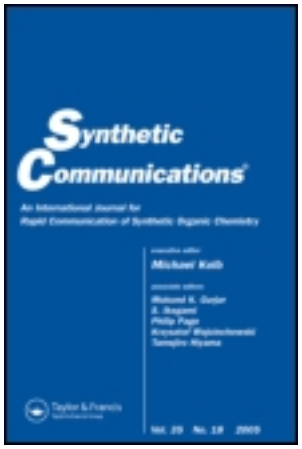

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Diastereoselective Synthesis of Novel Spiro-Isoxazolidines via [3 + 2] Cycloaddition

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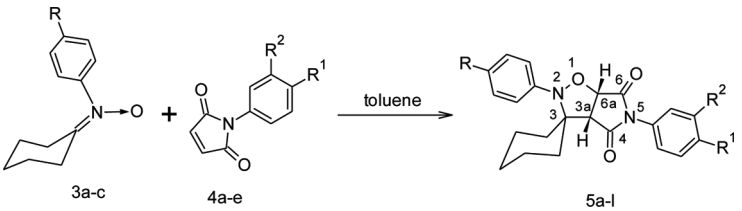
DIASTEREOSELECTIVE SYNTHESIS OF NOVEL SPIRO-ISOXAZOLIDINES VIA [3 + 2] CYCLOADDITION

Sakshi Shah, Rahul Badru, and Baldev Singh
Department of Chemistry, Punjabi University, Patiala, Punjab, India

GRAPHICAL ABSTRACT



Abstract *In this protocol, synthesis of novel 2,5-diphenyl-3,3-spiropentamethylene-5H-2,3,3a,6a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-diones through [3 + 2] cycloaddition of N-cyclohexylidene N-phenyl nitrones with cyclic dipolarophiles is described. 1,3-Dipolar cycloaddition of nitrones with substituted N-arylmaleimides gives exclusively* endo*-diastereoisomers of spiro-isoxazolidines and their stereochemistry was assigned using* ^{1}H *NMR and* ^{1}H-^{1}H *correlation spectroscopic studies.*

Keywords [3 + 2] Cycloaddition; N-arylmaleimides; N-cyclohexylidene n-phenyl nitrone; spiro-isoxazolidines

INTRODUCTION

Spiro compounds having cyclic structures fused at a central carbon are of current interest because of their interesting conformational features and their structural implications on biological systems. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the significant factors for the biological activities. Spiro compounds exhibit prominent pharmacological activities and have been used in the chemistry of natural products as more complex heterocycles.[1–3]

These can be synthesized through cycloaddition of 1,3-dipoles obtained from cyclic ketones, namely, nitrones and olefins.[4] Nitrones occupy a special position in 1,3-dipoles and dipolar cycloaddition reactions because of their greater stability, isolatability, and regioselective behavior in comparison to other 1,3-dipoles.[5,6]

Isoxazolidines are synthesized through 1,3-dipolar cycloaddition reactions of 1,3-dipoles and dipolarophiles [7,8] in a single concerted step with two or more

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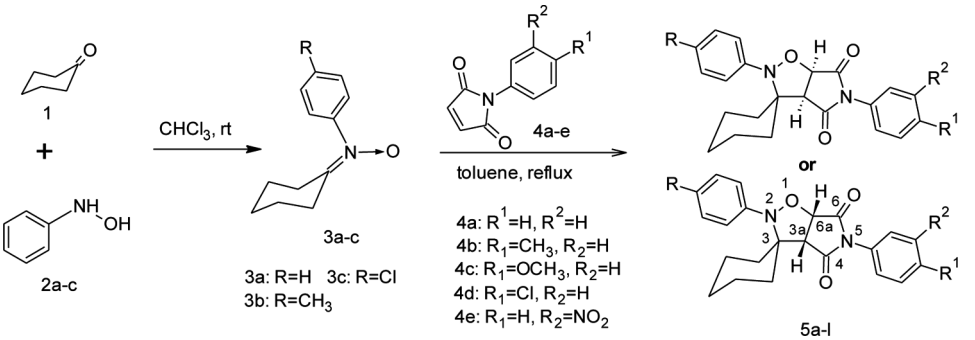
stereogenic centers[9,10] and are potential precursors for the synthesis of extremely useful natural products such as sugar derivatives, β-lactams, amino acids, and alkaloids.[11–16] They can be further explored into polyfunctional cyclic or acyclic bioactive molecules with complete control of relative stereochemistry.[17]

