HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 857 - 863
Received, 17th December, 2002, Accepted, 6th February, 2003, Published online, 10th February, 2003

DIASTEREOSELECTIVE SYNTHESIS AND STRUCTURE OF SPIRO-OXINDOLE DERIVATIVES

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Abstract-Spiroindolinonisoxazolines (**4** and **5h**) are prepared from (*E*)- **1** or (*Z*)-3-arylidene-2-oxindoles (**2**) by nitrile oxide cycloaddition reactions. Only one regioisomer is detected in all cases, and the observed complete diastereoselection is established by unambigous structural assignments.

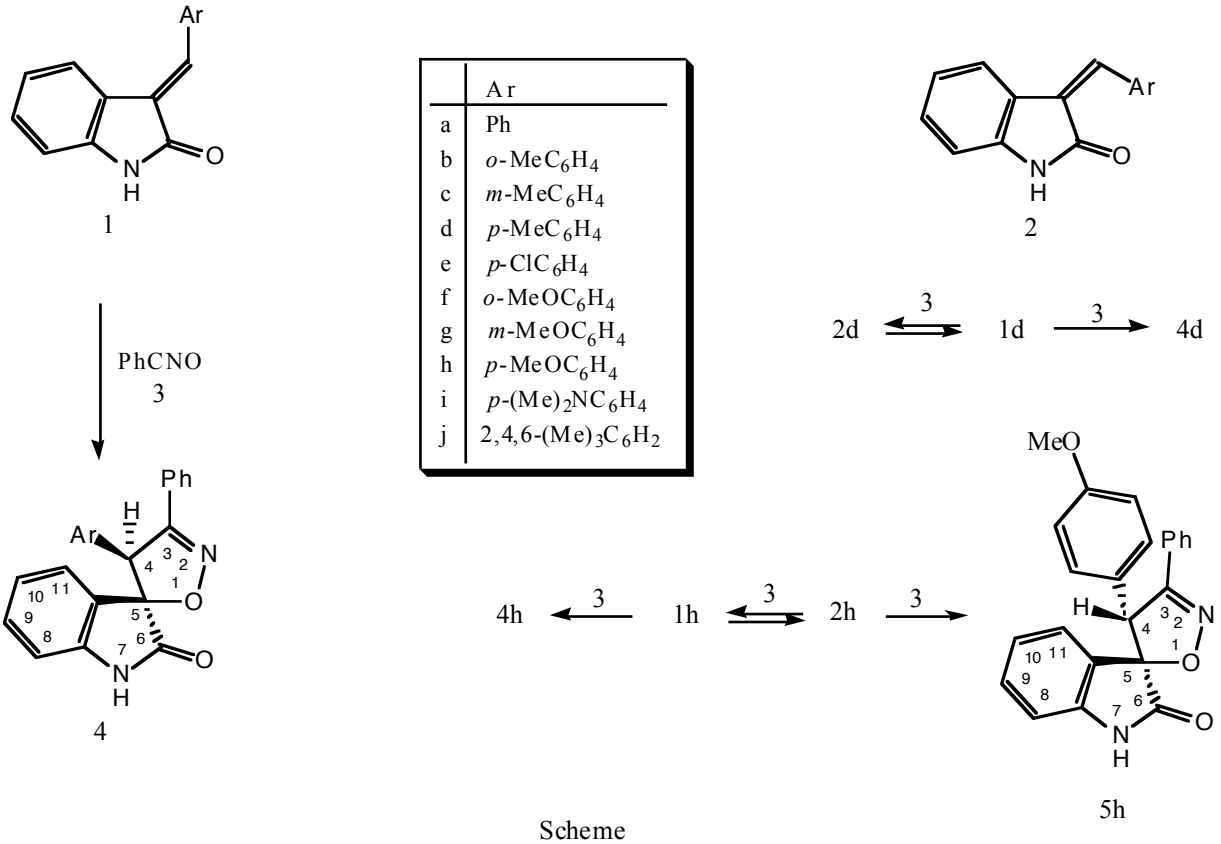
Spiroindoline derivatives are compound attractants of natural or synthetic origin[1] with promising properties both in terms of their potential bioactivity[2] and of their use as starting materials in the synthesis of alkaloids.[3] The simplest synthesis strategy in the construction of the spiroindole unit requires the use of 1,3-dipolar cycloaddition reactions to the exocyclic C-C double bond of specific indolinon-3-ylidene derivatives. But despite this apparently easy accessibility, few examples of synthesis of such systems by means of cycloaddition are reported in literature.[4]

