Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12220–12231

Sacrificial azomethine ylide cycloaddition controlled chemoselective nitrile oxide cycloaddition to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones: formation of mono-spiro-isoxazolines

Raju Ranjith Kumar and Subbu Perumal*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai, Tamil Nadu 625021, India

Received 16 June 2007; revised 31 August 2007; accepted 13 September 2007
Available online 22 September 2007

Abstract—The 1,3-dipolar cycloaddition of an azomethine ylide to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones afforded novel spiro-pyrrolidines in good yields. Further cycloaddition of these spiro-pyrrolidines with nitrile oxide afforded mono-spiro-isoxazolines in moderate yields (45–56%), presumably via a di-spiro intermediate, which undergoes a spontaneous cycloreversion of the spiro-pyrrolidine unit. In contrast, the direct cycloaddition of nitrile oxide to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones gave the mono-spiro-isoxazoline as the minor product, while the bis-spiro-isoxazolines are formed predominantly.

1. Introduction

1,3-Dipolar cycloaddition is a versatile synthetic strategy for the construction of five-membered ring heterocycles.[1] The 1,3-dipolar cycloaddition of azomethine ylide to alkenes affords pyrrolidines, which exhibit antiviral,[2] local anaesthetic,[3] potential antileukaemic[4] and anticonvulsant activities,[4] besides occurring in alkaloids.[5] The extensive use of isatin as a precursor for 1,3-dipolar cycloaddition stems from the fact that a wide variety of azomethine ylides with primary and secondary amines can be generated and trapped with suitable dipolarophiles.[6] The piperidine substructure displays spasmolytic[7] activity and potent cytotoxicity towards human Molt 4/C8 and CEM T-lymphocytes as well as murine P388 and L1210 leukaemic cells.[8]

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes and alkynes affords isoxazoles and isoxazolines.[9–11] It is pertinent to note that isoxazolines exhibit important biological activities such as antibacterial,[12] antiplatelet,[13] antiviral,[14] anticonvulsant[15] and immunostimulatory,[16] besides being valuable synthons in the synthesis of α,β-unsaturated ketones, β-hydroxy ketones and γ-amino alcohols.[17] The dipolar cycloaddition of nitrile oxides to dipolarophiles containing exocyclic double bonds and carbonyl moieties results in the formation of spiro-isoxazolines[18] and spiro-dioxazoles,[19] respectively. The spiro-isoxazolines exhibit antitumour[20] and anti-HIV activities against the Haitian RF strain of HIV-1[21] and are useful precursors for many synthetic intermediates.[22]

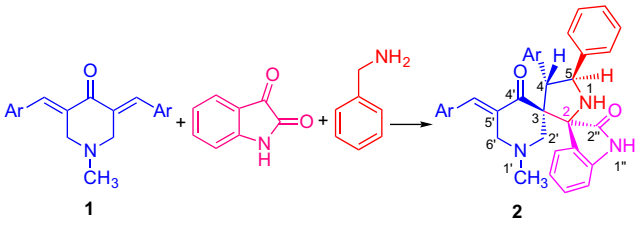
The above importance of pyrrolidines, piperidines, isoxazolines and dioxazoles led us to investigate the synthesis of novel spiro-pyrrolidines (**2** and **11**) via azomethine ylide cycloaddition to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**) and 1-cyano-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**10**) and their subsequent cycloaddition with nitrile oxide to obtain novel di-spiro heterocycles. Further, the 1,3-dipolar cycloaddition of nitrile oxide to **1** was also investigated and all these results are reported herein. Recently we have investigated the cycloaddition of (i) nitrile oxides to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones furnishing enantiomerically pure mono- and di-spiro compounds and (ii) nitrones to **1** affording novel mono- and di-spiro-isoxazolidines.[23] It is pertinent to note that the present work is the first report on the nitrile oxide cycloaddition to **1**.

2. Results and discussion

The 1,3-dipolar cycloaddition of the azomethine ylide generated in situ from isatin and benzylamine to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1a–i**) afforded novel 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(arylidene)piperidin-4-ones (**2a–i**) in good yields (80–93%) under solvent-free conditions

Keywords: Piperidone; 1,3-Dipolar cycloaddition; Azomethine ylide; Nitrile oxide; Isoxazolines; Dioxazoles.
* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.033



1 and 2	Ar	Yield (%)
a	*p*-$MeOC_6H_4$	93
b	*p*-MeC_6H_4	91
c	C_6H_5	90
d	*p*-FC_6H_4	90
e	*p*-ClC_6H_4	92
f	1-Naphthyl	80
g	*o*-ClC_6H_4	89
h	2-Thienyl	89
i	2-Furyl	80

Scheme 1. Synthesis of spiro-pyrrolidines **2**.

(Scheme 1). The reaction of an equimolar mixture of **1**, isatin and benzylamine at 85–90 °C for 10–15 s and at ambient temperature for 10 min led to a solid, which upon crystallization from ethanol led to pure **2**. This cycloaddition is chemoselective as it occurs on only one C=C of **1** furnishing exclusively the mono-spiro-pyrrolidines **2**, ascribable to the steric hindrance exerted by **2** for the second cycloaddition leading to bis-spiro-pyrrolidines. This reaction also proceeds (i) regioselectively, as the electron rich carbon of the dipole adds to the β carbon of **1** and (ii) stereoselectively, as only one diastereomer is obtained exclusively in high yield (80–93%), although four stereocentres are present in **2**. The structure of **2** is in accord with 1D and 2D NMR spectroscopic data. The HMBC correlations of **2c**, helpful in the assignment of the chemical shifts of **2**, are shown in Figure 1. The complete stereochemical information was obtained from an X-ray crystallographic study of a single crystal of **2c** (Fig. 2).[24] The piperidone and the pyrrolidine rings of **2c** are in half chair and envelope forms, respectively.

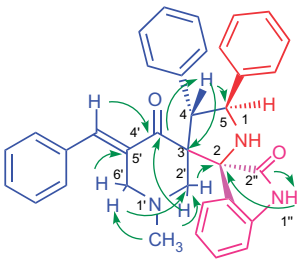


Figure 1. HMBC correlations of **2c**.

The spiro-pyrrolidines **2** were subsequently reacted with nitrile oxide (Scheme 2) generated in situ from 4-chlorobenzohydroximoyl chloride and triethylamine, with a view to obtaining di-spiro compounds **3**. However, this reaction furnished solely mono-spiro-isoxazolines **4a–h** in 45–56% yield along with unreacted **2** and a semi-solid from which no recognizable compound could be isolated and identified. The structure of **4a–h** was elucidated using NMR spectroscopic data and the HMBC correlations of **4c** are shown in Figure 3. The complete stereochemistry of **4c** was delineated by the X-ray crystallographic study of a single crystal (Fig. 4), which shows that (i) the piperidin-4-one ring adopts a half chair, while the isoxazoline ring is in an envelope conformation and (ii) the oxygen and the benzylic carbon of the isoxazoline ring are, respectively, oriented pseudo equatorially and pseudo axially from the nitrogen ring system.

Presumably, a tandem sequence comprising nitrile oxide cycloaddition to **2** to afford **3** and cycloreversion of the spiro-pyrrolidine unit of **3** to give **4** (Scheme 2) is involved in the above transformation, wherein the steric congestion in **3** might have triggered the cycloreversion. The alternative pathway for the reaction of **2** with nitrile oxide involving an initial cycloreversion of the spiro-pyrrolidine unit in **2** to **1** followed by nitrile oxide cycloaddition to **1** is ruled out by the absence of formation of a mixture of mono- and bis-spiro-isoxazolines and dioxazoles as found in the direct reaction of **1** with nitrile oxide (vide infra), wherein **4** is formed only as a minor product (10–20%) (Scheme 3). Thus, the overall transformation involving sacrificial azomethine ylide cycloaddition serves as a method to control the chemoselectivity of the nitrile oxide cycloaddition to **1**,

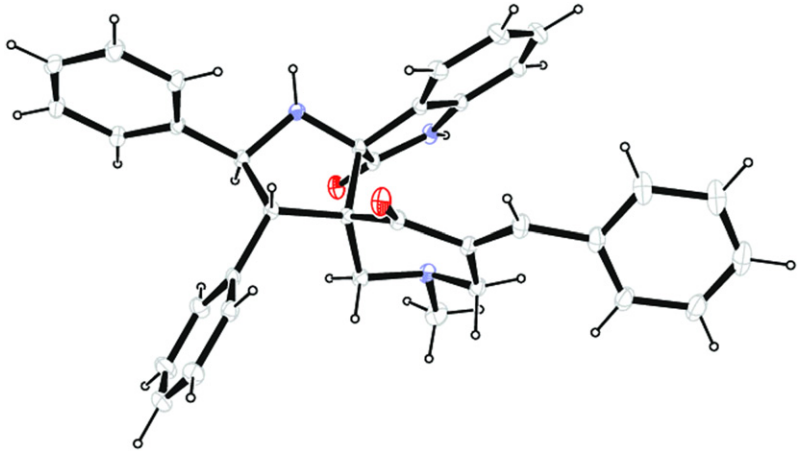
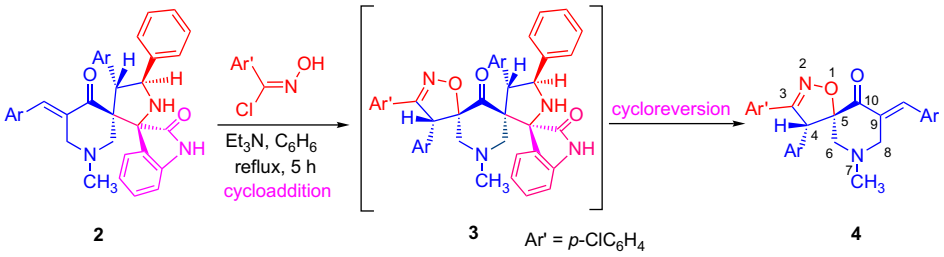


Figure 2. ORTEP diagram of **2c**.



