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REGIO- AND STEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF *C*-ARYL-*N*-PHENYLNITRONES OVER *(E)*-ARYLIDENE-*(2H)*-INDAN-1-ONES: SYNTHESIS OF HIGHLY SUBSTITUTED NOVEL SPIRO-ISOXAZOLIDINES

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Abstract – Synthesis of a series of novel spiro-isoxazolidines has been accomplished in good yields by regio- and diastereoselective 1,3-dipolar cycloaddition of *(E)*-2-arylidene-*(2H)*-indan-1-ones **1a-d** to *C*-aryl-*N*-phenylnitrones **2e-h**. The structure of the spiro-adducts **3ae-dh** was elucidated by ^{1}H and ^{13}C NMR spectroscopy. The proposed regio- and stereochemistry of spiranic compounds **3ae** and **3be** has been corroborated by two single crystal X-ray crystallographic analyses and by means of DFT calculations.

INTRODUCTION

The 1,3-dipolar cycloaddition reaction between nitrones and unsaturated systems is an efficient method for the organic synthesis of a wide variety of new heterocyclic derivatives structurally related to lactams, indolizidines, alkaloids[1] which have found application in the preparation of complex molecules with useful biological activities such as antibiotics and glycosidase inhibitors.[2] For example Januário-Charmier et al. [3–5] demonstrated that by conventional organic methods, chiral heterocycles of potential biological activity, can be synthesized, exploring the fact that addition of nucleophiles to a C=C double bond offers an attractive route for the creation of novel C–C, N–O and C–O bonds and for the generation of new isoxazolidine derivatives. These compounds have been for many products syntheses and can be converted to efficient precursors for many synthetic intermediates including *β*-amino alcohols,[6] *β*-amino acids[7] and *β*-lactams,[8] which are useful chiral building blocks for the synthesis of biologically active compounds. Although numerous reports are available for the synthesis of isoxazolidine derivatives,[9,10] relatively few work on spiro-isoxazolidine derivatives has been published.

Further, many more indanone derivatives have been used as versatile intermediates for many natural and pharmaceutical products.[11-13] The high synthetic utility and pharmacological importance have prompted us to synthesize some spiro-isoxazolidine derivatives which are potentially interesting in pharmaceutical industry.

Since several years, we have focused our studies on the reactivity of dipolarophiles bearing an exocyclic carbon-carbon double bond towards several 1,3-dipole such as nitrile oxides,[14] diazoalkanes[15] and diarylnitrilimines.[16] We particularly paid attention to the role played by the substituents of the dipolar entities on both chemical reactivity and stereochemistry.

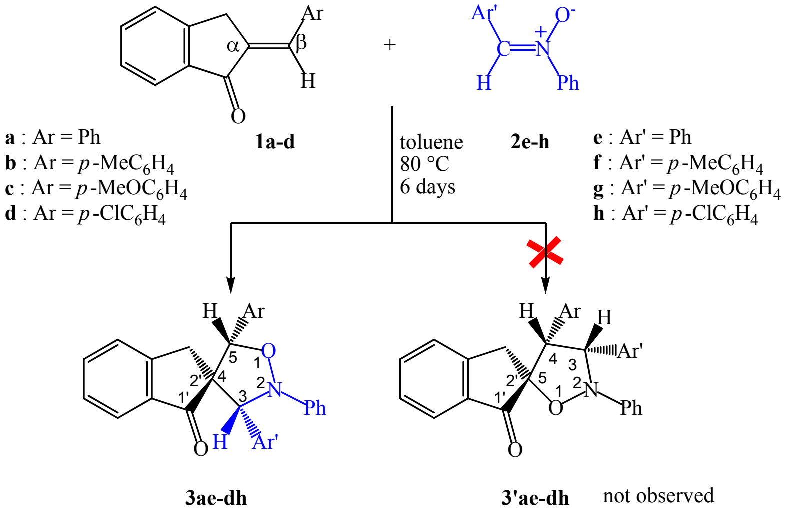
In continuation of our interest in the area of cycloaddition reactions, we present here the first examples where *C*-aryl-*N*-phenylnitrones **2e-h** reacted with (*E*)-2-arylidene-(*2H*)-indan-1-ones **1a-d** in regio selective manner. Previous to our investigation, to the best of our knowledge, there was only one report of nitrone cycloaddition to trisubstituted olefins where the dipolarophiles had the reacting double bond conjugated with an aryl group and a carbonyl group.[17] Note that in the latter work, formation of regioisomers has been observed.

