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Synthesis of 3'-allylindoline spirobenzopyrans derived from 3-allyl-3*H*-indoles

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ABSTRACT

In this study, 8 new spirobenzopyrans were synthesized. A novel, three-step, facile route for the synthesis of 3'-allylindoline spirobenzopyrans via 3-allyl-3*H*-indoles was developed. The newly synthesized spirobenzopyrans were evaluated for their photochromic properties. The presence of an allyl moiety at the 3' position did not disturb the photochromic response. The steric effects of the diallyl groups at the 3' position affected the interconversion between colored and colorless forms. Therefore, the allyl chain in 3'-allylindoline spirobenzopyrans can be utilized to attach these compounds to a molecular matrix. Consequently, this synthetic methodology could be readily applied to the creation of new photo-switchable materials.

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The photo-responsive behavior of indoline spirobenzopyrans (ISPs) and photochromic compounds (PCCs) has attracted significant attention from photochemists working in material sciences.^{1–3} ISPs impart biochemical materials with attributes such as photo-controlled color changes (photochromism),⁴ photo-induced interconversion,^{5–7} long wavelengths of absorption maxima, and promising thermosolvatochromism,^{8–10} while PCCs are extremely useful component parts for the synthesis of photo-switchable functional materials.^{11–13} According to current synthetic requirements in the biological applications of PCCs, entries involving new UVA-reactive ISPs are particularly welcome.

The indoline nucleus is an important substructure in ISP **1**, as it exhibits photo-induced isomerization to the indolenine (3*H*-indole) nucleus in merocyanine (MC) **2** (Fig. 1).^{14,15} Among various classes of ISPs, R¹ and R²-substituted derivatives on aromatic rings have been studied extensively as an effective modification in a shift of the absorbance spectrum associated with a color change.^{16–18} R³-Substituted derivatives are useful molecules that combine a photo-responsive ISP unit into polymer/nanoparticles utilized in biomedical applications such as targeted drug delivery and sensing.^{5,19–21} In most instances, R⁴,R⁵-dimethyl substitutions are commonly chosen and adopted into ISPs because commercially

available 2,3,3-trimethy-3*H*-indoles are easily obtained and used as starting substrates, which ensure the quick syntheses of ISPs. We thought, furthermore, that the lack of variation on $\mathbb{R}^4,\mathbb{R}^5$ -substitution in ISPs was caused by the synthetic difficulties of 2-methyl-3,3-disubstituted 3*H*-indole derivatives, which could be key intermediates for the synthesis of $\mathbb{R}^4,\mathbb{R}^5$ -substituted ISPs. To the best of our knowledge, the two major synthetic routes to 3*H*-indoles are Fisher indole synthesis and the β -substitution of indoles, although both of these methods present considerable limitations to the production of various 3,3-disubstituted 3*H*-indoles.^{22,23}

Based on the photochemical interest in compounds that belong to the ISP family, and considering that only a few examples have been reported for the syntheses of R^4 and R^5 -substituted (not methylated) derivatives,^{22,23} we present herein a novel three-step process for the synthesis of 3'-allylindoline spirobenzopyrans via



Figure 1. Photo-induced and reversible interconversion of ISP 1 and MC 2 isomers.

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a,h: R^3 = CH₂CH₂OH, R^4 = CH₃, R^5 = CH₂CH=CH₂

b: R^3 = CH₂CH₂OH, R^4 = CH₃, R^5 = CH₂CH=CHPh

c: R^3 = CH_2CH_2OH , R^4 = CH_3 , R^5 = CH_2CH = CHOAc

d: R^3 = CH₂CH₂OH, R^4 = R^5 = CH₂CH=CH₂

e: $R^3 = CH_3$, $R^4 = CO_2Et$, $R^5 = CH_2CH = CH_2$

Scheme 1. Synthesis of 3*H*-indoles 4, indolenium salts 5, oxazolidines 6, and ISP 1.

3-allyl-3*H*-indoles using β -allylation of 2,3-disubstituted indoles (Scheme 1).

Here, 3*H*-indoles **4a**–**b** were prepared in a classic method, starting from 2,3-dimethylindole **3a** under basic and nucleophilic conditions using a Grignard reagent and R⁵-halide in 91 and 80% yields for **4a** and **4b**, respectively. The major drawbacks to this method were low selectivities, excess use of reagents, functional group incompatibility, and complex operating conditions and workups. Grignard reagents are inexpensive, but their application to a large-scale preparation is difficult.

