrile oxides to alkenes is the most useful method of preparation for isoxazolines which can be easily converted to several synthetically important compounds such as β-hydroxy ketones, β-hydroxy esters, α,β-unsaturated carbonyl compounds [1-3]. The regio- and stereoselectivity of these reactions dramatically depends on the nature of the substituents on both the alkene and dipole [4,6]. The isoxazoline ring is present in a number of commercially available and clinically useful drugs, as well as in other biologically active compounds, acting as antibacterial, antitubercular, and antidepressant agents [7,8]. Most of the recently synthesized isoxazolines were prepared as antibacterial and antifungal compounds [9]. Based on an evaluation of the nitrile oxides cycloaddition, it was felt that the stereochemistry of these new centers could be controlled if the reaction system were properly designed. Pyrrolidinones are important precursors in organic synthesis and are found in many pharmaceuticals and active natural products [10,11].

As a continuation of our effort to utilize heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloaddition reactions, we report the asymmetric 1,3-cycloaddition of aromatic nitrile oxides with pyrrol-2-one derivatives [12-14].

Results and discussions

The labile nitrile oxides **2a-c** generated in situ were allowed to react with pyrrolidinones **1a,b** in toluene [15]. The reaction of 1,5-dihydropyrrol- 2-one derivatives **1** and the arylnitrile oxides **2** [5,6] proceeded with the formation of single diastereoisomers **3** (Scheme 1).

We now have to determine the addition mode of arylnitrile oxides with **1**. Unambiguous proofs for the obtained cycloadducts regiochemistry arose 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 [16].

The attack of the 1,3-dipole occurred from the less hindered face of the dipolarophile **1** giving the single isomer **3**. The electrostatic repulsion should account for

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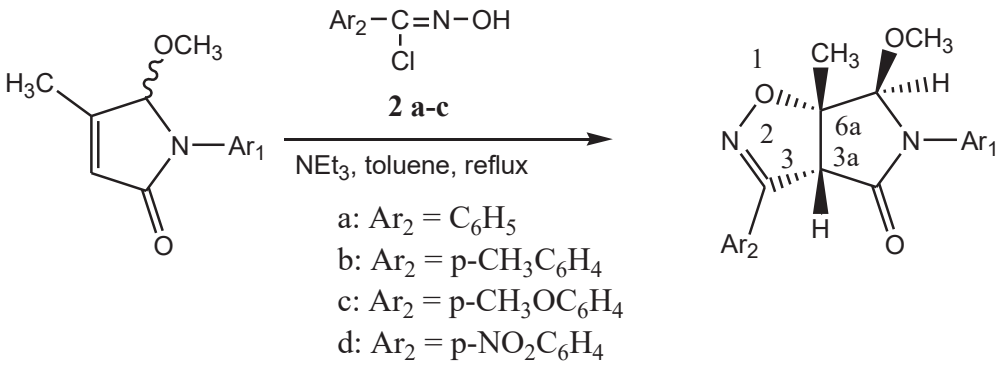

1a,b

a: $Ar_1 = C_6H_5$
b: $Ar_1 = p\text{-}CH_3OC_6H_4$

***Anti*-3**

Cycloadducts	Yield (%)
a: $Ar_1 = C_6H_5$, $Ar_2 = C_6H_5$	75
b: $Ar_1 = C_6H_5$, $Ar_2 = p\text{-}CH_3C_6H_4$	80
c: $Ar_1 = C_6H_5$, $Ar_2 = p\text{-}CH_3OC_6H_4$	65
d: $Ar_1 = C_6H_5$, $Ar_2 = p\text{-}NO_2C_6H_4$	70
e: $Ar_1 = p\text{-}CH_3OC_6H_4$, $Ar_2 = C_6H_5$	95
f: $Ar_1 = p\text{-}CH_3OC_6H_4$, $Ar_2 = p\text{-}CH_3C_6H_4$	70
g: $Ar_1 = p\text{-}CH_3OC_6H_4$, $Ar_2 = p\text{-}CH_3OC_6H_4$	80
h: $Ar_1 = p\text{-}CH_3OC_6H_4$, $Ar_2 = p\text{-}NO_2C_6H_4$	85

Scheme 1 Cycloaddition 1,3-dipolar of nitrile oxides with pyrrole-2-one derivatives.

the observed results. Moreover, *syn* orientation of the oxygen-containing pyrrolidinones to the oxygen atom of nitrile oxide leads to greater repulsion in the transition state (Figure 1) [17,18].