2 and 4	Ar	Yield (%)
a	*p*-$MeOC_6H_4$	45
c	C_6H_5	56
d	*p*-FC_6H_4	55
e	*p*-ClC_6H_4	50
g	*o*-ClC_6H_4	50
h	2-Thienyl	52

Scheme 2. Chemoselective synthesis of spiro-isoxazolines **4**.

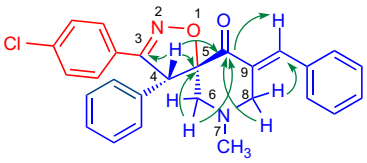


Figure 3. HMBC correlations of **4c**.

although this protocol militates against the tenet of atom economy.[25]

The 1,3-dipolar cycloaddition of nitrile oxide generated in situ from 4-chlorobenzohydroximoyl chloride and triethylamine to **1a–j** affords two diastereomeric spiro-dioxazoles (**5** and **6**), di-spiro-isoxazolines (**7**) and mono-spiro-

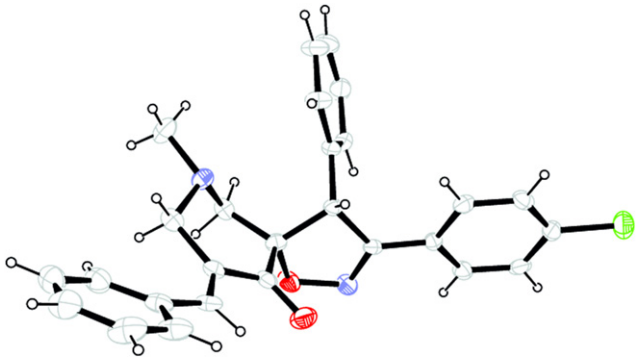
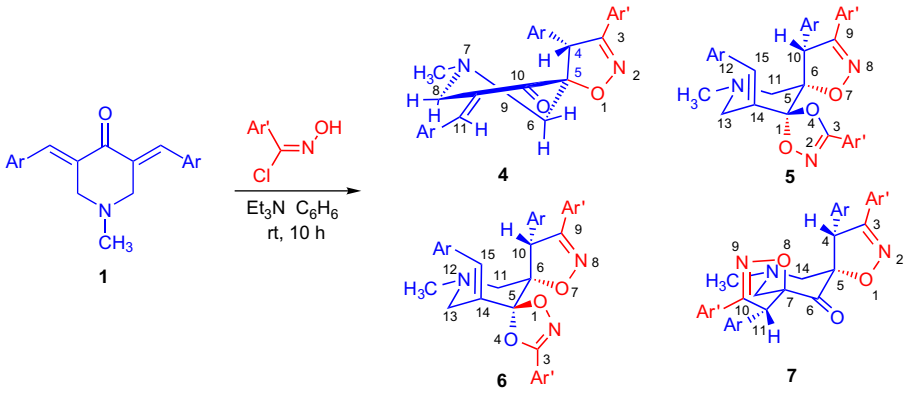


Figure 4. ORTEP diagram of **4c**.



Comp[a]	Ar	Comp[a]	Ar
a	*p*-$MeOC_6H_4$	**e**	*p*-ClC_6H_4
b	*p*-MeC_6H_4	**f**	1-Naphthyl
c	C_6H_5	**g**	*o*-ClC_6H_4
d	*p*-FC_6H_4	**j**	*m*-$NO_2C_6H_4$

[a] Ar'= *p*-ClC_6H_4 in all cases

Scheme 3. Synthesis of spiro-dioxazoles and isoxazolines.

isoxazolines (**4**) (Scheme 3). In general, **5** and **6** arising from the addition of two nitrile oxides are formed predominantly, among which, the former predominates (Table 1). Three di-spiro-isoxazolines **7b**, **7c** and **7f** were obtained in this series. The mono-spiro-isoxazolines **4** were obtained in all cases, except 1-naphthyl and *m*-nitro. No clear trend of the factors underlying the product distribution for the range of substituents in **1** is discernible from the available data (Table 1).

The structures of all the products of this cycloaddition are in accord with their NMR spectroscopic data. As representative cases, the HMBC correlations as well as the ^{1}H and ^{13}C NMR chemical shifts for **5g** and **7c** are shown in Figures 5 and 6, respectively. The di-spiro structures of **5** and **6** are clearly evident from the lack of a ^{13}C signal for carbonyl and the presence of a signal at 114 ppm due to a quaternary carbon of both compounds as expected for the spiro-dioxazoles. Also the 11-CH_2 protons show a HMBC (Fig. 5) correlation with C-5. The spiro-dioxazoles **5** and **6** also have very close ^{1}H and ^{13}C chemical shifts (Table 2) rendering their structural distinction difficult. Although the spiro-dioxazoles **5** and **6** could not be separated through column chromatography since their R_f values are almost identical, in one case, viz. **5g**, a single diastereomer was obtained on which a single crystal X-ray diffraction study could be performed (Fig. 7). The structure of **7c**[26] was also confirmed by a single crystal X-ray crystallographic study (Fig. 8). The complete stereochemistry of **6** could not be determined as pure crystals could not be obtained. However, the NMR spectroscopic

Table 1. Yield of dioxazoles and isoxazoles

Compd	Isolated yield of products (%)		
	5 and **6**[a]	**7**	**4**
a	—	—	20
b	—	28	17
c	53 (1:0.3)	20	10
d	57 (1:0.5)	—	10
e	—	—	20
f	<5 (**5**)	35	—
g	55 (**5**)	—	12
j	60 (1:0.6)	—	—

[a] Estimated from ^{1}H NMR spectra of the mixture.

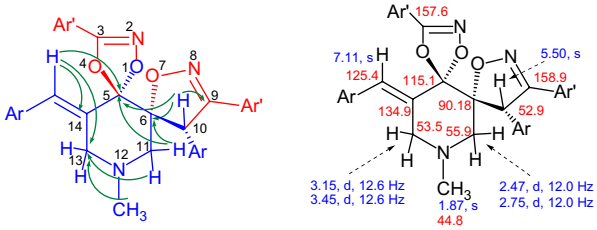


Figure 5. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **5g**.

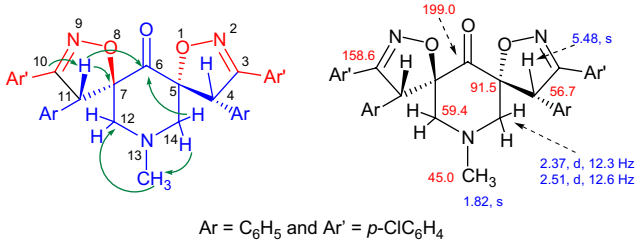


Figure 6. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **7c**.

Table 2. ^{1}H and ^{13}C NMR chemical shifts of **5d** and **6d**

Proton	δ (ppm)		Carbon	δ (ppm)	
	5d	**6d**		**5d**	**6d**
N–CH_3	2.00	1.97	N–CH_3	45.1	45.0
13-CH_2	2.37	2.31	13-CH_2	53.0	53.0
	2.57	2.66	11-CH_2	57.2	57.2
11-CH_2	3.31	3.31	7-*C*H	55.9	56.4
	3.34	3.34	6-*C*	89.1	89.4
7-*CH*	4.80	4.77	9-*C*	157.8	157.4
C=*CH*	7.00	7.00	3-*C*	158.3	158.1

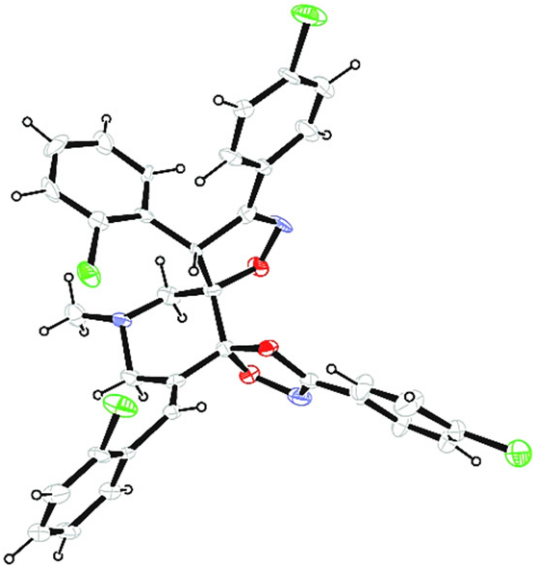


Figure 7. ORTEP diagram of **5g**.

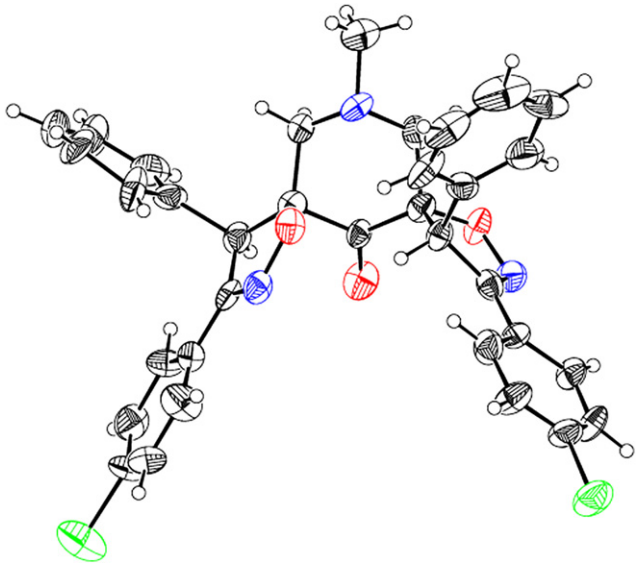


Figure 8. ORTEP diagram of **7c**.

