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Facile Isolation of Functionalized Spiropyran Mechanophores without Recrystallization

prepared by James F Berry
SURVICE Engineering
4695 Millennium Drive
Belcamp, MD

under contract W911QX-16-D-0014

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14. ABSTRACT The use of spiropyran in the fields of photoswitches, metal chelation, and dyes has been reported extensively in the literature. However, only within the last decade, as the field of mechanochemistry has evolved, have spiropyran found use as force-sensing molecules. Through this use of spiropyran as force-sensing molecules, observation of molecular-level bond breakage occurring in a sample is possible and can provide information about material failure before micro or macro cracks are formed in samples being impacted at ballistic velocities. To capture the onset of mechanophore activation due to impact at ballistic speeds, mechanophore purity is critical because it can influence the color of the polymer samples being tested, therefore influencing the accuracy of the observation being made. However, functionalized spiropyran isolation has proven to be challenging, and to date, recrystallization of the open form merocyanine in a nonpolar solvent has been the only way of obtaining the spiropyran form in acceptable purity. This method of purification can be very time consuming and difficult to reproduce for obtaining material useful for mechanochemical studies. This report describes new methods recently developed at the US Army Research Laboratory to isolate two different functionalized spiropyran molecules in high purity without recrystallization. These newly developed methods can provide hundreds of milligrams of functionalized spiropyran a few hours after reaction completion, as opposed to several days to greater than a week for recrystallization.						
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1. Introduction

Spiroyrans are a unique set of molecules that contain an indoline group fused to a chromene moiety through a spirocyclic center. These spiroyrans owe their unique chemistry to the labile carbon-oxygen bond between carbon 2 and the oxygen of the chromene (red bond, Fig. 1). Upon introduction of certain stimuli such as ultraviolet light or heat, this bond can be broken to form one of two different merocyanine isomers. Ultraviolet light promotes opening to the zwitterionic merocyanine structure, whereas heat promotes a 6- π electrocyclic ring opening to the quinoidal form (Fig. 1).¹ The true structure of the merocyanine is likely an average of the two isomers. Accompanying this transformation is a change in color to a shade of deep blue/purple. In essence, the extended conjugation of the open merocyanine form causes the molecule to absorb longer wavelengths of light, thus giving rise to the color change in the visible spectrum. On the other hand, exposure to visible light promotes ring closing back to the spiroyrans form. These unique properties allow spiroyrans and their derivatives to be used as photoswitches,^{1,2} metal chelation molecules,³ photochromic magnetic materials,⁴ and dyes.⁵

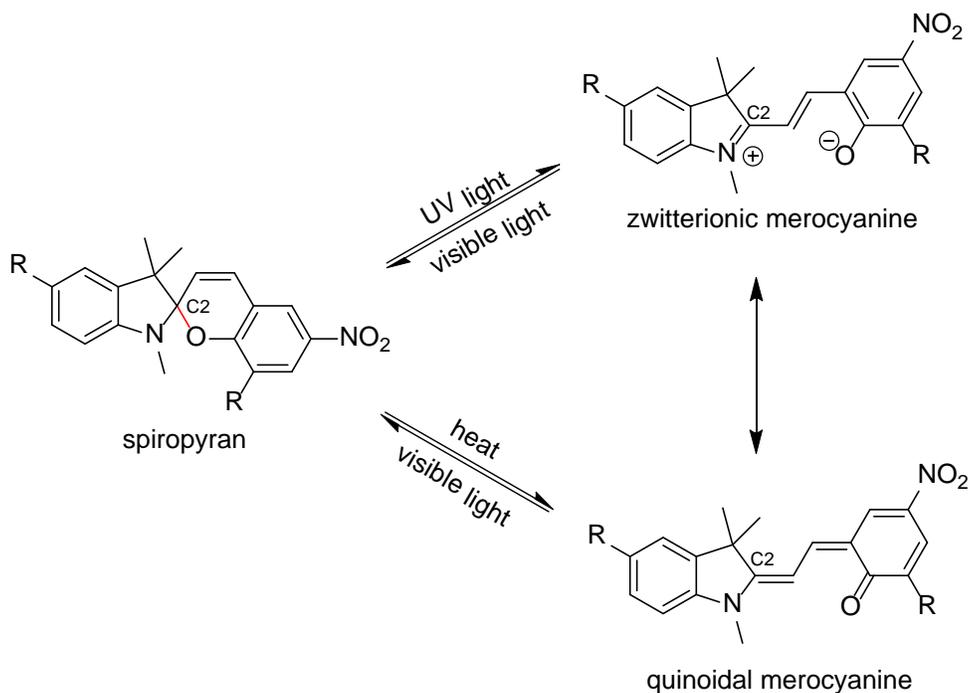


Fig. 1 Spiroyrans ring opening to merocyanine isomers

In a seminal report, Davis et al.⁶ disclosed the synthesis of a nitro-substituted functionalized spiroyrans that, when incorporated into an elastomeric or glassy polymer and exposed to force, could be “activated” and would exhibit a distinct color change from pale yellow to purple. However, to localize the force necessary

