

## Aryne approach towards 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles

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Reaction between 3-(2-pyridyl)-1,2,4-triazines and *in situ* generated 4,5-difluorobenzynes in toluene affords 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles. The structure of one representative compound was confirmed by X-ray diffraction analysis.

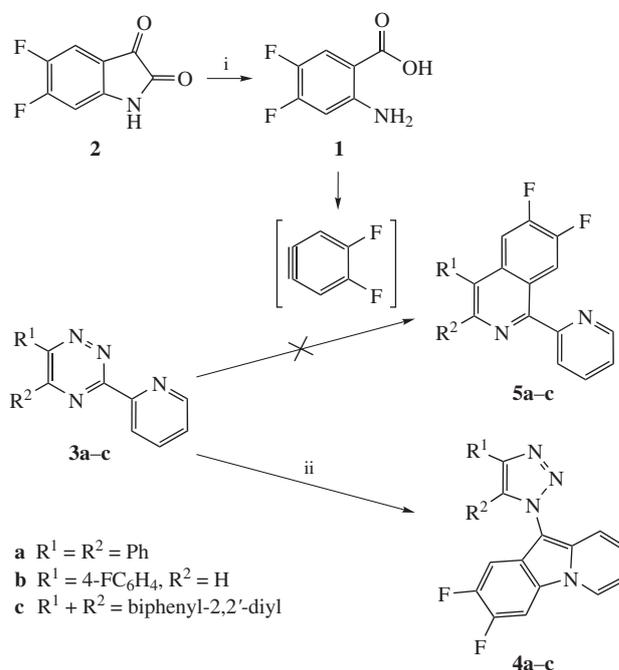
Pyrido[1,2-*a*]indoles are of practical interest due to their cytostatic,<sup>1</sup> antiviral<sup>2</sup> and antitumor<sup>3</sup> activities. Introduction of fluorine atoms into poly(hetero)cyclic systems in most cases improves their photophysical properties,<sup>4</sup> biological activity<sup>5</sup> and electrochemical properties.<sup>6</sup> For now fluorinated pyrido[1,2-*a*]indoles are known scarcely,<sup>7</sup> while substituted 2,3-difluoropyrido[1,2-*a*]indoles are not reported. As for 1,2,3-triazoles, they are of interest<sup>8</sup> as common pharmacophores<sup>9</sup> as well as components of photoluminescent sensors for various analytes,<sup>10</sup> including explosives.<sup>11</sup>

The methods for the synthesis of pyrido[1,2-*a*]indoles are mostly limited by availability of the starting materials and/or the application of harsh conditions.<sup>12</sup> As for 1,2,3-triazole-substituted pyrido[1,2-*a*]indoles, recently the convenient one-pot approach *via* the benzyne-mediated rearrangement of 3-(2-pyridyl)-1,2,4-triazines was reported by our group.<sup>13</sup> In this paper the convenient one-pot approach to 10-substituted 2,3-difluoropyrido[1,2-*a*]indoles by reaction between 3-(2-pyridyl)-1,2,4-triazines and 4,5-difluorobenzynes is reported.

During the last decade, aryne chemistry is experiencing a renaissance, due to the development of new methods for the smooth and effective aryne generation.<sup>14</sup> In particular, 4,5-difluorobenzynes can be generated from 4,5-difluoro-2-trimethylsilylphenyl trifluoromethanesulfonate<sup>15</sup> by the action of fluoride anion or from 1,2-dibromo-4,5-difluorobenzene<sup>16</sup> by the action of *n*-butyllithium. On the other hand, 3,4-difluoroanthranilic acid, which can be easily obtained by 3,4-difluoroaniline<sup>17–5,6-difluoroisatine</sup> sequence, is a rare 4,5-difluorobenzynes source.<sup>18</sup> In this work, 3,4-difluoroanthranilic acid-derived 4,5-difluorobenzynes is used to prepare 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles in one step in good yields.

For the synthesis of 3,4-difluoroanthranilic acid **1**, the modified method based on 5,6-difluoroisatine **2**<sup>19</sup> was used (Scheme 1).

1,2,4-Triazines **3** were synthesized according to reported procedures<sup>20</sup> by the reaction of isonitrosoacetophenone hydrazones with pyridine-2-carbaldehyde or by the reaction between  $\alpha$ -diketones and amidrazones. The fluorination of the aryl substituent of the triazine core as well as the aryl precursor of the 4,5-difluorobenzynes did not influence the reaction pathway giving 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **4** in moderate yields (see Scheme 1).<sup>†</sup> No isoquinolines **5** were observed in a



**Scheme 1** Reagents and conditions: i, NaOH, H<sub>2</sub>O<sub>2</sub>, 55°C, 2 h, then HCl, 15–20°C; ii, toluene, isoamyl nitrite, 110°C, 1.5 h.