The biological applications of spiro-compounds and (spiro) isoxazolidines[18–20] prompted us to synthesize spiro-isoxazolidines. In the present study synthesis of novel 2,5-diphenyl-3,3-spiropentamethylene-5H-2,3,3a,6a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-diones by reacting substituted N-arylmaleimides and N-cyclohexyldiene N-phenyl nitrones is described.

RESULTS AND DISCUSSION

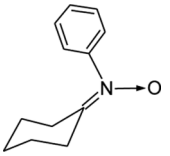
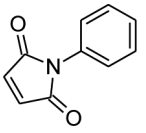
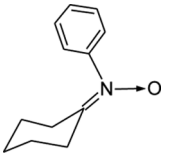
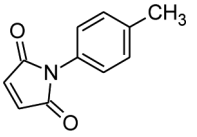
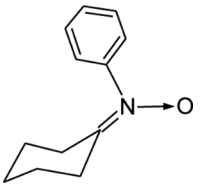
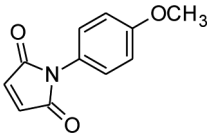
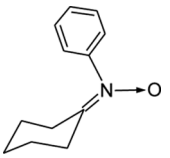
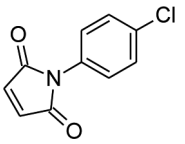
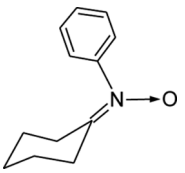
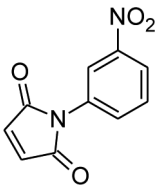
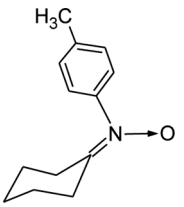
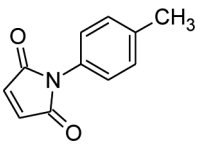
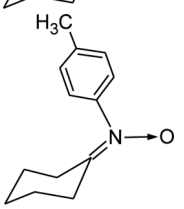
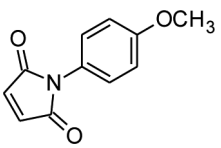
For these [3 + 2] cycloaddition reactions, an equimolar mixture of freshly prepared N-cyclohexyldiene N-phenyl nitrones (prepared from condensation of cyclohexanone **1** with phenylhydroxyamine, Scheme 1) **3** with N-phenylmaleimide **4** was refluxed in toluene to provide **single** *endo*-diastereoisomers **5** in good yields (Scheme 1, Table 1), which were characterized as substituted 3-spiro-isoxazolidines through their spectral analysis (i.e., IR, ^{1}H NMR, mass, etc). In their IR spectra, these derivatives show carbonyl stretching vibrations of succinimide moiety and strong absorption bands in the range of 1690–1786 cm^{-1}.

In ^{1}H NMR spectrum of 2-phenyl-5-*p*-tolyl-3,3-spiropentamethylene-5H-2,3,3a,6a-tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (5b), two doublets at δ 3.76 and δ 4.97 were observed for *cis*-protons C_{3a}-H and C_{6a}-H with coupling constants $J = 7.44$ Hz.($J_{3a\text{-}6a}$) for each proton. This was also supported by their ^{1}H-^{1}H correlation spectrum (COSY, Fig. 1) of product **5b**, which assigned them to H-3a and H-6a, respectively. A multiplet equivalent to 10 protons at δ 1.02–2.04 has been assigned to 10 methylenic protons of the cyclohexylidene moiety and another multiplet at δ 7.16–7.36 has been assigned to N-aryl protons. Proton C_{6a}-H shows a slight downfield chemical shift as compared to proton C_{3a}-H, due to the presence of an electronegative oxygen atom at 1-position and carbonyl group at 6-position. In its ^{13}C NMR spectrum, compound **5b** displays a signal at δ 21.3, which has been assigned to the methyl group. A multiplet signal at δ 23.1–32.2 has been assigned to five methylenic carbons of cyclohexyl moiety, while a signal at δ 53.0 has been



