Highly Efficient Synthesis of Hindered 3-Azoindoles via Metal-Free C–H Functionalization of Indoles

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Reversible modification of the key properties of a molecule, such as geometry, rigidity, dielectric constant, or refractive index under light irradiation is an intriguing feature of photochromic compounds with great potential applications in different fields.1 Thus, not surprisingly, molecular photoswitches have been attracting, over the last few decades, a growing attention and consequently these molecules have found numerous applications in light-triggered materials2 and machines,3 light driven molecular motors,4 polymers,5 drug delivery,6 and control of cell death.7 Such a large range of applications can be reached, because the physical properties of photoswitches, and in particular the thermal lifetime of the metastable Z-isomer (varying from nanosecond scale range to days), can be controlled by carefully selecting the appropriate photochromic scaffolds (Figure 1a). For example, if molecular storage,8 or biological applications in photomodulation of protein expression systems or oligonucleotide recognition applications are targeted,9 stable photoswitches will be selected (long thermal lifetime) while compounds characterized by short thermal lifetime are used in real-time optical information transmitting materials,10 in medicinal chemistry for neurons or ion channel stimulation purposes.11 Accordingly, several families of molecular photoswitches have been designed (Figure 1b) including spiro-pyranes,12 stilbenes13 and diarylethenes,14 but the azobenzenes15 are, by far, the most commonly applied ones (Figure 1a). More recently, indigos16 or Stenhouse adducts17 have been disclosed. Considerable attention has also been focused on heteroazoswitches,18 including compounds featuring pyridine, imidazole, pyrazole, and purine motifs.

In clear contrast, 3-arylazoindoles are relatively under-explored molecules.19 Surprisingly, only few literature reports disclose synthesis of indoles bearing a diazo moiety in C3 position20 and the recent methodologies request use of sophisticated coupling partners such as aryltriazenes21 in ionic liquid medium or arylhydrazine hydrochlorides22 under visible-light irradiation or heating at 90 °C. Very recently, a unique potential of 3-arylazoindole photoswitches has been demonstrated by König (Figure 1c)23 and thus development of truly efficient, sustainable and straightforward protocols delivering such compounds is timely. In particular, as the properties of azoswitches, and especially their thermal lifetime, are impacted by the substitution pattern around the azo moiety, synthesis of a library of 3-arylazoindoles bearing various substituents in proximity of N=N motif, on both C2 position of the indole and ortho-, ortho’-positions of the aromatic ring, seems very appealing (Figure 1d).24 Accordingly, we report herein an extremely simple but highly efficient strategy to prepare sterically hindered 2-substituted 3-arylazoindoles, the molecules with promising photochromic properties.

Our investigations began by exploring the coupling between 2-((tert-butyl)-1H-indole (1a) and electron-rich para-methoxyphenyldiazonium salt 2a. The reaction occurred...
smoothly in methanol medium and at room temperature, delivering the expected (E)-2-[(tert-butyl)-3-[4-methoxy-phenyl]diazenyl]-1H-indole (3a) in quantitative yield (Table 1, entry 1). Comparable results were obtained when using 2-(methyl)-1H-indole (1b) as substrate (entry 2). Besides, the reaction is extremely fast as full conversion of 1b could be achieved in less than 10 minutes (entry 3), even in the presence of equimolar amounts of both coupling partners (entry 4). Electron-poor Ac-substituted aryl diazonium salts may also be converted into 3-arylaizoidoles, but the reaction generally requires a slight excess of the diazonium salts coupling partners (entry 5). Accordingly, the general reaction conditions have been determined, that is, use of 1.3 equivalents of diazonium salt in MeOH medium and 30 minutes as standard reaction time (entry 6). Of note is that the desired products are isolated via simple filtration of the crude mixture through silica gel pad, further demonstrating the experimental simplicity and efficiency of this protocol. This transformation hence perfectly follows the requirements of sustainable and green chemistry, as neither a catalyst nor sophisticated additives or strong oxidants are required and this coupling is characterized by excellent atom economy. Finally, the reaction performed in water is sluggish and the desired product 4a was formed in only 68% NMR conversion after 4 days (entry 7).

