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Thin film microfluidic synthesis of fluorescent highly substituted pyridines†

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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 fluorescence intensity and excitation/emission parameters are 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] Triarylpyridines are structurally related to the symmetrical triaryl-thiopyrylium, triarylselenopyrylium, and triaryl-telluropyrylium 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 Kröhnke 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 (NH_4OAc). 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 $H_{14}[NaP_5W_{30}O_{110}]$,[19] bismuth triflate[20] and a Brønsted 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 thin films, which can allow for the 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 silica[30] 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 synthesis of amino functionalized 2,4,6-triarylpyridines, where formation of the thermodynamically favoured Schiff base adduct of the chalcone is avoided.[24] For the latter, the same outcome is possible when using a related spinning

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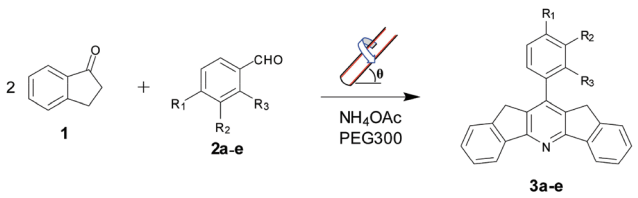
disc microfluidic platform, albeit due to the limited residence time of the liquid on the surface of the rapidly rotating disc as a strictly continuous flow process, several passes are required for a similar outcome relative to using the VFD.[35]

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 NH_4OAc, also in the continuous flow mode.[24] We have now expanded these strategies through a study involving the three component condensation involving 1-indanone **1** as the ketone with various aldehydes **2a–e**. This gains access to poly-substituted pyridines **3a–e** 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.



In a typical procedure for the synthesis of **3(a–e)**, 1-indanone **1** (1 mmol), the aldehyde **2a–e** (0.5 mmol) and NH_4OAc (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 NH_4OAc. Thus while continuous flow mode of the VFD has been used previously for the preparation of other 2,4,6-triarylpyridines,[24] it is not applicable for the present series of compounds here and those discussed below, and the synthetic

Table 1 Synthesis of various polysubstituted pyridines **3a–e** in PEG300 using the VFD operating at 7000 rpm and 45° tilt angle at 100 °C for 30 minutes in the confined mode

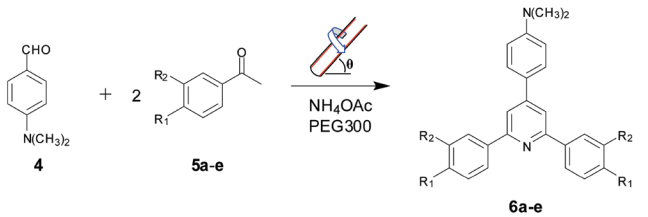
					Fluorescence	
Entry	R_1	R_2	R_3	Yield (%)	CH_3CN $\lambda_{exc}/\lambda_{em}$ (nm)	DMSO $\lambda_{exc}/\lambda_{em}$ (nm)
3a	OH	H	H	67	345/365	340/370
3b	H	$-C_4H_4-$		65	240/380	350/385
3c	OH	OCH_3	H	62	340/365	340/365
3d	OCH_3	OH	H	68	340/365	340/365
3e	$(CH_3)_2N$	H	H	60	340/475	340/480

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

				Fluorescence	
Entry	R_1	R_2	Yield (%)	CH_3CN $\lambda_{exc}/\lambda_{em}$ (nm)	DMSO $\lambda_{exc}/\lambda_{em}$ (nm)
6a	NO_2	H	66	330/460	—
6b	H	NO_2	59	—	—
6c	OCH_3	H	53	330/435	340/440
6d	CH_3	H	62	340/450	340/460
6e	NH_2	H	51	330/445	330/465

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,[2] and accordingly we also targeted the synthesis of 2,4,6-triarylpyridines using the three component condensation for 4-(dimethylamino)benzaldehyde **4** with different acetophenones **5a–e**. 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).



