JOC The Journal of Organic Chemistry

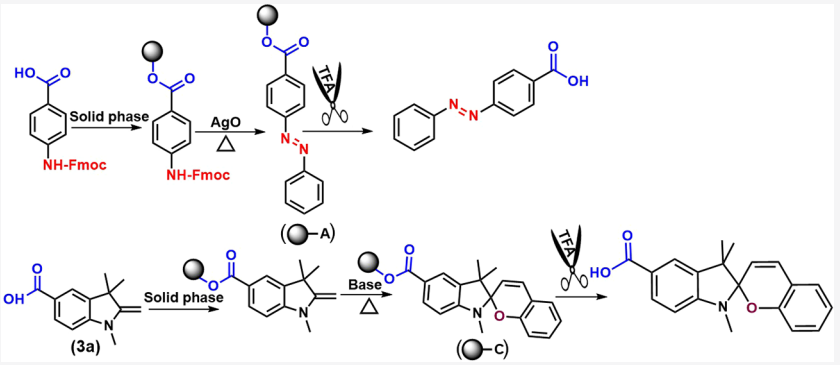
pubs.acs.org/joc Article

Direct and Divergent Solid-Phase Synthesis of Azobenzene and Spiropyran Derivatives

Ravichandran H. Kollarigowda and Paul V. Braun*

Cite This: J. Org. Chem. 2021, 86, 4391−4397 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Here, we report a solid-phase approach to synthesize azobenzene and spiropyran derivatives. The divergent synthesis process requires no purification steps to obtain the desired product with a 28−55% yield, depending on the specific compound. For the spiropyran compounds, solid-phase resin cleavage is performed under mild conditions to minimize spiropyran ring opening. The solid-phase method enables the synthesis of a library of azobenzene and spiropyran derivatives without the need to develop purification strategies for each derivative.

INTRODUCTION

Favorable features of solid-phase organic synthesis include the facile elimination and purification of intermediates, which allows the rapid synthesis of libraries of compounds.[1−3] In solid-phase organic synthesis, the product purification is simplified since filtration and washing rather than column chromatography can be used. This enables reactions to be driven to near completion by using excesses of reagents without causing separation problems. Inspired by the advantages of a solid-phase process, we developed a simple solid-phase method to synthesize azobenzene and spiropyran derivatives. We focus on azobenzene and spiropyran chemistries specifically due to their stimuli-responsive nature. These chemistries have been used for dyes and pigments,[4] smart textiles,[5] water purification,[6] dynamic surfaces for biological applications,[7,8] sensors,[9,10] and mechanophores.[11,12] The conformational changes of azobenzene and spiropyran chromophores upon exposure to external stimuli ranging from light and heat to mechanical force have been a primary driver of the interest in these systems.[13−15]

Solution synthesis of azobenzene and spiropyran derivatives is well established from the last two decades.[16]

Classical methods of preparing azobenzenes include azo coupling, Mills, oxidative, and Wallach reactions, which provide yields of 62−90% (Figure 1).[17−19]

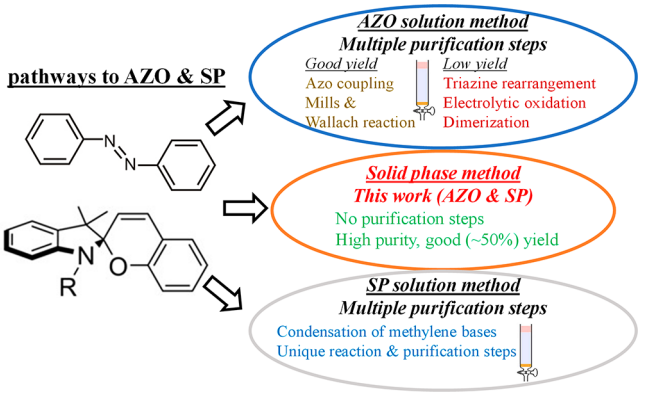


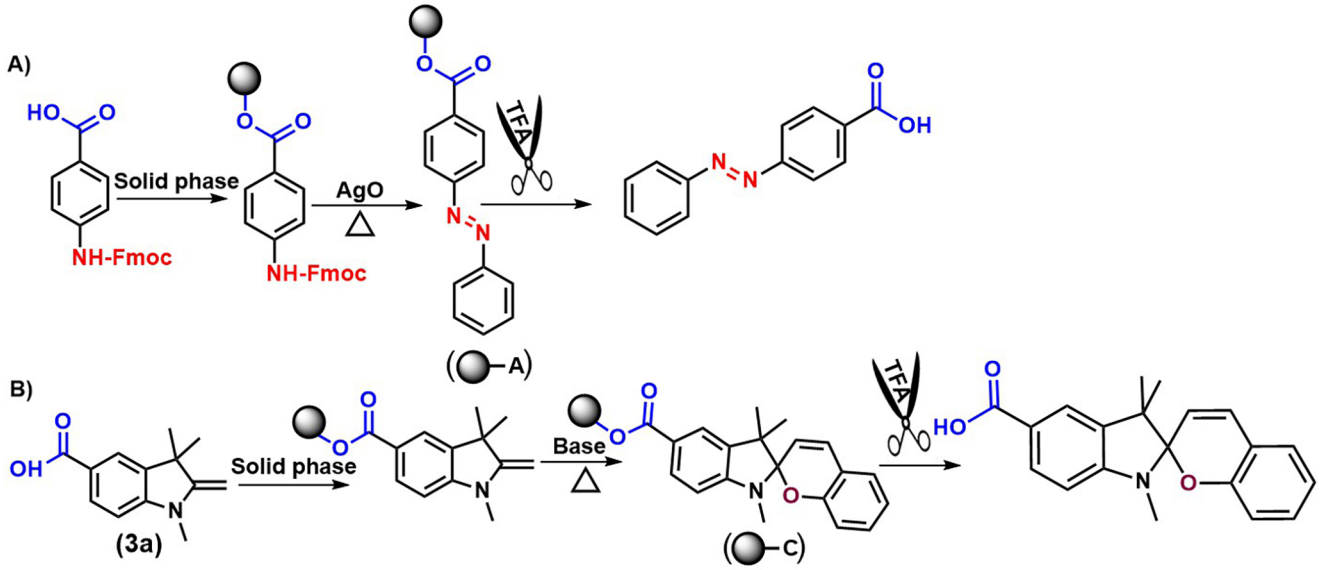
Figure 1. Synthetic pathways for azobenzene and spiropyrans contrasting solution and solid-phase (this work) methods.