The generality of this new protocol was subsequently explored (Scheme 1). Rewardingly, indole 1a bearing a highly hindering tert-butyl motif in C2 position could be coupled very smoothly with diverse diazo coupling partners, both electron-rich and electron-poor, affording the expected products in excellent yields and in short reaction time. Importantly, the presence of a substituent in the ortho-position of 2 is tolerated well, as 3b, 3c, and 3e could be isolated in almost quantitative yields. In addition, very congested azoindole 3g could also be synthesized following the standard procedure in 93% yield. Interestingly, our protocol also tolerates relatively well a halogen atom on the indole scaffold, as 3h could be isolated in 70% yield, albeit excess of 2 and prolonged reaction time were required in this case. Also, the coupling using mesityldiazonium salt was more sluggish; additional portion of the diazonium salt and longer reaction time (2 h) were needed to reach full conversion but, rewardingly, under such a modified protocol 3d was afforded in high 87% yield. The reaction occurs with a comparable outcome when using the less hindered 2-(methyl)-1H-indole (1b), furnishing the coupling products 4a–c in very high yields. The mesityl-derivized azoindole 4d was obtained in 85% yield using 2 equivalents of the diazo salt partner. Functionalized indole substrates bearing F, Cl, and Me motifs could also be converted into the expected products 4e–g in excellent yields. Of note is that this reaction is not specific to 1H-indoles, and diazo-(N-methyl)indoles 5a–c were also synthesized successfully. In contrast, acyl-

### Table 1 Optimization Study

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>3</th>
<th>x (equiv.)</th>
<th>Time</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>t-Bu</td>
<td>4-O-Me</td>
<td>3a</td>
<td>1.5</td>
<td>16 h</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>4-O-Me</td>
<td>4a</td>
<td>1.5</td>
<td>16 h</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>4-O-Me</td>
<td>3e</td>
<td>1.0</td>
<td>10 min</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>4-O-Me</td>
<td>4a</td>
<td>1.5</td>
<td>10 min</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
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<td>4-O-Me</td>
<td>4a</td>
<td>1.3</td>
<td>30 min</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>2-Ac</td>
<td>3e</td>
<td>1.5</td>
<td>16 h</td>
<td>99</td>
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<tr>
<td>7</td>
<td>Me</td>
<td>4-O-Me</td>
<td>4a</td>
<td>1.3</td>
<td>96 h</td>
<td>68</td>
</tr>
</tbody>
</table>

a Standard reaction conditions: 1 (0.115 mmol, 1 equiv.), 2 (0.150 mmol, 1.3 equiv.), MeOH (1 mL), rt, under air, approx. 30 min; isolated yield.

b Reaction performed in H2O, conversion determined by 1H NMR analysis.
protected indole turned out to be ineffective. Finally, under the standard reaction conditions, 2-phenylindole was converted into the corresponding diazo compound \(7a\) in 96% yield and pyrrole-derived substrate undergoes selective C2-functionalization delivering \(8a\) in quantitative yield.

Importantly, the reaction is also efficient even at 50 times larger scale (5.75 mmol, 754 mg of \(1b\)) and appealing product \(4a\) could hence be isolated in quantitative yield (Scheme 2). However, larger excess of \(2a\) (2 equiv.) and slightly longer reaction time (1 h) were critical to reach full conversion.

Subsequently, in order to gather additional information about the newly synthesized compounds, their UV/Vis absorption spectra were recorded (Figure 2). Interestingly, all compounds present rather similar absorption patterns, ranging from 353 nm (for 3-azaindoles bearing mesityl
motif such as 3d and 4d) to 393 nm (for 3-azoindole featuring 2-Ac phenyl motif such as 3e). Besides, the initial testes of cis–trans photoisomerization indicate that this process is relatively fast, inferior to the minute scale.