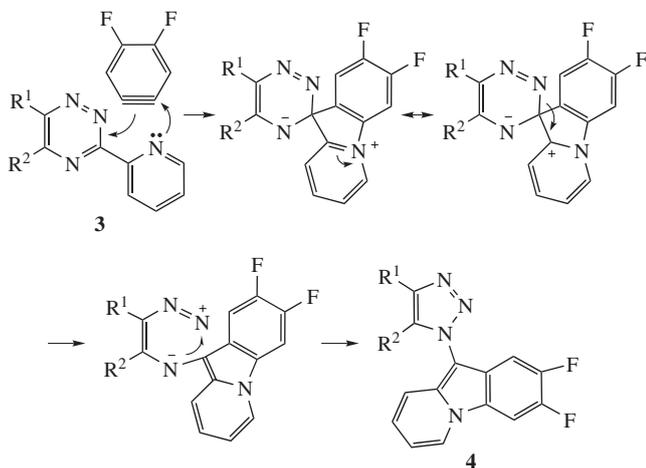
reaction mixture. A plausible mechanism of this transformation is represented in Scheme 2.

The structure of the products **4** was confirmed by <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR spectroscopy and mass spectrometry, and by comparison of their spectral data with the previously reported ones for non-fluorinated products.<sup>13</sup> Ultimately, the structure of the representative compound **4b** was confirmed by X-ray crystallography (Figure 1).<sup>‡</sup>

Compound **4b** is crystallized in trigonal system. Face-to-face  $\pi$ – $\pi$  stacking interactions between the pyrido[1,2-*a*]indole fragments are evident, the interplanar separations are in the range of

acid (2.08 g, 12 mmol) in dry 1,4-dioxane (15 ml) was added dropwise within 30 min. The reaction mixture was refluxed for 1 h, then cooled to room temperature and washed with 3 M KOH solution (3×75 ml), the organic layer was separated and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvents were removed under reduced pressure. Products **4** were isolated by column chromatography [silica gel, AcOEt–CH<sub>2</sub>Cl<sub>2</sub> (3:1) as eluent, R<sub>f</sub> = 0.8]. Analytically pure samples **4** were obtained by the recrystallization from dry acetonitrile. For the analytical data, see Online Supplementary Materials.

<sup>†</sup> 2,3-Difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **4**. Corresponding triazine **3** (3 mmol) was suspended in dry toluene (130 ml). Isoamyl nitrite (1.61 ml, 12 mmol) was added to this mixture. The mixture was stirred under reflux while solution of 3,4-difluoroanthranilic



Scheme 2

3.5 Å, and the glide-related molecules are linked in a head-to-tail fashion to generate a supramolecular architecture of infinite chains (see Figure S1, Online Supplementary Materials). Hydrogen bonds between fluorine and hydrogen atoms are also observed, distances between them are in a range of 2.5–2.6 Å (see Figure S2, Online Supplementary Materials). Similar cases of intermolecular and intramolecular hydrogen bonds involving fluorine atoms were reported.<sup>21</sup>

In conclusion, a convenient one-step approach towards novel 2,3-difluoro-10-(1H-1,2,3-triazol-1-yl)pyrido[1,2-a]indoles via the aryne chemistry has been developed. These compounds can be very promising in view of their biological activities.

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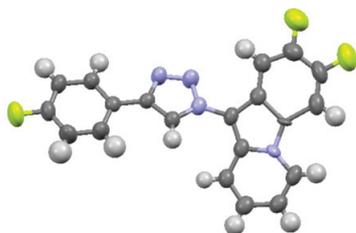


Figure 1 Molecular structure for product 4b.

‡ Crystal data for 4b. The single crystal (brown needle, 0.25×0.08×0.02 mm) of compound 4b (C<sub>20</sub>H<sub>11</sub>F<sub>3</sub>N<sub>4</sub>) was used for X-ray analysis. Analysis was performed at 295(2) K on an Xcalibur E diffractometer using graphite monochromated MoK $\alpha$  ( $\lambda$  = 71.073 pm) and CCD detector. Crystal is trigonal, space group *R*-3 with  $a = b = 47.097(5)$  and  $c = 3.8351(5)$  Å,  $\alpha = \beta = 90^\circ$ ,  $\gamma = 120^\circ$ ,  $V = 7367.1(15)$  Å<sup>3</sup>,  $Z = 18$ . On the angles  $2.29 < \theta < 26.36^\circ$  10 614 reflections were measured, among them 3323 unique reflections ( $R_{\text{int}} = 0.0490$ ), 1679 reflections with  $I > 2\sigma(I)$ . Completeness to  $\theta_{\text{max}} = 26.38$  is 99.3%. The structure was solved by direct method and refined by full-matrix least squares at  $F^2$  using the SHELXTL program package. All non-hydrogen atoms were refined anisotropically, the positions of the hydrogen atoms were calculated as a riding model in isotropic approximation. An absorption correction was not applied ( $\mu = 0.115$  mm<sup>-1</sup>). Goodness of fit at  $F^2$  1.003; final *R* values [ $I > 2\sigma(I)$ ],  $R_1 = 0.0548$ ,  $wR_2 = 0.0846$ ; *R* value (all reflections)  $R_1 = 0.1326$ ,  $wR_2 = 0.1024$ . Largest difference peak and hole were 0.143 and -0.139 eÅ<sup>-3</sup>.

CCDC 984078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.

### Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.01.003.

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