An alternative method is the electrolytic oxidation of aromatic amines; however, this only gave azo compounds in

Received: October 7, 2020
Published: March 3, 2021

https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397

Scheme 1. Examples of Solid-Phase Synthesis of (A) Azobenzene and (B) Spiropyran Compounds[a]



[a]In the final step, the product was cleaved from the polystyrene resin with TFA.

yields of 35−48%.[20] The azo formation mechanism generally involves N═N bond coupling with an aniline radical produced by one-electron transfer, followed by two-electron oxidation of hydrazobenzene.[21] For a review of azo formation methods, including recent advances, see Merino et al.[22] The traditional method of synthesizing spiropyran is the condensation of methylene bases (or their precursors) with *o*-hydroxy aromatic aldehydes. An alternative route is the condensation of *o*-hydroxy aromatic aldehydes with the salts of heterocyclic cations containing active methylene groups.[23−26] Many methods have been developed for the solution-phase synthesis of azobenzenes and spiropyran.[22−26] In most cases, the solution syntheses proceed in a linear way, but they require compound-specific purification steps. For each target, a unique set of starting materials, the sequence of chemical reactions, and purification procedures are generally required.

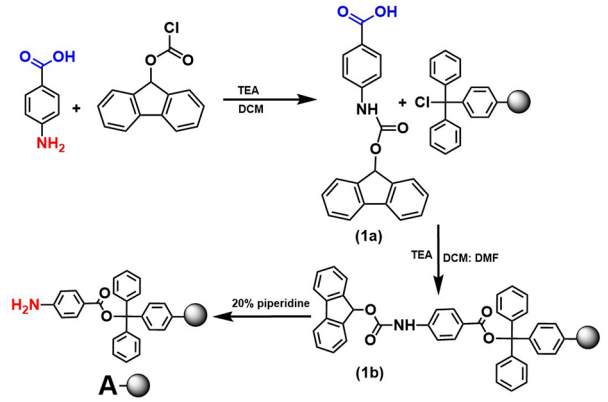
We suggest a solid-phase coupling approach may provide an opportunity for a more facile synthesis of families of azobenzenes and spiropyrans (Scheme 1), in particular, for compounds for which purification strategies have not already been developed. The solid-phase approach requires minimal purification steps and enables rapid access to a diversity of azobenzenes and spiropyrans in pure form. Moreover, this process can be automated, which enable the use of many reactions and starting materials and automation of generalized platforms that make many different targets using common coupling chemistry and building blocks.[27,28] It is our hope that these new strategies and methods for the synthesis of stimuli-responsive molecules will broaden access to these important chemistries.

RESULTS AND DISCUSSION

Building block **A** was synthesized using a solution method followed by solid-phase coupling and deprotection (Scheme 2).

Briefly, 4-aminobenzoic acid was protected with chloroformic acid 9-fluorenylmethyl ester ((9-fluorenylmethyl)-chloroformate (Fmoc-Cl)) forming compound **1a**. Next, a trityl chloride-functionalized resin was coupled with the

Scheme 2. Preparation of the A Block[a]



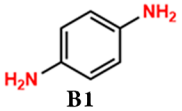
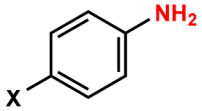
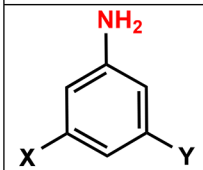
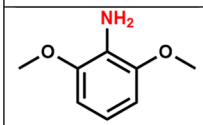
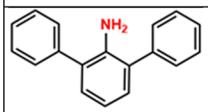
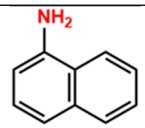
[a]Reaction conditions: (**1a**) ABA (3 mmol), TEA (5 mmol), Fmoc-cl (3 mmol) in 30 mL of DCM, 24 h, rt; (**1b**) **1a** (5 mmol), resin (1.1 mmol/g Cl loading), DMF/DCM, 12 h, rt.

unprotected acid functional group. Fmoc was cleaved with 20% (v/v) piperidine in dimethylformamide (DMF), forming the piperidine adduct.[29] Purification simply required washing with DMF and DCM to remove unreacted precursors and other noncovalent bonded impurities from the resin. The piperidine adduct exhibits two distinct UV absorbance maxima at λ = 301.0 and 289.8 nm. Absorption values measured at either of the piperidine absorbance maxima can be used, in combination with the respective molar absorption coefficient (following Beer's law), to calculate the substitution of Fmoc-deprotected resins.[2,29] The loading yield of the resin was over 60%.

Building block **B** (Table 1) was reacted with **A** to synthesize the family of azobenzenes shown in Scheme 3. The monosubstituted *p*-phenylenediamine was achieved at 0 °C with the slow addition of Fmoc-Cl (**B1**, Table 1). Monosubstitution (one-sided protection) with Fmoc was quite challenging, but the condition was optimized with low temperatures and with careful Fmoc addition. Lastly, the **A** and

