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# Indoleninyl-substituted pyrimido[1,2-*b*]indazoles via a facile condensation reaction†

 Abdul Qaiyum Ramle,<sup>\*a</sup> Chee Chin Fei,<sup>b</sup> Edward R. T. Tiekink<sup>id</sup><sup>c</sup>  
 and Wan Jeffrey Basirun<sup>id</sup><sup>\*a</sup>

A new series of pyrimido[1,2-*b*]indazoles bearing indolenine moieties was synthesized through a simple condensation reaction with up to 94% yield. The present method features the versatile formation of a pyrimidine ring with a broad range of substrates, great functional group compatibility and facile synthetic operation. The work offers opportunities in drug development as well as in materials science.

## Introduction

Pyrimido[1,2-*b*]indazoles are a class of fused nitrogen-containing tricyclic skeletons that have received significant attention as pharmacologically important molecules, *e.g.* as anti-cancer agents,<sup>1</sup> monoamine oxidase (MAO) inhibitors,<sup>2</sup> PDE10A inhibitors,<sup>3</sup> and for the treatment of hepatitis C virus (HCV) infection.<sup>4</sup> Despite their high bioactive potential, the preparation of pyrimido[1,2-*b*]indazoles is rarely documented due to the limited synthetic options and strategies. Hence, the development of new drugs with diverse substituted pyrimido[1,2-*b*]indazoles with feasible methods for their synthesis remains challenging.

A literature survey revealed that 3-amino-1*H*-indazole is an essential component for the preparation of pyrimido[1,2-*b*]indazole scaffolds. From a synthetic point of view, the condensation reaction of 3-amino-1*H*-indazole with various types of carbonyl compounds is the most frequent approach to access the structural motif.<sup>5</sup> The addition of metal catalysts such as CuSO<sub>4</sub>·5H<sub>2</sub>O, Al(OTf)<sub>3</sub>, and Cu(OAc)<sub>2</sub> also enhances the transformation of such products.<sup>6</sup> However, this method is only feasible with specific functional groups, hence there is a limitation in the synthesis of structurally diverse derivatives.

Since several years ago, some efforts have resulted in the facile synthesis of pyrimido[1,2-*b*]indazoles. In 2017, Li *et al.* performed a one-pot, three-component reaction utilising mixtures of aromatic aldehydes, 3-amino-1*H*-

indazoles and 3-oxopropanenitriles (Scheme 1a).<sup>7</sup> Later, a cost-effective method by Balwe *et al.* resulted in the preparation of four compounds of (2-hydroxyphenyl)(pyrimido[1,2-*b*]indazol-3-yl)methanones at room temperature with excellent yields (Scheme 1b).<sup>4</sup> Very recently, Jismy *et al.* investigated the treatment of 3-amino-1*H*-indazoles with 2-bromomalonaldehyde in ethanol in the presence of catalytic acetic acid which afforded the products in high yields (Scheme 1c).<sup>2</sup>

With growing interest in this area, the present work reports for the first time a new series of pyrimido[1,2-*b*]indazoles featuring indolenine scaffolds. The compounds were prepared *via* a simple condensation reaction between the substituted diformyl indolenines and 3-amino-1*H*-indazoles catalysed by acetic acid. The results of this investigation are described herein.

## Results and discussions

The starting materials, **1a–e** were prepared according to previous methods.<sup>8</sup> To begin the investigation, compounds **1a** and **2a** were selected as the model substrates. As tabulated in Table 1, preliminary results showed that the condensation reaction between **1a** and **2a** delivered the target product in 44% yield (entry 1). Treatment with a small amount of acetic acid and prolonged stirring at room temperature resulted in an 18% yield (entry 2). Further increase of the reaction temperature to 78 °C significantly improved the reaction efficiency to 61% yield (entry 3). On the other hand, the addition of a small amount of 37% hydrochloric acid catalyst to the reaction media decreased the product yield to only 12% (entry 4). However, the use of H<sub>2</sub>SO<sub>4</sub> catalyst failed to yield the target product **3a** (entry 5). Remarkably, increasing the amount of acetic acid catalyst afforded **3a** in 68% yield (entry 6). It was observed that replacing ethanol with acetonitrile, dioxane or methanol solvents decreased the reaction efficiency and gave poor yields (entries 7–9).