Thus, we turned our attention to the use of a palladium catalyst, in a mild, functional group tolerant method for the regioselective introduction of an allyl group on 2,3-disubstituted indoles **3d**–**e**.²⁴ Reactions were carried out via the addition of indole to a solution of $Pd_2(dba)_3$ (2.5 mol %), R^5 -OCO₂Me (2.0 equiv), and P(2-furyl)₃ (15 mol %) in CH₂Cl₂ at 20 °C. After the reaction completed, the solvent was evaporated to give a crude product, which was purified. This reaction provided the desired 3*H*-indoles 4d-e in 91% and 51% yields, respectively, depending on the R⁴-substitution on the 2-methylindoles **3d–e**. In particular, for indole **3e** wherein the nucleophilic reaction of a Grignard reagent with the substrate (CO₂Et) is faster than a substitution reaction with allyl bromide, the palladium-catalytic method proved to be effective since indole 3e was allylated to 3*H*-indole 4e without affecting the ethoxy carbonyl group. The 3H-indole 4c was derived from 3H-indole 4a via a cross-metathesis with allyl acetate (1 equiv) and 5 mol % of a Zhan 1B catalyst,²⁵ in a 10% yield, with a 80% recovery. When a Hoveyda-Grubbs catalyst 2nd generation was employed for the metathesis, the reaction proceeded much slower, while the yield of the product was almost the same (by 9%). These substituted 3H-indoles are useful intermediates for the synthesis of ISP 1. Therefore, 3*H*-indoles **4a**–**e** were *N*-alkylated with R³-halide to give indolenium salts 5a-e, which were very polar ionic liquid compounds those could be utilized for the next step without isolation. When 2-bromoethanol was used as a R³-halide, the indolenium

salts **5a–d** were treated with a solution of potassium hydroxide to give oxazolidines **6a–d**, which were purified by silica gel column chromatography in good yields (41–76% from **4a–d**) as an inseparable mixture of 2 stereoisomers for **6a–c**. The oxazolidines **6a–d** were condensed with 2-hydroxy-5-nitorobenzaldehyde **7a** ($R^2 = NO_2$) in refluxing ethanol to provide ISPs **1a–d** (62–78%) and treatment of **6a** with salicylaldehyde **7b** ($R^2 = H$) provided **1h** in 86% yield (Table 1).^{26,27} When iodomethane was used for 3*H*indole **4e**, the crude salt **5e** was condensed with **7a** in refluxing ethanol for 1 h to provide ISP **1e** (14% from **4e**). In addition, ISP **1a** was subjected to alkene metathesis with allyl acetate (6 equiv), forming ISP **1c** in 20% yield with 52% recovery.

In search of viable structural designs to attach the ISP with a biomolecule, a maleimide motif was introduced in the R³ side chain^{28,29} of ISPs **1f–g**, as shown in Figure 2, using a Mitsunobu reaction in the displacement of a primary alcohol of **1a** to maleimide or furan-protected maleimide.^{30,31} The deprotection of **1g** by retro Diels–Alder reaction afforded **1f** (41% from **1a**). This two-step method of the synthesis for **1f** achieved a better yield and successive removal of excess aldehyde **7a** in the crude product during column purification, compared with a direct transformation of **1a** to **1f** by Mitsunobu reaction (11%).^{29,32}