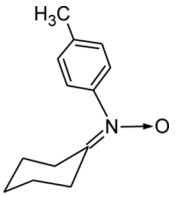
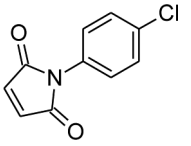
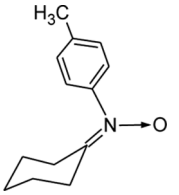
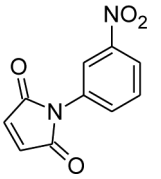
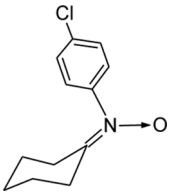
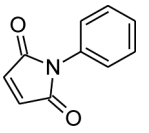
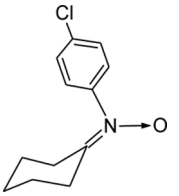
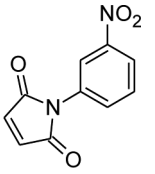
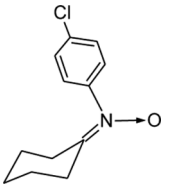
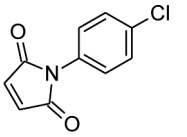
Scheme 1. Stereoselective synthesis of various 3-spiro-isoxazolidines.

Table 1. Synthesis of spiro-isoxazolidines with stereo-isomeric excess

Entry	Nitrone	Dipolarophile	Products[a]	Time (h)	Yield[b] (%)	Mp (°C)
1			**5a**	4.5	70	198–199
2			**5b**	5	72	195–197
3			**5c**	5.5	75	210–215
4			**5d**	6.5	69	190–192
5			**5e**	6.5	65	201–202
6			**5f**	5	69	200–202
7			**5 g**	5.5	65	193–195

(*Continued*)

Table 1. Continued

Entry	Nitrone	Dipolarophile	Products[a]	Time (h)	Yield[b] (%)	Mp (°C)
8			**5h**	6	67	183–184
9			**5i**	6.5	64	230–232
10			**5j**	4.5	72	194–195
11			**5k**	6.5	62	205–207
12			**5l**	6	61	185–187

[a]The products were characterized by spectral techniques like IR, ^{1}H NMR, ^{13}CNMR, and mass.
[b]Isolated yields after recrystallization.

assigned to the C_3-carbon. Another two signals at δ 72.4 and δ 74.4 have been assigned to $C_{\mathbf{3a}}$ and $\mathbf{C_{6a}}$ carbon atoms respectively. A multiplet signal at δ 123.0–143.2 has been assigned to aromatic carbon while two other signals at δ 173.9 and δ 174.3 have been assigned to two carbon atoms of the carbonyl group.

The only single isolated diastereoisomer seems to arise through *endo* transition state (TS 2, Scheme 2) where one of the carbonyl groups of succinimide moiety comes parallel to the N-phenyl moiety of nitrone during their approach to each other, thus stabilizing the *endo* transition state through maximum accumulation of