to rupture this spirocenter, the molecule needed to be covalently embedded into a long chain polymer, in this case either poly(methyl acrylate) (PMA) or poly(methyl methacrylate) (PMMA). The idea was to build up tensile force along the polymer chain to stress the weak spiro C-O bond over the other bonds in the molecule. This was carried out through placement of the spiropyran near the center of the polymer chain, as well as by the use of chain connections on opposite sides of the C-O spirocenter bond. Although the spiropyran motif had previously been shown to be light sensitive in the 1960s,⁷ the work by Davis⁶ was the first example of incorporation of a functionalized spiropyran⁸ as a mechanophore,⁹ a molecule containing a weak bond susceptible to force,^{9,10} into a bulk polymer.¹¹ A report by Hemmer et al.¹² described spiropyran mechanophore behavior in a glassy PMMA network at high strain rates. However, due to the brittle material properties of PMMA and the high strain rates employed, the specimens were damaged after use. Gossweiler et al.¹³ covalently incorporated a slightly different spiropyran molecule into an elastomeric polydimethylsiloxane (PDMS) framework. The embedded molecule was then activated repeatedly without discernable loss of activity or shape.

The synthesis of functionalized spiropyrans as mechanophores has been noted in the literature.^{6,9-14} However, isolation and purification have presented a formidable challenge due to spiropyrans exhibiting solvatochromism, which is the ability of a compound to absorb differing wavelengths of light depending on the polarity of the solvent used.¹⁵ This effect is due to the solvent's polarity inducing a change in the stabilization of the ground and excited states of the molecule. The solvents typically used (dichloromethane, tetrahydrofuran, ethyl acetate) to dissolve spiropyrans promote opening of the molecule to the merocyanine form. Therefore, previous isolation of functionalized spiropyrans (for embedding into a polymeric network) typically involved recrystallization in a nonpolar solvent.^{6,11-14} The challenge with recrystallization becomes employing the proper solvent, in ideal proportions to crystallize the molecule in its closed spiropyran form (yellow color). Compounding factors, such as the open merocyanine form being zwitterionic, as well as π -stacking that can result from intermolecular interactions of the planar π system, can cause aggregation¹ of the purple merocyanine form. In fact, several successive recrystallizations are typically needed to obtain pure material. These extra steps are time consuming and can negatively impact final product yield.

To be useful for impact studies, the functionalized spiropyran purity should be high to generate quality samples in which this molecule is embedded into a polymer matrix. The closer to colorless or pale yellow the samples are, the greater the contrast when activated to the purple merocyanine form. In working with these spiropyran molecules, the recrystallization step rarely yielded crystals that were

suitable for curing. In fact, this method could take a week or longer, depending on conditions. This lack of reproducibility prompted a workaround technique to obtain pure material suitable for curing into polymers for impact studies. In this report, methods are presented for rapid isolation of two different functionalized spiropyran mechanophores **1** and **2** (Fig. 2) in high purity without the use of recrystallization.

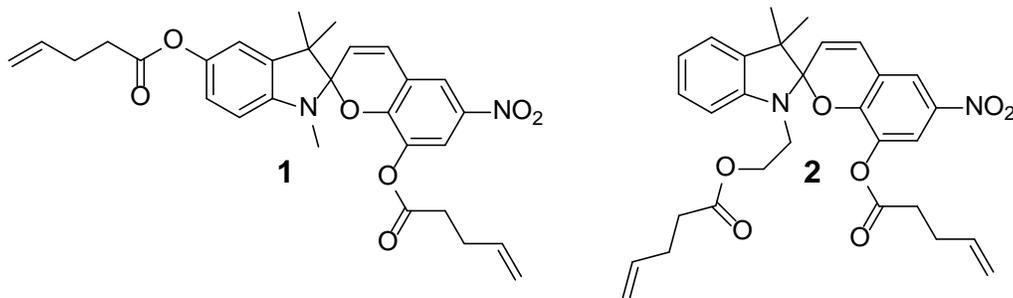
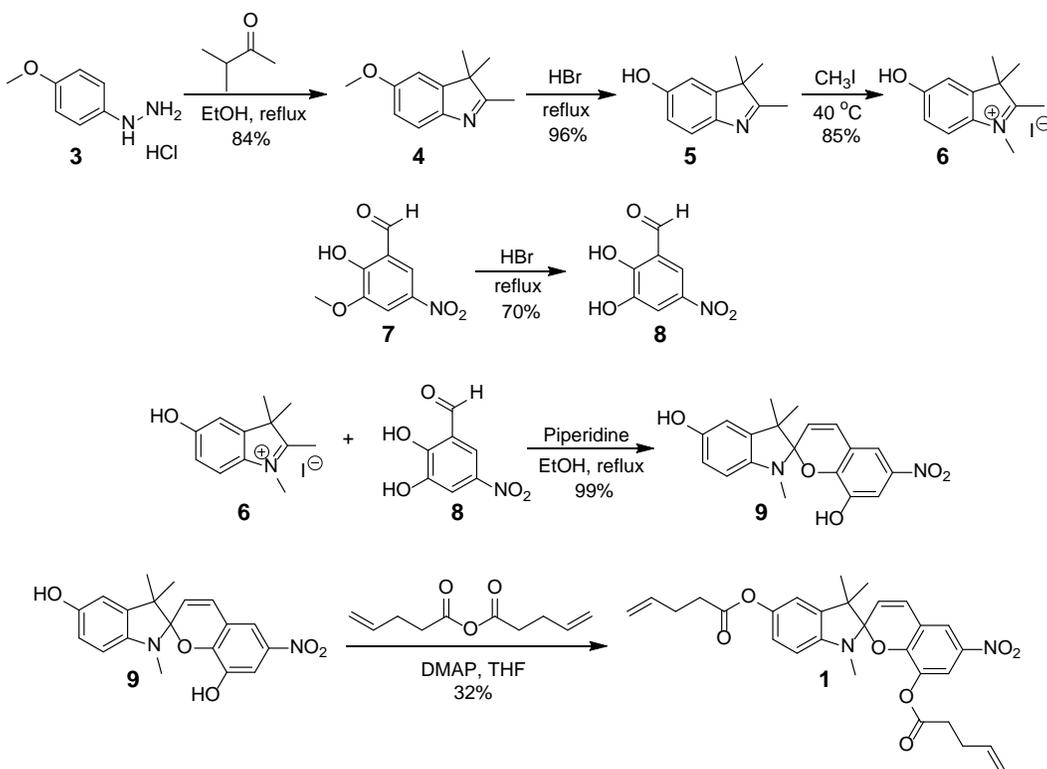


