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# Insertion–Coupling–Cycloisomerization Domino Synthesis and Cation-Induced Halochromic Fluorescence of 2,4-Diarylpyrano[2,3-*b*]indoles

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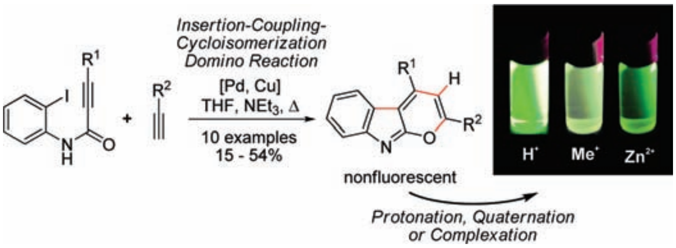
## ABSTRACT



**2,4-Diarylpyrano[2,3-*b*]indoles are formed via a Pd–Cu-catalyzed insertion–coupling–cycloisomerization domino reaction in moderate yields. Although the tricyclic systems are nonfluorescent in solution, protonation, quaternation, or complexation with metal ions induces intense green luminescence. Most strikingly, selective halochromic fluorescence of zinc and magnesium over calcium ions classify the title compounds as metal-selective luminescence sensors.**

The synthesis of novel functional organic molecules has become an important challenge at the cutting edge between organic chemistry and materials sciences.[1] For instance, functional chromophores are of particular interest in organic light-emitting diodes,[2] dye-sensitized organic solar cells,[3] organic field effect transistors,[4] or sensor arrays in bioanalytics or environmental analytical applications.[5] Hence the quest for rapid, flexible access to new tailor-made functional $\pi$-systems has become increasingly important. In particular, chromophores containing embedded recognition elements, such as basic nitrogen atoms or phenolic hydroxyl groups, for external stimuli are of paramount interest for advanced applications.[6] Typically, by addition of an analyte to a solution of the functional chromophore, significant changes in absorption or emission properties can be observed as instantaneous read-outs. Most prominently among recent examples based upon specific topologies of constituting subchromophores are cruciform fluorophores by Bunz,[7] tetraethynylethenes and diethynylethenes by Diederich,[8] or tetrakis(arylethynyl)benzenes by Haley.[9]

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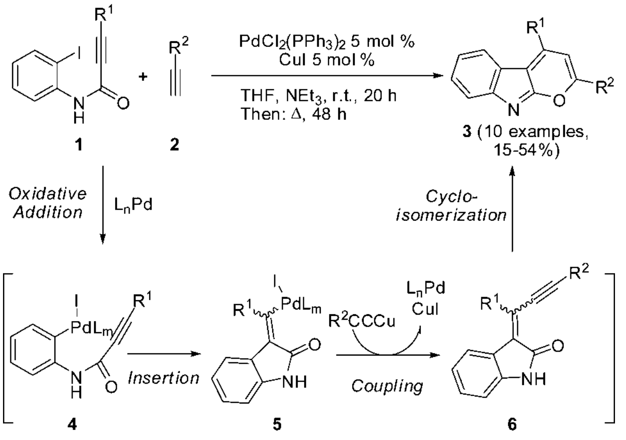
In the past years we have established and developed diversity-oriented syntheses of chromophores[10] based upon transition-metal catalysis as an entry to consecutive multicomponent[11] and domino reactions.[12] These concepts open excellent synthetic accesses to luminescent indolone terminated push−pull dienes, pyrazoles, benzodiazepines, furans, and pyrroles by multicomponent reactions[13] and to highly emissive spirocycles in a domino fashion.[12a,b] Here, we communicate a concise insertion−coupling−cycloisomerization domino synthesis of 2,4-diaryl-pyrano[2,3-*b*]indoles, a hitherto unknown substance class with peculiar halochromic luminescence. The vestigial literature precedence on pyranoindoles is limited to pyrano[3,4-*b*]indoles as useful precursors in the synthesis of carbazoles by Diels−Alder reactions[14] and a single paper on the synthesis of pyrano[2,3-*b*]indol-4-ones from oxindole and acetoacetate.[15] In a previous work we have already shown that alkynoyl *o*-iodo anilides **1** are useful building blocks for developing novel domino reactions.[12a,b] Now we have discovered a novel reaction starting from the same type of substrate.