RESULTS AND DISCUSSION

The synthetic route to the targeted spiro-isoxazolidines **3ae-dh** is outlined in Scheme 1. Dipolarophiles **1a-d** were obtained by the condensation of aromatic aldehydes with indanone.[18,19] *C*-aryl-*N*-phenylnitrones **2e-h** were easily generated by warming aryl aldehydes with *N*-phenylhydroxylamine in ethanolic solution following a known procedure.[20]

The initial investigation on the 1,3-dipolar cycloaddition of (*E*)-2-arylidene-(*2H*)-indan-1-ones **1a-d** with *C*-aryl-*N*-phenylnitrones **2e-h** involved the reaction of **1b** with **2e** at 110 °C in toluene solution for 24 h, compound **3be** was obtained in only 20% yield. Heating the same mixture at 80 °C for 24 h, afforded the product **3be** in 35% yield. Finally, the reaction of **1b** with nitrone **2e** in toluene at 80 °C for 6 days yielded **3be** (65%). Increase in reaction time from 6 days to 10 days did not allow improving the yield further. On the basis of these results, we performed all cycloaddition reactions of dipolarophiles **1a-d** with *C*-aryl-*N*-phenylnitrones **2e-h** at 80 °C in toluene for 6 days (Scheme 1). Yields of cycloadducts **3ae-dh** range between 45-70% (Table 1).

The reaction yielded exclusively in a regioselective manner, a series of the spiro-[3,5-diaryl-2-isoxazolidine-4:2'-indan-1'-ones] **3ae-dh**. The structure of each product was established on the basis of spectroscopic and crystallographic analysis. In each case, the presence of traces of starting reactants was also evidenced by TLC and ^{1}H NMR examination of the crude reaction mixture. These findings indicate that the reaction reaches an equilibrium state after 6 days. We suggest that the selectivity should be, at least in part, thermodynamically controlled.



Scheme 1. Reactions of *C*-aryl-*N*-phenylnitrones **2e-h** with *(E)*-2-arylidene-*(2H)*-indan-1-ones **1ad**

Table 1. Yields of spiro-isoxazolidines **3ae-dh**

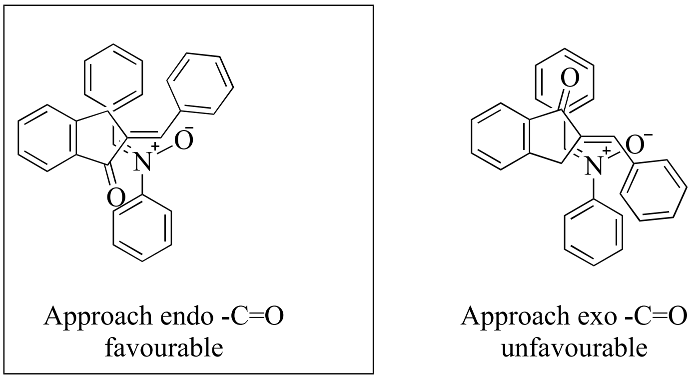
Entry	Dipolarophiles	Nitrones	Adducts[a]	Yield(%)
1	**1a**	**2e**	**3ae**	45
2	**1a**	**2f**	**3af**	64
3	**1a**	**2g**	**3ag**	60
4	**1a**	**2h**	**3ah**	50
5	**1b**	**2e**	**3be**	65
6	**1b**	**2f**	**3bf**	60
7	**1b**	**2g**	**3bg**	70
8	**1b**	**2h**	**3bh**	52
9	**1c**	**2e**	**3ce**	50
10	**1c**	**2f**	**3cf**	50
11	**1c**	**2g**	**3cg**	49
12	**1c**	**2h**	**3ch**	55
13	**1d**	**2e**	**3de**	60
14	**1d**	**2f**	**3df**	45
15	**1d**	**2g**	**3dg**	50
16	**1d**	**2h**	**3dh**	50

[a] Reaction in toluene at 80 °C during 6 days.

The reaction is: (i) regioselective, since **3ae-dh** with the oxygen of the nitrone added to the *β*-carbon of the dipolarophile and (ii) stereoselective, as the two aryl of isoxazolidine ring of **3ae-dh** are *cis*-arranged. The regioselectivity is not unexpected since many examples have been reported of nitrone additions to electron deficient alkenes to afford isoxazolidines with the oxygen in β-position to the electron-withdrawing group.[21-23]