Fig. 2 Functionalized spiropyran mechanophores **1** and **2** used in this study

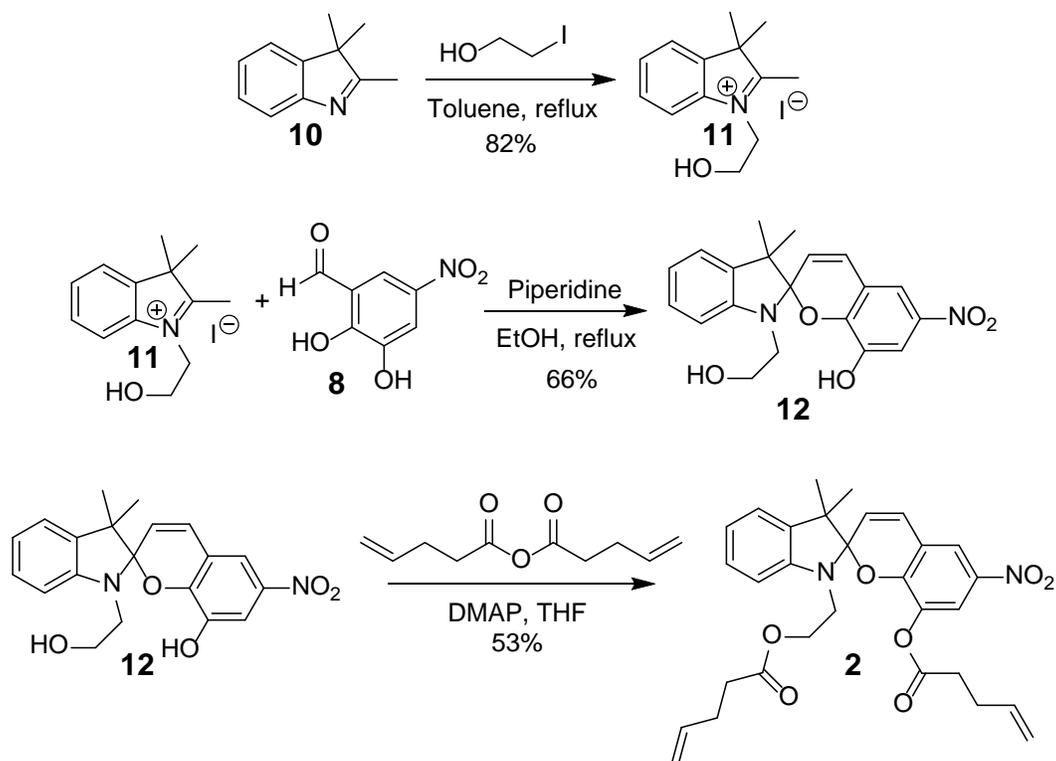
2. Synthesis of Functionalized Spiroyrans Containing Alkene Linkers

The synthetic route to functionalized spiropyran **1**, adapted from the literature,^{6,11–14} is outlined in Scheme 1. First, commercially available 4-methoxyphenylhydrazine hydrochloride **3** was reacted with methyl isopropyl ketone under refluxing conditions¹¹ to give indole **4**. Deprotection of the phenol group of compound **4** took place under acidic conditions to generate phenol **5** in high yield.⁶ Next, treatment of indole **5** with methyl iodide under slightly elevated temperatures¹¹ gave indolium iodide **6**. Concomitantly, the methyl group of commercially available 2-hydroxy-3-methoxy-5-nitrobenzaldehyde **7** was removed under acidic conditions¹² to give diol **8** in reasonable yield. Synthesis of spiropyran **9** took place through treatment of iodide **6** with diol **8** in the presence of base in refluxing ethanol.¹² Finally, the alkene side chains were added¹⁴ using 4-pentenoic anhydride in the presence of 4-dimethylaminopyridine (DMAP) to give functionalized spiropyran **1** (Scheme 1).