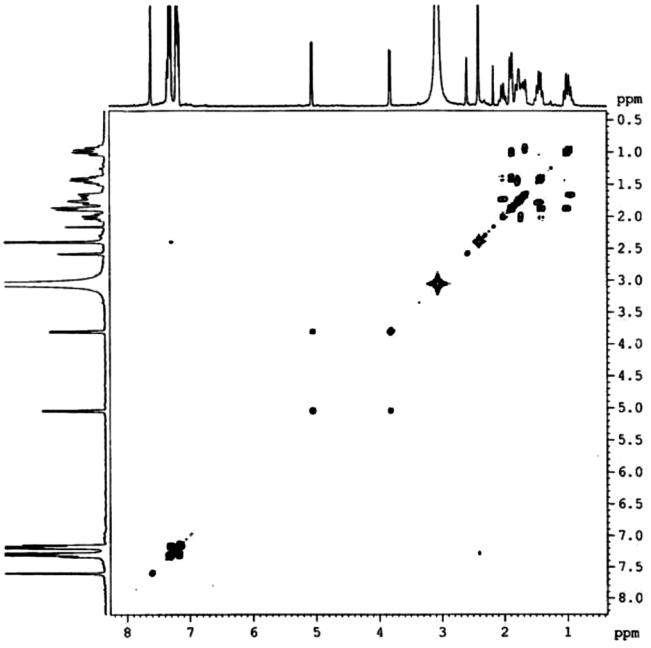
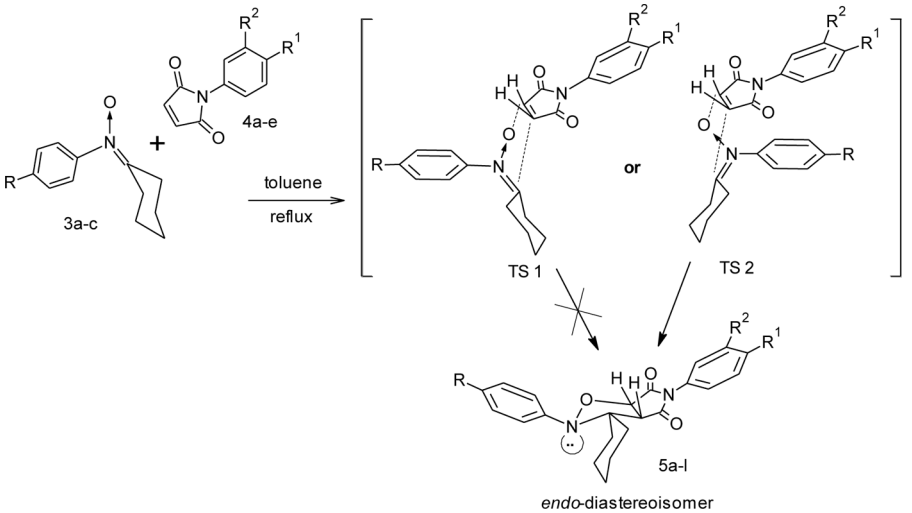


Figure 1. ^{1}H-^{1}H-COSY correlation spectrum of product **5b**.

double bond of dipole and dipolarophile as compared to the *exo* transition state (TS 1, Scheme 2) where the N-phenyl maleimide approaches from the other side of nitrone and no secondary interaction stabilization occurs. Thus, these 1,3-dipolar cycloadditions reported here are regioselective in nature, following the *cis-endo* addition rule.



Scheme 2. Possible transition state (TS).

In conclusion, the present method is facile, efficient, and catalyst-free for the synthesis of spiro-isoxazolidines cycloadduct with one *endo*-diastereoisomer. The employed N-oxide of cyclohexanone is very stable and affords end products in good yields. The attractive feature is the generation of only one stereoisomer without adopting any vigorous reaction conditions or chiral-catalyst/bio catalyst.

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT IR spectrophotometer using KBr pellets. ^{1}H NMR, ^{13}C NMR, and ^{1}H-^{1}H-COSY spectra were recorded on a 400-MHz Bruker spectrometer using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Waters Micromass Q-T of Micro (ESI) spectrometer. Elemental analysis was carried out using an Elementar Vario Micro cube CHN analyzer. Thin-layer chromatographic (TLC) plates were coated with silica gel G suspended in methanol–chloroform.