The ^{1}H NMR spectra (300 MHz) exhibits a singlet between 5.40 ppm and 5.65 ppm assigned to the 3-H proton. This excludes the presence of the inverse regioisomer, for which the NMR spectrum would exhibit a doublet for 3-H. This was confirmed by the ^{13}C NMR chemical shift of the spirocarbon (C-4,2') atoms of all adducts, which have been found between 68.69 ppm and 70.31 ppm. This range is in agreement with the remoteness from the isoxazolidinic oxygen atom.[24,25] In the case of the hypothetic isomeric structures **3'ae-dh,** the chemical shift values of spiro carbon atoms (C-5,2') should be around 82-84 ppm.[26-29] The cycloaddition of *(E)*-2-arylidene-*(2H)*-indan-1-ones **1a-d** with *C*-aryl-*N*-phenylnitrones **2e-h** led to cycloadducts **3ae-dh** with three new chiral centers, *i.e.* the quaternary spiroatom C-4,2'; C-3 and the C-5 of isoxazolidine ring (Scheme 1). The relative stereochemistry of these carbon [rel-(3S, 4,2'R, 5R)] results from (i) preservation of the *(E)* configuration of the initial olefin and (ii) concerted reaction of *(Z)*-nitrones **2e-h** over **1a-d** (Scheme 1). The formation of diastereoisomeric adducts has never been caused by any *Z/E* interconversion of nitrones,[27-29] the relative configuration *(Z)* of the dipole always being preserved in spiro-compounds (Figure 2, Scheme 1). Furthermore, the suggested regio- and stereochemistry of **3ae-dh** are supported by X-ray analyses carried out on **3ae** (Figure 2) and **3be** (Figure 3). Before commenting these structures, one may consider different approches during the course of the cycloaddition.

The two approach modes (*endo*-C=O and *exo*-C=O) of the *C*-aryl-*N*-phenylnitrones **2e-h** towards dipolarophiles **1a-d** are depicted in Scheme 2.



Approach endo -C=O
favourable

Approach exo -C=O
unfavourable

Scheme 2. *Endo*-C=O and *exo*-C=O transition states for the reaction

In order to clarify the origin of the selective formation of the *endo* –C=O product, we performed density functional theory (DFT) optimisations of the complex of reactants in toluene at the B3LYP/6-31G(d) level of theory. In these calculations the solvent was treated using the polarisable continuum dielectric model of Cossi *et al*.[30] The calculations were performed with the Gaussian 09 package.[31] We found that the reactants form a site-to-site complex of *endo* –C=O type (Figure 1) that is very likely the precursor of an *endo* –C=O transition state. It is well known that the site-to-site configuration is characteristic to complexes mainly stabilized by electrostatic interactions. In the present case the complex appears to be stabilized by hydrogen bonds involving the oxygen atoms carried by the two reactants. On the other hand, an analogous conformation of the complex of the *exo* –C=O type was not identified in the calculations. We conclude that the *endo* –C=O selectivity is due to a favourable electrostatic interaction between the two reactants.

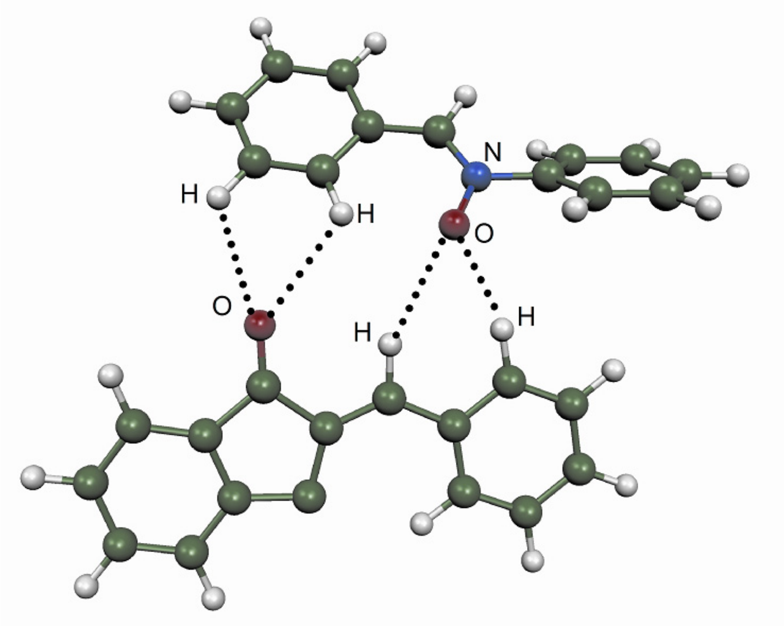


Figure 1. The calculations shows that the reactants form a site-to-site complex of *endo* –C=O type

Only diastereoisomers **3ae** and **3be** resulting from the cycloaddition of *(E)*-2-(benzylidene)-*(2H)*-indan-1-one **1a** and *(E)*-2-(*p*-methylbenzylidene)-*(2H)*-indan-1-ones **1b** with *C,N*-diphenylnitrone **2b** gave crystals of X-ray quality.

Because the space groups of the solid-state structures of both compounds contain the symmetry centres, the diastereoisomers *R*(C10)*S*(C23) and *S*(C10)*R*(C23) (X-ray ORTEP label C10 corresponds to C3, whereas C23 corresponds to C5 of Scheme 1) coexist in their racemic crystals. The H10 (3-H) and H23 (5-H) hydrogen atoms as well as the O2 one of carbonyl indanone ring point towards the same side of isoxazolidine ring. A resulting *endo* (or *cis*) type geometry is more favourable since repulsion between the O2 atom of indanone and the O1 and N1 atoms of central ring is thus avoided.

