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Thin film microfluidic synthesis of fluorescent highly
substituted pyridines

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Colin L. Raston a

A facile, one pot method for the synthesis of a series of
polysubstituted and 2,4,6-trisubstituted pyridines using a thin
film vortex fluidic device has been developed, with the
compounds obtained in good yield following simple purification
procedures. Changes in fluorescent intensity and
excitation/emission parameters is demonstrated through
variation of functional groups, without significantly impacting
on the synthetic yield.

Development of new fluorescent organic compounds with high
functionality has been the subject of intense study for more than a
decade because of rapidly increasing applications of organic
fluorescent materials for electroluminescence (EL), dye-lasers,
sensors, probes, and phototherapeutic agents. 1-3 Triaryl-
pyridines are structurally related to the symmetrical triaryl-thiopyrylium,
triarylseleopyrylium, and triaryl-selenuropyrylium photosensitizers,
which have been recommended for photodynamic cell specific
cancer therapy. 4

Also noteworthy is that the substituted pyridyl heterocyclic core
is an extensive sub-unit seen in numerous natural products 5, 6 and is a
versatile moiety in coordination chemistry, as well as in
supramolecular chemistry due to its ability to engage in π-stacking. 7-
9 This provides a compelling reason to explore alternative, more
efficient and more benign methods for the synthesis of such
heterocyclic compounds. Traditionally these compounds have been
prepared through the reaction of N-phenacylpyridinium salts with

α,β-unsaturated ketones, which is better known as the Kröhne
synthesis. 10, 11 More recently one-pot reactions have been developed
for the synthesis of some triarylpyridines, in a drive to improve the
associated green chemistry metrics, especially in avoiding the use of
pyridinium salts, which are derived from the reaction of an
halogenated-methyl ketone with pyridine. Such one-pot reactions
involve acetophenone, an aryl aldehyde, and ammonium acetate
(NH₂OAc). They include reactions under solventless conditions,12
the use of microwave irradiation,13-15 NaOH in PEG;16,17 catalytic
amounts of acetic acid,18 Preyssler-type heteropolyacid
H₃[NaP₃W₁₀O₄₀]19 bismuth trflate20 and a Bronsted acidic ionic
liquid.21 Although a variety of approaches toward gaining access to
substituted pyridines have been established, versatile and efficient
methods for the construction of the pyridine core which are
compatible with various functional groups remain highly desirable.
Given the aforementioned chemical and pharmacological
significance of the substituted pyridines, the synthesis of such types
of molecules is becoming an attractive area of research, in diverting
efforts to develop simple less waste generating routes for their
syntheses by further applying the principles of green chemistry.22

An alternative strategy in minimizing the generation of by-
products/waste, is the use of process intensification strategies,
beyond the use of solventless and microwave processing, as in
dynamic thins films, which can allow gaining control of formation of
the kinetic favoured product over the thermodynamic favoured
product.23 In the present study the process intensification device of
choice is a vortex fluidic device (VFD), where intense shear is
present for the device operating in both the so called continuous flow
and confined modes of operation, which have recently been studied
in detail.24 The thin film VFD is emerging as a versatile device for a
diverse range of applications, including exfoliation of laminar
material,25,26 controlled growth of nano-particles,27,28 disassembly of
self-organised systems,29 preparing mesoporous silica30 entrapping
microalgal cells, 31,32 and in controlling reactivity and selectivity in
organic synthesis, notably in accelerating Diels-Alder reactions,33
stereochemical control of the synthesis of calixarenes,34 and the

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supplementary information available should be included here]. See
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synthesis of amino functionalized 2,4,6-triarylpyridines, where formation of the thermodynamically favoured Schiff base adduct of the aldehyde is avoided. For the latter, the same outcome is possible when using a related spinning disc microfluidic platform, albeit due to the limited residence time of the liquid on the surface of the rapidly rotating disc as a strictly continuous flow process, several passes are required for a similar outcome relative to using the VFD.