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 (Fig. 1). Indeed the aromatic rings are essentially co-planar, as would be expected for the maximum overlap of elec-

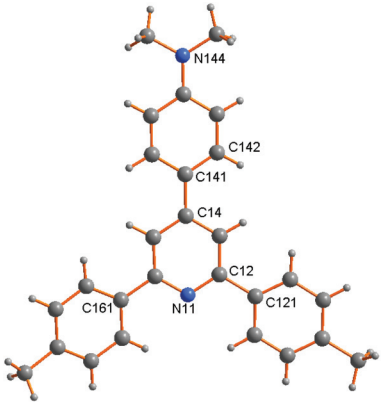


Fig. 1 Crystal structure of **6d** projected onto the plane of the central ring.‡

tron 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 Fig. 2, the fluorescence spectra of the compounds in series **3** displayed an increase in emission wavelength in the order **3a** < **3b** < **3e**. The fluorescence intensity in series **3** followed the order **3b** < **3d** < **3c** < **3a** < **3e** 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 acetophenone group not bearing strong electron withdrawing groups. Also, the 3D fluorescent plots (see ESI†) 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[15] this probably arises from a π–π* and a n–π* electronic transition.

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,[24] in contrast to mechanoenergy used in driving solventless reactions and high energy microwave processing,[15] (ii) establishing a one pot reaction of the tri-substituted pyridines in PEG which is a benign reaction medium,[16] 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

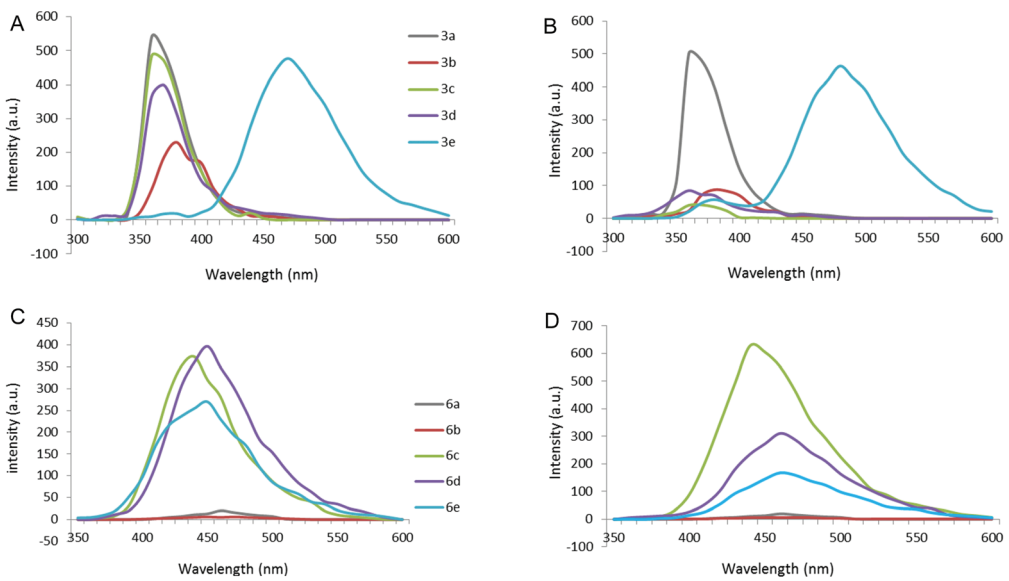


Fig. 2 (a) Fluorescence spectra for **3a–e** in acetonitrile. (b) Fluorescence spectra for **3a–e** in DMSO. (c) Fluorescence spectra for **6a–e** in acetonitrile. (d) Fluorescence spectra for **6a–e** in DMSO.

intermediate chalcone *en route* to the 1,5-diketone for conversion to the corresponding pyridine, and competing formation of cyclohexyl ring systems,[16] 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.[17] 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.

Acknowledgements

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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.

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