Scheme 1. The synthetic route of functionalized spiropyran **1**, adapted from existing literature

The synthesis of functionalized spiropyran **2** commenced with alkylation of 2,3,3-trimethyl-3*H*-indole **10** with 2-iodoethanol¹³ to give iodolium iodide **11**. This iodide salt was then coupled with diol **8** under basic conditions to give spiropyran **12** in moderate yield¹³ as an emerald colored solid. The alkene linkers were then added through acylation¹³ of compound **12** with 4-pentenoic anhydride in the presence of DMAP to give functionalized spiropyran **2** (Scheme 2).



Scheme 2. The synthetic route of functionalized spiropyran **2**, adapted from existing literature

3. Isolation of Functionalized Spiropyran Mechanophores

While the synthesis of compounds **1** and **2** was straightforward, their isolation from the reaction mixture as pure functionalized spiropyrans proved to be a challenge. After the reaction was filtered through a small plug of basic alumina to remove any single alkylation products that formed, attempts to recrystallize in nonpolar solvents such as hexane and petroleum ether were mostly unsuccessful. During this process, the solution would slowly turn purple and either oil out or solidify as a purple solid, most likely due to aggregation of the open merocyanine form. Use of completely dry glassware, dry solvents, and sodium sulfate to dry the spiropyran recrystallization solution rarely resulted in the requisite crystals. Finally, slow evaporation of the solvent also did not result in any crystalline spiropyran product.

While interaction of a spiropyran with mildly acidic silica gel does promote opening to the merocyanine form,^{16,17} resulting in a loss in yield, it was hypothesized that a mostly nonpolar solution (3%–6% ethyl acetate in petroleum ether) would be sufficient to quickly elute the relatively nonpolar product from the column. Therefore, this process was performed rapidly to minimize contact time with the silica gel. The crude reaction mixture was dissolved in dichloromethane, evaporated to silica gel, and dry packed onto a small column of silica gel. The

mobile phase was increased in polarity (from 3% ethyl acetate in petroleum ether to 6% ethyl acetate in petroleum ether) until the product had eluted from the column, as shown by thin layer chromatography (TLC). Combining fractions followed by rotary evaporation of approximately 90% of the solvent resulted in a blue colored solution, due to the remaining solvent being comprised mostly of ethyl acetate. At this point, additional petroleum ether was added, which resulted in the solution changing from blue to colorless due to the increased nonpolar petroleum ether solvent content favoring the closed spiropyran form. As the solvent was slowly removed under reduced pressure via rotary evaporation, the solution turned a yellow color, followed by precipitation of the functionalized spiropyran product as a yellow solid (Figs. 3 and 4). The solid was then stirred in a small amount of petroleum ether to give the product as a fine, yellow powder in high purity. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ are in agreement with previously reported material.^{13,14,*}

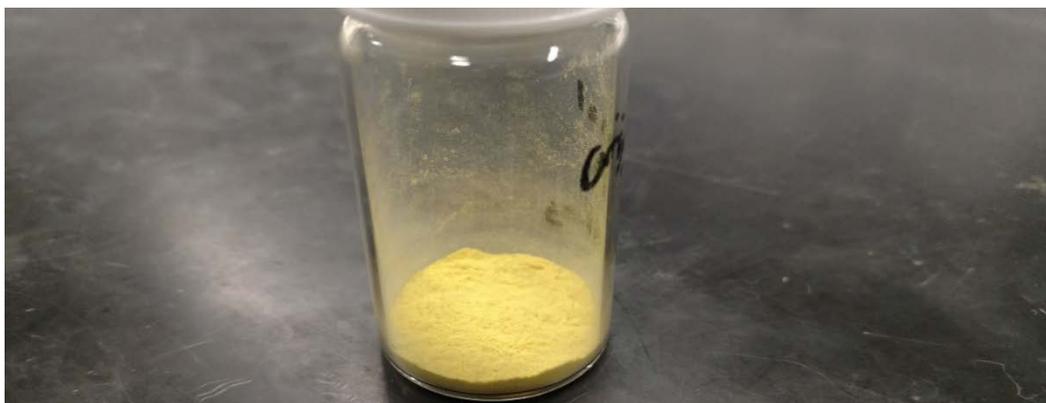


Fig. 3 Functionalized spiropyran 1 as a yellow powder



Fig. 4 Functionalized spiropyran 2 as a yellow powder

Isolation of compounds **1** and **2** without column chromatography¹⁷ would make it even more attractive as a method for production of functionalized spiropyrans.

* The original material synthesized in reference 14 contained a heptenoate ester as the linker, whereas the product synthesized in this report contains a pentenoate ester linker.

From experimentation on the crude reaction mixture of **1** with several solvents, it was found that, after evaporation of the reaction solvent to dryness, stirring with a small amount of methanol to break up the solids followed by cooling in an ice bath (with stirring) lead to the precipitation of **1** as a red solid. Washing the solid with small aliquots of ice cold methanol resulted in a dark yellow solid, which was then stirred in a small amount of petroleum ether to give **1** as a dark yellow powder. Unfortunately, the same procedure carried out on spiropyran **2** with various solvents did not successfully precipitate any solid material, necessitating the use of column chromatography for this substrate.

While recrystallization of compounds in the solid state can be a useful method of producing high-purity samples in organic synthesis, additional factors such as solvatochromic effects can complicate this process for certain substrates. Although higher yields have been reported previously^{13,14} for these functionalized spiropyrans, several recrystallizations would have been necessary to produce the requisite high-purity material needed for ballistic testing. On the other hand, the techniques developed in this report can provide quantities of several hundred milligrams of compounds **1** and **2** in high purity, with greater consistency than what has been reported. These molecules can be isolated in powder form only a few hours from the quenching of the final acylation reaction (see Schemes 1 and 2), which is in contrast to the days-to-weeks' timescale that may be required for recrystallization.

