Supporting Information

MediaChrom: discovering a class of pyrazinoindolone based polarity-sensitive dyes

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Attempts to obtain 2-trifluoromethanesulfoniloxindole derivative 4.

We tried different reaction conditions in order to introduce the triflate group in the position 2 of the indolinone 3 but any reaction gave the desired product (see the following table):

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (Eq.)</th>
<th>Triflating agent (Eq.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Main product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIPEA (1.3)</td>
<td>Tf$_2$O (1.5)</td>
<td>CH$_2$Cl$_2$</td>
<td>0 °C</td>
<td>Blue dimer</td>
</tr>
<tr>
<td>2</td>
<td>DIPEA (1.5)</td>
<td>Tf$_2$O (1.3)</td>
<td>CH$_2$Cl$_2$</td>
<td>-78 °C</td>
<td>Blue dimer</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (1.5)then KHMDS (1.0)</td>
<td>PhNTf$_2$ (1.3)</td>
<td>CH$_2$Cl$_2$</td>
<td>-78 °C</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>KHMDS (1.25)</td>
<td>PhNTf$_2$ (1.25) then Tf$_2$O (1.0)</td>
<td>THF</td>
<td>-78 °C</td>
<td>Blue polymer</td>
</tr>
<tr>
<td>5</td>
<td>/</td>
<td>Tf$_2$O (1.1)</td>
<td>CH$_2$Cl$_2$</td>
<td>0 °C</td>
<td>3 + Blue dimer</td>
</tr>
<tr>
<td>6</td>
<td>DTBMP (1.5)</td>
<td>Tf$_2$O (1.2)</td>
<td>DCE</td>
<td>0 °C</td>
<td>Blue polymer</td>
</tr>
</tbody>
</table>

Firstly, we tried the strategy already developed in our laboratory for analogous substrates, by using DIPEA (pKa = 11) as base and Tf$_2$O as triflating reagent (entries 1-2). The reaction led to the formation of an unidentified blue product, in both tested conditions, i.e., by changing the molar ratio between base and Tf$_2$O and decreasing the reaction temperature. The blue product is probably a dimer with a similar-indigo structure. On the basis of these results and literature findings, we can argue that the diethylamino function at the position 6 of indole nucleus increases the reactivity of indoles, especially activating the position 3. To overcome this drawback we tried a milder triflating reagent, such as PhNTf$_2$, in the presence of the same base. However under these conditions no product was obtained (entry 3), and the starting material was recovered unreacted even after the addition of a stronger base, such as KHMDS (pKa = 28). The direct use of a strong base together with the mild triflating reagent (entry 4) did not lead to any reaction product, whereas a subsequent addition of Tf$_2$O led to the formation of an unidentified dark-blue dimerization/polymerization product. On the basis of these data we concluded that the use of the mild triflating reagent (PhNTf$_2$) always leads to the recovery of the starting material, regardless of strength of the base used. Conversely, the use of the strong triflating agent Tf$_2$O, leads always to the formation of unidentified blue dimers/polymers depending of the strength of the base used. As further attempt, we performed the reaction in the presence of the strong triflating reagent without the base (entry 5), and in this case we recovered the starting material beside traces of dimerization product. Finally, the use of an even weaker base such as DTBMP (pKa ≈ 6) with Tf$_2$O at 0 °C resulted in the isolation of a dark-blue polymerization product (entry 6).
Therefore, we planned an alternative strategy involving a double triflation of the 6-(diethylamino)indolin-2-one. This path seemed to be feasible taking advantage from the absence of deactivating group on the nitrogen of indolinone and the chance to modulate the strength of the base and of the triflating reagent. The results are shown in following table:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (Eq.)</th>
<th>Triflating agent (Eq.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Main product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEA (2.3)</td>
<td>Tf₂O (2.2)</td>
<td>THF</td>
<td>rt</td>
<td>Blue polymer</td>
</tr>
<tr>
<td>2</td>
<td>DTBMP (3.0)</td>
<td>Tf₂O (3.0)</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>Blue polymer</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (3.0)</td>
<td>PhNTf₂ (3.0)</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>2</td>
</tr>
</tbody>
</table>

In the presence of TEA (pKa = 10.6, entry 1) or DTBMP (pKa ≈ 6, entry 2) and Tf₂O we obtained only the polymerization product. Conversely, with DIPEA (pKa = 11, entry 3) and PhNTf₂ we only recovered the starting material, as in all previous cases in which the mild triflating reagent was used.

**Study on the Au-catalyzed cycloisomerization.**

Under a nitrogen atmosphere, to a solution of 14a (0.10 mmol) in the proper solvent (3.5 mL, see table below) the catalyst (0.005 mmol) was added. The reaction mixture was heated at 80 °C for the time reported in the table below. The reaction mixture was evaporated to dryness and the crude was purified by flash chromatography over a silica gel column.

<table>
<thead>
<tr>
<th>Cat.</th>
<th>Solv.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AuClPPh₃ (5 mol%), AgOTf (5 mol%)</td>
<td>Toluene</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>AgOTf (10 mol%)</td>
<td>DCE</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>PPh₃AuNTf₂ (5 mol%)</td>
<td>DCE</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>IPrAuSbF₆ (5 mol%)</td>
<td>DCE</td>
<td>6</td>
<td>53</td>
</tr>
</tbody>
</table>

*The starting material was almost quantitatively recovered.*
**Table S1:** Changes in dipole moments of MediaChrom 15a-f.