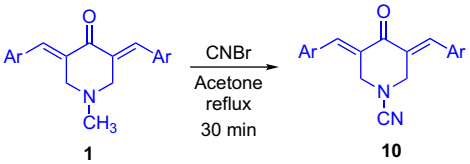
data suggest that **6** is a diastereomer of **5** and hence **6** has been tentatively assigned the structure shown in Scheme 3.

All the di-spiro compounds, **5–7** presumably arise from the cycloaddition of an initially formed isoxazoline or dioxazole. With a view to finding out which are formed from the isoxazoline **4** and/or dioxazole **8**, a separate reaction of **4c** with nitrile oxide was conducted. This reaction afforded only **7c** along with unreacted **4c** which discloses that (i) **4** serves as an intermediate for the formation of **7** alone and (ii) both **5** and **6** are formed from the cycloaddition of nitrile oxide to dioxazole **8** and its conformational diastereomer **8′** but not to **4**. The reaction of **4g** with nitrile oxide also failed to afford **5g** and **6g** in accord with the earlier conclusion that **5** and **6** are not formed via **4**.

The formation of **5** and **6** is explicable on the basis that the dioxazole can exist in the form of two interconvertible diastereomeric conformations, **8** and **8′** (Scheme 4). Presumably, the nitrile oxide adds to **8** and **8′** from the less hindered bottom side. Further, nitrile oxide cycloaddition to **8** is probably more facile than to **8′** as in the former the nitrile oxide approach is likely to be less hindered by the aryl ring of the dioxazole ring than that in the latter affording **5** more predominantly than **6**. The fact that **8** could not be found in the reaction mixture of **1** with nitrile oxide suggests that, probably, **8** is very reactive towards further cycloaddition and hence it is completely converted into **5** and **6**.

The facial selectivity involved in the formation of **7** suggests that the cycloaddition of nitrile oxide to **4** preferentially occurs from the top side of the C=C bond. This is explicable by the fact that **7** is likely to be more stable than **9**, as the latter is bound to suffer from greater 1,3-diaxial interactions than **7** (Scheme 5).

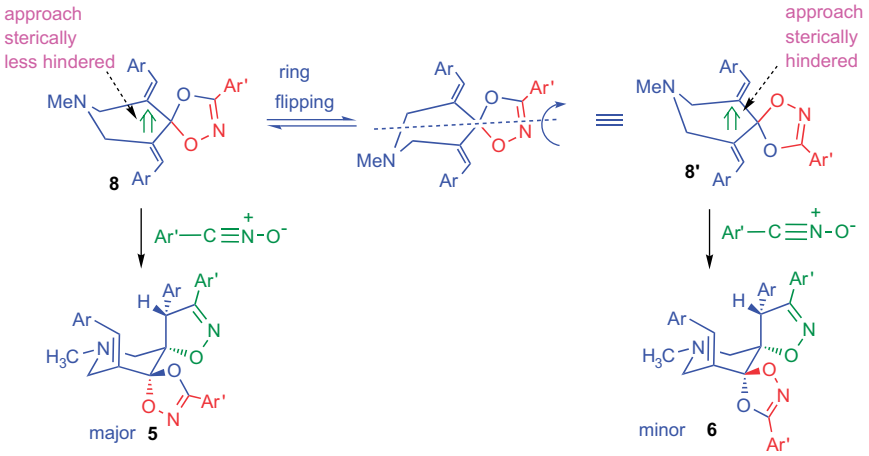
The 1-cyano-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **10** were obtained in excellent yields from the reaction of **1** with cyanogen bromide (Scheme 6) and the structural features were studied with the help of ^{1}H, ^{13}C NMR spectroscopic study and X-ray crystallography (Fig. 9).[27] The azomethine ylide cycloaddition of **10b–f**, which failed to occur under thermal conditions, led to the formation of **11b–f** in diminished yields (55–65%) under microwave irradiation (Scheme 7). The structure of **11** was elucidated using ^{1}H and ^{13}C NMR spectroscopic studies and the relative configurations at the stereocentres were assigned with the help of X-ray crystallography (Fig. 10).



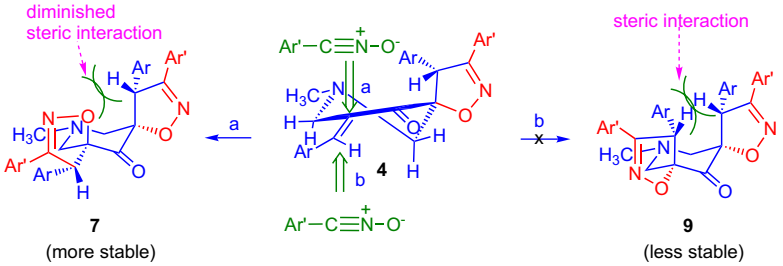
1 **10**

10	Ar	Yield (%)
b	*p*-MeC_6H_4	92
c	C_6H_5	93
e	*p*-ClC_6H_4	90
f	1-Naphthyl	90

Scheme 6. Synthesis of **10**.



Scheme 4. Conformational equilibrium of **8** and formation of **5** and **6**.



Scheme 5. Product development control in the formation of **7**.

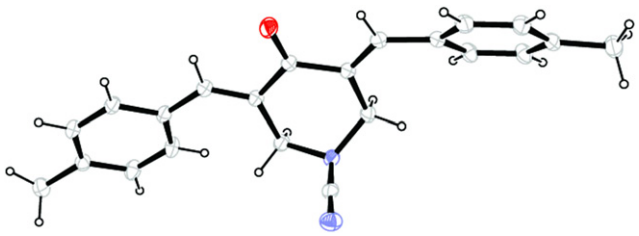
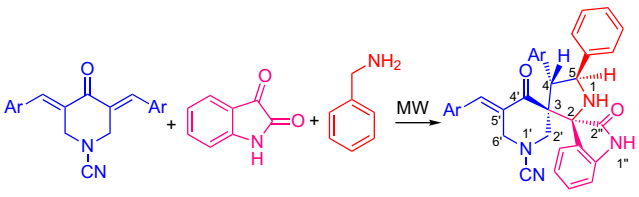


Figure 9. ORTEP diagram of **10b**.



10 **11**

11	Ar	Yield (%)	Irradiation time (min)
b	*p*-MeC_6H_4	60	3
c	C_6H_5	65	4
e	*p*-ClC_6H_4	63	5
f	1-Naphthyl	55	6

Scheme 7. Synthesis of spiro-pyrrolidines **11**.

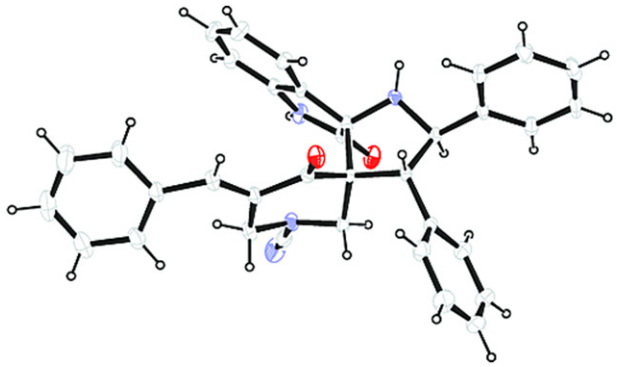


Figure 10. ORTEP diagram of **11c**.

The spiro-pyrrolidines **11** are found to be inert towards further reaction with the nitrile oxide suggesting that the cyano group attached to the nitrogen probably diminishes the transannular/homoconjugative interactions of nitrogen in **1** and **10** attenuating their reactivity relative to **1**. Similar influence of these interactions on the cycloaddition of nitrones to **1** has been inferred by our group recently.[23a]

3. Conclusions

The present work describes the 1,3-dipolar cycloaddition of azomethine ylide to 1-methyl-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones affording novel spiro-pyrrolidines in excellent yields. These spiro-pyrrolidines led to the synthesis of mono-spiro-isoxazolines, via cycloaddition–cycloreversion tandem sequence, which are otherwise obtained as a minor product in the direct nitrile oxide cycloaddition with 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones. Further cycloadditions of these dipolarophiles with other dipoles are under progress in our research group.

4. Experimental

4.1. General

The melting points were measured in open capillary tubes and are uncorrected. The ^1H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. ^{19}F NMR spectra were recorded on a Bruker DRX-500 MHz NMR spectrometer using trifluorotoluene as internal standard and $CDCl_3$ as solvent. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyzer. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and $CHCl_3$ in case of viscous liquids).The dipolarophiles **1** were synthesized according to the literature procedure.[28]

4.2. General procedure for the synthesis of 4-aryl-5-phenylpyrrolo(spiro[2.3″]-oxindole)-spiro[3.3′]-1′-methyl-5′-(arylidene)piperidin-4-ones (2)

1-Methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**1**, 1 mmol), benzylamine (1 mmol) and isatin (1 mmol) were taken in a glass tube and mixed thoroughly. The tube was placed in a water bath at 85–90 °C for 10–15 s until the mixture became a viscous paste to ensure thorough mixing and left aside for 10 min at ambient temperature. The solidified reaction mixture was warmed in ethanol (10 mL) and allowed to cool to afford pure **2**.

4.2.1. 4-(4-Methoxyphenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(4-methoxyphenylmethylidene)piperidin-4-one (2a). Obtained as yellow solid (0.156 g, 93%), mp 190–192 °C. R_f (petroleum ether/EtOAc, 4:1) 0.26; found C, 75.97; H, 5.95; N, 7.10. $C_{37}H_{35}N_3O_4$ requires C, 75.88; H, 6.02; N, 7.17; ν_{max} (KBr) 3199, 1698, 1606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54 (1H, br s, 1″-NH), 6.59–7.52 (18H, m, Ar–H), 5.35 (1H, d, *J* 11.0 Hz, 5-CH), 4.67 (1H, d, *J* 11.0 Hz, 4-CH), 3.79 (3H, s, Ar–OCH_3), 3.75 (3H, s, Ar–OCH_3), 3.43 (1H, d, *J* 13.0 Hz, 6′-CH_2), 2.97 (1H, d, *J* 13.0 Hz, 6′-CH_2), 2.14 (3H, s, N–CH_3), 1.84 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.1, 180.4, 160.2, 160.0, 141.0, 140.8, 137.1, 136.0, 132.3, 132.0, 131.7, 131.3, 130.6, 128.3, 128.0, 127.7, 127.5, 126.9, 113.7, 113.5, 108.8, 71.4, 67.1, 63.8, 57.2, 57.0, 55.3, 55.2, 44.9.