Herein, we further develop the utility of the VFD in gaining access to a series of poly-substituted and N,N-dimethyl containing 2,4,6-trisubstituted pyridines, and investigate the fluorescent properties of these new molecules. The choice of the VFD in the present study relates to its ability to scale down under constant shear using the confined mode, in further mapping out the novel capabilities of the microfluidic platform in general, as well the potential to develop a robust benign method for gaining access to a diverse range of fluorescence molecules.

Previously we reported two synthetic strategies for preparing 2,4,6-triaryl pyridines. The first involved two steps, initially forming the 1,5-diketone via a sequential aldol and Michael addition reactions using the VFD in the continuous flow mode. The second method was a one step method using the VFD, as a three component condensation in the presence of NH₄OAc, also in the continuous flow mode. We have now expanded these strategies through a study involving the three component condensation involving 1-indanone as the ketone with various aldehydes. This gains access to poly-substituted pyridines under the confined mode of operation of the VFD, where the intense shear arises from the cross vector of centrifugal force and gravity, for a tube rotating at 45° tilted relative to the horizontal position.

![Diagram](Image)

**Figure 1.** Crystal structure of 6d projected onto the plane of the central ring.

In a typical procedure for the synthesis of 3(a–e), 1-indanone 1 (1 mmol), the aldehyde 2a–e (0.5 mmol) and NH₄OAc (2 mmol) in PEG300 (1 mL) were treated in the confined mode of VFD at 100 °C for 30 minutes. As a control the reaction was also carried out in a round bottom flask with a stirrer bar under the same reaction conditions and no product formation was observed, as determined using thin layer chromatography. The yields of the reactions undertaken using the VFD were good (Table 1) with little to no by-products observed. Also the scope of the reaction regarding the different aldehydes was found to be excellent, with a variety of different compounds prepared. Of note is that using this three component system in the continuous flow mode of the VFD resulted in low yields, in consequence of the limited residence time of the liquid in the tube for less reactive aldehydes/ketones in the presence of NH₄OAc. Thus while continuous flow mode of the VFD has been used previously for the preparation of other 2,4,6-triarylpyridines, it is not applicable for the present series of compounds here and those discussed below, and the synthetic findings further highlight the versatility of the VFD in controlling chemical reactions which operate beyond conventional diffusion control. In principle, the confined mode lends itself to robotic control for scaling up for a large number of sequential reactions of small aliquots of a reacting liquid.

The literature suggests that N,N-dimethylamino-containing triarylpyridines are potentially efficient fluorophores, and accordingly we also targeted the synthesis of 2,4,6-triarylpyridines using the three component condensation for 4-(dimethylamino)benzaldehyde 4 with different acetonophenones. Using the method established for the preparation of 3a–e we found that this confined mode method using the VFD was also suitable for the preparation of 6a–e, which were obtained in good yield (Table 2).

**Table 2.** Synthesis of various 2,4,6-triarylpyridines 6a–e in PEG300 using the VFD operating at 7000 rpm and 45° tilt angle at 100 °C for 30 minutes in the confined mode.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>CH₃CN λₑₓ/λₑₛ (nm)</th>
<th>DMSO λₑₓ/λₑₛ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>NO₂</td>
<td>H</td>
<td>66</td>
<td>330/460</td>
<td>+/-</td>
</tr>
<tr>
<td>6b</td>
<td>H</td>
<td>NO₂</td>
<td>59</td>
<td>330/345</td>
<td>340/440</td>
</tr>
<tr>
<td>6c</td>
<td>OCH₃</td>
<td>H</td>
<td>53</td>
<td>330/435</td>
<td>340/440</td>
</tr>
<tr>
<td>6d</td>
<td>CH₃</td>
<td>H</td>
<td>62</td>
<td>340/450</td>
<td>340/460</td>
</tr>
<tr>
<td>6e</td>
<td>NH₂</td>
<td>H</td>
<td>51</td>
<td>330/445</td>
<td>330/465</td>
</tr>
</tbody>
</table>