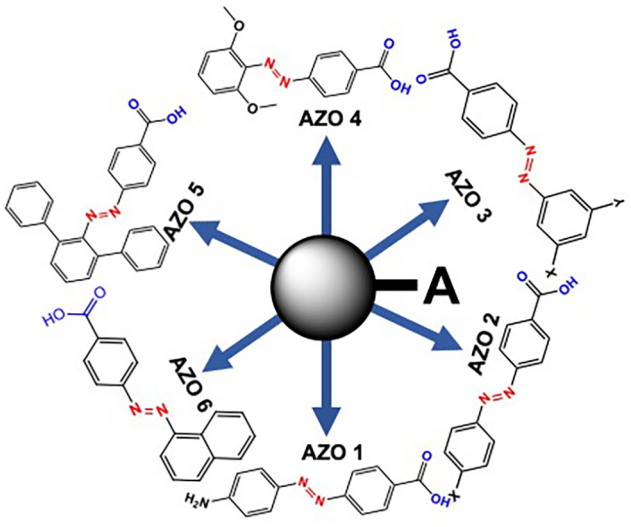
https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397

Table 1. Azobenzene Building Blocks, Reaction Conditions, and Yields for Final Azobenzene Products (X−OH, Y−Br)[a]

Building block **B**	Product	Yield[a] (%)	Conditions
 **B1**	AZO 1	55	DMF: DCM 40°C
 **B2**	AZO 2	50	DMF: DCM 40°C
 **B3**	AZO 3	43	DMF: THF: DCM 40°C
 **B4**	AZO 4	40	DMF: DCM 40°C
 **B5**	AZO 5	30	DMF: DCM 40°C
 **B6**	AZO 6	38	DMF: DCM 40°C

[a]The yield was the average of 3 batches ±4%.

Scheme 3. Synthesized Azobenzenes

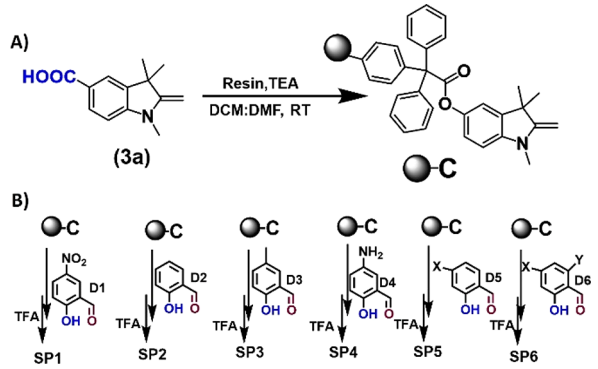


B blocks were coupled following standard amine−amine diazo coupling using silver oxide as a catalyst in DMF/DCM solvent mixtures. Colorimetric Kaiser tests were performed to check for reaction completion.[30] Once the reaction was complete, Fmoc was deprotected by following the piperidine procedure, and the resin was cleaved with 15% trifluoroacetic acid, TFA.[30]

The synthesis of AZO 1 to AZO 6 was performed under similar conditions. The yield of AZO 1 was 55% and AZO 2 was 50% (yields are almost equivalent to the solution method).[23] The yield of AZO 3 was 43%, AZO 4 was 40%, AZO 5 was 30%, and AZO 6 was 38% (Table 1). In AZO 5 synthesis of **B5**, we suspect the two benzene rings in [1,1′:3′,1″-terphenyl]-2′-amine] result in steric hindrance, which lowers the yield.

We now describe the solid-phase synthesis of a library of spiropyrans (Scheme S1). 1,3,3-Trimethyl-2-methyleneindoline-5-carboxylic acid (**3a**) was prepared using a reported protocol.[31] The resin was reacted with **3a** to form building block **C**. As a test, **C** was reacted with 2-hydroxy-5-nitrobenzaldehyde, **D1**, Scheme 4 under classical basic conditions,[26] successfully yielding SP1.

Scheme 4. (a) Synthesis of Building Block C; (b) Solid-Phase Reaction of C with Building Blocks D1−D6, Yielding Spiropyrans SP1−SP6 (X−OH, Y−Br)



For solid-phase SP1−SP6 spiropyran synthesis, building blocks **D1−D6** were reacted with **C** at 55 °C in a basic (piperidine) DMF/DCM/EtOH solvent mixture (Scheme 4, Table 2). An important consideration is the use of TFA to cleave SP from the resin. Acid can open the spiropyran ring structure to the merocyanine (MC ∼ 8−10%) form, but we found by using dilute TFA that this was minimized. We noticed the formation of the merocyanine once the concentration of TFA was increased. While, in principle, treatment of the MC form with a base will lead to conversion

Table 2. SP Building Blocks, Reaction Conditions, and Yields for Final SP Products[a]

building block **D**	product no.	yield[a] (%)	conditions
D1	SP1	45	DCM/DMF/EtOH; 55 °C
D2	SP2	40	DCM/DMF/EtOH; 55 °C
D3	SP3	40	DCM/DMF/EtOH; 60 °C
D4	SP4	28	DCM/DMF/EtOH; 55 °C
D5	SP5	40	DCM/DMF/EtOH; 55 °C
D6	SP6	35	DCM/DMF/EtOH; 55 °C

[a]The yield was the average of 3 batches ±3%.

https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397

back to SP, we suggest avoiding this rather by the use of a low concentration of acid to cleave SP from the resin.

The reported yield for the solution methods was about 72% for the azobenzene derivatives and 65% for the spiropyran derivatives with purities generally of +90%.[21−26] The yield for the solid-phase technique reported here was generally 40−50%. One reason for the difference in the yield is that the solution syntheses were run at 90 °C, but the solid-phase syntheses were performed at 40−60 °C (the resin begins to break at ∼70 °C). While a higher temperature resin might provide an enhanced yield, we did not investigate this, as the focus of this study was to use the solid-phase approach to simplify the purification process and provide a high purity product. Here we generally achieved +95% purity (see HPLC reports in Supporting Information) without column chromatography, indicating the solid-phase approach may be attractive for the simple synthesis of pure forms of these types of chromophores.