4.2.2. 4-(4-Methylphenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(4-methylphenylmethylidene)piperidin-4-one (2b). Obtained as yellow solid (0.159 g, 91%), mp 170–171 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 80.17; H, 6.29; N, 7.67. $C_{37}H_{35}N_3O_2$ requires C, 80.26; H, 6.37; N, 7.59; ν_{max} (KBr) 3168, 1695, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, br s, 1″-NH),

6.60–7.54 (18H, m, Ar–H), 5.37 (1H, d, *J* 11.1 Hz, 5-CH), 4.69 (1H, d, *J* 11.1 Hz, 4-CH), 3.41–3.50 (2H, m, 6′-CH_2 and 2′-CH_2), 2.95 (1H, d, *J* 14.4 Hz, 6′-CH_2), 2.32 (3H, s, Ar–CH_3), 2.27 (3H, s, Ar–CH_3), 2.13 (3H, s, N–CH_3), 1.82 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.8, 180.7, 141.1, 140.7, 139.0, 137.3, 136.2, 134.0, 132.9, 132.3, 130.1, 129.6, 129.4, 129.0, 128.9, 128.7, 128.2, 127.8, 127.5, 126.9, 121.9, 108.8, 71.2, 67.4, 63.6, 56.8, 55.2, 44.8, 21.3, 21.0.

4.2.3. 4-Phenyl-5-phenylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(phenylmethylidene)piperidin-4-one (2c). Obtained as yellow solid (0.163 g, 90%), mp 176–177 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 79.88; H, 6.02; N, 7.90. $C_{35}H_{31}N_3O_2$ requires C, 79.97; H, 5.94; N, 7.99; ν_{max} (KBr) 3199, 1743, 1695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.62–7.54 (21H, m, Ar–H), 5.41 (1H, d, *J* 11.0 Hz, 5-CH), 4.73 (1H, d, *J* 11.0 Hz, 4-CH), 3.50 (1H, d, *J* 12.3 Hz, 2′-CH_2), 3.43 (1H, d, *J* 14.3 Hz, 6′-CH_2), 2.94 (1H, d, *J* 14.3 Hz, 6′-CH_2), 2.42 (1H, br s, 1-NH), 2.12 (3H, s, N–CH_3), 1.80 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.8, 180.5, 141.1, 140.5, 137.2, 137.1, 135.1, 133.7, 129.9, 129.7, 129.5, 128.8, 128.6, 128.3, 128.2, 127.7, 127.5, 127.0, 126.7, 121.9, 108.9, 71.1, 67.4, 63.5, 56.9, 56.7, 55.6, 44.8.

4.2.4. 4-(4-Fluorophenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(4-fluorophenylmethylidene)piperidin-4-one (2d). Obtained as yellow solid (0.155 g, 90%), mp 169–171 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 74.94; H, 5.14; N, 7.55. $C_{35}H_{29}F_2N_3O_2$ requires C, 74.85; H, 5.20; N, 7.48; ν_{max} (KBr) 3181, 1697, 1600 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.60 (1H, br s, 1″-NH), 6.63–7.53 (18H, m, Ar–H), 5.35 (1H, d, *J* 10.8 Hz, 5-CH), 4.68 (1H, d, *J* 10.8 Hz, 4-CH), 3.45 (1H, d, *J* 12.4 Hz, 2′-CH_2), 3.40 (1H, d, *J* 14.4 Hz, 6′-CH_2), 2.93 (1H, d, *J* 14.4 Hz, 6′-CH_2), 2.14 (3H, s, N–CH_3), 1.79 (1H, d, *J* 12.4 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.7, 180.5, 121.9, 108.9, 71.1, 67.0, 63.8, 56.9, 56.7, 55.0, 44.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −135.2 (s), −130.5 (s).

4.2.5. 4-(4-Chlorophenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(4-chlorophenylmethylidene)piperidin-4-one (2e). Obtained as yellow solid (0.153 g, 92%), mp 189–190 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 70.79; H, 4.99; N, 7.00. $C_{35}H_{29}Cl_2N_3O_2$ requires C, 70.71; H, 4.92; N, 7.07; ν_{max} (KBr) 3126, 1708, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.56 (1H, br s, 1″-NH), 6.62–7.52 (18H, m, Ar–H), 5.35 (1H, d, *J* 10.8 Hz, 5-CH), 4.67 (1H, d, *J* 10.8 Hz, 4-CH), 3.45 (1H, d, *J* 12.3 Hz, 2′-CH_2), 3.38 (1H, d, *J* 14.4 Hz, 6′-CH_2), 2.93 (1H, dd, *J* 14.4, 2.4 Hz, 6′-CH_2), 2.41 (1H, br s, 1-NH), 2.14 (3H, s, N–CH_3), 1.79 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.5, 180.4, 141.1, 140.2, 135.6, 136.0, 134.8, 134.0, 133.4, 132.7, 131.1, 131.0, 129.3, 129.0, 128.6, 128.4, 128.3, 127.8, 127.7, 127.0, 122.0, 109.0, 67.1, 71.1, 63.6, 56.9, 56.7, 55.0, 44.8.

4.2.6. 4-(1-Naphthyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(1-naphthylmethylidene)piperidin-4-one (2f). Obtained as yellow solid (0.129 g, 80%), mp 220–221 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 82.61; H, 5.57; N, 6.79. $C_{43}H_{35}N_3O_2$ requires C, 82.53; H, 5.64; N, 6.72; ν_{max} (KBr) 3056, 1712, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.09 (1H, br s, 1″-NH), 6.75–8.25 (24H, m, Ar–H), 5.77 (1H, d, *J* 10.0 Hz, 5-CH), 5.60 (1H, d, *J* 10.0 Hz, 4-CH), 3.44 (1H, d, *J* 12.6 Hz, 2′-CH_2), 3.11 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.71 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 2.20 (3H, s, N–CH_3), 1.61 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.7, 179.6, 141.7, 140.9, 136.5, 134.6, 134.0, 133.9, 133.4, 133.3, 132.3, 131.3, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 127.6, 127.5, 127.4, 127.0, 126.7, 126.4, 126.3, 126.2, 125.3, 125.0, 124.9, 124.4, 122.3, 109.3, 73.1, 65.7, 65.5, 58.0, 56.9, 50.9, 45.1.

4.2.7. 4-(2-Chlorophenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(2-chlorophenylmethylidene)piperidin-4-one (2g). Obtained as yellow solid (0.148 g, 89%), mp 193–194 °C. R_f (petroleum ether/EtOAc, 4:1) 0.25; found C, 70.67; H, 4.83; N, 7.14. $C_{35}H_{29}F_2N_3O_2$ requires C, 70.71; H, 4.92; N, 7.07; ν_{max} (KBr) 3060, 1704, 1637 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.80 (1H, br s, 1″-NH), 6.69–7.65 (18H, m, Ar–H), 5.62 (1H, d, *J* 9.6 Hz, 5-CH), 5.13 (1H, d, *J* 9.6 Hz, 4-CH), 3.45 (1H, d, *J* 12.9 Hz, 2′-CH_2), 3.20 (1H, d, *J* 14.7 Hz, 6′-CH_2), 3.00 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.39 (3H, s, N–CH_3), 1.31 (1H, d, *J* 12.9 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.8, 178.7, 141.5, 140.8, 136.2, 135.1, 134.6, 133.8, 133.5, 130.5, 129.9, 129.7, 129.2, 128.6, 128.5, 128.2, 127.9, 127.7, 126.7, 126.5, 126.2, 122.6, 109.0, 74.4, 65.2, 64.2, 57.9, 57.1, 53.8, 45.6.

4.2.8. 4-(2-Thienyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(2-thienylmethylidene)piperidin-4-one (2h). Obtained as yellow solid (0.159 g, 89%), mp 175–177 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 69.34; H, 5.15; N, 7.89. $C_{31}H_{27}N_3O_2S_2$ requires C, 69.25; H, 5.06; N, 7.81; ν_{max} (KBr) 3189, 1697, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.69 (1H, br s, 1″-NH), 6.65–7.61 (16H, m, Ar–H), 5.32 (1H, d, *J* 10.3 Hz, 5-CH), 4.94 (1H, d, *J* 10.3 Hz, 4-CH), 3.43–3.51 (2H, m, 2′- and 6′-CH_2), 3.04 (1H, d, *J* 15.3 Hz, 6′-CH_2), 2.22 (3H, s, N–CH_3), 2.07 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 197.6, 180.0, 141.1, 140.5, 140.0, 138.4, 132.9, 130.6, 129.7, 129.5, 128.9, 128.3, 127.8, 127.7, 126.8, 126.7, 126.6, 124.1, 121.9, 108.9, 71.9, 66.3, 65.8, 56.8, 55.9, 51.7, 45.0.