In conclusion, we have described herein a very efficient synthesis of original, highly substituted 3-azoindoles. The coupling occurs via metal-free C–H diazonylation of indoles, using aryldiazonium salts as coupling partners. Remarkably, the reaction does not require addition of a catalyst and performs smoothly at room temperature within few minutes delivering the expected products in quantitative yields in most of the cases. This sustainable, particularly mild and atom-economic protocol is highly tolerant towards various functionalities, furnishing a library of interesting scaffolds. These unprecedented molecules appear as privileged candidates for original photoswitch design. Besides, the simplicity of this protocol renders it perfectly suitable to be used in late-modification of sophisticated indole-containing drugs.

All the reactions were performed under air atmosphere, using tube reactors (10 mL). Chemicals and solvents (suppliers: Aldrich, Alfa Aesar, Fluorochem, TCI) were directly used without further purification. Technical grade solvents for purification were used without further purification or distillation. \(^1\)H, \(^13\)C and \(^19\)F NMR spectra were recorded in CDCl\(_3\) or acetone-\(d_6\) at rt on Bruker, Avance 400 (400 MHz) or Avance III-HD (500 MHz) spectrometers and FID was processed in MestreNova software. Chemical shifts were referenced to residual solvent peaks and reported in ppm (i.e., CDCl\(_3\) referenced at 7.26 and 77.16 ppm respectively and acetone-\(d_6\) referenced at 2.05 ppm). Standard abbreviations were used for NMR spectra to represent the signal multiplicity. The coupling constants were reported in hertz (Hz). Thin-layer chromatography (TLC) were carried out on precoated aluminum sheets (Merck 60-F254 plates) and the components were visualized by observation under UV light at 254 nm. Products were purified by column chromatography on 40–63 mesh silica gel, SiO\(_2\). HRMS measurements were carried out by Service de Spectrométrie de Masse de l’Institut de Chimie at the University of Strasbourg.

The preparation of starting aryldiazonium tetrafluoroborates 2 and indoles 1 are provided in the Supporting Information.

3-Azindoones; General Procedure

A 10 mL reaction tube equipped with magnetic stir bar was filled with indole derivative 1 (0.115 mmol, 1 equiv.) and diazonium tetrafluoroborate salt 2 (0.150 mmol, 1.3 equiv.) under air. Then, anhydrous Mo(O\(_2\)) (1 mL) was added, the reaction mixture turned immediately to a deep dark red color. The resulting mixture was stirred at rt for 30 min. Afterwards, the reaction mixture was filtered through a short pad of silica gel. The reaction tube and the pad of silica gel were washed with DCM until the disappearance of color of the filtrate (~100 mL). The solvent was removed under reduced pressure and the resulting highly colored solid was dried under vacuum to give the expected pure product.

(E)-2-((tert-Butyl)-3-[(4-methoxyphenyl)diazenyl]-1H-indole (3a)

Deep orange solid; yield: 35 mg (99%, 0.114 mmol).

(E)-2-((tert-Butyl)-3-[(4-methoxyphenyl)diazenyl]-1H-indole (3b) Deep orange solid; yield: 35 mg (95%, 0.110 mmol).

(E)-2-((tert-Butyl)-3-[(o-tolyl diazenyl)]-1H-indole (3b) Deep orange solid; yield: 32 mg (95%, 0.110 mmol).

(E)-2-((tert-Butyl)-3-[(2-methoxyphenyl)diazenyl]-1H-indole (3c) Deep red solid; yield: 35 mg (99%, 0.114 mmol).

(E)-2-((tert-Butyl)-3-[(mesityldiazenyl)]-1H-indole (3d) Prepared according to the general procedure, with a following modification: an additional portion of 0.7 equiv. of mesityldiazonium tetrafluoroborate was added after 30 min; stirred for 2 h; deep orange solid; yield: 32 mg (87%, 0.100 mmol).

(E)-1-[(2-((tert-Butyl)-1H-indol-3-yl)diazenyl)phenyl]ethan-1-one (3e) Deep orange solid; yield: 36 mg (98%, 0.113 mmol).

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HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{21}BrN_3O: 386.0863; found: 386.1076.