In principle, the evaluation of the present results suggests that the VFD operates as a novel chemical reactor to prepare diverse functionalized heteroaromatic compounds. Furthermore, the present study highlights the potential of the VFD as a platform for the large-scale production of functionalized analytes. An important feature is the ability to operate beyond conventional diffusion control, which is of significant benefit for the preparation of new intermediates and/or products which may be otherwise inaccessible. In this paper, the VFD was used to explore the potential of the confined mode for the preparation of diverse 2,4,6-triarylpyridines, which is a new concept that may be of broad utility in generating a wide range of new chemical space for the design and synthesis of new functionalized heteroaromatic compounds.
The crystal structure of 6d was also established using single crystal diffraction data, as a representative of the atom-to-atom connectivity, but more importantly to establish the orientation of the planar aromatic rings relative to the central pyridine ring (Figure 1). Indeed the aromatic rings are essentially co-planar, as would be expected for the maximum overlap of electron density from one ring to another, which relates to the electronic properties of the molecules, including fluorescence. The dihedral angles between the peripheral phenyl rings and the central pyridine ring are 7.3(1), 6.4(1), 14.8(1)° for rings 12, 14 and 16.

With the availability of these compounds, we set out to gain a preliminary insight into their fluorescent properties. As shown in Table 1 and Figure 2, the fluorescence spectra of the compounds in series 3 displayed an increase in emission wavelength in the order 3a<3b<3c. The fluorescence intensity in series 3 followed the order 3b<3d<3e<3a<3c in acetonitrile, but compounds 3b, 3c and 3a were quenched significantly in DMSO. This data strongly suggests that strong electron donating groups in the parent aldehyde are a key factor to increasing the fluorescence intensity in this class of compounds. For the 2,4,6-triarylpyridine derivatives 6a-e the fluorescence intensity decreases in the order 6d<6c<6e<6a<6b in acetonitrile. In DMSO the fluorescent intensity of 6c was enhanced over acetonitrile whilst 6d and 6e were mildly quenched. This data establishes that the fluorescent intensity is dependent on the parent acetonophene group not bearing strong electron withdrawing groups. Also, the 3D fluorescent plots (See supplementary information) indicate that the majority of the compounds synthesised show two excitation peaks resulting in one emission peak. As first indicated by a paper focused on similar compounds, this probably arises from a π-π* and a n-π* electronic transition.

![Figure 2](image-url)

**Figure 2.** (a) Fluorescence spectra for 3a-e in acetonitrile. (b) Fluorescence spectra for 3a-e in DMSO. (c) Fluorescence spectra for 6a-e in acetonitrile. (d) Fluorescence spectra for 6a-e in DMSO.

**Conclusions**

We have developed a convenient, relatively low cost, one pot preparation of polysubstituted and 2,4,6-triaryl pyridines from readily available starting materials using the confined mode of operation of the VFD. This is more versatile than using the continuous flow mode of the device, where the additional shear associated with the viscous drag as the liquid whirls along the tube is insufficient in further accelerating the reactions to overcome the consequential short residence time in the VFD. The photo-physical properties displayed by these compounds demonstrate that they may be promising candidates for the development of putative fluorescent probes.

The green chemistry metrics of the syntheses relative to earlier studies include, (i) efficient energy usage, as a constant safe and ‘soft’ form of energy, in contrast to mechanoenergy used in driving solventless reactions and high energy microwave processing, (ii) establishing a one pot reaction of the tri-substituted pyridines in PEG which is a benign reaction medium, in avoiding the use of toxic volatile solvents, (iii) avoiding the use of concentrated basic solutions as an inherently safer process, (iv) circumventing the formation of intermediate chalcone en route to the 1,5-diketone for conversion to the corresponding pyridine, and competing formation of cyclohexyl ring systems, in minimising the generation of waste, and (v) the thin film ensures that there is rapid heat dissipation for highly exothermic and otherwise waste generating reactions which have been noted in the formation of such pyridines. Moreover, the present findings further highlight the application of the VFD, with the ability to scale up under continuous flow, or scale down in confined mode, yet with dynamic thin films present for controlling reactions beyond conventional batch processing.

**Acknowledgments**

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**Notes and references**

*Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 972818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk)."†Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/*

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Fluorescent polysubstituted pyridines are readily accessible as a single process using a thin film vortex fluidic device, with the compounds obtained in good yield following simple purification procedures.