4.2.9. 4-(2-Furyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)spiro[3.3′]-1′-methyl-5′-(2-furylmethylidene)-piperidin-4-one (2i). Obtained as yellow solid (0.150 g, 80%), mp 200–202 °C. R_f (petroleum ether/EtOAc, 4:1) 0.36; found C, 73.54; H, 5.45; N, 8.23. $C_{31}H_{27}N_3O_2S_2$ requires C, 73.65; H, 5.38; N, 8.31; ν_{max} (KBr) 3087, 1714, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, br s, 1″-NH), 6.05–7.71 (16H, m, Ar–H), 5.36 (1H, d, *J* 10.3 Hz, 5-CH), 4.68 (1H, d, *J* 10.3 Hz, 4-CH), 3.60 (1H, d, *J* 15.6 Hz, 6′-CH_2), 3.45 (1H, d, *J* 12.4 Hz, 2′-CH_2), 3.04 (1H, d, *J* 15.6 Hz, 6′-CH_2), 2.19 (3H, s, N–CH_3), 2.01 (1H, d, *J* 12.4 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 199.2, 179.7, 153.2, 152.5, 143.1, 142.6, 141.1, 140.0, 130.6, 129.7, 129.5, 128.9, 126.8, 126.6, 124.1, 121.9, 114.5, 110.3, 109.8, 108.1, 108.9, 70.2, 65.7, 64.1, 55.1, 54.7, 50.9, 44.8.

4.3. Synthesis of 3-(4-chlorophenyl)-7-methyl-4-aryl-9-[(*E*)-arylmethylidene]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-ones (4)

General procedure. A mixture of 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methyl-5′-(arylmethylidene)piperidin-4-one (**2**) (1 mmol), 4-chloro-*N*-hydroxybenzenecarboximidoyl chloride (4 mmol) and triethylamine (4 mmol) in benzene (10 mL) was heated to reflux for 5 h on a water bath. The reaction mixture was filtered to remove the triethylammonium hydrochloride and the solvent evaporated in vacuo. The residue upon column chromatography on silica gel using a petroleum ether/ethyl acetate (10:1 v/v) mixture afforded pure **4**.

4.3.1. 3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-9-[(*E*)-(4-methoxyphenyl)methylidene]-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4a). Obtained as viscous paste (0.039 g, 45%). R_f (petroleum ether/EtOAc, 4:1) 0.40; found C, 69.32; H, 5.34; N, 5.50. $C_{29}H_{27}ClN_2O_4$ requires C, 69.25; H, 5.41; N, 5.57; ν_{max} ($CHCl_3$) 1625, 1608, 1511 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, s, C═CH), 6.77–7.47 (12H, m, Ar–H), 4.93 (1H, s, 4-CH), 3.78 (3H, s, Ar–OCH_3), 3.72 (3H, s, Ar–OCH_3), 3.66 (1H, d, *J* 14.6 Hz, 8-CH_2), 3.54 (1H, d, *J* 14.6 Hz, 8-CH_2), 2.57 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.42 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.10 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 194.9, 158.2, 160.7, 159.4, 138.0, 136.8, 132.6, 131.2, 129.4, 128.8, 128.7, 127.4, 127.2, 125.3, 114.2, 114.1, 88.9, 57.9, 57.6, 56.9, 55.3, 55.2, 45.8.

4.3.2. 3-(4-Chlorophenyl)-7-methyl-4-phenyl-9-[(*E*)-phenylmethylidene]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4c). Obtained as yellow solid (0.047 g, 56%), mp 155–156 °C. R_f (petroleum ether/EtOAc, 4:1) 0.52; found C, 73.30; H, 5.15; N, 6.27. $C_{27}H_{23}ClN_2O_2$ requires C, 73.21; H, 5.23; N, 6.32; ν_{max} (KBr) 1671, 1571, 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.59 (1H, s, C═CH), 7.15–7.48 (14H, m, Ar–H), 5.00 (1H, s, 4-CH), 3.68 (1H, d, *J* 14.5 Hz, 8-CH_2), 3.55 (1H, d, *J* 14.5 Hz, 8-CH_2), 2.59 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.44 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.04 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 193.5, 157.2, 137.0, 134.9, 133.7, 132.3, 130.8, 129.5, 128.5, 128.0, 127.8, 127.6, 127.3, 126.0, 88.1, 57.0, 56.9, 55.6, 44.7.

4.3.3. 4-(4-Chlorophenyl)-4-(4-fluorophenyl)-9-[(*E*)-(4-fluorophenyl)methylidene]-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4d). Obtained as viscous paste (0.047 g, 55%). R_f (petroleum ether/EtOAc, 4:1) 0.52; found C, 67.77; H, 4.48; N, 5.92. $C_{27}H_{21}ClF_2N_2O_2$ requires C, 67.71; H, 4.42; N, 5.85; ν_{max} ($CHCl_3$) 1666, 1598, 1508 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.53 (1H, s, C═CH), 6.96–7.45 (12H, m, Ar–H), 4.97 (1H, s, 4-CH), 3.61 (1H, d, *J* 14.4 Hz, 8-CH_2), 3.53 (1H, d, *J* 14.4 Hz, 8-CH_2), 2.57 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.41 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.05 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 194.5, 158.0, 88.9, 57.7, 57.3, 56.5, 45.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −133.2 (s), −131.9 (s).

4.3.4. 3,4-Bis(4-chlorophenyl)-9-[(*E*)-(4-chlorophenyl)-methylidene]-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4e). Obtained as yellow solid (0.043 g, 50%), mp 183–185 °C. R_f (petroleum ether/EtOAc, 4:1) 0.52; found C, 63.30; H, 4.21; N, 5.55. $C_{27}H_{21}Cl_3N_2O_2$ requires C, 63.36; H, 4.14; N, 5.47; ν_{max} (KBr) 1650, 1594, 1490 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.51 (1H, s, C═CH), 7.13–7.48 (12H, m, Ar–H), 4.97 (1H, s, 4-CH), 3.63 (1H, d, *J* 14.4 Hz, 8-CH_2), 3.52 (1H, d, *J* 14.4 Hz, 8-CH_2), 2.58 (1H, d, *J* 12.7 Hz, 6-CH_2), 2.42 (1H, d, *J* 12.7 Hz, 6-CH_2), 2.07 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 193.3, 157.0, 135.6, 135.2, 133.5, 132.0, 131.1, 130.7, 130.6, 129.8, 128.3, 127.9, 127.7, 127.6, 127.0, 125.6, 88.0, 56.9, 56.2, 55.5, 44.8.

4.3.5. 4-(2-Chlorophenyl)-3-(4-chlorophenyl)-9-[(*E*)-(2-chlorophenyl)methylidene]-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4g). Obtained as yellow solid (0.043 g, 50%), mp 175–177 °C. R_f (petroleum ether/EtOAc, 4:1) 0.52; found C, 63.29; H, 4.07; N, 5.51. $C_{27}H_{21}Cl_3N_2O_2$ requires C, 63.36; H, 4.14; N, 5.47; ν_{max} (KBr) 1700, 1625, 1594 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82 (1H, s, C═CH), 7.01–7.52 (12H, m, Ar–H), 5.74 (1H, s, 4-CH), 3.67 (1H, d, *J* 14.3 Hz, 8-CH_2), 3.39 (1H, d, *J* 14.3 Hz, 8-CH_2), 2.66 (1H, d, *J* 12.9 Hz, 6-CH_2), 2.49 (1H, d, *J* 12.6 Hz, 6-CH_2), 2.10 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 193.1, 157.7, 140.2, 137.0, 135.0, 133.7, 133.1, 132.6, 132.4, 132.1, 130.4, 129.0, 128.7, 126.9, 126.5, 124.7, 127.4, 126.4, 88.9, 58.4, 57.7, 53.5, 45.3.

4.3.6. 3-(4-Chlorophenyl)-7-methyl-4-(2-thienyl)-9-[(*E*)-2-thienylmethylidene]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (4h). Obtained as yellow solid (0.044 g, 52%), mp 159–161 °C. R_f (petroleum ether/EtOAc, 4:1) 0.52; found C, 60.65; H, 4.12; N, 6.25. $C_{23}H_{19}ClN_2O_2S_2$ requires C, 60.71; H, 4.21; N, 6.16; ν_{max} (KBr) 1617, 1571, 1492 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.80 (1H, s, C═CH), 6.80–7.58 (10H, m, Ar–H), 5.24 (1H, s, 4-CH), 3.69 (1H, d, *J* 16.8 Hz, 8-CH_2), 3.63 (1H, d, *J* 16.8 Hz, 8-CH_2), 2.71 (1H, d, *J* 12.6 Hz, 6-CH_2), 2.59 (1H, d, *J* 12.6 Hz, 6-CH_2), 2.22 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 194.2, 157.5, 138.2, 136.0, 135.6, 134.2, 131.7, 130.7, 128.8, 128.7, 128.5, 128.1, 127.8, 127.5, 127.0, 126.5, 88.5, 57.2, 56.9, 53.2, 46.1.

4.4. Cycloaddition of 4-chlorobenzohydroximoyl chloride with 3,5-bis(arylidene)-1-methylpiperidin-4-ones

General procedure. 1-Methyl-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinone (**1**, 1 mmol) was dissolved in benzene (15 mL). To this solution, 4-chlorobenzohydroximoyl chloride (5 mmol) was added and the mixture was stirred at room temperature. Triethylamine (5 mmol) dissolved in benzene (10 mL) was added dropwise to the above mixture and stirring continued for 9–10 h. The reaction mixture was filtered to remove the triethylamine hydrochloride, the solvent evaporated in vacuo and the residue subjected to column chromatography on silica gel (petroleum ether/EtOAc, 10:1).

4.4.1. Diastereoisomers of 3,9-bis(4-chlorophenyl)-12-methyl-10-phenyl-14-[(*E*)-phenylmethylidene]-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene (5c/6c). Obtained as white solid, overall yield 53%. R_f (petroleum ether/EtOAc, 4:1) 0.72; found C, 68.59; H, 4.41; N, 7.12. $C_{34}H_{27}Cl_2N_3O_3$ requires C, 68.46; H, 4.56; N, 7.04; ν_{max} (KBr) 1678, 1610, 1545, 1510, 1410, 1402 cm^{-1}.