General Procedure for the Synthesis of 3-Spiro-isoxazolidines

Nitrones **3a–c** (10 mmol) and substituted N-aryl maleimides **4a–e** (10 mmol) were refluxed in toluene (20 ml) for 4.5–6.5 h (Table 1). Reaction completion was monitored by TLC using mobile phase (ethyl acetate–petroleum ether; 1:9). After the completion of the reaction, excess solvent was pulled off under vacuum, providing crude products, which were purified using silica-gel column chromatography employing ethyl acetate–petroleum ether (1:9) as eluent and recrystallized from a mixture of ethyl acetate–petroleum ether to provide only *cis* products in 61–75% yields (Table 1).

2,5-Diphenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5a)

IR (KBr): $\nu_{max} = 1786$, 1697, 1610, 1410–1220 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01–2.07 (m, 10H), 3.71 (d, 3a-H, 1H, $J = 7.58$ Hz), 4.93 (d, 6a-H, 1H, $J = 7.58$ Hz), 7.16–7.51 (m, Ar-H, 10H) ppm;^{13}C NMR ($CDCl_3$): δ 23.3, 23.5, 25.7, 28.6, 32.5, 53.2, 72.5, 74.7, 123.1, 124.2, 126.0, 126.2, 128.1, 128.9, 137.2, 143.4, 174.0, 174.5 ppm; MS: m/z: 362 $[M]^+$. Anal. calcd. for $C_{22}H_{22}N_2O_3$: C, 72.93; H, 6.08; N, 7.74. Found: C, 72.82; H, 6.18; N, 7.66.

2-Phenyl-5-p-tolyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5b)

IR (KBr): $\nu_{max} = 1785$, 1692, 1600, 1410–1220 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.02–2.04 (m, 10H), 2.38 (s, 3H), 3.76 (d, 3a-H, 1H, $J = 7.48$ Hz), 4.97 (d, 6a-H, 1H, $J = 7.44$ Hz), 7.16–7.36 (m, Ar-H, 9H) ppm;^{13}C NMR ($CDCl_3$): δ 21.3, 23.1, 23.5, 25.4, 28.9, 32.2, 53.0, 72.4, 74.4, 123.0, 126.0, 126.2, 128.1, 128.9, 129.9, 139.0, 143.2, 173.9, 174.3 ppm; MS: m/z: 376 $[M]^+$. Anal. calcd. for $C_{23}H_{24}N_2O_3$: C, 73.40; H, 6.38; N, 7.45. Found: C, 73.48; H, 6.26; N, 7.53.

2-Phenyl-5-p-anisyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5c)

IR (KBr): $\nu_{max} = 1783, 1706, 1605, 1410–1225\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.02–2.05 (m, 10H), 3.8 (s, 3H), 4.1 (d, 3a-H, 1H, $J = 7.46$ Hz), 5.3 (d, 6a-H, 1H, $J = 7.46$ Hz), 7.10-7.43 (m, Ar-H, 9H) ppm;^{13}C NMR ($CDCl_3$): δ 23.0, 23.3, 25.6, 29.0, 32.5, 53.5, 55.6, 72.2, 74.7, 113.8, 123.5, 126.2, 128.2, 128.1, 133.4, 139.4, 158.3, 173.7, 174.8 ppm; MS: m/z: 392 $[M]^+$. Anal. calcd. for $C_{23}H_{24}N_2O_4$: C, 70.41; H, 6.12; N, 7.14. Found: C, 70.35; H, 6.27; N, 7.22.

2-Phenyl-5-p-cl-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5d)

IR (KBr): $\nu_{max} = 1766, 1700, 1610, 1210–1070\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.01–2.04 (m, 10H), 4.2 (d, 3a-H, 1H, $J = 7.40$ Hz), 5.4 (d, 6a-H, 1H, $J = 7.41$ Hz), 7.25–7.55 (m, Ar-H, 9H) ppm; ^{13}C NMR ($CDCl_3$): δ 22.8, 24.0, 25.3, 28.7, 32.2, 53.7, 72.7, 74.9, 123.8, 124.2, 126.0, 126.7, 128.1, 135.0, 139.6, 143.7, 174.2, 174.8 ppm; MS: m/z: 397 $[M]^+$. Anal. calcd. for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.30; N, 7.06. Found: C, 66.61; H, 5.24; N, 7.19.