The *anti* stereochemistry of the 2-isoxazolines **3** was deduced from the NOES spectrum which allowed us to distinguish a clear spatial correlation between the CH_3 protons (5.4 ppm), H-3a (4.14) and the methoxy proton (3.8 ppm). Also, the absence of any nOe between the methoxy H-6 proton (6.9 ppm) and the methyl protons (1.6 ppm) of the dipolarophile moiety, confirms the structure of the obtained compounds **3** (Figure 2).

Conclusion

Our studies have shown that methoxy group is extremely effective in affording complete stereoselectivity for 1,3-dipolar cycloaddition reactions between nitrile oxides and pyrrolidinones. This synthesis allows us to obtain one diastereoisomer of isoxazolines. Finally, the electrostatic repulsion between oxygen-containing pyrrolidinones and the oxygen atom of nitrile oxide are the main reasons for the observed anti-selectivity.

Experimental details

General

Infrared spectra were recorded on a Perkin-Elmer IR-197 spectrophotometer in KBr disks. NMR spectra were obtained with a Bruker AC 300 spectrometer operating at 300 MHz for 1 H and at 75.64 MHz for 13C using TMS as the internal standard. Elemental analysis was performed with a Perkin–Elmer 240B microanalyzer. The melting points, thermal transitions, and mesomorphic textures were determined using an Olympus BX50 microscope equipped with a Mettler Toledo FP-82 hot-stage and a PM-30 exposure control unit.

Materials

All the reagents were obtained from commercial sources and used without further purification. The organic solvents were of commercial grade quality and all were dried by traditional methods. In general, all the compounds were purified by column chromatography on silica gel (60–120 mesh), and crystallization from analytical grade