In view of our interest in reactions of nitrile oxides with exo- or endo-cyclic double bonds or with nucleophilic centres present on cyclic or acyclic systems,[5] we decided to investigate the behavior of these dipoles towards selected 2-indolinone derivatives. This approach also allows access to spirocycles which can be suitably manipulated in order to obtain useful natural indolinone products through the selective possibilities of isoxazoline ring opening.[6] Thus, we now describe an efficient and practical procedure for generating the desired spiro derivatives (**4**) and (**5**) starting from suitable *N*-unsubstituted 3-arylmethylene-2-indolinone derivatives (**1**) or (**2**) and nitrile oxide (**3**).

(*E*)- **1** or (*Z*)-3-arylidene-2-oxindoles (**2**) were prepared according to methods described in literature[7] and reacted with benzonitrile oxide (BNO) generated *in situ* directly from benzaldoxime with *N*-chlorosuccinimide and triethylamine (TEA) according to the procedure refined by Thomsen and Torsell.[8] As summarized in Scheme and in Table, with **1** only one detectable adduct was formed in each case; in general yields seem to be quite good regardless of the nature and position of the substituents on Ar except for the mesitylene derivative (**1j**) whose poor yields are probably due to the strong steric congestion of the exocyclic double bond.

In line with observations made using 1,1-disubstituted or trisubstituted olefins,[9] where dipole orientation is dominated by the tendency of the most substituted C-atom to adopt 5-position in the ring that is formed, the structure of the expected spiroisoxazolines (**4**) was assigned on the basis of analytical and spectroscopic data. Elemental analysis and the appearance of strong carbonyl absorption at 1722-1742 cm^{-1} in IR spectrum are consistent with the addition of a BNO molecule to the C=C exocyclic double

bond of **1**. The benzylic H-4 signal in the ^{1}H NMR spectra at around δ 5.00 and the spiran-C signal in the ^{13}C NMR spectra at around δ 89 are consistent with the spiro-atom at 5-position in the isoxazoline ring, while the displacement of the doublet relative to H-11 to unusually high fields (around δ 6.20) shows that this H-atom is close to the aryl at 4-position of the isoxazoline ring and that, therefore, benzonitrile oxide cycloaddition proceeds with retention of configuration at the starting double bond of **1**.



	Ar
a	Ph
b	*o*-MeC_6H_4
c	*m*-MeC_6H_4
d	*p*-MeC_6H_4
e	*p*-ClC_6H_4
f	*o*-$MeOC_6H_4$
g	*m*-$MeOC_6H_4$
h	*p*-$MeOC_6H_4$
i	*p*-$(Me)_2NC_6H_4$
j	2,4,6-$(Me)_3C_6H_2$

Scheme

Scheme also describes the stereochemical outcome of the reaction and is fully supported by NOE measurements. Thus, irradiation of H-11 in **4** resulted in NOE enhancement for the *ortho*-protons of the aryl at C-4, indicating a close spatial proximity between these protons. The configurational features of spirans (**4**) were again verified by an X-Ray analysis carried out on **4d** (Figure). In the light of these results spirans (**4**) have 4S* and 5R* configuration.