2-Phenyl-5-m-nitro-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5e)

IR (KBr): $\nu_{max} = 1784, 1699, 1610, 1410–1060\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.03–2.06 (m, 10H), 4.25 (d, 3a-H, 1H, $J = 7.45$), 5.5 (d, 6a-H, 1H, $J = 7.45$ Hz), 7.26–7.87 (m, Ar-H, 9H) ppm; ^{13}C NMR ($CDCl_3$): δ 23.1, 23.5, 25.4, 28.9, 32.2, 53.0, 72.4, 74.4, 120.1, 123.6, 125.5, 126.1, 127.1, 128.3, 132.9, 137.2, 143.2, 148.6, 173.9, 174.3 ppm; MS: m/z: 407 $[M]^+$. Anal. calcd. for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.16; N, 10.32. Found: C, 64.75; H, 5.31; N, 10.41.

2,5-p-Ditolyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5f)

IR (KBr): $\nu_{max} = 1783, 1702, 1600, 1200–1030\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.02–2.03 (m, 10H), 2.46 (s, 6H), 3.7 (d, 3a-H, 1H, $J = 7.56$ Hz), 4.6 (d, 6a-H, 1H, $J = 7.56$ Hz), 7.16–7.36 (m, Ar-H, 8H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.3, 21.8, 23.1, 23.2, 25.7, 28.8, 32.6, 53.4, 72.8, 74.7, 126.0, 126.4, 128.1, 128.6, 129.4, 129.7, 138.7, 142.9, 174.9, 175.3 ppm; MS: m/z: 390 $[M]^+$. Anal. calcd. for $C_{24}H_{26}N_2O_3$: C, 73.85; H, 6.67; N, 7.18. Found: C, 73.77; H, 6.71; N, 7.27.

2-Tolyl-5-p-anisyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5g)

IR (KBr): $\nu_{max} = 1776, 1700, 1610, 1225–1035\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.03–2.05 (m, 10H), 3.6 (d, 3a-H, 1H, $J = 7.49$ Hz), 4.8 (d, 6a-H, 1H, $J = 7.49$ Hz), 2.53 (s, 3H), 3.87 (s, OCH3, 3H), 7.12–7.45 (m, Ar-H, 8H) ppm;^{13}C NMR ($CDCl_3$): δ 22.0, 23.1, 23.0, 25.6, 29.0, 32.3, 53.3, 55.4, 72.4, 74.5, 113.5, 126.5, 127.3, 128.5,

129.5, 133.6, 139.5, 158.2, 173.7, 174.6 ppm; MS: m/z: 406 $[M]^+$. Anal. calcd. for $C_{24}H_{26}N_2O_4$: C, 70.94; H, 6.40; N, 6.90. Found: C, 71.06; H, 6.32; N, 6.98.

2-Tolyl-5-p-cl-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5h)

IR (KBr): $\nu_{max} = 1784, 1699, 1610, 1200–1070\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.06–2.07 (m, 10H), 2.83 (s, 3H), 3.9 (d, 3a-H, 1H, J = 7.44 Hz), 5.2 (d, 6a-H, 1H, J = 7.44 Hz), 7.16–7.65 (m, Ar-H, 8H) ppm;^{13}CNMR ($CDCl_3$): δ 21.8, 23.7, 23.9, 25.6, 28.8, 32.7, 53.8, 72.6, 74.4, 126.1, 126.4, 127.9, 128.5, 129.0, 134.9, 139.6, 143.2, 174.1, 174.7 ppm; MS: m/z: 411 $[M]^+$. Anal. calcd. for $C_{23}H_{23}N_2O_3Cl$: C, 67.24; H, 5.60; N, 6.82. Found: C, 67.36; H, 5.48; N, 6.87.