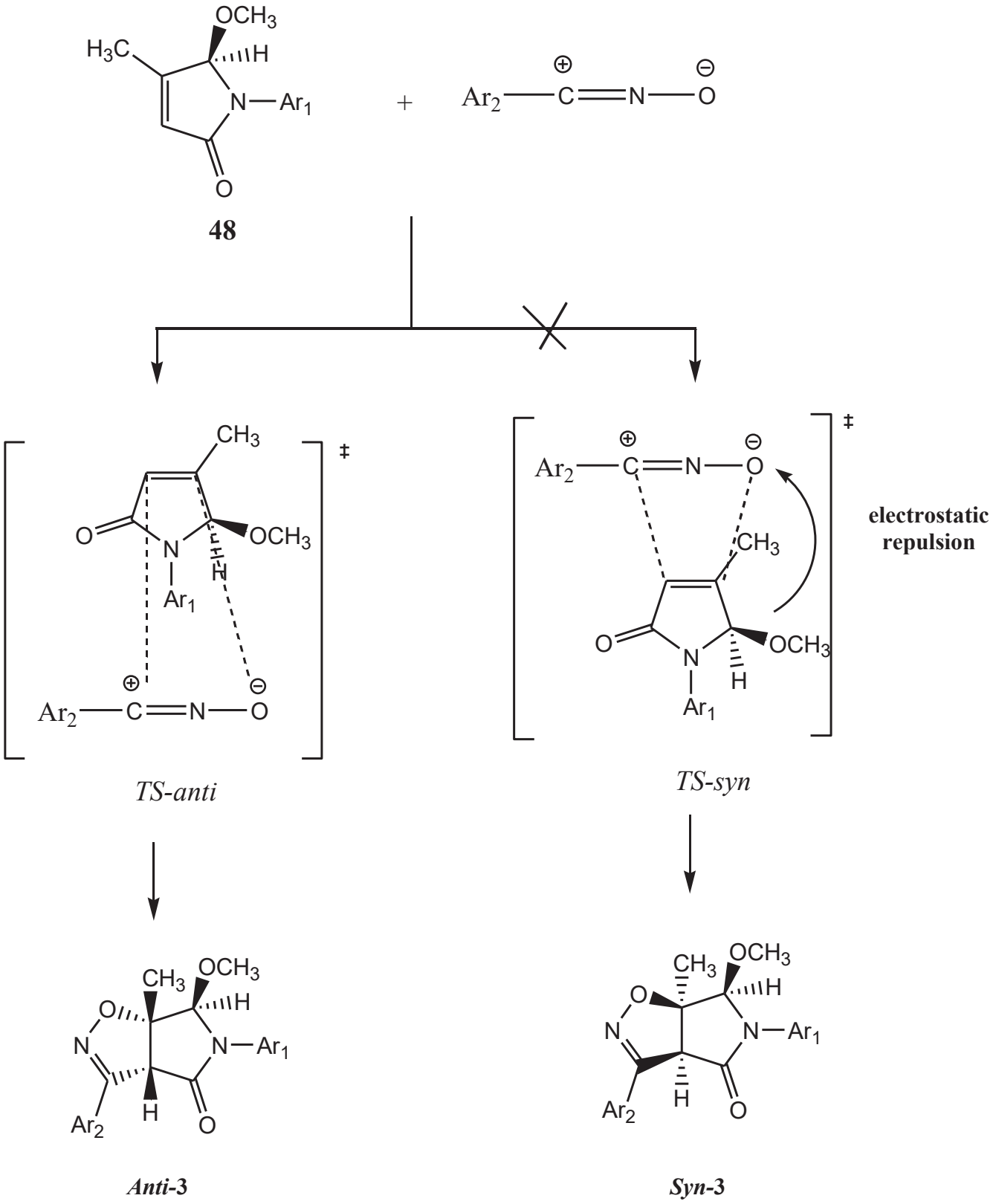

Figure 1 Stereochemistry of the 2-isoxazolines **3**.

solvents. The purity of the sample was checked by thin-layer chromatography (Merck Kieselgel 60F254).

Addition of aromatic nitrile oxides to dihydropyrrol-2-one derivatives

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 **3a–f**.

6-Methoxy-6a-methyl-3,5-diphenyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoxazole-4-one (3a)

Yield = 75% white solid. mp = 221-222 °C. IR (KBr) ymax/cm^{-1}: 1645 (C=N); 1735 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm} : 1.61 (s, 3H, CH_3); 3,80 (s, 3H, OCH_3); 4.12 (s, 1H, 3a–H); 6.47 (s, 1H, 6-H); 7.27–7.87 (m, 10H, Harom). ^{13}C NMR (75.47 MHz; DMSO-d6) δ_{ppm} : 19.5; 55.5; 61.5; 89.5; 91.4; 122.6–137.0; 153.8; 170.1. Elemental analysis: $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%; Found: C, 70.81; H, 5.60; N, 8.73%.

6-Methoxy-6a-methyl-3-(4-methylphenyl)-5-phenyl-3a,5,6,6a-tetrahydro-4Hpyrrolo[3,4-d]isoxazole-4-one (3b)

Yield = 80% white solid. mp = 191-192 °C. IR (KBr) ymax/cm^{-1}: 1635 (C=N); 1735 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm} : 1.68 (s, 3H, CH_3); 2.54 (s, 3H, CH_3); 3.77 (s, 3H, OCH_3); 4.21 (s, 1H, 3a-H); 6,61 (s, 1H, 6-H); 7,36–7,80 (m, 9H, Harom). ^{13}C NMR (75.47 MHz; DMSO-d6) δ_{ppm} : 19.1; 21.0; 55.8; 60.2; 89.5; 91.1; 123.4–141.9; 154.3; 168.9. Elemental analysis: $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%; Found: C, 71.46; H, 5.96; N, 8.34%.

6-Methoxy-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-d]isoxazole-4-one (3c)

Yield = 65% white solid. mp = 199-200 °C. IR (KBr) ymax/cm^{-1}: 1630 (C=N); 1745 (C=O). ^{1}H NMR (300 MHz; DMSO) δ_{ppm} : 1.68 (s, 3H, CH_3); 3.81 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 4.18 (s, 1H, 3a-H); 6.53 (s, 1H, 6-H); 7.17–7.87 (m, 9H,