(E)-2-(tert-Butyl)-3-[(4-fluorophenyl)diazenyl]-1H-indole (3f)
Deep yellow solid; yield: 28 mg (82%, 0.095 mmol).

1H NMR (CDCl_3, 500 MHz): δ = 8.57–8.50 (m, 1 H), 8.18 (br s, 1 H), 7.89–7.85 (m, 2 H), 7.30–7.23 (m, 2 H), 7.20–7.12 (m, 2 H), 1.85 (s, 9 H).

13C NMR (CDCl_3, 126 MHz): δ = 162.97 (d, J = 19.1 Hz, 1 H), 133.70, 131.57, 133.59, 133.55, 131.56, 127.71, 128.11, 127.33, 126.78, 123.75, 123.72, 123.40, 121.10, 117.33, 34.26, 30.94, 19.47.

HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{21}FN_3: 296.1557; found: 296.1544.

HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{21}BrN_3O: 386.0863; found: 386.1076.

(E)-2-(tert-Butyl)-3-[(2-chloro-6-methylphenyl)diazenyl]-1H-indole (3g)
Deep orange solid; yield: 35 mg (93%, 0.107 mmol).

1H NMR (CDCl_3, 500 MHz): δ = 8.56 (dd, J = 6.5, 2.1 Hz, 1 H), 8.39 (br s, 1 H), 7.38–7.34 (m, 2 H), 7.30–7.24 (m, 2 H), 7.17 (dd, J = 7.6, 1.5, 0.7 Hz, 1 H), 7.09 (t, J = 7.8 Hz, 1 H), 2.39 (s, 3 H), 1.65 (s, 9 H).

13C NMR (CDCl_3, 126 MHz): δ = 153.84, 158.04, 133.59, 132.55, 131.56, 127.94, 128.11, 127.33, 126.78, 123.75, 123.72, 123.40, 120.17, 110.73, 34.26, 30.94, 19.47.

HRMS (ESI): m/z [M + H]^+ calcld for C_{20}H_{22}N_3O: 320.1757; found: 320.1744.

(E)-2-(tert-Butyl)-3-[(2-methoxyphenyl)diazenyl]-1H-indole (4a)
Prepared according to the general procedure, with a following modification: two additional portions of 0.7 equiv of mesityldiazonium tetrafluoroborate were added after 30 min and 1 h; stirred for 2 h; deep orange solid; yield: 31 mg (85%, 0.099 mmol).

1H NMR (CDCl_3, 500 MHz): δ = 8.47–8.41 (m, 1 H), 8.20 (br s, 1 H), 7.33–7.23 (m, 3 H), 6.95 (s, 2 H), 2.77 (s, 3 H), 2.45 (s, 6 H), 2.33 (s, 3 H).

13C NMR (CDCl_3, 126 MHz): δ = 150.36, 142.10, 136.47, 135.06, 133.41, 130.79, 129.94, 123.47, 122.92, 122.37, 119.50, 110.56, 21.15, 19.68, 11.58.

HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{18}N_3O: 284.0949; found: 284.0946.

(E)-3-(Mesityldiazenyl)-2-methyl-1H-indole (4d)
Prepared according to the general procedure, with a following modification: an additional portion of 0.7 equiv of mesityldiazonium tetrafluoroborate was added after 30 min; stirred for 2 h.

Deep yellow solid; yield: 27 mg (85%, 0.097 mmol).

1H NMR (CDCl_3, 500 MHz): δ = 8.47–8.41 (m, 1 H), 8.20 (br s, 1 H), 7.33–7.23 (m, 3 H), 6.95 (s, 2 H), 2.77 (s, 3 H), 2.45 (s, 6 H), 2.33 (s, 3 H).

13C NMR (CDCl_3, 126 MHz): δ = 150.24, 142.10, 136.47, 135.06, 133.41, 130.79, 129.94, 123.47, 122.92, 122.37, 119.50, 110.56, 21.15, 19.68, 11.58.

HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{18}N_3O: 278.1652; found: 278.1648.