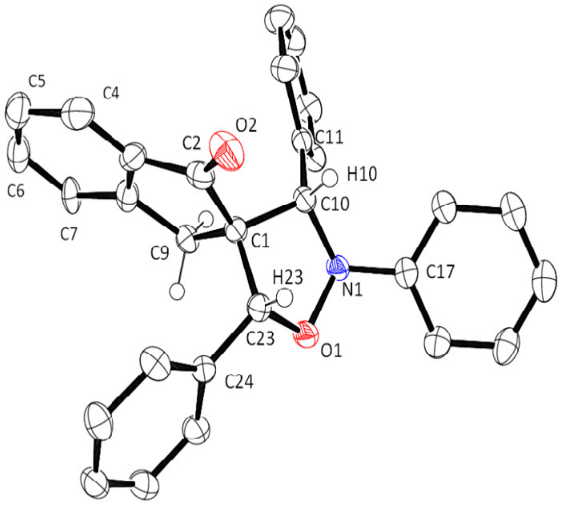


Figure 2. ORTEP drawing of **3ae** (50% probability level). One diastereoisomer (R(C10)S(C23); 3R5S) is shown. Selected bond lengths (Å) and angles (°): N1-O1 1.462(2), C1-C10 1.546(2), C1-C23 1.545(3), C1-C2 1.531(3), C1-C9 1.536(3), C10-N1 1.475(2), C23-O1 1.428(2); C2-C1-C9 105.94(15), C10-C1-C23 97.83(14), C1-C10-N1 102.96(14), C1-C23-O1 103.26(15)

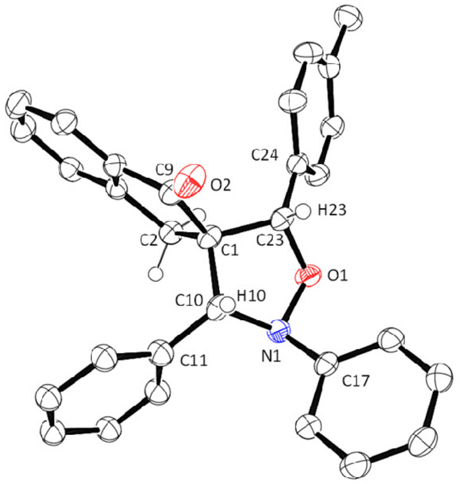


Figure 3. ORTEP drawing of **3be** (50% probability level). One diastereoisomer (S(C10)R(C23); 3S5R) is shown. Selected bond lengths (Å) and angles (°): N1-O1 1.4488(15), C1-C10 1.552(2), C1-C23 1.544(2), C1-C2 1.537(2), C1-C9 1.537(2), C10-N1 1.492(2), C23-O1 1.4368(17), C2-C1-C9 105.32(12), C10-C1-C23 98.74(11), C1-C10-N1 104.16(11), C1-C23-O1 102.37(11)

Because of the presence of three adjacent sp^3 carbon atoms (C10, C1 and C23), the isoxazolidine rings deviate strongly from planarity. The C10/N1/O1/C23 fragment is planar within 0.05 and 0.10 Å in **3ae** and **3be**, respectively. The dihedral angles with the C10/C1/C23 plane are equal to 42.4(9) and 40.1(1)° in **3ae** and **3be**, respectively. Contrary to the isoxazolidine ring, the five-membered indanone ring (one sp^3 carbon) fits very well the best least-square plane with highest deviations from reaching only 0.01 and 0.009 Å, respectively. The spiranic dihedral angles of 89.5(1) **3ae** and 87.8(1)° **3be** are close to the ideal value of 90° for regular tetrahedral T_d spirane. The metric parameters are normal in both structures.

CONCLUSION

In conclusion, we have shown that cycloaddition reaction of *(E)*-2-arylidene-*(2H)*-indan-1-ones **1a-d** with nitrones **2e-h** leads regio- and diastereoselectively (100%) to spiro-[3,5-diaryl-2-isoxazolidine-4:2'-indan-1'-ones]. The regiochemistry of the reaction is independent to the electronic nature of the substituents at the *para*-position on the dipolarophile as well as on the dipole. The exclusive stereoselectivity of the reaction has been rationalised to be a consequence of combined electronic and steric interactions of the reagents during their approaches. The diastereoisomers **3ae-dh** are the result of the preferential approach directing the indanone carbonyl group in the *endo* position relative to the dipolar linkage. Apart from the regioselectivity aspect, the novel spiro-isoxazolidines presented in this work should be of interest as precursors for the synthesis of a variety of amino-alcohols derivatives.

EXPERIMENTAL

General Remarks: Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use.