CONCLUSIONS

In summary, we have developed a simple and effective solid-phase approach to synthesize a library of azobenzenes and spiropyrans using a common protocol. The method described requires minimal purification steps and enables rapid access to a diversity of azobenzenes and spiropyrans in pure form.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents were purchased from Sigma-Aldrich at the highest purity available and used without further purification unless otherwise indicated. Thin-layer chromatography was performed on LC silica gel 60G F_{254} glass plates. ^{1}H and ^{13}C NMR spectra were recorded with a spectrometer operating at 500 MHz for proton and carbon nuclei, respectively, using either tetramethylsilane or residual protons of the deuterated solvent used (in parentheses) as an internal reference. High-resolution mass spectra (HRMS) were obtained using positive electrospray ionization by the TOF method. Compounds **B2**−**B6** were purchased from Sigma-Aldrich. Compounds **D1**, **D2**, **D3**, and **D5** were purchased from Sigma-Aldrich. Compounds **D4** and **D6** were purchased from AKos Consulting & Solutions. A digital dry bath (heating mantle, Thomas Scientific) was used for heating the reaction tubes.

*Synthesis of **1a** (Fmoc-aminobenzoic acid).* 4-Aminobenzoic acid (412 mg, 3 mmol) and triethyl amine (TEA, 0.69 mL, 5 mmol) were dissolved in 30 mL of DCM. The solution of chloroformic acid 9-fluorenylmethyl ester (778 mg, 3 mmol in 20 mL of DCM) was added dropwise at 0 °C, and the reaction continued for 24 h at rt. The reaction was monitored by thin-layer chromatography (TLC). The mixture was washed with a saturated solution of bicarbonate, and then the product was extracted with DCM and washed again with a saturated sodium chloride solution. Finally, the DCM layer was dried over sodium sulfate and filtered. The DCM was evaporated, yielding a fluffy red powder. Further purification of the product was done by column chromatography with a mixture of hexane/ethyl acetate, 70:30 (v/v). The yield was 360 mg, 88%. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{17}NO_4Na$, 382.1055; found, 382.1050. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.68 (d, J = 2.5 Hz, 1H), 10.08 (s, 1H), 7.92 (d, 2H, J = 7.6 Hz), 7.90−7.84 (m, 2H), 7.76 (d, 2H, J = 7.4 Hz), 7.56 (s, 2H), 7.43 (t, 2H, J = 7.4 Hz), 7.36 (td, 2H, J = 7.5, 1.1 Hz), 4.54 (d, 2H, J = 6.6 Hz), 4.34 (t, 1H, J = 6.5 Hz). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 167.4, 153.7, 144.1, 143.7, 141.3, 130.9, 128.1, 127.6, 125.5, 124.8, 120.6, 117.9, 66.2, 47.0.

*Synthesis of Compound **A**.* A total of 500 mg of trityl chloride resin (1.1 mmol/g Cl loading) was loaded, activated, and washed with DMF/DCM. Compound **1a** was loaded and allowed to react for 12 h. After 12 h, the unreacted material is washed out, and the reaction was monitored by UV absorption and a Kaiser test. The reacted resin beads were treated with 20% piperidine, and the deprotected FMOC was calculated using Beer's law. If the percentage substitution is lower than expected, FMOC is reloaded to yield the desired substitution. The amine-terminated resin was obtained after cleaving with 20% piperidine, and the product was confirmed via the UV/Kaiser test. Note, **A** is a resin and, thus, cannot be characterized via solution NMR.

Synthesis of B1 (N-BOC-1,4-phenylenediamine). *p*-Phenylenediamine (1.08 g, 10 mmol) and triethylamine (0.4 mL, 30 mmol) were dissolved in 25 mL of dry tetrahydrofuran (THF). Di-*tert*-butyl dicarbonate (4.35 g, 2 mmol) was dissolved in 15 mL of THF and added dropwise to the reaction mixture at 0 to 4 °C. The reaction was continued for 6 h. The reaction was monitored by TLC. Reaction completion was confirmed by TLC. The mixture was washed with a saturated solution of bicarbonate, and then the product was extracted with DCM and washed again with a saturated sodium chloride solution. Finally, the DCM layer was dried over sodium sulfate and filtered. Further, purification of the product was done by column chromatography with a mixture of hexane/ethyl acetate, 70:30 (v/v), yielding an off-white powder. The yield was 0.91 g, 85%. The product was characterized by MS and NMR. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{16}N_2O_2Na$, 231.1109; found, 231.1105. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.16 (s, 1H), 7.30 (s, 2H), 1.46 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 153.3, 134.46, 79.1, 28.6.

General Procedure for Azobenzene (AZO) Synthesis. A total of 500 mg of compound **A** resin was loaded and activated by washing with DCM/DMF, and 300 mg (1.4 mmol) of **B** (**B1**, *N*-BOC-1,4-phenylenediamine, **B2**, 4-aminophenol (215 mg, 2 mmol), **B3**, 3-amino-5-bromophenol (335 mg, 1.8 mmol), **B4**, 3,5-dimethoxyaniline (307 mg, 2 mmol), **B5**, [1,1′:3′,1′′-terphenyl]-2′-amine (615 mg, 2.5 mmol), **B6**, naphthalen-1-amine (267 mg, 2 mmol)), silver oxide (0.21 mmol), and 5 mL of DMF/DCM 50:50 v/v were added. The mixture was heated to 50 °C and kept for 12 h. A microwave oven can also be used to provide this product, and the conversion is much faster. After 12 h, any unreacted compound was washed out, and a few beads were removed to check with the Kaiser reagent. The resin beads and the solution turn dark blue when a primary amine is present, which means there was still some unreacted resin present. In this situation, we reload the compound and repeat the same procedure until the primary amines are completely consumed. The resin beads remain the same color, and the solution stays yellow when no free primary amine is present (expected result after successful coupling). A recoupling step is necessary when a slight blue color is detected in the solution and/or on beads. In the final step, the resin was cleaved by 15% TFA in DCM. The resulting compound was analyzed with NMR and mass spectrometry for product confirmation.