The reactions described therefore seem to be highly site-, regio- and stereoselective. The regioselectivity observed is not encountered in other analogous exocyclic alkenes[10] or in the only currently known example[4a] of BNO cycloaddition to 3-arylmethyleneindolin-2-one (**1**) (Ar = COOEt) where the formation of spiro regioisomer mixtures generally prevails. Orientation in these cycloadditions is unambiguous and is the same as that with other arylmethylene derivatives of benzofused heterocycles with five and six members.[11] Evidently, in these BNO cycloadditions the approach of the C end of the 1,3-dipole, which has greater steric sensitivity,[12] to the less hindered β-carbon of **1** is the only explanation for the complete regioselectivity of the reaction with formation of the 5-acyl cycloadduct regardless of frontier orbital expectations.[13]

Table. Selected Data for Compounds (**4**) and (**5**)

Compd (Formula)	Mp °C	Yield (%)	Calcd/Found C	H	N	IR[a] $\nu_{C=O}$	^{1}H NMR[b] H-4	H-7	H-8	H-9	H-10	H-11	^{13}C NMR[b]
4a $C_{22}H_{16}N_2O_2$	244	82	77.55 (77.63)	4.68 (4.74)	8.12 (8.23)	1740	5.06	8.28	6.77	7.08	6.59	6.22	62.35, 87.75, 158.23, 176.35
4b $C_{23}H_{18}N_2O_2$	248	74	77.99 (77.95)	5.20 (5.12)	7.82 (7.90)	1722	5.24	7.31	6.75	7.11	7.01	6.10	18.81, 60.18, 88.83, 159.06, 176.31
4c $C_{23}H_{18}N_2O_2$	245	70	77.77 (77.95)	5.01 (5.12)	8.01 (7.90)	1727	4.99	8.20	6.76	7.09	6.61	6.24	20.37, 63.72, 88.15, 158.85, 175.47
4d $C_{23}H_{18}N_2O_2$	241	71[c]	77.83 (77.95)	5.04 (5.12)	7.80 (7.90)	1738	5.02	8.14	6.79	7.05	6.92	6.27	20.67, 63.81, 89.22, 159.01, 176.08
4e $C_{22}H_{15}ClN_2O_2$	240	72	70.65 (70.50)	4.08 (4.03)	7.22 (7.47)	1739	5.03	8.49	6.80	7.00	6.67	6.28	63.19, 87.85, 157.09, 168.81
4f $C_{23}H_{18}N_2O_3$	235	70	74.43 (74.58)	4.84 (4.90)	7.67 (7.56)	1735	5.10	8.37	6.78	7.03	6.81	6.25	53.95, 63.05, 88.98, 158.99, 173.11
4g $C_{23}H_{18}N_2O_3$	233	73	74.45 (74.58)	4.79 (4.90)	7.72 (7.56)	1742	5.00	7.80	6.78	7.15	7.12	6.65	54.21, 64.14, 89.14, 159.22, 174.09
4h $C_{23}H_{18}N_2O_3$	220	71	74.65 (74.58)	4.99 (4.90)	7.48 (7.56)	1726	5.01	8.18	6.74	7.08	6.63	6.29	55.01, 64.91, 89.37, 159.88, 174.08
4i $C_{24}H_{21}N_3O_2$	242	69	75.34 (75.18)	5.57 (5.52)	10.82 (10.96)	1732	4.96	8.79	6.96	7.05	6.87	6.30	44.52(2), 63.22, 87.61, 164.58, 172.74
4j $C_{25}H_{22}N_2O_2$	239	20	78.39 (78.51)	5.71 (5.80)	7.49 (7.33)	1727	5.40	7.80	6.75	7.00	6.80	6.60	18.88, 21.15, 22.31, 55.62, 89.81, 158.91, 171.81
5h $C_{23}H_{18}N_2O_3$	241	70	74.69 (74.58)	4.97 (4.90)	7.69 (7.56)	1738	5.20	7.52	6.79	7.26	7.10	7.46	54.95, 64.01, 89.35, 159.34, 173.25