4.4.1.1. Data for compound 5c. δ_H (300 MHz, $CDCl_3$) 7.10–7.67 (18H, m, Ar–H), 7.00 (1H, s, C═CH), 4.74 (1H, s, 7-CH), 3.37 (1H, d, *J* 13.4 Hz, 11-CH_2), 3.27 (1H, d, *J* 13.4 Hz, 11-CH_2), 2.49 (1H, d, *J* 12.9 Hz, 13-CH_2), 2.31 (1H, d, *J* 12.9 Hz, 13-CH_2), 1.89 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 157.3, 156.9, 136.9, 135.0, 134.8, 134.3, 131.9, 129.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 127.0, 126.8, 126.0, 119.8, 113.8, 88.3, 56.3, 55.6, 52.0, 44.0.

4.4.1.2. Data for compound 6c. δ_H (300 MHz, $CDCl_3$) 7.20–7.67 (18H, m, Ar–H), 7.00 (1H, s, C═CH), 4.72 (1H, s, 7-CH), 3.37 (1H, d, *J* 13.3 Hz, 11-CH_2), 3.27 (1H, d, *J* 13.3 Hz, 11-CH_2), 2.58 (1H, d, *J* 12.9 Hz, 13-CH_2), 2.36 (1H, d, *J* 12.9 Hz, 13-CH_2), 1.34 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 157.3, 156.9, 137.2, 135.0, 134.9, 134.3, 132.0, 126.0, 88.4, 56.3, 55.1, 52.0, 43.7.

4.4.2. Diastereoisomers of 3,9-bis(4-chlorophenyl)-10-(4-fluorophenyl)-14-[(*E*)-(4-fluorophenyl)methylidene]-12-methyl-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene (5d/6d). Obtained as white solid, overall yield 57%. R_f (petroleum ether/EtOAc, 4:1) 0.72; found C, 64.43; H, 4.10; N, 6.73. $C_{34}H_{25}Cl_2F_2N_3O_3$ requires C, 64.57; H, 3.98; N, 6.64; ν_{max} (KBr) 1629, 1600, 1562, 1513, 1432, 1402 cm^{-1}.

4.4.2.1. Data for compound 5d. δ_H (300 MHz, $CDCl_3$) 7.03–7.75 (16H, m, Ar–H), 7.00 (1H, s, C═CH), 4.80 (1H, s, 7-CH), 3.34 (1H, d, *J* 12.9 Hz, 11-CH_2), 3.31 (1H, d, *J* 12.9 Hz, 11-CH_2), 2.57 (1H, d, *J* 12.9 Hz, 13-CH_2), 2.37 (1H, d, *J* 12.9 Hz, 13-CH_2), 2.00 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 158.3, 157.8, 136.0, 127.6, 114.6, 89.1, 57.2, 56.4, 53.0, 45.1.

4.4.2.2. Data for compound 6d. δ_H (300 MHz, $CDCl_3$) 7.03–7.75 (16H, m, Ar–H), 7.00 (1H, s, C═CH), 4.77 (1H, s, 7-CH), 3.34 (1H, d, *J* 12.9 Hz, 11-CH_2), 3.31 (1H, d, *J* 12.9 Hz, 11-CH_2), 2.66 (1H, d, *J* 13.3 Hz, 13-CH_2), 2.31 (1H, d, *J* 13.3 Hz, 13-CH_2), 1.97 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 158.1, 157.4, 136.1, 127.0, 115.3, 89.5, 55.9, 55.9, 53.0, 45.0.

4.4.3. 10-(2-chlorophenyl)-3,9-bis(4-chlorophenyl)-14-[(*E*)-(2-chlorophenyl)methylidene]-12-methyl-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene (5g). Obtained as white solid (0.256 g, 55%), mp 197–199 °C. R_f (petroleum ether/EtOAc, 4:1) 0.72; found C, 61.46; H, 3.72; N, 6.25. $C_{34}H_{25}Cl_4N_3O_3$ requires C, 61.37; H, 3.79; N, 6.32%; ν_{max} (KBr) 1627, 1596, 1494, 1403 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.15–7.64 (16H, m, Ar–H), 7.11 (1H, s, C═CH), 5.50 (1H, s, 7-CH), 3.45 (1H, d, *J* 12.3 Hz, 11-CH_2), 3.15 (1H, d, *J* 12.3 Hz, 11-CH_2), 2.75 (1H, d, *J* 12.6 Hz, 13-CH_2), 2.47 (1H, d, *J* 12.6 Hz, 13-CH_2), 1.87 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 158.9, 157.6, 137.8, 136.2, 134.9, 134.0, 133.7, 131.6, 131.4, 130.8, 130.4, 129.7, 129.6, 129.3, 129.2, 129.1, 129.0, 128.4, 128.0, 127.0, 126.6, 126.5, 125.4, 121.0, 115.1, 90.2, 55.9, 53.5, 52.9, 44.8.

4.4.4. Diastereoisomers of 3,9-bis(4-chlorophenyl)-12-methyl-10-(3-nitrophenyl)-14-[(*E*)-(3-nitrophenyl)methylidene]-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene (5h/6h). Obtained as white solid, overall yield 60%. R_f (petroleum ether/EtOAc, 4:1) 0.68; found C, 59.40; H, 3.71; N, 10.33. $C_{34}H_{25}Cl_2N_5O_7$ requires C, 59.49; H, 3.67; N, 10.20; ν_{max} (KBr) 1596, 1529, 1509, 1492, 1402, 1439 cm^{-1}.

4.4.4.1. Data for compound 5h. δ_H (300 MHz, $CDCl_3$) 7.21–8.22 (16H, m, Ar–H), 7.20 (1H, s, C═CH), 4.93 (1H, s, 7-CH), 3.56 (1H, d, *J* 12.9 Hz, 11-CH_2), 3.22 (1H, d, *J* 12.9 Hz, 11-CH_2), 2.66 (1H, d, *J* 13.3 Hz, 13-CH_2), 2.36 (1H, d, *J* 13.3 Hz, 13-CH_2), 1.92 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 158.3, 157.2, 148.3, 148.1, 138.3, 136.6, 136.5, 135.0, 132.6, 129.7, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 128.3, 128.0, 126.0, 123.9, 123.2, 122.9, 120.4, 127.0, 114.2, 89.2, 56.7, 56.4, 52.8, 44.9.

4.4.4.2. Data for compound 6h. δ_H (300 MHz, $CDCl_3$) 7.21–8.22 (16H, m, Ar–H), 7.20 (1H, s, C═CH), 4.93 (1H, s, 7-CH), 3.56 (1H, d, *J* 12.0 Hz, 11-CH_2), 3.22 (1H, d, *J* 12.0 Hz, 11-CH_2), 2.73 (1H, d, *J* 12.0 Hz, 13-CH_2), 2.27 (1H, d, *J* 12 Hz, 13-CH_2), 1.92 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 157.5, 157.4, 132.7, 127.1, 114.5, 89.7, 56.7, 56.4, 52.8, 44.9.

4.4.5. 3,10-Bis(4-chlorophenyl)-13-methyl-4,11-bis(4-methylphenyl)-1,8-dioxa-2,9,13-triazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (7b). Obtained as viscous paste (0.138 g, 28%). R_f (petroleum ether/EtOAc, 4:1) 0.54; found C, 69.29; H, 5.07; N, 6.65. $C_{36}H_{31}Cl_2N_3O_3$ requires C, 69.23; H, 5.00; N, 6.73%; ν_{max} ($CHCl_3$) 1717, 1598, 1490, 1450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.00–7.53 (16H, m, Ar–H), 5.36 (2H, s, 1,8-CH), 2.43 (2H, d, *J* 12.9 Hz, 12-CH_2 and 14-CH_2), 2.31 (2H, d, *J* 12.9 Hz, 12-CH_2 and 14-CH_2), 2.23 (6H, s, Ar–CH_3) 1.77 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 198.2, 157.7, 138.9, 135.1, 129.9, 128.6, 127.8, 127.7, 126.2, 90.4, 58.4, 55.4, 44.1, 20.1.

4.4.6. 3,10-Bis(4-chlorophenyl)-13-methyl-4,11-diphenyl-1,8-dioxa-2,9,13-triazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (7c). Obtained as white solid (0.103 g, 20%), mp 180–182 °C. R_f (petroleum ether/EtOAc, 4:1) 0.54; found C, 68.51; H, 4.52; N, 7.12. $C_{34}H_{27}Cl_2N_3O_3$ requires C, 68.46; H, 4.56; N, 7.04%; ν_{max} (KBr) 1729, 1594, 1492, 1455 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.22–7.53 (18H, m, Ar–H), 5.48 (2H, s, 1,8-CH), 2.51 (2H, d, *J* 12.9 Hz, 12-CH_2 and 14-CH_2), 2.37 (2H, d, *J* 12.9 Hz, 12-CH_2 and 14-CH_2), 1.83 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 199.0, 158.6, 136.3, 132.3, 129.0, 128.9, 128.8, 128.4, 126.6, 91.5, 59.4, 56.7, 45.0.

4.4.7. 3,10-Bis(4-chlorophenyl)-13-methyl-4,11-di(1-naphthyl)-1,8-dioxa-2,9,13-triazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (7f). Obtained as viscous paste (0.157 g, 35%). R_f (petroleum ether/EtOAc, 4:1) 0.54; found C, 72.48; H, 4.56; N, 6.12. $C_{42}H_{31}Cl_2N_3O_3$ requires C, 72.41; H, 4.49; N, 6.03%; ν_{max} ($CHCl_3$) 1729, 1627, 1596, 1492 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.97–8.58 (22H, m, Ar–H), 6.30 (2H, s, 1,8-CH), 2.37 (2H, d, *J* 13.3 Hz, 12-CH_2 and 14-CH_2), 2.12 (2H, d, *J* 13.3 Hz, 12-CH_2 and 14-CH_2), 1.75 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 198.3, 158.6, 135.2, 133.1, 130.7, 128.2, 127.9, 127.7, 127.6, 126.6, 126.2, 125.6, 125.2, 124.9, 124.3, 122.9, 91.4, 57.9, 50.7, 43.3.