4. Experimental

Most solvents were purchased from either Sigma-Aldrich or VWR International and used as is except tetrahydrofuran (THF), which was dried on an MBraun, Inc., Solvent Purification System prior to use. Absolute ethanol was purchased from Koptec, Inc., and petroleum ether was purchased from GFS Chemicals, Inc. CDCl₃ was purchased from Sigma-Aldrich, and DMSO-*d*₆ was purchased from Cambridge Isotope Laboratories. All other reagents were purchased from either Sigma-Aldrich or Alfa Aesar. All glassware was dried in an oven set to 110 °C, and reactions were stirred magnetically under an argon atmosphere. Thin layer chromatography (TLC) was performed using EMD/Millipore Silica Gel 60 TLC plates (250 μm, F₂₅₄ indicator) and viewed under UV light (254 nm). Column chromatography was performed using SiliCycle SiliaFlash F60 silica gel (40–63 μm particle size, 230–400 mesh). ¹H-NMR and ¹³C-NMR were performed on a Bruker 400-MHz nuclear magnetic resonance (NMR) system. NMR values are reported in parts per million (ppm) as compared to the reference peaks of CDCl₃ (7.26 ppm for ¹H and 77.16 ppm for ¹³C) and DMSO-*d*₆ (2.50 ppm for ¹H and 39.52 ppm for ¹³C). ¹H-NMR values are reported as (chemical shift in parts per million, multiplicity,

coupling constant in hertz, relative integral). ¹H-NMR multiplicities are indicated as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet) and b (broad). EtOH is ethanol, EtOAc is ethyl acetate, DCM is dichloromethane, Et₂O is diethyl ether, THF is tetrahydrofuran, MeOH is methanol, PE is petroleum ether, HBr is hydrobromic acid, NaHCO₃ is sodium bicarbonate.

5-methoxy-2,3,3-trimethyl-3H-indole (4)

Following the literature procedure,¹¹ 4-methoxyphenylhydrazine hydrochloride **3** (5.00 g, 28.7 mmol, 1 equiv.) was stirred in 133 mL absolute EtOH, and methyl isopropyl ketone (3.07 mL, 28.7 mmol, 1 equiv.) was added. The mixture was then refluxed overnight in an oil bath set to 100 °C. After cooling and removal of the solvent, the product was purified via column chromatography (product *R_f* = 0.14 in 3:1 hexane:EtOAc) to give 5-methoxy-2,3,3-trimethyl-3H-indole **4** (4.57 g, 84% yield) as a red oil that solidified upon standing. ¹H-NMR and ¹³C-NMR were in agreement with the previously reported material.¹¹ ¹H-NMR (400 MHz, CDCl₃) δ 7.41 (d, *J* = 8.2 Hz, 1H), 6.84-6.78 (m, 2H), 3.81 (s, 3H), 2.23 (s, 3H), 1.27 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ 185.8, 158.0, 147.6, 147.4, 120.2, 112.1, 108.2, 55.8, 53.9, 23.3, 15.4.

2,3,3-trimethyl-3H-indol-5-ol (5)

Following the literature procedure,⁶ 5-methoxy-2,3,3-trimethyl-3H-indole **4** (4.50 g, 23.8 mmol, 1 equiv.) was stirred with 90 mL of 48% aq. HBr and heated to reflux (bath temperature 140 °C) for 5 h. After cooling to room temperature, the mixture was slowly diluted with 300 mL of water and then solid NaHCO₃ was slowly added in small portions with vigorous stirring until the reaction became basic and the evolution of gas stopped. The solid product was filtered and washed with water. The filtrate was extracted three times with DCM and after removal of the solvent, the solids were combined to give 2,3,3-trimethyl-3H-indol-5-ol **5** (4.01 g, 96% yield) as a light brown powder that was used without further purification. ¹H-NMR (400 MHz, CDCl₃) δ 8.93 (bs, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.4 Hz, 1H), 2.26 (s, 3H), 1.28 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ 185.9, 155.6, 147.5, 145.5, 120.1, 114.3, 109.9, 53.8, 23.3, 15.1.

5-hydroxy-1,2,3,3-tetramethyl-3H-indolium iodide (6)

Following a modified literature procedure,¹¹ 2,3,3-trimethyl-3H-indol-5-ol **5** (4.00 g, 22.8 mmol, 1 equiv.) was stirred with methyl iodide (21.3 mL, 0.34 mol, 15 equiv.) and the mixture heated to 40 °C for 24 h. The reaction was cooled to room temperature, and the solid was filtered and washed with 300 mL of benzene. The solid was then triturated with hot EtOH, filtered, then triturated twice with Et₂O

to give 5-hydroxy-1,2,3,3-tetramethyl-3*H*-indolium iodide **6** (6.15 g, 85% yield) as a light brown powder. ¹H-NMR and ¹³C-NMR were in agreement with the previously reported material.¹¹ ¹H-NMR (400 MHz, DMSO-*d*₆) δ 10.23 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.90 (s, 3H), 2.68 (s, 3H), 1.47 (s, 6H). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 191.9, 159.0, 143.7, 134.1, 116.1, 115.0, 110.3, 53.4, 34.6, 21.9, 13.7.