Melting points were determined on a Kofler bank. IR spectra were recorded from KBr on a Perkin-Elmer 197 spectrometer; only structurally significant bands are reported. NMR spectra were recorded with a Bruker-Spectrospin AC 300 spectrometer operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C using tetramethylsilane (TMS) as the internal standard (0.00 ppm) in $CDCl_3$ as solvent. Chemical shifts were reported in ppm (δ) downfield from TMS. The following abbreviations were used to explain the multiplicities: s =singlet, d = doublet, t = triplet, m = multiplet.

Elemental analyses (C, H, N) were conducted on a Leco Elemental CHN 900; values were in satisfactory agreement with the calculated ones (0.30%). Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm.

(*E*)-2-Arylidene-(*2H*)-indan-1-ones **1a-d** were obtained by condensation of aldehydes ArCHO with respectively indanone according to reported methods.[28,29,32] *C*-Aryl-*N*-phenylnitrones **2e-h** was synthesized as reported by condensation of aldehydes Ar'CHO with phenylhydroxylamine.[33]

General procedure for the preparation of the cycloadducts (3ae-dh)

A solution of dipolarophiles **1a-d** (3 mmol) and *C*-aryl-*N*-phenylnitrones (3 mmol) **2e-h** in dry toluene (10 mL), was stirred at 80 °C for 6 days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (20:80) to afford compounds **3ae-dh**.

Spiro[3,5-diphenyl -2-isoxazolidine-4:2'-indan-1'-ones] (3ae)

Yield 0.56 g (45%); white solid; mp 122 °C; IR (KBr, cm^{-1}): 1751, 1615; ^{1}H NMR (CDCl$_3$): δ 2.75 (d, J= 18 Hz, 3'-H); 2.85 (d, J= 18 Hz, 3'-H); 5.45 (s, 3-H); 5.60 (s, 5-H); 6.78-8.30 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 30.57 (C-3'); 70.31 (C-4.2'); 79.20 (C-3); 86.64 (C-5); 114.95-154.24 (aromatic C); 204.36 (C-1'); Anal. Calcd for $C_{29}H_{23}NO_2$: C, 83.43; H, 5.55; N, 3.35. Found: C, 83.25; H, 5.40; N, 3.21.

Spiro[3-phenyl-5-(*p*-tolyl)-2-isoxazolidine-4:2'-indan-1'-one] (3af)

Yield 0.82 g (64%); yellow solid; mp 126 °C; IR (KBr, cm^{-1}): 1740, 1613; ^{1}H NMR (CDCl$_3$): δ 2.20 (s, CH$_3$); 2.75 (d, J= 18 Hz, 3'-H); 2.85 (d, J= 18 Hz, 3'-H); 3'-H); 5.40 (s, 3-H); 5.60 (s, 5-H); 6.85-7.75 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 21.44 (CH$_3$); 30.53 (C-3'); 70.25 (C-4,2'); 79.02 (C-3); 86.62 (C-5); 114.96-154.32 (aromatic C); 204.40 (C-1'). Anal. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25. Found: C, 83.29; H, 5.96; N, 3.34.

Spiro[5-(*p*-anisyl)-3-phenyl-2-isoxazolidine-4:2'-indan-1'-one] (3ag)

Yield 0.80 g (60%); yellow solid; mp 165 °C; IR (KBr, cm^{-1}): 1742, 1612; ^{1}H NMR (CDCl$_3$): δ 2.83 (d, J= 18 Hz, 3'-H); 2.93 (d, J= 18 Hz, 3'-H); 3.75 (s, OCH$_3$); 5.47 (s, 3-H); 5.50 (s, 5-H); 6.75 -7.70 (m, aromatic H);^{13}C NMR (CDCl$_3$): δ 30.19 (C-3'); 55.30 (s, OCH$_3$); 69.90 (C-4,2'); 78.45 (C-3); 86.57 (C-5); 113.40-159.20 (aromatic C); 204.28 (C-1'). Anal. Calcd for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63; N, 3.13. Found: C, 80.25; H, 5.35; N, 2.97.

Spiro[5-(*p*-chlorophenyl)-3-phenyl-2-isoxazolidine-4:2'-indan-1'-one] (3ah)

Yield 0.67g (50%); white solid; mp 149 °C; IR (KBr, cm^{-1}): 1753, 1613; ^{1}H NMR (CDCl$_3$): δ 2.90 (d, J= 18 Hz, 3'-H); 3.00 (d, J= 18 Hz, 3'-H); 5.63 (s, 3-H); 5.72 (s, 5-H); 7.03-7.85 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 29.06 (C-3'); 68.69 (C-4,2'); 77.72 (C-3); 83.95 (C-5); 113.60-152.64 (aromatic C); 202.67 (C-1'). Anal. Calcd for $C_{29}H_{22}NO_2Cl$: C, 77.07; H, 4.91; N, 3.10. Found: C, 76.89; H, 4.72; N, 3.33.