All new compounds were characterized by NMR and IR spectroscopy, as well as by mass spectrometry. Regarding the structures of products **4** and **6**, their ¹H NMR spectra showed signals that could be attributed to an alkene with reasonable coupling constants. In the ¹³C NMR spectra of 3*H*-indoles **4a**–**e**, a prominent carbon signal appeared, which was ascribed to the imino carbon at position 2 of the indole (**4a**: *δ* 186.4, **4b**: *δ* 186.3, **4c**: *δ* 186.0, **4d**: δ 184.8, and **4e**: δ 179.3), while during the following cyclization the same carbon was remarkably shielded (**6a**: δ 108.8, 108.6, **6b**: δ 108.8, 108.4, **6c**: δ 108.7, 108.4, and **6d**: δ 108.5). The ¹H NMR spectra of compounds **1a-h** exhibited signals for the H-3 protons of the chromene ring at 5.87-6.00 ppm as characteristic doublets with J = 10-11 Hz, which indicated a *cis* conformation. The ¹H NMR and ¹³C NMR spectra for the 6 ISPs, **1a-c** and **1f-h**, revealed that the 2 adjacent stereogenic centers in the structure caused an inseparable mixture of diastereomers in unequal ratios. As for ISP **1e**, the 1D NMR (¹H, ¹³C, and DEPT) spectra showed that all signals could be assigned to a single stereoisomer. The assignment of the signals was achieved with the aid of the 2D NMR (¹H-¹H COSY, HMQC, and HMBC) spectra. The stereochemistry of 1e was confirmed via NOEs and X-ray crystallography (Fig. 3). To assess the relative stability of **1e** for 2',3'-cis-substituted stereoisomer against 2',3'-trans, optimized structures was calculated at the Hartree–Fock/3-21G(*) level utilizing the Spartan program. The 2',3'-cis isomer **1e** was 17.2 kJ mol⁻¹ lower in energy than the 2',3'-trans isomer (see Supplementary material).

To characterize the photochromic properties of ISPs 1a-h, the UV-vis absorption spectra were measured in chloroform solution both before and after UV light irradiation (Fig. 4). The results showed the UV-vis absorption spectra of **1a-h** at a concentration of 1×10^{-4} mol/L, in which characteristic peaks were clearly shown at 565–569 nm for **1a-d** and at 593–595 nm for **1e-g** after UV light irradiation (Table 1). The peaks appeared as a result of 366 nm UV light irradiation for 3 min, indicating the photoisomerization from ISP form **1** to MC form **2**, as shown in Figure 1.³³ The colored solution after UV light irradiation was stored in the dark, and the absorption spectra were measured as a function of concurrent time (Fig. 5). The absorption at 560-595 nm gradually decreased as time increased (Fig. 4c and Fig. 5). For ISPs 1a-g, the intensity of the peaks was completely repeatable with the UV light irradiation (Table 1). The maximum absorption at 560–595 nm of **1a-g** during irradiation of 366 nm proved to be a trans-trans-cis conformation of MC chromophores, which has been suggested to be the thermodynamically stable version of

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1	15	5 1		1 1 1		
Product	R ²	R ³	R^4	R ⁵	Photochromism [stectra] ^a	$\lambda (nm)^{b}$
1a	6-NO ₂	CH ₂ CH ₂ OH	CH ₃	CH ₂ CH=CH ₂	Yes [Fig. 5a]	565
1b	6-NO ₂	CH ₂ CH ₂ OH	CH ₃	CH ₂ CH=CH-Ph	Yes [Fig. 5b]	566
1c	6-NO ₂	CH ₂ CH ₂ OH	CH ₃	CH ₂ CH=CHCH ₂ OAc	Yes [Fig. 5c]	569
1d	6-NO ₂	CH ₂ CH ₂ OH	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	Yes [Fig. 5d]	568
1e	6-NO ₂	CH ₃	CO ₂ Et	CH ₂ CH=CH ₂	Yes [Fig. 5e]	595
1f	6-NO ₂	CH ₂ CH ₂ NR ₂ ^c	CH ₃	CH ₂ CH=CH ₂	Yes [Fig. 5f]	593
1g	6-NO ₂	CH ₂ CH ₂ NR ₂ ^d	CH ₃	CH ₂ CH=CH ₂	Yes [Fig. 5g]	594
1h	Н	CH ₂ CH ₂ OH	CH ₃	CH ₂ CH=CH ₂	No ^e	_
2i	6-NO ₂	CH ₃	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	No ^f	429

Indoline spirobenzopyrans 1a-h and mero	cyanine 2i produced via Scheme	, and their photochromic properties

^a Irradiation with 366 nm was carried out in a chloroform solution of each substrates.

^b Wavelengths at a maximum peak for the corresponding MC 2 forms.

^c A unit of maleimide was attached (Fig. 2).

^d A unit of protected maleimide was attached (Fig. 2).

^e Color change was not observed.

Table 1

^f Conversion from MC to ISP was observed, but it was not reversible.



Figure 2. Structure of ISPs 1f and 1g.