[a] Nujol, cm^{-1}. [b] $CDCl_3$/TMS, δ. [c] 37% starting from **2**

With isomeric (*Z*)-ylidene derivatives (**2d**) and (**2h**) (see Scheme), however, the reaction seems to proceed with loss of stereochemical integrity: only spiroisoxazoline (**4d**) is isolated from **2d**, while from **2h** a mixture of diastereisomers (**4h**) and (**5h**) are obtained in a ratio of *4:1*. This ratio was determined by integration of the benzylic proton signals in the NMR spectra of the crude mixture and closely corresponds to those obtained in the separation. The structure of **5h** was established on the basis of analytical and spectroscopic data. The ^{1}H NMR spectrum is similar to that of isomeric cycloadduct (**4h**) but shows more deshielded signals both for H-4 (δ 5.20), because of the neighbhoring indole system's benzene ring, and for H-11 in the range typical for H-Ar (δ 7.20), while its ^{13}C NMR spectrum contains two signals at δ 64.01and δ 89.35, which can respectively be assigned to the C-4 and spiran-C, as with those found for **4d**. NOE experiment provided significant proof that the isolated product (**5h**) has the benzylic H-4 and the indolinone carbonyl opposite: irradiation of H-4 resulted in increased H-11.

Since, under the same reaction conditions and times, no isomerization from **5h** to **4h** was observed, we can certainly rule out the hypothesis that cycloadduct (**4h**) is derived from *in situ* thermal epimerization of the initially formed isomer (**5h**) after a retro-1,3-dipolar reaction. Thus the anomalous behaviour observed may be ascribed to the poor reactivity of the ylidene derivative (**2**) towards BNO, probably due to

insufficient steric tension, which is fundamental to controlling the dipolarophilic activity of an olefin substrate.

Crystal structures and in solution investigations[7b] confirm little tension in the *Z*-isomers (**2**) and considerable steric congestion in the corresponding E-isomers (**1**). In such a situation BNO has difficulty cycloadding itself to the *Z*-derivative (**2**), though it helps in some way to induce the isomerization of **2** to the more reactive dipolarophile (**1**), to which, therefore, BNO cycloadds exclusively (d case) or chemoselectively (h case).

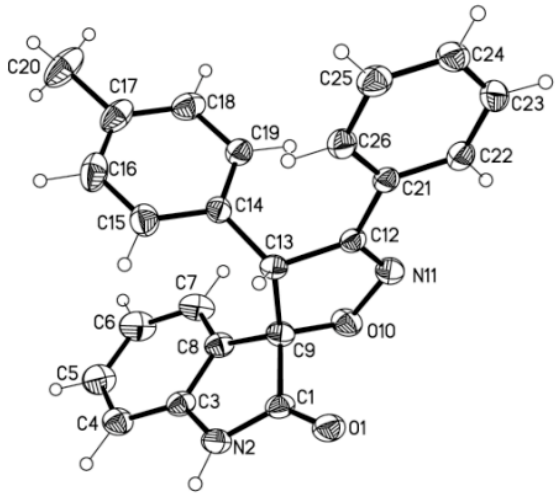


Figure. Molecular structure of **4d**, showing the atom labelling. Displacement ellipsoids of non-H atoms are drawn at 40% probability level and H-atoms as spheres with arbitrary radius.

EXPERIMENTAL

Melting points were determined with Reichert-Kofler hot stage apparatus and are uncorrected. IR spectra were performed on Nicolet FT-IR Impact 400D spectrophotometer and microanalyses on a Carlo Erba 1102 element analyser. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker ARX 300 spectrometer, in the solvent indicated. Chemical shifts (□) refer to TMS, which was used as an internal reference. Flash column chromatography was performed using silica gel (Merck, 40-64 mesh). (*E*)- **1** and (*Z*)-arylidenindol-2-ones (**2**) were prepared by standard procedures.[7] All solvents and reagents were obtained from commercial sources and purified before use if necessary.