Upon reacting alkynoyl *o*-iodo anilides **1** with terminal arylacetylenes **2** under the Sonogashira conditions[16] in a mixture of THF and triethylamine, first at room temperature and then at reflux temperature, the novel class of 2,4-diaryl-pyrano[2,3-*b*]indoles **3** were formed in moderate yields (Scheme 1, Table 1). The structures of the 2,4-diaryl-pyrano[2,3-*b*]indoles **3** were unambiguously supported by $^{1}$H and $^{13}$C NMR spectroscopy, by EI-MS spectrometry, and by elemental analysis. Additionally, the structure of **3a** was later corroborated by an X-ray structure analysis (Figure 1).[17]

**Scheme 1.** One-Pot Insertion−Coupling−Cycloisomerization Synthesis of Novel 2,4-Diphenylpyrano[2,3-*b*]indoles



On the basis of the product analysis and the possibility to isolate the conjugated enynes **6** after a room temperature reaction,[12a] the mechanistic rationale of this one-pot sequence can be rationalized as follows (Scheme 1). After oxidative addition an aryl-Pd species **4** readily inserts into the tethered amido alkynyl triple bond to furnish vinyl-Pd species **5**. Subsequent alkynylation with the copper acetylide concludes the coupling by forming conjugated enyne **6** as a mixture of geometrical isomers, presumably as a consequence of a precoupling stereomutation from the expected initial *syn*-insertion product **5**-*E*. For geometrical reasons only the *Z*-configured stereoisomer **6**-*Z* can participate in the final cycloisomerization. A post-coupling *E*/*Z*-isomerization of **6** can be excluded due to the failure of attempted triethylamine catalyzed equilibration with isolated **6**-*E*. The concluding cycloisomerization furnishes, as supported by DFT calculations (see Supporting Information), the thermodynamically most stable isomer in a series of isomers, i.e., the 2,4-diarylpyrano[2,3-*b*]indole **3**. Within this efficient sequence four new bonds, i.e., two carbon−carbon bonds, a carbon−oxygen, and a carbon−hydrogen bond, are formed with an average yield per bond-forming step ranging from 62% to 86%. Already, upon workup of the reaction mixture under mildly acidic conditions (silica gel flash chromatography) the peculiar appearance of green luminescence prompted us to more closely scrutinize this phenomenon instead of pushing forward the methodological and mechanistic studies on the formation of 2,4-diarylpyrano[2,3-*b*]indoles **3**.

The UV−vis spectra of the pure compounds **3** show two intense major absorption maxima around 380 and 280 nm (Table 2). Moreover the free bases **3** fluoresce neither in solution nor in the solid state. However, upon protonation of the 2,4-diarylpyrano[2,3-*b*]indoles **3** with trifluoroacetic acid a significant bathochromic and hyperchromic shift of the longest wavelength absorption maxima between 403 and 465 nm with large molar extinction coefficients appears in

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(17) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 785242 (**3a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk).

**Table 1.** Domino Reaction Consisting of Insertion, Coupling, and Cycloisomerization Steps Yielding 2,4-Diarylpyrano[2,3-*b*]indoles **3**

| entry | *o*-iodo alkynylanilide **1** | alkyne **2** | 2,4-diarylpyrano[2,3-*b*]indole **3**[a] |
|---|---|---|---|
| 1 | $R^1$ = Ph (**1a**) | $R^2$ = Ph (**2a**) | **3a** (35%) |
| 2 | **1a** | $R^2$ = *p*-$NCC_6H_4$ (**2b**) | **3b** (15%) |
| 3 | **1a** | $R^2$ = *p*-$MeOC_6H_4$ (**2c**) | **3c** (54%) |
| 4 | **1a** | $R^2$ = *p*-$ClC_6H_4$ (**2d**) | **3d** (32%) |
| 5 | $R^1$ = *p*-$ClC_6H_4$ (**1b**) | **2c** | **3e** (41%) |
| 6 | $R^1$ = *p*-$ClC_6H_4$ (**1b**) | **2a** | **3f** (24%) |
| 7 | $R^1$ = *p*-$ClC_6H_4$ (**1b**) | **2d** | **3g** (24%) |
| 8 | **1a** | $R^2$ = *p*-$^t$Bu-$C_6H_4$ (**2e**) | **3h** (14%) |
| 9 | **1a** | $R^2$ = *p*-Me-$C_6H_4$ (**2f**) | **3i** (25%) |
| 10 | **1a** | $R^2$ = *p*-$CO_2Me$-$C_6H_4$ (**2g**) | **3j** (17%) |

[a] Reaction conditions: 1.00 equiv of alkynoyl *o*-iodo anilides **6** (0.1 M in THF/$NEt_3$ 1:1), 1.10 equiv of terminal alkynes **2**, 0.05 equiv of $PdCl_2(PPh_3)_2$, 0.05 equiv of CuI; after stirring for 20 h at room temp heating to 85 °C temp for 48 h in a sealed tube.