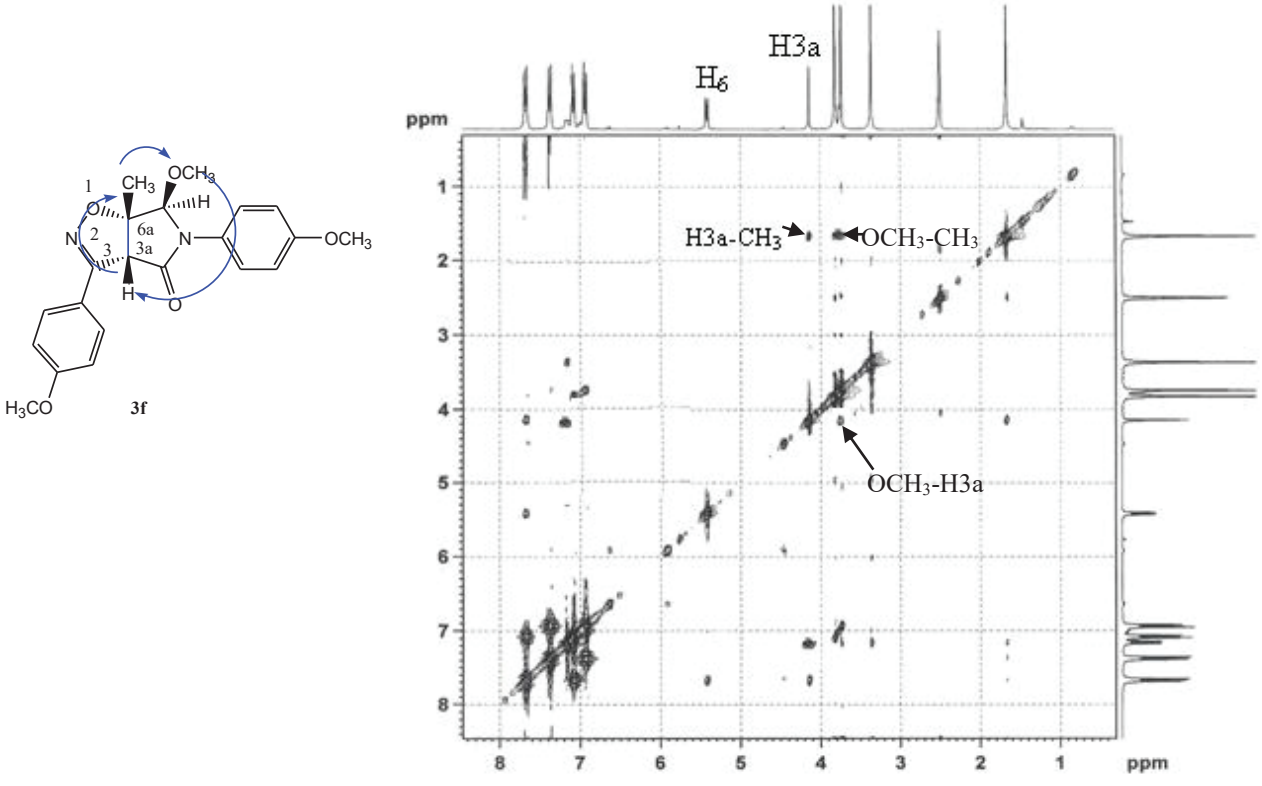

Figure 2 NOESY spectrum of isoxazoline **3f**.

Harom). ^{13}C NMR (75,47 MHz; DMSO) δ_{ppm}: 20.2; 55.7; 55.9; 60.4; 85.4; 89.3; 113.9–162.4; 157.2; 171.5.
Elemental analysis: $C_{20}H_{20}N_2O_4$ requires C, 68.17; H, 5.72; N, 7.95%; Found: C, 68.20; H, 5.69; N, 7.99%.

6-Methoxy-6a-methyl-3-(4-nitro-phenyl)-5-phenyl-3a,5,6,6a-tetrahydro-pyrrolo[3,4-d]isoxazol-4-one (3d)

Yield = 70% white solid. mp = 201-202 °C. IR (KBr) ymax/cm^{-1}: 1635 (C=N); 1740 (C=O). ^{1}H NMR (300 MHz; DMSO) δ_{ppm}: 1.66 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 4.21 (s, 1H, 3a-H); 6.48 (s, 1H, 6-H); 7.17–8.11 (m, 9H, Harom). ^{13}C NMR (75,47 MHz; DMSO) δ_{ppm}: 20.1; 55.8; 60.5; 85.1; 88.9; 116.49–149.4; 157.4; 170.9.
Elemental analysis: $C_{19}H_{17}N_3O_5$ requires C, 62.12; H, 4.66; N, 11.44%; Found: C, 62.14; H, 4.59; N, 11.38%.