General procedure for the preparation of compounds (4)

Benzaldoxime (2.42 g, 20 mmol) was added in one portion to a stirred solution (2.67 g, 20 mmol) of *N*-chlorosuccinimide in chloroform (18 mL) and pyridine (0.1 mL). The reaction mixture was stirred at rt until the solution became colourless and indol-2-one (**1**) (20 mmol) was then added in one portion and

stirring was continued at 50°C. Triethylamine (2,15 g, 21 mmol) was then added dropwise and the mixture was refluxed for 30 min. The solvent was removed in vacuo and the residue dissolved in chloroform(30 mL)–water(10 mL). The aqueous layer was extracted with chloroform (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The pure products (**4**) were obtained from the residue by either crystallisation (methanol) or by flash column chromatography using chloroform as eluent.

Cycloaddition reactions of 2d and 2h

The reaction of **2d** (4.70 g, 20 mmol) or **2h** (5.02 g, 20 mmol) with BNO generated *in situ* from benzaldoxime (2.42 g, 20 mmol) and *N*-chlorosuccinimide (2.67 g, 20 mmol) was carried out in the same manner as the corresponding reaction of **1**. Purification of the reaction mixture by silica gel chromatography eluting with chloroform provided: **4d** (37%), in d case; **4h** (58%) and **5h** (14%) as separate fractions, in h case.

Crystal structure determination of compound (4d)

Crystal data. $C_{23}H_{18}N_2O_2$, M = 354.39, Monoclinic, $P2_1/c$ (ITC N. 14), a = 11.719(2), b = 5.6055(9), c = 27.071(5) Å, b = 97.295(11), V = 1763.9(5) $Å^3$, Z = 4, r_{calcd}= 1.334 g cm^{-3}, F(000) = 744, m (MoKa) = 3.31 cm^{-1}, R1 = 0.0466 / 0.0840 and *w*R2 = 0.1000 / 0.1183 for 2065 / 3112 obs [I>2s(I)] / all independent reflections, respectively, GOF = 1.024.

Data collection and processing. Diffraction data were collected at room temperature from a colorless 0.58 x 0.30 x 0.20 mm^3 prismatic crystal sample by using a Siemens P4 automated four-circle single-crystal diffractometer with graphite-monochromated MoK_a radiation (l = 0.71073 Å). Lattice parameters were obtained from least-squares refinement of the setting angles of 39 reflections within $3.03 \leq 2q \leq 14.16°$ range. 3112 reflections were measured by the fixed speed w scan technique up to 2q=50°. No crystal decay was evidenced by the check reflections monitored each 197 measurements. Intensities were evaluated by profile fitting of a 96-steps peak scan among 2q shells procedure[14] and then corrected for Lorentz polarization effects. Absorption correction was not necessary. Data-collection and reduction with the profile fitting has been performed by XSCANS[15] and SHELXTL package[16]. Structure was solved by a combination of standard Direct Methods[17] and Fourier synthesis, and refined by minimizing the function $\sum w(Fo^2-Fc^2)^2$ with the full matrix least-square technique based on all 3112 independent F^2 [R_{int}= 0.0213], by using SHELXL97[18]. All non-hydrogen atoms were treated as anisotropic. Hydrogen atoms were located on the difference Fourier maps and, because of the goodness of distance and thermal parameters, left free in the model refinement except for the methyl group. Because of the motions of this fragment the hydrogens were placed in ideal positions with the "riding model" technique, moreover, since there is free methyl rotation, 6 ideal positions for 3 hydrogen atoms were set, each with 0.5 of structural factor (AFIX 127 in the shelxl command). An empirical extinction parameter was included in the last refinement cycles [0.0063(12)].

The last difference map showed no significant electron density residuals (max and min value are 0.16 and -0.16 e $Å^{-3}$). The Final geometrical calculations and drawings were carried out with the PARST program[19] and the XPW utility of the Siemens package, respectively.

Further details on the crystal structure (**4d**) are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail:deposit@ccdc.ac.uk) on quoting the depository number CCDC 192726.

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