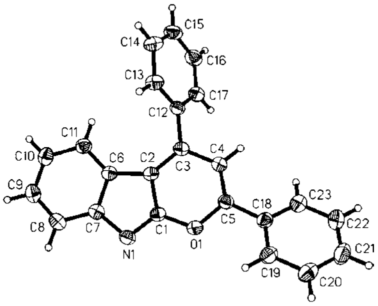


**Figure 1.** ORTEP plot of the crystal structure of the 2,4-diphenylpyrano[2,3-*b*]indole (**3a**).

the UV−vis spectra and a distinct second absorption band around 355 nm is detected.

Most interestingly, the protonated 2,4-diarylpyrano[2,3-*b*]indoles **3-H**$^+$ display an intense green luminescence with a narrow, unstructured longest wavelength maximum around 520 nm (Figure 2). This protochromicity is most pronounced for the donor-substituted diphenyl-pyrano[2,3-*b*]indoles **3c-H**$^+$ and **3e-H**$^+$, also with respect to the efficacy of the fluorescence as represented by the considerable higher fluorescence quantum yields $\Phi_f$, determined with coumarin 153 as a standard.[18]

The Stokes shifts $\Delta\tilde{\nu}$ ($\lambda_{max,abs} - \lambda_{max,em}$) are dependent on the electronic nature of the 2-aryl substituents and range from 2300 cm$^{-1}$ for electron-rich anisyl substituents to 5000 cm$^{-1}$ for electron-deficient and electro-neutral moieties. The electron-deficient *p*-cyano substituent (compound **3b-H**$^+$) causes a hypsochromic shift in comparison to the electro neutral phenyl derivative **3a-H**$^+$, whereas the electron-rich anisyl moiety (compound **3c-H**$^+$) leads to a considerable red shift. As indicated by the emission data, the electronic structure in the vibrationally relaxed excited state of **3-H**$^+$ is essentially unaffected by substitution. A stronger push−pull character as in the cases of **3c-H**$^+$ and **3e-H**$^+$also results in smaller Stokes shifts. Since trifluoroacetic acid is completely dissociated in dichloromethane[19] a p$K_a$ value of 4.53 of the protonated species **3d-H**$^+$ was determined in a titration experiment. This p$K_a$ value is comparable to that of a pyridinium ion,[20] and thus, protonation of the pyranoindoles **3** on the indole nitrogen atom can be assumed.

In addition, the efficacy of the emission (vide supra) strongly depends on the electronic nature of the substituent in position 2. In contrast, caused by conformational torsion out of coplanarity with the pyranoindole, only a minor

**Table 2.** Photophysical Data of the 2,4-Diarylpyrano[2,3-*b*]indoles **3a**−**e** Recorded in Dichloromethane at 298 K

| compound | $\lambda_{max,abs}$ [nm] ($\varepsilon$) [L cm$^{-1}$ mol$^{-1}$] unprotonated | $\lambda_{max,abs}$ [nm] ($\varepsilon$) [L cm$^{-1}$ mol$^{-1}$] protonated | $\lambda_{max,em}$ [nm] ($\Phi_f$)[a] protonated | Stokes shift $\Delta\tilde{\nu}$[b] |
|---|---|---|---|---|
| **3a** | 383 (17400) | 415 (19600) | 522 (0.1%) | 5000 |
| **3b** | 383 (19300) | 403 (19300) | 513 (0.1%) | 5400 |
| **3c** | 393 (17200) | 462 (26400) | 519 (15.0%) | 2300 |
| **3d** | 384 (26700) | 417 (28900) | 523 (0.1%) | 4800 |
| **3e** | 397 (25200) | 465 (39100) | 522 (11.2%) | 2300 |
| **3f** | 384 (26700) | 417 (28900) | 523 (0.1%) | 4800 |
| **3g** | 386 (20500) | 421 (23400) | 523 (0.1%) | 4600 |
| **3h** | 385 (22300) | 428 (30600) | 511 (0.1%) | 3800 |
| **3i** | 386 (19700) | 430 (25900) | 511 (0.1%) | 3700 |
| **3j** | 389 (18700) | 413 (18200) | 519 (0.1%) | 4900 |

[a] Determined against coumarin 153 as a standard ($\Phi_f$ = 38%); [b] Stokes shift only for protonated pyranoindoles.