Spiro[5-phenyl-3-(*p*-tolyl)- 2-isoxazolidine-4:2'-indan-1'-one] (3be)

Yield 0.84g (65%); yellow solid; mp 126 °C; IR (KBr, cm^{-1}): 1755, 1613; ^{1}H NMR (CDCl$_3$): δ 2.27 (s, CH$_3$); 2.84 (d, J= 18 Hz, 3'-H); 2.94 (d, J= 18 Hz, 3'-H); 5.54 (s, 3-H); 5.63 (s, 5-H); 6.91-7.76 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 21.19 (CH$_3$); 30.16 (C-3'); 69.86 (C-4,2'); 78.69 (C-3); 86.31 (C-5);

114.57-154.01 (aromatic C); 204.14 (C-1’). Anal. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25. Found: C, 83.33; H, 5.58; N, 3.06.

Spiro[3,5-di(*p*-tolyl)-2-isoxazolidine-4:2’-indan-1’-one] (3bf)

Yield 0.80 g (60%); yellow solid; mp 195 °C; IR (KBr, cm^{-1}): 1757, 1614; ^1H NMR ($CDCl_3$): δ 2.40 (s, CH_3); 2.42 (s, CH_3); 2.80 (d, J= 18 Hz, 3’-H); 2.90 (d, J= 18 Hz, 3’-H); 5.45 (s, 3-H); 5.59 (s, 5-H); 6.87-7.77 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 21.30 (s, CH_3); 21.35 (s, CH_3); 30.33 (C-3’); 70.14 (C-4,2’); 78.74 (C-3); 86.42 (C-5); 114.62-154.24 (aromatic C); 204.26 (C-1’). Anal. Calcd for $C_{31}H_{27}NO_2$: C, 83.57; H, 6.11; N, 3.14. Found: C, 83.75; H, 6.25; N, 2.97.

Spiro[5-(*p*-anisyl)-3-(*p*-tolyl)-2-isoxazolidine-4:2’-indan-1’-one] (3bg)

Yield 0.96 g (70%); yellow solid; mp 190 °C; IR (KBr, cm^{-1}): 1754, 1614; ^1H NMR ($CDCl_3$): δ 2.40 (s, CH_3); 2.96 (d, J= 18 Hz, 3’-H); 3.06 (d, J= 18 Hz, 3’-H); 3.80 (s, OCH_3); 5.46 (s, 3-H); 5.63 (s, 5-H); 6.70-7.75 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 21.51 (s, CH_3); 30.35 (C-3’); 55.61 (s, OCH_3); 70.10 (C-4,2’); 78.35 (C-3); 85.98 (C-5); 113.62-158.54 (aromatic C); 204.26 (C-1’). Anal. Calcd for $C_{31}H_{27}NO_3$: C, 80.67; H, 5.90; N, 3.03. Found: C, 80.82; H, 5.62; N, 2.91.

Spiro[5-(*p*-chlorophenyl)-3-(*p*-tolyl)- 2-isoxazolidine-4:2’-indan-1’-one] (3bh)

Yield 0.72 g (52%); white solid; mp 175 °C; IR (KBr, cm^{-1}): 1735, 1612; ^1H NMR ($CDCl_3$): δ 2.45 (s, CH_3); 3.07 (d, J= 18 Hz, 3’-H); 3.17 (d, J= 18 Hz, 3’-H); 5.61 (s, 3-H); 5.73 (s, 5-H); 7.26-7.85 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 22.40 (CH_3); 30.40 (C-3’); 68.77 (C-4,2’); 77.73 (C-3); 85.45 (C-5); 115.64-153.30 (aromatic C); 204.20 (C-1’). Anal. Calcd for $C_{30}H_{24}NO_2Cl$: C, 77.33; H, 5.19; N, 3.01. Found: C, 77.13; H, 5.04; N, 3.20.

Spiro[3-(*p*-anisyl)-5-phenyl-2-isoxazolidine-4:2’-indan-1’-one] (3ce)

Yield 0.67 g (50%); yellow solid; mp 186 °C; IR (KBr, cm^{-1}): 1732, 1615; ^1H NMR ($CDCl_3$): δ 2.84 (d, J= 18 Hz, 3’-H); 2.94 (d, J= 18 Hz, 3’-H); 3.77 (s, OCH_3); 5.48 (s, 3-H); 5.52 (s, 5-H); 6.73 -7.85 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 30.25 (C-3’); 55.31 (s, OCH_3); 69.95 (C-4,2’); 78.46 (C-3); 86.60 (C-5); 113.45-159.25 (aromatic C); 204.30 (C-1’). Anal. Calcd for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63; N, 3.13. Found: C, 80.34; H, 5.37; N, 2.94.