2,3-dihydroxy-5-nitrobenzaldehyde (8)

Following the literature procedure,¹² 90 mL of 48% aq. HBr was added to 2-hydroxy-3-methoxy-5-nitrobenzaldehyde **7** (5.00 g, 25.4 mmol, 1 equiv.) in a round bottom flask and heated to 140 °C for 5.5 h. After cooling to room temperature, the reaction mixture was added to 120 mL of cold water. The suspension was filtered and washed with water to give a brown solid. This solid was dissolved in 150 mL of hot EtOAc, activated carbon was added and, after brief stirring, the solution was passed through a small plug of silica gel. The filtrate was then placed into a -40 °C freezer to cool overnight. The precipitated solids were filtered off to give 2,3-dihydroxy-5-nitrobenzaldehyde **8** as light yellow needles. Additional product was obtained through rotary evaporation of the supernatant. Total yield 3.27 g, 70% yield. ¹H-NMR and ¹³C-NMR matched that of the previously reported material.¹¹ ¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.18 (bs, 2H), 10.30 (s, 1H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.78 (d, *J* = 2.8 Hz, 1H). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 189.8, 156.0, 147.2, 139.2, 121.8, 114.6, 113.2.

1',3',3'-trimethyl-6-nitrospiro[chromene-2,2'-indoline]-5',8-diol (9)

Following the literature procedure,¹² 5-hydroxy-1,2,3,3-tetramethyl-3*H*-indol-1-ium iodide **6** (2.73 g, 8.61 mmol, 1 equiv.) and 2,3-dihydroxy-5-nitrobenzaldehyde **8** (1.57 g, 8.61 mmol, 1 equiv.) were combined with 86 mL of absolute EtOH and stirred for 5 min. Piperidine (1.70 mL, 17.2 mmol, 2 equiv.) was added dropwise, and the mixture turned black. The reaction was heated to reflux (100 °C oil bath) and stirred for 3 h, then removed from the oil bath and allowed to cool to room temperature. The reaction mixture was further cooled in an ice bath for 20 min, then filtered and washed with small aliquots of ice cold EtOH to give 1',3',3'-trimethyl-6-nitrospiro[chromene-2,2'-indoline]-5',8-diol **9** (3.01 g, 99% yield) as a dark green/black powder. This material was used directly without purification.

1',3',3'-trimethyl-6-nitrospiro[chromene-2,2'-indoline]-5',8-diyl bis(pent-4-enoate) (1)

Following a modified literature procedure,¹⁴ a mixture of 1',3',3'-trimethyl-6-nitrospiro[chromene-2,2'-indoline]-5',8-diol **9** (1.50 g, 4.24 mmol, 1 equiv.) and 4-dimethylaminopyridine (DMAP, 1.55 g, 12.72 mmol, 3 equiv.) was combined with

42 mL of dry DCM. 4-Pentenoic anhydride (2.00 mL, 11.02 mmol, 2.6 equiv.) was added dropwise at room temperature over 5 min. The mixture changed from blue to purple and was stirred for 72 h at room temperature (product $R_f = 0.79$ in 4:1 PE:EtOAc). Then, 1.5 mL of MeOH was added to the solution, which was stirred for 10 min. The reaction mixture was then filtered through a small plug of basic alumina, and the column washed with 200 mL of DCM. The filtrate was rotary evaporated to dryness and dried under high vacuum. MeOH (20 mL) was added to the purple solid and stirred for 20 min at 0 °C, causing a red solid to precipitate out of the solution. The precipitate was then filtered and washed with a small amount of ice cold MeOH until the red color disappeared, leaving a dark yellow solid. The precipitate was then stirred in petroleum ether and filtered to give 1',3',3'-trimethyl-6-nitrospiro[chromene-2,2'-indoline]-5',8-diyl bis(pent-4-enoate) **1** (0.706 g, 32% yield) as a dark yellow powder. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.94 (d, $J = 2.6$ Hz, 1H), 7.82 (d, $J = 2.6$ Hz, 1H), 6.97 (d, $J = 10.4$ Hz, 1H), 6.84 (dd, $J = 8.2, 2.2$ Hz, 1H), 6.80 (d, $J = 2.2$ Hz, 1H), 6.48 (d, $J = 8.3$ Hz, 1H), 5.96-5.86 (m, 1H), 5.90 (d, $J = 10.4$ Hz, 1H), 5.68-5.58 (m, 1H), 5.17-5.06 (m, 2H), 4.96-4.92 (m, 2H), 2.68-2.61 (m, 5H), 2.54-2.46 (m, 2H), 2.32-2.15 (m, 2H), 2.00-1.92 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 172.0, 170.6, 151.1, 145.3, 144.5, 140.3, 137.7, 137.4, 136.6, 136.5, 128.6, 121.1, 120.3, 120.2, 119.5, 119.3, 116.0, 115.5, 115.5, 107.8, 107.5, 52.0, 33.8, 32.9, 29.1, 29.0, 28.5, 25.7, 19.6.