AZO 1 (4-((4-Aminophenyl)diazenyl)benzoic acid). The general procedure resulted in a fluffy orange powder with 55% (132.5 mg) yield of the title product. Mp: 248−255 °C. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{11}N_3O_2Na$, 264.0749; found, 264.0745. ^{1}H NMR (500 MHz, DMSO): δ 7.76−7.74 (m, 1H), 7.69−7.65 (m, 2H), 7.51 (dd, 2H, J = 8.5, 7.0 Hz), 7.44−7.40 (m, 1H), 6.84−6.59 (m, 2H), 6.10 (s, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO): δ 153.3, 152.9, 143.2, 129.8, 129.6, 125.6, 122.1, 113.8.

AZO 2 (4-((4-Hydroxyphenyl)diazenyl)benzoic acid)). The general procedure resulted in an orange solid with 50% (121.3 mg) yield of the title product. Mp: 270−280 °C. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{10}N_2O_3Na$, 265.0589; found, 265.0585. ^{1}H NMR (500 MHz, DMSO): δ 10.46 (s, 1H), 8.19−8.06 (m, 2H), 7.93−7.82 (m, 4H), 7.03−6.94 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO): δ 167.2, 162.1, 155.0, 145.7, 132.3, 131.0, 125.8, 122.5, 116.5.

AZO 3 (4-((3-Bromo-4-hydroxyphenyl)diazenyl)benzoic acid). The general procedure resulted in an orange-reddish powder with 43% (137.66 mg) yield of the title product. Mp: 225−230 °C. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}BrN_2O_3$, 320.9875; found, 320.9870. ^{1}H NMR (500 MHz, DMSO): δ 9.88 (s, 1H), 8.38−8.28 (m, 2H), 8.22−8.14 (m, 1H), 7.13 (t, 1H, J = 8.0 Hz), 6.96−6.94 (m, 2H), 6.76 (ddd, 1H, J = 8.1, 2.3, 1.0 Hz). $^{13}C\{^{1}H\}$

https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397

NMR (126 MHz, DMSO): δ 166.2, 159.0, 150.5, 136.8, 131.6, 131.1, 124.2, 122.2, 122.1, 118.5, 115.0.

AZO 4 (4-((2,6-Dimethoxyphenyl)diazenyl)benzoic acid). The general procedure resulted in an orange solid with 40% (114.5 mg) yield of the title product. Mp: 175−180 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{14}N_2O_4Na$, 309.0851; found, 309.0849. ^1H NMR (500 MHz, acetone-d_6): δ 8.43−8.36 (m, 2H), 8.34−8.28 (m, 2H), 6.69 (d, 2H, *J* = 2.3 Hz), 6.54 (t, 1H, *J* = 2.2 Hz), 3.88 (d, 6H, *J* = 1.3 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 168.1, 161.4, 153.5, 134.7, 131.7, 117.3, 113.1, 107.0, 99.7, 56.0.

AZO 5 (4-([1,1′:3′,1′′-Terphenyl]-2′-yldiazenyl)benzoic acid). The general procedure resulted in a red powder with 30% (113 mg) yield of the title product. Mp: 350−360 °C. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{19}N_2O_2$, 379.1447; found, 379.1443. ^1H NMR (500 MHz, acetone-d_6): δ 8.40−8.34 (m, 2H), 8.32−8.26 (m, 2H), 7.92 (t, 1H, *J* = 1.8 Hz), 7.79−7.64 (m, 8H), 7.58 (t, 1H, *J* = 7.7 Hz), 7.54−7.47 (m, 2H), 7.44−7.37 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, acetone): δ 205.2, 166.9, 153.0, 141.8, 140.7, 140.3, 140.1, 131.8, 131.5, 129.5, 129.0, 128.8, 127.5, 127.0, 126.3, 125.7, 125.4, 121.2, 117.8, 112.9.

AZO 6 (4-(Naphthalen-1-yldiazenyl)benzoic acid). The general procedure resulted in a red powder with 38% (89 mg) yield of the title product. Mp: 290−295 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{12}N_2O_2Na$, 299.0796; found, 299.0791. ^1H NMR (500 MHz, DMSO): δ 15.78 (s, 1H), 8.56 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.98 (d, *J* = 9.4 Hz, 1H), 7.91−7.85 (m, 2H), 7.80 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.63 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.59−7.52 (m, 2H), 7.52−7.44 (m, 1H), 7.43−7.36 (m, 1H), 6.94 (d, *J* = 9.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 169.2, 163.7, 145.5, 140.4, 133.2, 130.3, 129.6, 129.6, 129.3, 128.5, 128.3, 126.3, 124.3, 121.7, 119.4.

General Procedure for Azobenzene (AZO) Solution Synthesis. A total of 300 mg (1.4 mmol) of **B** (**B1**, *N*-BOC-1,4-phenylenediamine, AZO 1; **B2**, 4-aminophenol (215 mg, 2 mmol), AZO 2; **B3**, 3-amino-5-bromophenol (335 mg, 1.8 mmol), AZO 3; **B4**, 3,5-dimethoxyaniline (307 mg, 2 mmol), AZO 4; **B5**, [1,1′:3′,1′′-terphenyl]-2′-amine (615 mg, 2.5 mmol), AZO 5; **B6**, naphthalen-1-amine (267 mg, 2 mmol), AZO 6), silver oxide (0.21 mmol), and 15 mL of acetone at 4 °C (for AZO 5 and AZO 6, THF, and heated at 85 °C) were reacted for 24 h. The reaction was monitored by TLC. Reaction completion was confirmed by TLC. The purification of the product was done by column chromatography with a mixture of dichloromethane/methanol, 90:10 (v/v), yielding the resultant compound. The yield was 193 mg (80% AZO 1), 192 mg (80% AZO 2), 228 mg (71% AZO 3), 214.7 mg (75% AZO 4), 227 mg (60% AZO 5), and 182.2 mg (66% AZO 6).

Synthesis of ***C****.* A total of 500 mg of trityl chloride resin (1.1 mmol/g Cl loading) was loaded, activated, and washed with DMF/DCM. Compound **3a** (synthesized by following the procedure from ref 31) (650 mg, 3 mmol) and triethyl amine (TEA, 0.65 mL, 5 mmol) were dissolved in 30 mL of DCM. This mixture was loaded onto the resin and allowed to react for 12 h. After 12 h, unreacted material is washed out. The reaction was monitored by UV absorption and the Kaiser test. Note that **C** is a resin and, thus, cannot be characterized via solution NMR.