2-Tolyl-5-m-nitro-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5i)

IR (KBr): $\nu_{max} = 1786, 1677, 1600, 1210–1170\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.05–2.12 (m, 10H), 2.77 (s, 3H), 4.20 (d, 3a-H, 1H, $J = 7.49$), 5.43 (d, 6a-H, 1H, $J = 7.48$ Hz), 7.16–7.67 (m, Ar-H, 8H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.4, 23.2, 23.5, 25.7, 28.7, 32.25, 53.3, 73.0, 74.3, 120.8, 126.0, 126.6, 127.9, 128.1, 129.6, 132.9, 139.0, 142.7, 146.2, 173.6, 174.3 ppm; MS: m/z 421 $[M]^+$. Anal. calcd. for $C_{23}H_{23}N_3O_5$: C, 65.56; H, 5.46; N, 9.98. Found: C, 65.42; H, 5.58; N, 10.09.

2-Cl-5-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5j)

IR (KBr): $\nu_{max} = 1783, 1694, 1600, 1210–1070\,cm^{-1}$; ^1H NMR ($CDCl_3$) δ 1.07–2.09 (m, 10H), 4.1(d, 3a-H, 1H, J = 7.55 Hz), 5.3 (d, 6a-H, 1H, J = 7.55 Hz), 7.32–7.76 (m, Ar-H, 9H) ppm; ^{13}CNMR ($CDCl_3$): δ 22.9, 23.5, 25.4, 27.9, 33.0, 52.9, 73.0, 74.2, 123.3, 124.2, 126.3, 126.9, 128.4, 135.5, 138.9, 143.6, 174.3, 175.0 ppm; MS: m/z: 397 $[M]^+$. Anal. calcd. for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.30; N, 7.06. Found: C, 66.65; H, 5.21; N, 7.17.

2-Cl-phenyl-5-m-nitro-phenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo [3,4-d]isoxazole-4,6-diones (5k)

IR (KBr): $\nu_{max} = 1765, 1690, 1600, 1400–1150\,cm^{-1}$; ^1H NMR ($CDCl_3$): δ 1.03–2.06 (m,10H), 4.22 (d, 3a-H, 1H, $J = 7.48$), 5.53 (d, 6a-H, 1H, $J = 7.48$ Hz), 7.19–7.77 (m, Ar-H, 8H) ppm; ^{13}C NMR ($CDCl_3$): δ 23.4, 23.2, 24.4, 28.6, 32.7, 53.0, 72.4, 74.4, 120.4, 123.0, 126.0, 126.2, 128.1, 128.9, 129.9, 132.8, 139.0, 143.2, 149.3, 174.9, 175.7 ppm; MS: m/z: 442 $[M]^+$. Anal. calcd. for $C_{22}H_{20}N_3O_5Cl$: C, 59.80; H, 4.53; N, 9.51. Found: C, 59.73; H, 4.66; N, 9.62.

2,5-p-Dichloro-diphenyl-3,3-spiropentamethylene-5H-2,3,3a, 6a-tetrahydropyrrolo[3,4-d]isoxazole-4,6-diones (5l)

IR (KBr): $\nu_{max} = 1776, 1695, 1600, 1200–1040\,cm^{-1}$; ^1H NMR ($CDCl_3$): 1.09–2.10 (m, 10H), 4.2 (d, 3a-H, 1H, $J = 7.57$ Hz), 5.4 (d, 6a-H, 1H, $J = 7.57$ Hz),

7.35–7.65 (m, 8H) ppm;^{13}CNMR ($CDCl_3$): δ 23.8, 23.7, 25.4, 28.9, 33.2, 52.9, 72.4, 73.8, 126.3, 126.5, 127.8, 128.0, 135.3, 135.6, 142.9, 143.2, 173.3, 174.6 ppm; MS: *m/z*: 431 $[M]^+$. Anal. calcd. for $C_{22}H_{20}N_2O_3Cl_2$: C, 61.25; H, 4.64; N, 6.50. Found: C, 61.41; H, 4.57; N, 6.63.

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