4.4.8. 3-(4-Chlorophenyl)-7-methyl-4-(4-methylphenyl)-9-[(*E*)-(4-methylphenyl)methylidene]-1-oxa-2,7-

diazaspiro[4.5]dec-2-en-10-one (4b). Obtained as yellow solid (0.063 g, 17%), mp 162–164 °C. R_f (petroleum ether/EtOAc, 4:1) 0.54; found C, 74.02; H, 5.70; N, 5.87. $C_{29}H_{27}ClN_2O_2$ requires C, 73.95; H, 5.78; N, 5.95%; ν_{max} (KBr) 1675, 1560, 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.00–7.53 (12H, m, Ar–H), 7.56 (1H, s, C═CH), 4.96 (1H, s, 1-CH), 3.67 (1H, d, *J* 14.2 Hz, 8-CH_2), 3.51 (1H, d, *J* 14.2 Hz, 8-CH_2), 2.57 (1H, d, *J* 13.3 Hz, 6-CH_2), 2.42 (1H, d, *J* 13.3 Hz, 6-CH_2), 2.30 (3H, s, Ar–CH_3), 2.23 (3H, s, Ar–CH_3), 2.05 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 193.8, 157.3, 138.9, 137.0, 137.2, 135.1, 134.8, 131.0, 129.6, 129.5, 129.2, 128.3, 128.2, 127.8, 127.7, 125.7, 88.0, 57.1, 56.7, 55.8, 44.8, 21.1, 20.4.

4.5. General procedure for the synthesis of 1-cyano-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones (10)

General procedure. A mixture of 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**1**, 1 mmol), cyanogen bromide (1 mmol) and potassium carbonate (1 mmol) in acetone (20 mL) was refluxed for 30 min. After completion of the reaction as judged by TLC (petroleum ether/ethyl acetate, 4:1), the mixture was poured into water (50 mL) and the precipitated **10** was filtered and washed with water (100 mL). *Caution! cyanogen bromide is a poison, may be fatal if inhaled or swallowed; causes burns and severe irritation*.

4.5.1. 1-Cyano-3,5-bis[(*E*)-(4-methylphenyl)methylidene]tetrahydro-4(1*H*)-pyridinone (10b). Obtained as yellow solid (0.476 g, 92%), mp 146–147 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45; found C, 80.37; H, 6.23; N, 8.47. $C_{22}H_{20}N_2O$ requires C, 80.46; H, 6.14; N, 8.53; ν_{max} (KBr) 2211, 1594 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (2H, s, C═CH), 7.26 (8H, s, Ar–H), 4.55 (4H, s, 2-CH_2 and 6-CH_2), 2.41 (6H, s, Ar–CH_3); δ_C (75 MHz, $CDCl_3$) 184.0, 140.4, 139.3, 131.2, 130.4, 129.5, 128.6, 116.8, 50.6, 21.4.

4.5.2. 1-Cyano-3,5-bis[(*E*)-phenylmethylidene]tetrahydro-4(1*H*)-pyridinone (10c). Obtained as yellow solid (0.483 g, 93%), mp 141–143 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45; found C, 79.90; H, 5.46; N, 9.40. $C_{20}H_{16}N_2O$ requires C, 79.98; H, 5.37; N, 9.33; ν_{max} (KBr) 2215, 1608 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.96 (2H, s, C═CH), 7.33–7.48 (10H, m, Ar–H), 4.55 (4H, s, 2-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$) 184.1, 139.5, 134.0, 130.3, 130.0, 129.4, 128.9, 116.7, 50.6.

4.5.3. 3,5-Bis[(*E*)-(4-chlorophenyl)methylidene]-1-cyanotetrahydro-4(1*H*)-pyridinone (10e). Obtained as yellow solid (0.465 g, 90%), mp 198–199 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45; found C, 65.14; H, 3.90; N, 7.49. $C_{20}H_{14}Cl_2N_2O$ requires C, 65.06; H, 3.82; N, 7.59; ν_{max} (KBr) 2217, 1606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.89 (2H, s, C═CH), 7.44 (4H, d, *J* 8.1 Hz, Ar–H), 7.28 (4H, d, *J* 8.1 Hz, Ar–H), 4.51 (4H, s, 2-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$) 183.7, 138.4, 136.3, 132.3, 131.6, 129.7, 129.3, 116.5, 50.6.

4.5.4. 1-Cyano-3,5-bis[(*E*)-1-naphthylmethylidene]tetrahydro-4(1*H*)-pyridinone (10f). Obtained as yellow solid (0.463 g, 90%), mp 142–144 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45; found C, 84.05; H, 4.97; N, 7.09. $C_{28}H_{20}N_2O$ requires C, 83.98; H, 5.03; N, 7.00; ν_{max} (KBr) 2210, 1600 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.61 (2H, s, C═CH), 7.24–8.02 (14H, s, Ar–H), 4.39 (4H, s, 2-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$) 184.1, 138.1, 133.5, 131.6, 131.3, 131.0, 130.3, 128.7, 127.1, 127.0, 126.6, 124.9, 124.4, 116.5, 50.7.

4.6. General procedure for the synthesis of 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-cyano-5′-(arylidene)piperidin-4-ones (11)

General procedure. In a glass tube, 1-cyano-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**10**, 1 mmol), benzylamine (1 mmol) and isatin (1 mmol) were thoroughly mixed and the open glass tube was partially immersed in a silica bath in a microwave oven (IFB, model-Electron of 1000 W capacity and microwave frequency of 2450 MHz) and irradiated in 1 min durations for 3–6 min at power level 5. After each irradiation, the reaction mixture was cooled to room temperature and mixed well. The maximum temperature of the silica bath, measured immediately after irradiation by stirring the silica bath with a thermometer, was found to be 85 °C. The reaction mixture was then subjected to column chromatography on silica gel employing petroleum ether/ethyl acetate mixture (10:1 v/v) as eluent to obtain **11**.

4.6.1. 4-(4-Methylphenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-cyano-5′-(4-methylphenylmethylidene)piperidin-4-one (11b). Obtained as yellow solid (0.206 g, 60%), mp 188–190 °C. R_f (petroleum ether/EtOAc, 4:1) 0.32; found C, 78.77; H, 5.64; N, 9.85. $C_{37}H_{32}N_4O_2$ requires C, 78.70; H, 5.71; N, 9.92; ν_{max} (KBr) 3390, 3310, 2205, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.39 (1H, s, 1″-NH), 7.47 (1H, s, C═CH), 6.84–7.79 (17H, m, Ar–H), 5.53 (1H, d, *J* 10.8 Hz, 5-CH), 4.67 (1H, d, *J* 10.8 Hz, 4-CH), 4.09 (1H, dd, *J* 15.6, 2.4 Hz, 6′-CH_2), 4.02 (1H, d, *J* 14.3 Hz, 2′-CH_2), 3.61 (1H, d, *J* 15.6 Hz, 6′-CH_2), 2.74 (1H, d, *J* 14.3 Hz, 2′-CH_2), 2.64 (1H, br s, 1-NH), 2.33 (3H, s, Ar–CH_3), 2.28 (3H, s, Ar–CH_3); δ_C (75 MHz, $CDCl_3$) 195.5, 179.8, 141.5, 140.5, 139.4, 137.0, 132.9, 130.8, 130.3, 129.6, 129.4, 128.4, 128.2, 127.9, 127.6, 127.5, 127.3, 126.9, 122.3, 116.8, 110.0, 71.6, 65.0, 64.2, 56.1, 51.4, 49.1, 21.4, 21.0.

4.6.2. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-cyano-5′-(phenylmethylidene)piperidine-4-one (11c). Obtained as yellow solid (0.232 g, 65%), mp 170–173 °C. R_f (petroleum ether/EtOAc, 4:1) 0.32; found C, 78.26; H, 5.19; N, 10.53. $C_{35}H_{28}N_4O_2$ requires C, 78.34; H, 5.26; N, 10.44; ν_{max} (KBr) 3380, 3324, 2215, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (1H, s, 1″-NH), 7.45 (1H, s, C═CH), 6.97–7.59 (19H, m, Ar–H), 5.58 (1H, d, *J* 10.0 Hz, 5-CH), 4.70 (1H, d, *J* 10.0 Hz, 4-CH), 4.11 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 4.03 (1H, d, *J* 14.3 Hz, 2′-CH_2), 3.60 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.73 (1H, d, *J* 14.3 Hz, 2′-CH_2), 2.60 (1H, br s, 1-NH); δ_C (75 MHz, $CDCl_3$) 195.4, 179.6, 141.5, 140.8, 140.7, 136.1, 133.6, 130.1, 129.9, 129.8, 129.7, 128.7, 128.3, 127.7, 127.5, 127.4, 127.1, 126.9, 122.4, 116.6, 110.1, 71.5, 64.6, 64.1, 56.4, 51.4, 49.0.

4.6.3. 4-(4-Chlorophenyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)-spiro[3.3′]-1′-cyano-5′-(4-chlorophenylmethylidene)piperidin-4-one (11e). Obtained as yellow solid (0.207 g, 63%), mp 200–202 °C. R_f (petroleum ether/EtOAc, 4:1) 0.32; found C, 69.49; H, 4.26; N, 9.33. $C_{35}H_{26}Cl_2N_4O_2$ requires C, 69.42; H, 4.33; N, 9.25; ν_{max} (KBr) 3385, 3330, 2210, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.39 (1H, s, 1″-NH), 7.49 (1H, s, C=CH), 6.91–7.77 (17H, m, Ar–H), 5.48 (1H, d, *J* 10.3 Hz, 5-CH), 4.64 (1H, d, *J* 10.3 Hz, 4-CH), 4.06 (1H, dd, *J* 15.3, 2.4 Hz, 6′-CH_2), 4.01 (1H, d, *J* 14.0 Hz, 2′-CH_2), 3.57 (1H, d, *J* 15.3 Hz, 6′-CH_2), 2.73 (1H, d, *J* 14.0 Hz, 2′-CH_2), 2.62 (1H, br s, 1-NH); δ_C (75 MHz, $CDCl_3$) 195.0, 179.7, 141.7, 140.3, 139.5, 136.2, 133.4, 131.3, 130.8, 129.9, 129.3, 129.0, 128.9, 128.6, 128.5, 127.9, 127.4, 126.9, 122.4, 116.5, 110.3, 71.5, 64.9, 64.4, 55.8, 51.3, 48.9.