Synthesis of Spiropyran (SP1) General Procedure. A total of 500 mg of compound **C** resin was loaded and activated by washing with DCM/DMF/EtOH, 300 mg (1.8 mmol) of **D** (**D1**, 2-hydroxy-5-nitrobenzaldehyde; **D2**, 2-hydroxybenzaldehyde (244 mg, 2 mmol); **D3**, 2-hydroxy-5-methylbenzaldehyde (273 mg, 2 mmol); **D4**, Boc-amino-2-hydroxybenzaldehyde (475 mg, 2 mmol); **D5**, 2,4-dihydroxybenzaldehyde (276 mg, 2 mmol); **D6**, 2-bromo-4,6-dihydroxybenzaldehyde (434 mg, 1.9 mmol)). Piperidine (85 mg, 1 mmol) was added, and the reaction was heated to 60 °C for 6 h. The unreacted compound was washed out, and a few beads were taken out with the Kaiser reagent. The resin beads and the solution turn dark blue when a primary amine is present, which means some unreacted resin is present. In this situation, we reload the compound and repeated the same procedure until no unreacted resin is present. The resin beads retain their color, and the solution stays yellow when no free primary amines are present (expected result after successful coupling). A recoupling step is necessary when a slight blue color is detected in the solution and/or on beads. In the final step, the resin was cleaved by 15% trifluoroacetic acid in DCM. The resulting compound was analyzed via NMR and mass spectrometry for product confirmation.

SP1 (1′,3′,3′-Trimethyl-6-nitrospiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a dark green powder with 45% (165 mg) yield of the title product. Mp: 177−180 °C. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_5$, 367.1294; found, 367.1290. ^1H NMR (500 MHz, DMSO): δ 8.22 (d, 1H, *J* = 2.8 Hz), 8.00 (dd, 1H, *J* = 9.0, 2.8 Hz), 7.23 (d, 1H, *J* = 10.4 Hz), 7.17−7.13 (m, 1H), 6.89 (d, 1H, *J* = 9.0 Hz), 6.81 (td, 1H, *J* = 7.4, 0.9 Hz), 6.62 (dd, 1H, *J* = 7.6, 1.1 Hz), 5.99 (d,1H, *J* = 10.4 Hz), 2.68 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 163.5, 159.8, 147.8, 140.9, 136.3, 128.7, 128.1, 126.2, 123.2, 122.0, 121.9, 119.8, 119.3, 115.8, 107.5, 106.6, 52.3, 28.9, 26.1, 20.1.

SP2 (1′,3′,3′-Trimethylspiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a red powder with 40% (128 mg) yield of the title product. Mp: 170−175 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3Na$, 344.1263; found, 344.1265. ^1H NMR (500 MHz, DMSO): δ 7.17 (dd, 1H, *J* = 7.5, 1.7 Hz), 7.12−7.08 (m, 2H), 7.01 (d, 1H, *J* = 10.2 Hz), 6.83 (td, 1H, *J* = 7.4, 1.1 Hz), 6.77 (td, 1H, *J* = 7.4, 1.0 Hz), 6.66 (d, 1H, *J* = 8.1 Hz), 6.56 (d, 1H, *J* = 7.6 Hz), 5.76 (d, 1H, *J* = 10.2 Hz), 2.65 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 163.5, 154.4, 148.3, 136.7, 130.2, 129.7, 127.9, 127.3, 121.9, 120.6, 119.7, 119.3, 119.0, 114.7, 107.2, 104.2, 51.8, 29.0, 26.1, 20.3.

SP3 (1′,3′,3′,6-Tetramethylspiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a red powder with 40% (135 mg) yield of the title product. Mp: 168−173 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{21}NO_3Na$, 358.1419; found, 358.1416. ^1H NMR (500 MHz, DMSO): δ 7.91 (d, 1H, *J* = 2.6 Hz), 7.66 (d, 1H, *J* = 2.6 Hz), 7.19 (d, 1H, *J* = 10.4 Hz), 7.17−7.09 (m, 2H), 6.81 (td,1H, *J* = 7.4, 1.1 Hz), 6.62 (d, 1H, *J* = 7.8 Hz), 5.97 (d, 1H, *J* = 10.4 Hz), 3.78 (s, 3H), 2.69 (s, 3H), 1.74 (s, 1H), 1.20 (s, 3H), 1.10 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 169.2, 169.1, 157.3, 155.5, 151.3, 148.7, 140.3, 137.1, 136.6, 131.4, 123.2, 123.0, 122.9, 120.9, 97.6, 57.5, 51.7, 49.1, 44.5, 43.9, 43.5, 31.1, 31.1, 2.1, 23.9, 23.2, 22.0.

SP4 (6-Amino-1′,3′,3′-trimethylspiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a reddish-range powder with 40% (134 mg) yield of the title product. Mp: 175−178 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{20}N_2O_3Na$, 359.1372; found, 359.1370. ^1H NMR (500 MHz, DMSO): δ 7.77−7.71 (m, 1H), 7.56 (d, 1H, *J* = 2.7 Hz), 7.16−7.10 (m, 3H), 6.80 (t, 1H, *J* = 7.4 Hz), 6.61 (d, 1H, *J* = 7.7 Hz), 5.94 (d, 1H, *J* = 10.2 Hz), 3.85 (s, 1H), 3.02 (d, 1H, *J* = 18.3 Hz), 2.83 (s, 1H), 2.68 (s, 3H), 1.21 (s, 3H), 1.10 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 163.6, 148.5, 148.0, 145.1, 140.2, 136.4, 128.8, 128.0, 122.0, 121.9, 119.6, 119.4, 111.2, 107.3, 106.0, 52.2, 28.8, 26.2, 19.9.