<table>
<thead>
<tr>
<th>MediaChrom</th>
<th>$\mu^* - \mu$ (Debye)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>13.0</td>
</tr>
<tr>
<td>15b</td>
<td>-</td>
</tr>
<tr>
<td>15c</td>
<td>13.3</td>
</tr>
<tr>
<td>15d</td>
<td>13.4</td>
</tr>
<tr>
<td>15e</td>
<td>13.0</td>
</tr>
<tr>
<td>15f</td>
<td>13.4</td>
</tr>
</tbody>
</table>

**Table S2:** Comparison between fluorescent emission peaks of MediaChrom 15c and 15’c.\(^a\)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>MediaChrom 15c (benzyl ester)</th>
<th>MediaChrom 15’c (carboxyl free)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hexane</td>
<td>490 nm</td>
<td>487 nm</td>
</tr>
<tr>
<td>$n$-octanol</td>
<td>525 nm</td>
<td>520 nm</td>
</tr>
<tr>
<td>ethanol</td>
<td>540 nm</td>
<td>537 nm</td>
</tr>
<tr>
<td>DMF</td>
<td>565 nm</td>
<td>563 nm</td>
</tr>
</tbody>
</table>

\(^a\) excitation wavelength: 393 nm
**Chromatogram and Mass spectra of 15’c-Cro:1**: $M = 2837.9$. ESI-MS m/z (%): 1419.8 [(M + 2)/2]⁺ (100), 946.9 [(M + 3)/3]⁺.

**Info**: analitica 95% A for 5 min 30%A at 25 min

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area[mAu,Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>19,467</td>
<td>7995,500</td>
<td>100</td>
</tr>
</tbody>
</table>

**Injection Date**: 29-Mag-2015 13:32:06  
**Curr. Date**: 29-Mag-2015 14:02:00
References


$\text{H}_3\text{C} - \text{NH} - \text{NH}$

$2'$

$200 \text{ MHz, DMSO-}d_6$

$\text{H}_3\text{C} - \text{NH} - \text{NH}$

$2'$

$200 \text{ MHz, DMSO-}d_6$
50.3 MHz, CDCl₃
traces of indoline

50.3 MHz, CDCl₃

S19
$^{1}H$ NMR spectrum of compound 7 in CDCl$_3$ (200 MHz):

- Peaks at 7.84 ppm, 7.83 ppm, 7.41 ppm, 7.32 ppm, 6.69 ppm, 6.66 ppm, 6.65 ppm, 6.51 ppm, 5.49 ppm, 3.45 ppm, 3.42 ppm, 3.38 ppm, 3.33 ppm.

- Additional peaks at 6.49 ppm, 6.51 ppm, 6.65 ppm, 6.66 ppm, 6.69 ppm, 6.70 ppm, 7.26 ppm, 7.32 ppm, 7.34 ppm, 7.41 ppm, 7.45 ppm, 7.48 ppm, 7.51 ppm, 7.83 ppm, 7.84 ppm, 7.87 ppm.

- Assignment of peaks corresponds to the chemical shifts of different functional groups and protons in the compound.

- Water (H$_2$O) peak at 5.84 ppm.
50.3 MHz, CDCl₃
12a

50.3 MHz, CDCl₃
S38

12d

50.3 MHz CDCl₃
200 MHz, CDCl₃

12e

grease

S39
12f
$12f$

50.3 MHz, CDCl$_3$
$\text{H}_3\text{C}\text{N}\text{H}_3$ $13a$

50.3 MHz, CDCl$_3$
The image contains an NMR spectrum of compound 13b. The spectrum displays various peaks at different ppm values, indicating the chemical shifts of different protons in the molecule. The peaks are labeled with their corresponding ppm values, such as 8.23, 8.19, 7.63, 7.58, 7.46, 7.41, 6.81, 6.75, 6.70, 6.64, 3.46, 3.42, 3.39, 3.35, 1.23, 1.20, 1.16, and others. The spectrum is recorded at 200 MHz in CDCl₃. The compound structure is also shown, with elements like nitrogen (N), oxygen (O), and carbon (C) highlighted in the diagram. The structure includes a nitrogen-containing ring and a nitro group (-NO₂) attached to a phenyl ring.
50.3 MHz, DMSO-d$_6$

C-F:

J$_1$
J$_2$
J$_3$

S54
14a

$200 \text{ MHz, CDCl}_3$

$H_2O$
50.3 MHz, CDCl$_3$

14a
50.3 MHz, CDCl₃
15b

75.5 MHz, C₆D₆
The image shows a proton NMR spectrum of compound 15e. The spectrum is recorded at 200 MHz in C₆D₆. The chemical shifts are indicated by peaks at various ppm values. The peaks are labeled with their corresponding chemical shifts, and the structural formula of the compound is shown in the upper right corner of the image. The compound is a heterocyclic molecule with several functional groups, including ester and amide functionalities. The spectrum includes signals for EtOAc groups at around 1.01 ppm and 1.18 ppm, and the methyl group at 2.33 ppm. The spectrum also shows a broad signal around 6.76 ppm, likely due to the aromatic protons.
COSY, acetone-\textit{d}_6
HSQC, acetone-$d_6$
HSQC, acetone-$d_6$
HSQC, acetone-\textit{d}_6

![HSQC spectrum diagram](image)

15\textsuperscript{c}
NOESYPH, acetone-$d_6$
$T = 300K, t_{mix} = 800$ ms

$15^c$
NOESYPH, acetone-$d_6$
$T = 300K$, $t_{\text{mix}} = 800$ ms
NOESYPH, acetone-$d_6$
T = 300K, $t_{mix} = 800$ ms