MC-isomers.^{34–36} It also showed that the hydroxyethyl group on N did not form an oxazolidine intramolecularly in a ring-opened isomer. There was, however, the possibility that the hydroxyethyl group contributed something to the processes of ring opening

and closing.³⁷ It should be noted that ISP **1h** was distinct from **1a–g** for its lack of a nitro group. The photoconversion of **1h** into colored forms did not occur with light at 366 nm since no absorption for excitation was observed in the spectrum of **1h**, as shown in Figure 4a (brown). In the case of 3',3'-diallyl ISP, some interesting observations were made. Left in the dark after irradiation of ISP **1d**, the lifetime of 3',3'-diallyl MC **2d** was the longest based on the fact that the absorption of a maximum peak (568 nm for **2d**) decreased into a pre-irradiation levels at a much slower rate compared with other examples of MC **2** (Fig. 4c, Fig. 5d). Furthermore, a 3',3'-diallyl derivative with R³ = CH₃ was isolated dominantly as the MC form **2i**, which was confirmed by NMR.³⁸ The chloroform solution of this compound was gradually changed to the ISP form **1i** by the irradiation of light at 365 nm. The NMR measurement revealed that a negative type of photoisomerization, from the MC to the



Figure 3. ORTEP diagram of 1e, assigned as a 2',3'-cis diastereomer.



Figure 4. UV-vis spectra of ISP **1a-h** in solutions [a], after irradiation of **1a-h**. [b] Time dependence of the absorption at a maximum peak of **1a-g**. [c] The concentration of **1a-h** was 1×10^{-4} M in chloroform at 293 K. The solutions were stored in the dark after irradiation at 366 nm for 3 min.

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Figure 5. Evolution of UV-vis absorption spectrum of 1a [a], 1b [b], 1c [c], 1d [d], 1e [e], 1f [f], and 1g [g] in solutions after removing the UV light irradiation (366 nm, 3 min). The concentration of 1a-g was 1×10^{-4} M in chloroform at 293 K.

ISP with UV irradiation, had occurred.¹⁹ However, the phenomenon was not reversible, and complete conversion required more than 1 h of irradiation. These results implied that diallyl substitution at the 3' position led to a steric effect during the process of interconversion between the colored and colorless forms. The ratios between two isomers were determined by ¹H NMR in favor of colorless-form ISPs and corresponded to the equilibrium constants (K_1) of 9.8 × 10⁻³ (for **1a**) and 5.0 × 10⁻² (for **1d**) at 298 K (see Supplementary material). From the concentration dependence of the absorbance and the K_1 , the molar extinction coefficients of MC 2a and **2d** were estimated to be 3.3×10^4 and 1.7×10^4 M⁻¹ cm⁻¹, respectively.²⁷ Moreover, the time dependence of the absorbance in Figure 5a indicated that estimates for the rate constant (k_1) for the thermal interconversion of ISP **1a** into MC **2a** and that (k_{-1}) for the opposite process should be 3.9×10^{-5} and $4.0\times 10^{-3}\,s^$ respectively. Similarly, the k_1 and k_{-1} between **1d** and **2d** were estimated to be 4.7×10^{-5} and 9.5×10^{-4} s⁻¹ (Fig. 5d), respectively.³⁷

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In summary, a novel, three-step, facile synthesis of 3'-allylindoline spirobenzopyrans enhanced by palladium-catalyzed β -allylation was accomplished via their 3-allyl-3*H*-indoles. The reactions occurred selectively under mild conditions using accessible 2methylindoles, and 5 types of 3-allyl-3*H*-indoles were isolated. These 5 types were transformed into 8 ISPs, which contained allyl moieties at the 3' position. Most of the compounds proved to have photochromic properties, indicating that the presence of an allyl moiety at the 3' position did not disturb the photochromic response. This result allowed us to propose these compounds as attachable templates in the structural design of new photo-switchable materials.

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Supplementary data

Supplementary data (experimental details, characterization data, NMR spectra for **4a–e**, **6a–d**, and **1a–h**) associated with this article can be found, in the online version, at http://dx.doi.org/ 10.1016/j.tetlet.2014.09.121. (CCDC n.-1012225–1012226, contain the crystallographic data for this article. These data can be obtained, free of charge, from the *Cambridge Crystallographic Data Centre* via: www.ccdc.cam.ac.uk/data_request/cif) These data include MOL files and InChiKeys of the most important compounds described in this article.

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- 38. In the ¹H NMR spectrum for 2i, the doublets of signal for a proton appeared at 8.48 ppm with J = 16 Hz, which confirmed the *trans*-configuration of the associated double bond.