SP5 (7-Hydroxy-1′,3′,3′-trimethylspiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a red solid powder with 40% (135 mg) yield of the title product. Mp: 169−173 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_4Na$, 360.1211; found, 360.1215. ^1H NMR (500 MHz, DMSO): δ 9.87 (s, 1H), (d, 2H, *J* = 1.7 Hz), 7.75−7.52 (m, 3H), 7.16 (d, 1H, *J* = 10.4 Hz), 6.71 (d, 1H, *J* = 8.2 Hz), 6.05 (d, 1H, *J* = 10.4 Hz), 2.79 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ 167.8, 155.6, 151.5, 136.3, 135.3, 131.2, 129.7, 128.4, 123.9, 123.3, 122.9, 121.7, 112.5, 106.7, 106.0, 52.0, 28.9, 25.9, 20.4.

SP6 (5-Bromo-7-hydroxy-1′,3′,3′-trimethylspiro[chromene-2,2′-indoline]-5′-carboxylic acid). The general procedure resulted in a red powder with 30% (125 mg) yield of the title product. Mp: 160−164 °C. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{18}BrNO_4Na$, 438.0317; found, 438.0319. ^1H NMR (500 MHz, DMSO): δ 10.27 (s, 1H), 8.29 (d, 1H, *J* = 16.1 Hz), 8.19 (d,1H, *J* = 2.8 Hz), 8.01 (d, 1H, *J* = 16.2 Hz), 7.87 (d, 1H, *J* = 2.8 Hz), 7.65 (d, 1H, *J* = 8.7 Hz), 7.15 (d, 1H, *J* = 2.3 Hz), 6.95 (dd, 1H, *J* = 8.7, 2.3 Hz), 3.97 (s, 3H), 1.71 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO):

https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397

δ 179.4, 170.2, 169.0, 159.3, 147.8, 145.9, 137.3, 137.2, 134.4, 125.5, 122.0, 116.2, 115.8, 111.7, 110.2, 105.12 51.7, 46.2, 34.2, 26.6, 9.1.

Synthesis of Spiropyran (SP) General Solution Method. Compound **3a** (synthesized by following the procedure found in ref 31) (434 mg, 2 mmol), 334 mg (2 mmol) of **D** (**D1**, 2-hydroxy-5-nitrobenzaldehyde; **D2**, 2-hydroxybenzaldehyde (244 mg, 2 mmol); **D3**, 2-hydroxy-5-methylbenzaldehyde (273 mg, 2 mmol); **D4**, Boc-amino-2-hydroxybenzaldehyde (475 mg, 2 mmol); **D5**, 2,4-dihydroxybenzaldehyde (276 mg, 2 mmol); **D6**, 2-bromo-4,6-dihydroxybenzaldehyde (434 mg,1.9 mmol)), and piperidine (85 mg-1 mmol) were added, and the reaction was heated to 90 °C for 6 h. The reaction was monitored by TLC. The purification of the product was done by column chromatography with a mixture of dichloromethane/methanol, 90:10 (v/v), yielding a resultant compound. The yield was 281 mg (76% SP 1), 250 mg (77% SP 2), 238 mg (70.9% SP 3), 200 mg (59.4% SP 4), 249 mg (73% SP 5), and 260 mg (62% AZO 6).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02375.

NMR, mass spectra, and HPLC of azo and spiropyran derivatives (PDF)

FAIR data, including the primary NMR FID files, for compounds AZO 1−6 and SP1−6 (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Paul V. Braun − *Beckman Institute for Advanced Science and Technology, Department of Materials Science and Engineering, Department of Chemistry, and Materials Research Laboratory, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States;* orcid.org/0000-0003-4079-8160; Email: pbraun@illinois.edu

Author

Ravichandran H. Kollarigowda − *Beckman Institute for Advanced Science and Technology, Department of Materials Science and Engineering, and Materials Research Laboratory, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States;* orcid.org/0000-0001-8376-218X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02375

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Department of Defense/US Army W911NF-17-1-0351 through the Materials Research Laboratory at the University of Illinois. The authors thank to Ms. Chen Chen for helping with NMR analysis.

■ REFERENCES

(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. Applications of Combinatorial Technologies to Drug Discovery.1. Background and Peptide Combinatorial Libraries. *J. Med. Chem.* **1994**, *37* (9), 1233−1251.

(2) Sebestyen, F.; Dibo, G.; Kovacs, A.; Furkua, A. Chemical Synthesis of Peptide Libraries. *Bioorg. Med. Chem. Lett.* **1993**, *3* (3), 413−418.

(3) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic-Synthesis, Library Screening Strategies, and Future-Directions. *J. Med. Chem.* **1994**, *37* (10), 1385−1401.

(4) Zollinger, H. Color Chemistry-Synthesis, Properties and Applications of Organic-Dyes and Pigments. *Leonardo* **1989**, *22*, 456.

(5) Hu, J. L.; Meng, H. P.; Li, G. Q.; Ibekwe, S. I. A Review of Stimuli-Responsive Polymers for Smart Textile Applications. *Smart Mater. Struct.* **2012**, *21* (5), 053001−053023.

(6) Kollarigowda, R. H.; Bhyrappa, H. M.; Cheng, G. Stimulus-Responsive Biopolymeric Surface: Molecular Switches for Oil/Water Separation. *ACS Appl. Bio Mater.* **2019**, *2* (10), 4249−4257.

(7) Rianna, C.; Rossano, L.; Kollarigowda, R. H.; Formiggini, F.; Cavalli, S.; Ventre, M.; Netti, P. A. Spatio-Temporal Control of Dynamic Topographic Patterns on Azopolymers for Cell Culture Applications. *Adv. Funct. Mater.* **2016**, *26* (42), 7572−7580.

(8) Kollarigowda, R. H.; Fedele, C.; Rianna, C.; Calabuig, A.; Manikas, A. C.; Pagliarulo, V.; Ferraro, P.; Cavalli, S.; Netti, P. A. Light-Responsive Polymer Brushes: Active Topographic Cues for Cell Culture Applications. *Polym. Chem.* **2017**, *8* (21), 3271−3278.