6-Methoxy-5-(4-methoxyphenyl)-6a-methyl-3-phenyl-3a,5,6,6atetrahydro-4*H* pyrrolo[3,4- d]isoxazole-4-one (3e)

Yield = 95% white solid. mp = 178-179 °C. IR (KBr) ymax/cm^{-1}: 1635 (C=N); 1737 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm}: 1.43 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 4.67 (s, 1H, 3a–H); 6.94 (s, 1H, 6-H); 7.02 (d, 2H, *J* = 9 Hz) and 7.80 (d, 2H, *J* = 9 Hz):; 7.22–7.55 (m, 5H, Harom). ^{13}C NMR (300 MHz; DMSO-d6) δ_{ppm}: 19.2; 55.7; 55.60; 59.4; 88.8; 91.9; 114.6–162.7; 156.3; 168.7. Elemental analysis: $C_{20}H_{20}N_2O_4$ requires C, 68.17; H, 5.72; N, 7.95%; Found: C, 68.15; H, 5.65; N, 8.03%.

6-Methoxy-5-(4-methoxyphenyl)-6a-methyl-3-(4-methylphenyl)-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4-one (3f)

Yield = 70% white solid. mp = 168-169°C. IR (KBr) ymax/cm^{-1}: 1640 (C=N); 1745 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm}: 1.46 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 3.81 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 4.65 (s, 1H, 3a-H); 6.91 (s, 1H, 6-H); 6.96 (d, 2H, *J* = 9 Hz) and 7.43 (d, 2H, *J* = 9 Hz); 7.27 (d, 2H, *J* = 7.8 Hz) and 7.83 (d, 2H, *J* = 7.8 Hz); ^{13}C (300 MHz; DMSO-d6) δ_{ppm}: 19.2; 21.5; 55.6; 55.8; 59.6; 88.3; 92.2; 114.4–157.3; 154.3; 168.5.
Elemental analysis: $C_{21}H_{22}N_2O_4$ requires C, 68.84; H, 6.05; N, 7.65%; Found: C, 68.81; H, 5.99; N, 7.59%.

6-Methoxy-3,5-di(4-methoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-d]isoxazole-4-one (3g)

Yield = 80% white solid. mp = 179-180 °C. IR (KBr) ymax/cm^{-1}: 1640 (C=N); 1740 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm}: 1.69 (s, 3H, CH_3); 3.74 (s, 6H, OCH_3); 3.79 (s, 3H, OCH_3); 4.16 (s, 1H, 3a-H); 7.17 (s, 1H, 6-H); 6.93 (d, 2H, *J* = 9 Hz) and 7.38 (d, 2H, *J* = 9 Hz); 7.08 (d, 2H, *J* = 8.7 Hz) and 7.68 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR (300 MHz; DMSO-d6) δ_{ppm}: 20.5; 55.6; 55.8; 60.9; 84.8; 89.9; 114.7–161.3; 157.9; 171.2. Elemental analysis: $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.80; N, 7.33%; Found: C, 65.89; H, 5.78; N, 7.37%.

6-Methoxy-5-(4-methoxy-phenyl)-6a-methyl-3-(4-nitro-phenyl)-3a,5,6,6a-tetrahydro-pyrrolo[3,4-d]isoxazol-4-one (3h)

Yield = 85% white solid. mp = 227-228 °C. IR (KBr) ymax/cm^{-1}: 1645 (C=N); 1745 (C=O). ^{1}H NMR (300 MHz; DMSO-d6) δ_{ppm}: 1.69 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 4.17 (s, 1H, 3a-H); 7.23–8.03 (m, 9H, Harom). ^{13}C NMR (300 MHz; DMSO-d6) δ_{ppm}: 20.4; 55.7; 55.8; 61.0; 84.9; 90.9; 115.1–160.9; 157.8; 170.8. Elemental analysis: $C_{20}H_{19}N_3O_6$ requires C, 60.45; H, 4.82; N, 10.57%; Found: C, 60.40; H, 4.79; N, 10.55%.

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