1-(2-hydroxyethyl)-2,3,3-trimethyl-3H-indolium iodide (11)

Following a modified literature procedure,¹³ 2-iodoethanol (7.36 mL, 94.3 mmol, 1.5 equiv.) was added dropwise over 5 min to a solution of 2,3,3-trimethyl-3H-indole **10** (10.0 g, 62.9 mmol, 1 equiv.) in 100 mL of toluene. The mixture was heated to reflux (bath temperature 120 °C) and stirred for 20 h. After cooling to room temperature, the mixture was further cooled to 0 °C in an ice bath, then filtered to give a dark purple solid, which was washed with ice cold toluene. The solid was triturated several times with acetone to give 1-(2-hydroxyethyl)-2,3,3-trimethyl-3H-indolium iodide **11** (17.08 g, 82% yield) as a light pink solid. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ were in agreement with the previously reported material.¹³ $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 7.97-7.94 (m, 1H), 7.86-7.84 (m, 1H), 7.64-7.60 (m, 2H), 4.60 (t, $J = 5.0$ Hz, 2H), 3.88 (t, $J = 5.0$ Hz, 2H), 2.82 (s, 3H), 1.55 (s, 6H). $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ 197.8, 141.8, 141.1, 129.3, 128.8, 123.4, 115.6, 57.8, 54.2, 50.2, 22.0, 14.4.

1'-(2-hydroxyethyl)-3',3'-dimethyl-6-nitrospiro[chromene-2,2'-indolin]-8-ol (12)

Following a slightly modified literature procedure,¹³ 1-(2-hydroxyethyl)-2,3,3-trimethyl-3H-indol-1-ium iodide **11** (2.71 g, 8.19 mmol, 1 equiv.) and 2,3-dihydroxy-5-nitrobenzaldehyde **8** (1.50 g, 8.19 mmol, 1 equiv.) were combined in

a round bottom flask along with 82 mL of absolute EtOH. Piperidine (1.62 mL, 16.4 mmol, 2 equiv.) was added dropwise over 5 min with stirring, and the mixture turned black. The flask was then heated (oil bath) to 100 °C and stirred at this temperature for 3 h. The mixture was removed from the oil bath and cooled to room temperature, then further cooled to 0 °C in an ice bath and filtered to give a black solid. The filtered solid was washed with small aliquots of ice cold EtOH to give 1'-(2-hydroxyethyl)-3',3'-dimethyl-6-nitrospiro[chromene-2,2'-indolin]-8-ol **12** (2.01 g, 66% yield) as an emerald green solid. This material was used directly without purification.

3',3'-dimethyl-6-nitro-1'-(2-(pent-4-enoyloxy)ethyl)spiro[chromene-2,2'-indolin]-8-yl pent-4-enoate (2)

Following a modified literature procedure,¹³ a mixture of 1'-(2-hydroxyethyl)-3',3'-dimethyl-6-nitrospiro[chromene-2,2'-indolin]-8-ol **12** (0.50 g, 1.36 mmol, 1 equiv.) and 4-dimethylaminopyridine (DMAP, 0.298 g, 2.44 mmol, 1.8 equiv.) was combined with 14 mL of dry THF and stirred for 5 min. 4-Pentenoic anhydride (0.65 mL, 3.54 mmol, 2.6 equiv.) was added dropwise at room temperature over 5 min. The solution changed from blue to purple and was stirred overnight at room temperature. Then, 1 mL of MeOH was added to the solution, which was stirred for 10 min. The reaction mixture was then filtered through a small plug of basic alumina, and the column washed with 200 mL of DCM. Silica gel was added to the solution, and the solvent removed under reduced pressure. Column chromatography using a solvent system ranging from 3% EtOAc/PE to 6% EtOAc/PE was used to elute the product from the column. The fractions containing product (product $R_f = 0.81$ in 3:1 PE:EtOAc) were combined, and solvent was removed (through rotary evaporation) until the solution started turning a darker shade of blue (about 10% of original volume). PE (~100 mL) was then added to the solution and stirred. After removing some of the solvent under reduced pressure, the solution turned a bright yellow color and the product precipitated out as a yellow solid. The remaining solvent was removed, and the product was triturated with PE and filtered to give 3',3'-dimethyl-6-nitro-1'-(2-(pent-4-enoyloxy)ethyl)spiro[chromene-2,2'-indolin]-8-yl pent-4-enoate **2** (358 mg, 53% yield) as a bright yellow powder. ¹H-NMR and ¹³C-NMR were in agreement with the previously reported material.¹³ ¹H-NMR (400 MHz, CDCl₃) 7.94 (d, $J = 2.6$ Hz, 1H), 7.82 (d, $J = 2.6$ Hz, 1H), 7.16 (td, $J = 7.7, 1.1$ Hz, 1H), 7.06 (dd, $J = 7.3, 1.0$ Hz, 1H), 6.96 (d, $J = 10.4$ Hz, 1H), 6.86 (td, $J = 7.5, 1.0$ Hz, 1H), 6.65 (d, $J = 7.8$ Hz, 1H), 5.96 (d, $J = 10.4$ Hz, 1H), 5.82-5.71 (m, 1H), 5.61-5.49 (m, 1H), 5.04-4.86 (m, 4H), 4.28-4.10 (m, 2H), 3.33 (t, $J = 6.1$ Hz, 2H), 2.38-2.30 (m, 4H), 2.25-2.10 (m, 2H), 1.88-1.83 (m, 2H), 1.26 (s, 3H), 1.18 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 172.9, 170.5, 150.9, 146.7, 140.4, 137.8, 136.6, 136.4, 135.9, 128.5, 127.9, 121.7, 121.6,

120.3, 120.2, 119.3, 119.3, 115.7, 115.6, 107.5, 107.2, 62.6, 52.3, 42.6, 33.6, 33.0, 28.8, 28.4, 26.0, 19.5.