4.6.4. 4-(1-Naphthyl)-5-phenylpyrrolo(spiro[2.3″]-oxindole)-spiro[3.3′]-1′-cyano-5′-(1-naphthylmethylidene)piperidin-4-one (11f). Obtained as yellow solid (0.175 g, 55%), mp 194–196 °C. R_f (petroleum ether/EtOAc, 4:1) 0.32; found C, 81.19; H, 5.00; N, 8.86. $C_{43}H_{32}N_4O_2$ requires C, 81.11; H, 5.07; N, 8.80; ν_{max} (KBr) 3382, 3329, 2215, 1710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.62 (1H, s, 1″-NH), 8.35 (1H, s, C=CH), 6.81–8.38 (19H, m, Ar–H), 5.97 (1H, d, *J* 10.8 Hz, 5-CH), 5.54 (1H, d, *J* 10.8 Hz, 4-CH), 3.79 (1H, dd, *J* 15.6, 2.4 Hz, 6′-CH_2), 3.76 (1H, d, *J* 14.3 Hz, 2′-CH_2), 3.21 (1H, d, *J* 15.6 Hz, 6′-CH_2), 2.49 (1H, d, *J* 14.3 Hz, 2′-CH_2), 2.78 (1H, br s, 1-NH); δ_C (75 MHz, $CDCl_3$) 196.9, 179.6, 141.1, 139.7, 138.3, 136.1, 134.0, 133.6, 133.4, 133.3, 132.5, 131.4, 130.8, 130.5, 130.3, 129.9, 128.6, 128.5, 128.3, 128.0, 127.6, 127.2, 127.0, 126.9, 126.7, 126.6, 125.8, 125.0, 124.5, 124.2, 123.3, 122.6, 116.5, 110.5, 72.8, 65.0, 64.3, 51.4, 50.9, 48.4.

4.7. X-ray crystal structure determination of 4c

The unit cell was measured by centring 25 reflections and refined by full-matrix least-squares on F^2. Empirical formula $C_{27}H_{23}ClN_2O_2$; formula weight 442.92; crystal system monoclinic; space group *P*21/*n*. The unit cell dimensions are *a*=10.564(6) Å, *b*=17.656(9) Å, *c*=12.512(7) Å, α=90.00°, β=95.110(12)°, γ=90.00°, *V*=2324(2) $Å^3$, *Z*=4, D_{calcd}=1.266 Mg m^{-3}, μ=0.191 mm^{-1}, *T*=293(2) K, *F*(000)=928. The reflections collected were 4623 of which 4082 unique [R_{int}=0.1244]; 1203 $I>2\sigma(I)$, R_1=0.0770 and ωR_2=0.1616 for 1203 [$I>2\sigma(I)$] and R_1=0.2750, ωR_2=0.2407 for all (4623) intensity data. Goodness of fit=0.951, residual electron density in the final Fourier map was 0.253 and −0.278 e$Å^{-3}$. CCDC number is 644050. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].

4.8. X-ray crystal structure determination of 5g

The unit cell was measured by centring 25 reflections and refined by full-matrix least-squares on F^2. Empirical formula $C_{34}H_{25}Cl_4N_3O_3$; formula weight 665.37; crystal system monoclinic; space group *P*21/*n*. The unit cell dimensions are *a*=11.196(8) Å, *b*=12.578(9) Å, *c*=25.102(15) Å, α=90.00°, β=92.20(3)°, γ=90.00°, *V*=3532(4) $Å^3$, *Z*=4, D_{calcd}=1.251 Mg m^{-3}, μ=0.371 mm^{-1}, *T*=293(2) K, *F*(000)=1368. The reflections collected were 3483 of which 2775 unique [R_{int}=0.0843]; 1596 $I>2\sigma(I)$, R_1=0.0911 and ωR_2=0.2417 for 1596 [$I>2\sigma(I)$] and R_1=0.2210, ωR_2=0.2931 for all (3483) intensity data. Goodness of fit=1.099, residual electron density in the final Fourier map was 0.491 and −0.348 e$Å^{-3}$. CCDC number is 648539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].

Acknowledgements

S.P. thanks the Department of Science and Technology, New Delhi, for funding for a major research project (No. SR/S1/OC-70/2006) and for funds under (i) IRHPA program for the purchase of a high resolution NMR spectrometer and (ii) FIST program and the University Grants Commission, New Delhi, for funds under the DRS and ASIST programs.

References and notes

1. (a) Jiang, H.; Zhao, J.; Han, X.; Zhu, S. *Tetrahedron* **2006**, *62*, 11008; (b) Coutouli-Argyropoulou, E.; Lianis, P.; Mitakou, M.; Giannoulis, A.; Nowak, J. *Tetrahedron* **2006**, *62*, 1494; (c) Gomes, P. J. S.; Nunes, C. M.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D.; Arnaut, L. G. *Tetrahedron Lett.* **2006**, *47*, 5475.
2. Lundahl, K.; Schut, J.; Schlatmann, J. L. M. A.; Paerels, G. B.; Peters, A. *J. Med. Chem.* **1972**, *15*, 129.
3. Kornett, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
4. Abou-Gharbia, M. A.; Doukas, P. H. *Heterocycles* **1979**, *12*, 637.
5. (a) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447; (b) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135; (c) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605.
6. da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273.
7. Abignente, E.; Biniecka-Picazio, M. *Acta Pol. Pharm.* **1977**, *34*, 241.
8. Dimmock, J. R.; Jha, A.; Zello, G. A.; Sharma, R. K.; Shrivastav, A.; Selvakumar, P.; Allen, T. M.; Santos, C. L.; Balzarini, J.; De Clercq, E.; Manavathu, E. K.; Stables, J. P. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 325.
9. (a) Caramella, P.; Grunanger, P. *Nitrile Oxides and Imines*; Padwa, A., Ed.; 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, NY, 1984; Vol. 1, Chapter 3, pp 291–392; (b) Kudyba, I.; Jozwik, J.; Romanski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257; (c) Padwa, A. *Angew. Chem.* **1976**, *88*, 131; (d) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.
10. Torssell, K. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, NY, 1988.
11. Grunanger, P.; Vita-Finzi, P. *Isoxazoles—Part 1*; Chemistry of Heterocyclic Compounds; Wiley: New York, NY, 1991; Vol. 49.
12. Kang, Y. K.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Hong, C. Y.; Lee, C.; Park, S. Y.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 95.
13. Xue, C.; Roderick, J.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499.

14. Diana, G. D.; McKinlay, M. A.; Brisson, C. J.; Zalay, E. S.; Miralles, J. V.; Salvador, U. J. *J. Med. Chem.* **1985**, *28*, 748.
15. Lepage, F.; Tombert, F.; Cuvier, G.; Marivain, A.; Gillardin, J. M. *Eur. J. Med. Chem.* **1992**, *27*, 581.
16. Ryng, S.; Machon, Z.; Wieczorek, Z.; Zimecki, M.; Mokrosz, M. *Eur. J. Med. Chem.* **1998**, *33*, 831.
17. Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, NY, 1984.
18. (a) Risitano, F.; Grassi, G.; Foti, F.; Bruno, G.; Rotondo, A. *Heterocycles* **2003**, *60*, 857; (b) Pirc, S.; Recnic, S.; Skof, M.; Steve, J.; Golic, L.; Meden, A.; Stanovnick, B. *J. Heterocycl. Chem.* **2002**, *39*, 411; (c) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603; (d) Baba, N.; Soufiaoui, M. *Tetrahedron Lett.* **1990**, *31*, 1709.
19. Nair, V.; Radhakrishnan, K. V.; Sheela, K. C.; Rath, N. P. *Tetrahedron* **1999**, *55*, 14199.
20. Liu, K. C.; Howe, R. K. *J. Org. Chem.* **1983**, *48*, 4590.
21. (a) Ichiba, T.; Scheuer, P. J. *J. Org. Chem.* **1993**, *58*, 4149; (b) Lacy, C.; Scheuer, P. J. *J. Nat. Prod.* **2000**, *63*, 119.
22. (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213; (b) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270.
23. (a) Ranjith Kumar, R.; Perumal, S.; Kagan, H. B.; Guillot, R. *Tetrahedron* **2006**, *62*, 12380; (b) Suresh Kumar, R.; Perumal, S.; Kagan, H. B.; Guillot, R. *Tetrahedron: Asymmetry* **2007**, *18*, 170; (c) Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 7850.
24. Ravi Kumar, B.; Pandiarajan, S.; Ramakrishnan, V.; Ranjith Kumar, R.; Perumal, S. *Acta Crystallogr., Sect. E* **2007**, *63*, 3221.
25. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
26. Ravi Kumar, B.; Pandiarajan, S.; Ramakrishnan, V.; Ranjith Kumar, R.; Perumal, S., unpublished results.
27. Subha Nandhini, M.; Srinivasan, N.; Ranjith Kumar, R.; Perumal, S.; Krishnakumar, R. V. *Acta Crystallogr., Sect. E* **2007**, *63*, 3749.
28. El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-Obaid, A. M. *J. Med. Chem.* **2000**, *43*, 2915.