(E)-3-(2-Chlorophenyl)diazenyl)-5-fluoro-2-methyl-1H-indole (4e)
Deep yellow solid; yield: 32 mg (97%, 0.111 mmol).

1H NMR (CDCl_3, 500 MHz): δ = 8.32 (dd, J = 9.7, 2.7 Hz, 1 H), 8.29 (br s, 1 H), 7.80 (dd, J = 7.9, 1.8 Hz, 1 H), 7.55 (dd, J = 7.8, 1.5 Hz, 1 H), 7.34–7.30 (m, 1 H), 7.28 (dd, J = 7.7, 1.8 Hz, 1 H), 7.19 (dd, J = 8.7, 4.3 Hz, 1 H), 6.98 (td, J = 8.9, 2.6 Hz, 1 H), 2.82 (s, 3 H).

13C NMR (CDCl_3, 126 MHz): δ = 160.30 (d, J = 237.9 Hz), 149.83, 145.08, 134.19 (d, J = 3.9 Hz), 134.10, 131.48, 130.56, 129.58, 127.19, 120.02 (d, J = 11.3 Hz), 116.95, 111.81 (d, J = 26.3 Hz), 111.23 (d, J = 9.5 Hz), 108.63 (d, J = 25.6 Hz, 1 H), 11.81.

19F NMR (CDCl_3, 376 MHz): δ = -120.04 (s, 1 F).

HRMS (ESI): m/z [M + H]^+ calcld for C_{19}H_{18}BrN_3O: 386.0863; found: 386.0847.

(E)-5-Chloro-3-[(4-methoxyphenyl)diazenyl]-2-methyl-1H-indole (4f)
Prepared according to the general procedure, but by using another 0.7 equiv of the corresponding aryldiazonium tetrafluoroborate after 30 min; stirred for 30 min.

Deep orange solid; yield: 28 mg (84%, 0.097 mmol).
Deep orange solid; yield: 33 mg (quant, 0.115 mmol).  
1H NMR (CDCl₃, 400 MHz): δ = 8.51 (dd, J = 1.9, 0.8 Hz, 1 H), 8.26 (br s, 1 H), 7.88 (d, J = 9.0 Hz, 2 H), 7.19 (d, J = 0.8 Hz, 1 H), 7.18 (d, J = 1.9 Hz, 1 H), 7.00 (d, J = 9.0 Hz, 2 H), 3.89 (s, 3 H), 2.80 (s, 3 H).

13C NMR (CDCl₃, 101 MHz): δ = 160.60, 148.22, 142.74, 133.42, 132.03, 128.28, 123.62, 123.38, 122.14, 114.23, 111.54, 55.68, 11.73.


(E)-1-{[(2,5-Dimethyl-1H-indol-3-yl)diazonyl]phenyl}ethan-1-one (4g)

Deep orange solid; yield: 33.5 mg (90%, 0.112 mmol).
1H NMR (CDCl₃, 500 MHz): δ = 8.15 (s, 1 H), 8.03 (d, J = 8.3 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H), 7.63 (ddd, J = 8.5, 7.2, 1.5 Hz, 1 H), 7.39 (d, J = 7.9 Hz, 1 H), 7.22–7.18 (m, 2 H), 2.72 (s, 3 H), 2.65 (s, 3 H), 2.53 (s, 3 H) (NH proton not detected).


(E)-3-{[(4-Methoxyphenyl)diazonyl]-1,2-dimethyl-1H-indole (5a)

Deep orange solid; yield: 29 mg (90%, 0.104 mmol).
1H NMR (CDCl₃, 500 MHz): δ = 8.59–8.54 (m, 1 H), 7.87 (d, J = 9.0 Hz, 2 H), 7.34–7.26 (m, 3 H), 7.00 (d, J = 8.9 Hz, 2 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 2.82 (s, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 160.10, 148.72, 143.88, 136.96, 132.30, 123.11, 122.69, 122.66, 119.27, 114.16, 108.85, 55.66, 29.98, 10.30 (1 C undetected due to overlapping).


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Supporting Information
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References