5. Conclusion

Isolation of the spiropyran moiety can be problematic due to its propensity to undergo a ring-opening transformation to the purple merocyanine form. While recrystallization from the merocyanine isomer using a nonpolar solvent has been previously reported to give functionalized spiropyran crystals, this method did not produce much of the requisite material. Here, new methods were developed where two different functionalized spiropyran mechanophores, compounds **1** and **2**, can be isolated through adjustment of the reaction workup conditions. These methods allow for consistent production of hundreds of milligrams of high-purity material in a fraction of the time that would be needed for recrystallization.

6. References

1. Klajn R. Spiropyran-based dynamic materials. *Chem Soc Rev.* 2014;43(1):148–184.
2. Minkin VI. Photoswitchable molecular systems based on spiropyrans and spirooxazines. In: Faringa BL, Browne WR, editors. *Molecular Switches*, Volume 1. 2nd ed. Weinheim (Germany): Wiley-VCH Verlag GmbH & Co.; c2011. p. 37–80.
3. Fries KH, Sheppard GR, Bilbrey JA, Locklin J. Tuning chelating groups and comonomers in spiropyran-containing copolymer thin films for color-specific metal ion binding. *Polym Chem.* 2014;5(6):2094–2102.
4. Nakatani K, Yu P. Photochromic magnetic materials. *Adv Mater.* 2001;13(18):1411–1413.
5. Corns SN, Partington SM, Towns AD. Industrial organic photochromic dyes. *Color Tech.* 2009;125(5):249–261.
6. Davis DA, Hamilton A, Yang J, Cremer LD, Van Gough D, Potisek SL, Ong MT, Braun PV, Martinez TJ, White SR, Moore JS, Sottos NR. Force-induced activation of covalent bonds in mechanoresponsive polymeric materials. *Nature.* 2009;459:68–72.
7. Bercovici T, Fischer E. Photosensitized coloration of photochromic spiropyrans. *J Am Chem Soc.* 1964;86(24):5687–5688.
8. For the first example of a spiropyran being incorporated into a bulk polymer for photochemical studies, see: Smets G, De Blauwe F. Chemical reactions in solid polymeric systems: photochemical phenomena. *Pure App Chem.* 1974;39(1–2):225–238.
9. Li J, Nagamani C, Moore JS. Polymer mechanochemistry: from destructive to productive. *Acc Chem Res.* 2015;48(8):2181–2190.
10. Caruso MM, Davis DA, Shen Q, Odom SA, Sottos NR, White SR, Moore JS. Mechanically-induced chemical changes in polymeric materials. *Chem Rev.* 2009;109(11):5755–5798.
11. For the first example of a spiropyran used as a mechanophore in solution, see: Potisek SL, Davis DA, Sottos NR, White SR, Moore JS. Mechanophore-linked addition polymers. *J Am Chem Soc.* 2007;129(45):13808–13809.

12. For a work in which a spiropyran was embedded in a glassy PMMA polymer and tested at high rate, see: Hemmer JR, Smith PD, van Horn M, Alnemrat S, Mason BP, de Alaniz JR, Osswald S, Hooper JP. High strain-rate response of spiropyran mechanophores in PMMA. *J Poly Sci, Part B: Poly Phys.* 2014;52(20):1347–1356.
13. Gossweiler GR, Hewage GB, Soriano G, Wang Q, Welshofer GW, Zhao X, Craig SL. Mechanochemical activation of covalent bonds in polymers with full and repeatable macroscopic shape recovery. *ACS Macro Lett.* 2014;3(3):216–219.
14. Gossweiler GR, Kouznetsova TB, Craig SL. Force rate characterization of two spiropyran-based molecular force probes. *J Am Chem Soc.* 2015;137(19):6148–6151.
15. Rauf MA, Hisaindee S. Studies on solvatochromic behavior of dyes using spectral techniques. *J Mol Struct.* 2013;1042:45–56.
16. Schulz-Senft M, Gates PJ, Sönnichsen FD, Staubitz A. Diversely halogenated spiropyrans – useful synthetic building blocks for a versatile class of molecular switches. *Dyes and Pigments.* 2017;136:292–301.
17. Kinashi K, Nakamura S, Imamura M, Ishida K, Ueda Y. The mechanism for negative photochromism of spiropyran in silica. *J Phys Org Chem.* 2012;25(6):462–466.

List of Symbols, Abbreviations, and Acronyms

DCM	dichloromethane
DMAP	dimethylaminopyridine
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
HBr	hydrobromic acid
MeOH	methanol
NMR	nuclear magnetic resonance
NaHCO ₃	sodium bicarbonate
PDMS	polydimethylsiloxane
PE	petroleum ether
PMA	poly(methyl acrylate)
PMMA	poly(methyl methacrylate)
ppm	parts per million
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

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