Spiro[3-(*p*-anisyl)-5-(*p*-tolyl)-2-isoxazolidine-4:2’-indan-1’-one] (3cf)

Yield 0.69 g (50%); yellow solid; mp 180 °C; IR (KBr, cm^{-1}): 1754, 1612; ^1H NMR ($CDCl_3$): δ 2.39 (s,

CH_3); 2.92 (d, J= 18 Hz, 3'-H); 3.02 (d, J= 18 Hz, 3'-H); 3.85 (s, OCH_3); 5.48 (s, 3-H); 5.60 (s, 5-H); 6.70-7.75 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 21.50 (s, CH_3); 30.89 (C-3'); 55.65 (s, OCH_3); 70.12 (C-4,2'); 78.40 (C-3); 85.97 (C-5); 113.62-158.55 (aromatic C); 204.27 (C-1'). Anal. Calcd for $C_{31}H_{27}NO_3$: C, 80.67; H, 5.90; N, 3.03. Found: C, 80.79; H, 6.03; N, 2.88.

Spiro[3,5-di(*p*-anisyl)-2-isoxazolidine-4:2'-indan-1'-one] (3cg)

Yield 0.70 g (49%); yellow solid; mp 138 °C; IR (KBr, cm^{-1}): 1752, 1613; ^{1}H NMR ($CDCl_3$): δ 2.84 (d, J= 18 Hz, 3'-H); 2.94 (d, J= 18 Hz, 3'-H); 3.70 (s, OCH_3); 3.74 (s, OCH_3); 5.47 (s, 3-H); 5.59 (s, 5-H); 6.68-7.73 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 30.04 (C-3'); 55.23 (OCH_3); 55.28 (OCH_3); 69.97 (C-4,2'); 78.52 (C-3); 86.14 (C-5); 113.54-159.31 (aromatic C); 204.29 (C-1'). Anal. Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93. Found: C, 78.14; H, 5.44; N, 2.67.

Spiro[3-(*p*-anisyl)-5-(*p*-chlorophenyl)-2-isoxazolidine-4:2'-indan-1'-one] (3ch)

Yield 0.79 g (55%); white solid; mp 196 °C; IR (KBr, cm^{-1}): 1753, 1613; ^{1}H NMR ($CDCl_3$): δ 2.85 (d, J= 18 Hz, 3'-H); 2.95 (d, J= 18 Hz, 3'-H); 3.84 (s, OCH_3); 5.49 (s, 3-H); 5.61 (s, 5-H); 6.72-7.75 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 30.42 (C-3'); 55.25 (OCH_3); 70.12 (C-4,2'); 78.55 (C-3); 85.30 (C-5); 113.62-160.40 (aromatic C); 204.25 (C-1'). Anal. Calcd for $C_{30}H_{24}NO_3Cl$: C, 74.76; H, 5.02; N, 2.91. Found: C, 74.63; H, 5.23; N, 2.67.

Spiro[3-(*p*-chlorophenyl)-5-phenyl-2-isoxazolidine-4:2'-indan-1'-one] (3de)

Yield 0.81 g (60%); yellow solid; mp 176 °C; IR (KBr, cm^{-1}): 1755, 1614; ^{1}H NMR ($CDCl_3$): δ 2.84 (d, J= 18 Hz, 3'-H); 2.94 (d, J= 18 Hz, 3'-H); 5.65 (s, 3-H); 5.69 (s, 5-H); 6.99-7.80 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 29.26 (C-3'); 68.73 (C-4,2'); 77.68 (C-3); 83.98 (C-5); 114.30-155.25 (aromatic C); 203.99 (C-1'). Anal. Calcd for $C_{29}H_{22}NO_2Cl$: C, 77.07; H, 4.91; N, 3.10. Found: C, 76.90; H, 4.73; N, 3.30.

Spiro[3-(*p*-chlorophenyl)-5-(*p*-tolyl)-2-isoxazolidine-4:2'-indan-1'-one] (3df)

Yield 0.62 g (45%); yellow solid; mp 230 °C; IR (KBr, cm^{-1}): 1753, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, CH_3); 3.09 (d, J= 18 Hz, 3'-H); 3.19 (d, J= 18 Hz, 3'-H); 5.63 (s, 3-H); 5.70 (s, 5-H); 7.26-7.85 (m, aromatic H); ^{13}C NMR ($CDCl_3$): δ 22.39 (CH_3); 30.36 (C-3'); 68.75 (C-4,2'); 77.70 (C-3); 85.41 (C-5); 115.63-155.27 (aromatic C); 202.71 (C-1'). Anal. Calcd for $C_{30}H_{24}NO_2Cl$: C, 77.33; H, 5.19; N, 3.01. Found: C, 77.10; H, 5.06; N, 3.19.