(9) Radu, A.; Scarmagnani, S.; Byrne, R.; Slater, C.; Tong Lau, K.; Diamond, D. Photonic Modulation of Surface Properties: A Novel Concept in Chemical Sensing. *J. Phys. D: Appl. Phys.* **2007**, *40* (23), 7238.

(10) Fries, K. H.; Driskell, J. D.; Sheppard, G. R.; Locklin, J. Fabrication of Spiropyran-Containing Thin Film Sensors Used for the Simultaneous Identification of Multiple Metal Ions. *Langmuir* **2011**, *27* (19), 12253−12260.

(11) Lee, C. K.; Davis, D. A.; White, S. R.; Moore, J. S.; Sottos, N. R.; Braun, P. V. Force-Induced Redistribution of a Chemical Equilibrium. *J. Am. Chem. Soc.* **2010**, *132* (45), 16107−16111.

(12) Lee, C. K.; Beiermann, B. A.; Silberstein, M. N.; Wang, J.; Moore, J. S.; Sottos, N. R.; Braun, P. V. Exploiting Force Sensitive Spiropyrans as Molecular Level Probes. *Macromolecules* **2013**, *46* (10), 3746−3752.

(13) Bandara, H. M. D.; Burdette, S. C. Photoisomerization in Different Classes of Azobenzene. *Chem. Soc. Rev.* **2012**, *41* (5), 1809−1825.

(14) Hamon, F.; Djedaini-Pilard, F.; Barbot, F.; Len, C. Azobenzenes-Synthesis And Carbohydrate Applications. *Tetrahedron* **2009**, *65* (49), 10105−10123.

(15) Kollarigowda, R. H.; De Santo, I.; Rianna, C.; Fedele, C.; Manikas, A. C.; Cavalli, S.; Netti, P. A. Shedding Light on Azopolymer Brush Dynamics by Fluorescence Correlation Spectroscopy. *Soft Matter* **2016**, *12* (34), 7102−7111.

(16) Davey, M. H.; Lee, V. Y.; Miller, R. D.; Marks, T. J. Synthesis of Aryl Nitroso Derivatives by Tert-Bbutyl hypochlorite Oxidation in Homogeneous Media. Intermediates for the Preparation of High-hyperpolarizability Chromophore skeletons. *J. Org. Chem.* **1999**, *64* (13), 4976−4979.

(17) Haghbeen, K.; Tan, E. W. Facile Synthesis of Catechol Azo Dyes. *J. Org. Chem.* **1998**, *63* (13), 4503−4505.

(18) Merrington, J.; James, M.; Bradley, M. Supported Diazonium Salts-Convenient Reagents for the Combinatorial Synthesis of Azo Dye. *Chem. Commun.* **2002**, No. 2, 140−141.

(19) Fry, H. S.; Bowman, P. E. The Effect of Organic Bases Upon the Extent and Mechanism of the Reducing Action of Sodium Methylate on Nitrobenzene and Azoxybenzene. *J. Am. Chem. Soc.* **1930**, *52*, 1531−1536.

(20) Wawzonek, S.; Mcintyre, T. W. Electrolytic Preparation of Azobenzenes. *J. Electrochem. Soc.* **1972**, *119* (10), 1350−1350.

(21) Grirrane, A.; Corma, A.; Garcia, H. Gold-Catalyzed Synthesis of Aromatic Azo Compounds from Anilines and Nitroaromatics. *Science* **2008**, *322* (5908), 1661−1664.
(22) Merino, E. Synthesis of Azobenzenes: The Coloured Pieces of Molecular Materials. *Chem. Soc. Rev.* **2011**, *40* (7), 3835−3853.
(23) Chernyshev, A. V.; Voloshin, N. A.; Raskita, I. M.; Metelitsa, A. V.; Minkin, V. I. Photo- and Ionochromism of 5′-(4,5-diphenyl-1,3-oxazol-2-yl) Substituted Spiro[indoline-naphthopyrans]. *J. Photochem. Photobiol., A* **2006**, *184* (3), 289−297.
(24) Dürr, H.; Bouas-Laurent, H. *Photochromism: Molecules and Systems*; Elsevier, 2003.
(25) Li, X. L.; Li, J. L.; Wang, Y. M.; Matsuura, T.; Meng, J. B. Synthesis of Functionalized Spiropyran and Spirooxazine Derivatives and Their Photochromic Properties. *J. Photochem. Photobiol., A* **2004**, *161* (2−3), 201−213.
(26) Lukyanov, B. S.; Lukyanova, M. B. Spiropyrans: Synthesis, Properties, and Application. *Chem. Heterocycl. Compd.* **2005**, *41* (3), 281−311.
(27) Trobe, M.; Burke, M. D. The Molecular Industrial Revolution: Automated Synthesis of Small Molecules. *Angew. Chem., Int. Ed.* **2018**, *57* (16), 4192−4214.
(28) Lehmann, J. W.; Blair, D. J.; Burke, M. D. Towards the Generalized Iterative Synthesis of Small Molecules. *Nat. Rev. Chem.* **2018**, *2* (2), 1.
(29) Eissler, S.; Kley, M.; Bachle, D.; Loidl, G.; Meier, T.; Samson, D. Substitution Determination of Fmoc-Substituted Resins at Different Wavelengths. *J. Pept. Sci.* **2017**, *23* (10), 757−762.
(30) Lansbury, P. T.; Hendrix, J. C.; Coffman, A. I. A Practical Method for the Preparation of Protected Peptide-Fragments Using the Kaiser Oxime Resin. *Tetrahedron Lett.* **1989**, *30* (37), 4915−4918.
(31) Tomasulo, M.; Kaanumal, S. L.; Sortino, S.; Raymo, F. M. Synthesis and Properties of Benzophenone-Spiropyran and Naphthalene-Spiropyran Conjugates. *J. Org. Chem.* **2007**, *72* (2), 595−605.

https://dx.doi.org/10.1021/acs.joc.0c02375
J. Org. Chem. 2021, 86, 4391−4397