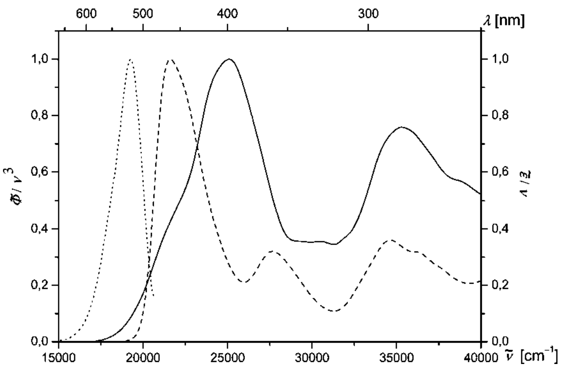
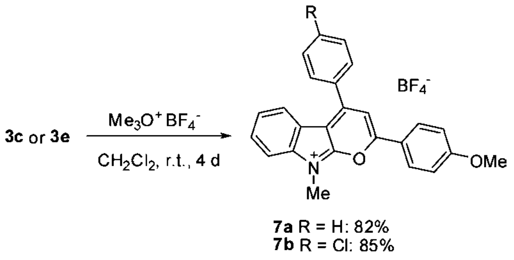


**Figure 2.** UV−vis and emission spectra of **3c** and **3c-H**$^+$ recorded in CH$_2$Cl$_2$ at 298 K. Absorption spectra of **3c** (solid line) and **3c-H**$^+$ (after protonation with TFA, dashed line); emission spectrum of **3c-H**$^+$ (dotted line).

substituent effect can be expected at position 4. This prediction is supported by the comparison of compounds **3c** and **3e**, where the electron-withdrawing *p*-chlorophenyl substituent causes only a slight bathochromic shift of the absorption and emission bands. Finally, the influence of substituents on the absorption maxima of the neutral and the protonated pyrano[2,3-*b*]indoles can easily rationalized by ZINDO-CI calculations. The experimental spectra are reproduced in good agreement and the calculated maxima only deviate in a range of a few nanometers (see also Supporting Information).

Encouraged by the observation of the protonation induced emission enhancement of the pyranoindoles, we decided to prepare the corresponding quaternized derivatives **7** by reacting the pyranoindoles **3c** and **3e** in dichloromethane with an equimolar amount of trimethyloxonium tetrafluoroborate (Scheme 2). After stirring at room temperature for 4 days, precipitation, and washing with diethyl ether, the *N*-methyl pyranoindolium tetrafluoroborates **7a** and **7b** were obtained in good yields. The quaternized derivatives **7** display almost superimposable absorption and emission spectra with the analogous protonated pyranoindoles **3c-H**$^+$ and **3e-H**$^+$ (see Supporting Information), and the fluorescence quantum yields of **7a** and **7b** appear with $\Phi_f = 10\%$ just in the same range.

**Scheme 2.** Quaternation of Pyranoindoles **3c** and **3e** by Methylation with Trimethyloxonium Tetrafluoroborate



The peculiar halochromic luminescence behavior of pyranoindoles **3** with donor substituents in position 2 prompted us to check if this turning on of fluorescence could also be effective for sensing cations. Therefore, solutions of pyranoindole **3c** were exposed to biologically relevant metal ions in the form of their salts, such as zinc triflate, calcium triflate, or magnesium triflate. Upon eyesight (Figure 3) but also confirmed by fluorescence spectroscopy, intense green fluorescence can be observed with pronounced selectivity for the biologically relevant cations zinc and magnesium over calcium. As shown before in the protonation experiments the absorption maximum was shifted bathochromically with concomitant switching on green light emission.

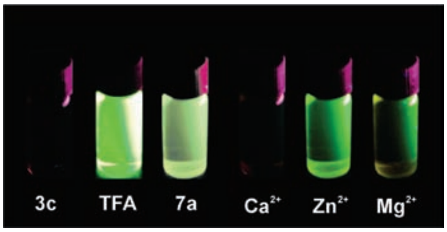


**Figure 3.** From left to right: compound **3c** dissolved in CH$_2$Cl$_2$; compound **3c** after the addition of trifluoroacetic acid; compound **7a**, compound **3c** after the addition of Ca$^{+II}$ triflate; compound **3c** after the addition of Zn$^{+II}$ triflate; compound **3c** after the addition of Mg$^{+II}$ triflate; (irradiation at $\lambda_{exc} = 354$ nm).

In conclusion we have developed a domino synthesis of hitherto unknown 2,4-diarylpyrano[2,3-*b*]indoles, a class of compounds with unique photophysical properties. Displaying no fluorescence as a free base halochromic green fluorescence can be switched on upon protonation, methylation, or complexation with various metal cations, also displaying considerable fluorescence sensitivity. Since the 2,4-diarylpyrano[2,3-*b*]indoles are also readily soluble in an aqueous solution containing 1% of 2-propanol, more detailed studies of the complexation behavior of metal salts various solvents and solvent systems such as cell buffers are currently underway.

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**Supporting Information Available:** Experimental details, NMR and selected absorption and emission spectra of compounds **3** and **7**, computational data and X-ray data of compound **3a** including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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