Spiro[5-(*p*-anisyl)-3-(*p*-chlorophenyl)-2-isoxazolidine-4:2'-indan-1'-one] (3dg)

Yield 0.72 g (50%); yellow solid; mp 188 °C; IR (KBr, cm^{-1}): 1752, 1615 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.87 (d, J= 18 Hz, 3'-H); 2.97 (d, J= 18 Hz, 3'-H); 3.82 (s, OCH$_3$); 5.50 (s, 3-H); 5.62 (s, 5-H); 7.71-7.77 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 30.140 (C-3'); 55.26 (OCH$_3$); 70.10 (C-4,2'); 78.48 (C-3); 85.37 (C-5); 113.60-160.43 (aromatic C); 203.98 (C-1'). Anal. Calcd for $C_{30}H_{24}NO_3Cl$: C, 74.76; H, 5.02; N, 2.91. Found: C, 74.62; H, 5.25; N, 2.68.

Spiro[3,5-di(*p*-chlorophenyl)-2-isoxazolidine-4:2'-indan-1'-one] (3dh)

Yield 0.72 g (50%); white solid; mp 170 °C; IR (KBr, cm^{-1}): 1751, 1615; ^{1}H NMR (CDCl$_3$): δ 2.90 (d, J= 18 Hz, 3'-H); 3.00 (d, J= 18 Hz, 3'-H); 5.62 (s, 3-H); 5.71 (s, 5-H); 7.69-7.79 (m, aromatic H); ^{13}C NMR (CDCl$_3$): δ 30.15 (C-3'); 70.16 (C-4,2'); 78.52 (C-3); 85.91 (C-5); 113.58-160.40 (aromatic C); 204.18 (C-1'). Anal. Calcd for $C_{29}H_{21}NO_2Cl_2$: C, 71.61; H, 4.35; N, 2.88. Found: C, 71.43; H, 4.44; N, 2.76.

X-Ray structure analyses

X-Ray quality colorless crystals of **3ae** (0.42x0.20x0.20 mm) and **3be** (0.30x0.25x0.07 mm), grown from ethanol solutions, were mounted on a Nonius KappaCCD diffractometer. Intensity data were collected at 115 K with Mo-K$_\alpha$ radiation. The crystal structures were solved by direct methods[34] and refined with full-matrix least squares on F^2.[35] Anisotropic thermal parameters were applied for non-hydrogen atoms. All H atoms were placed in calculated positions and included in final refinements in a riding model with isotropic temperature factors related to the carbon atoms bearing them: $U_{iso}(H) = 1.2U_{eq}(C)$. There is a slight disorder in both structures. It concernes the four aromatic CH groups of indanone ring in **3ae** (refined occupancies are 0.55/0.45), whereas in **3be** the disorder is observed for phenyl group bound to C10 atom of the central ring with occupancies 0.61/0.39. These disorders are certainly due to the crystal packing.

X-Ray crystal structure analyses of compounds (**3ae**) and (**3be**):

For $C_{29}H_{23}NO_2$: M = 417.48, monoclinic, space group P2$_1$/c, a = 10.2526(1) Å, b = 19.8492(3) Å, c = 11.1911(2) Å, β = 104.151(1)°, V = 2208.34(6) Å^3, Z = 4, D_c = 1.256 Mg/m^3, λ(Mo-Kα) = 0.71073 Å, F(000) = 880, μ(Mo-Kα) = 0.078 mm^{-3}, T = 115(2) K. 9878 reflections collected, 5022 unique and 3881 with $I>2\sigma(I)$. Final residuals ρ_{max} = 0.247, ρ_{min} = -0.192 e$^-$/Å^3. Final agreement factors: $R(F)$ = 0.0555 and 0.0757, $wR(F2)$ = 0.1259 and 0.1325 for $I>2\sigma(I)$ and all data, respectively, GOF = 1.143.

For $C_{30}H_{25}NO_2$: M = 431.51 triclinic, space group P-1, a = 8.3336(2) Å, b = 9.5701(3) Å, c = 15.3515(4) Å, α = 81.393(2)°, β = 79.535(2)°, γ = 68.349(1)°, V = 1114.44(5) Å^3, Z = 2, D_c = 1.286 Mg/m^3, λ(MoKα) = 0.71073 Å, F(000) = 456, μ(Mo-Kα) = 0.080 mm^{-3}, T = 115(2) K. 9798 reflections collected, 5101 unique and 3448 with $I>2\sigma(I)$. Final residuals $\rho_{max} = 0.328$, $\rho_{min} = -0.298$ $e^-/Å^3$. Final agreement factors: $R(F) = 0.0496$ and 0.0845, $wR(F2) = 0.1195$ and 0.1360 for $I>2\sigma(I)$ and all data, respectively, $GOF = 1.050$.

Crystallographic data for the structures of **3ae** and **3be** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 782615 and 782616. Copy of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK, fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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