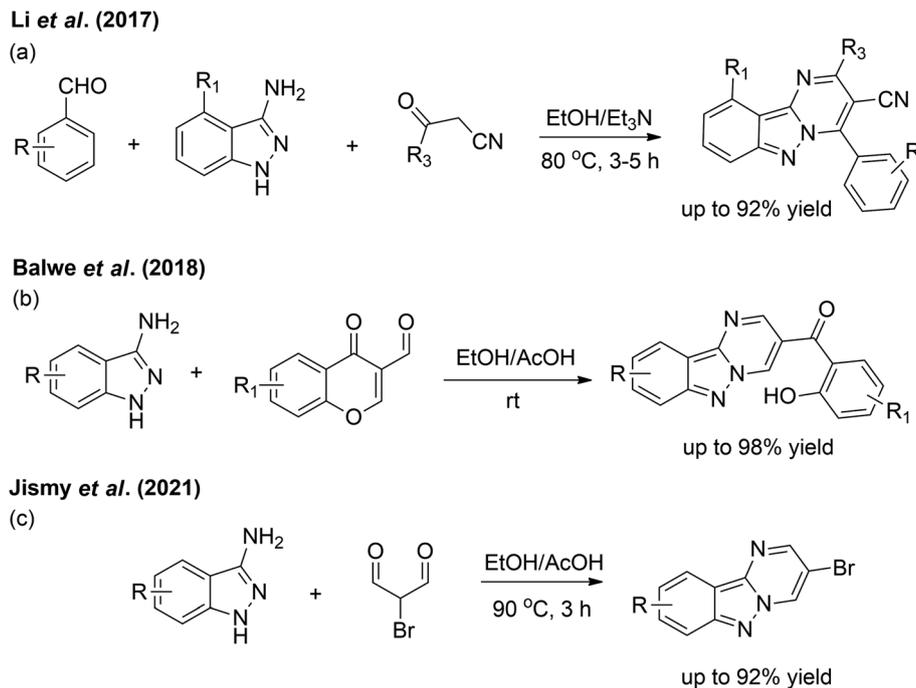
<sup>a</sup>Department of Chemistry, University of Malaya, Kuala Lumpur, 50603, Malaysia. E-mail: qaiyum@um.edu.my; jeff@um.edu.my

<sup>b</sup>Nanotechnology and Catalysis Research Centre, University of Malaya, Kuala Lumpur, 50603, Malaysia

<sup>c</sup>Research Centre for Crystalline Materials, School of Science and Technology, Sunway University, Bandar Sunway, Selangor Darul Ehsan, 47500, Malaysia

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Scheme 1 Efficient methods for the synthesis of substituted pyrimido[1,2-*b*]indazoles.

The substrate scope of **1a–e** and **2a–d** were investigated in optimised reaction conditions. As illustrated in Scheme 2, the reactions between **1a–e** and **2a** afforded the products **3a–e** in reasonable yields (47–68%). Furthermore, the presence of a bromo group in substrate **2b** was also compatible under this synthetic protocol, affording the desired products **3f–j** in good yields (67–78%). It is interesting to note that the presence of a methoxy group in substrate **2c** was also effective under typical conditions to yield the desired products **3k–o** in moderate to high yields (61–94%). Substrate **2d**, bearing a strong electron-withdrawing trifluoromethyl substituent, also reacted well with **1a–e** to furnish the corresponding products **3p–t** in good yields (50–79%). These results demonstrated that these facile syntheses were tolerable to various substituents regardless of their electronic nature, whether on the indolenine and indazole rings.

Table 1 Screening the reaction conditions for the preparation of **3a**<sup>a</sup>

Entry	Solvent/acid	Time (h)	Temperature (°C)	Yield (%)
1	EtOH	5	78	44
2	EtOH/AcOH (99 : 1)	72	25	18
3	EtOH/AcOH (99 : 1)	5	78	61
4	EtOH/37% HCl (99 : 1)	5	78	12
5	EtOH/H <sub>2</sub> SO <sub>4</sub> (99 : 1)	5	78	—
6	EtOH/AcOH (4 : 1)	5	78	68
7	MeCN/AcOH (4 : 1)	5	82	5
8	Dioxane/AcOH (4 : 1)	5	101	16
9	MeOH/AcOH (4 : 1)	5	65	5

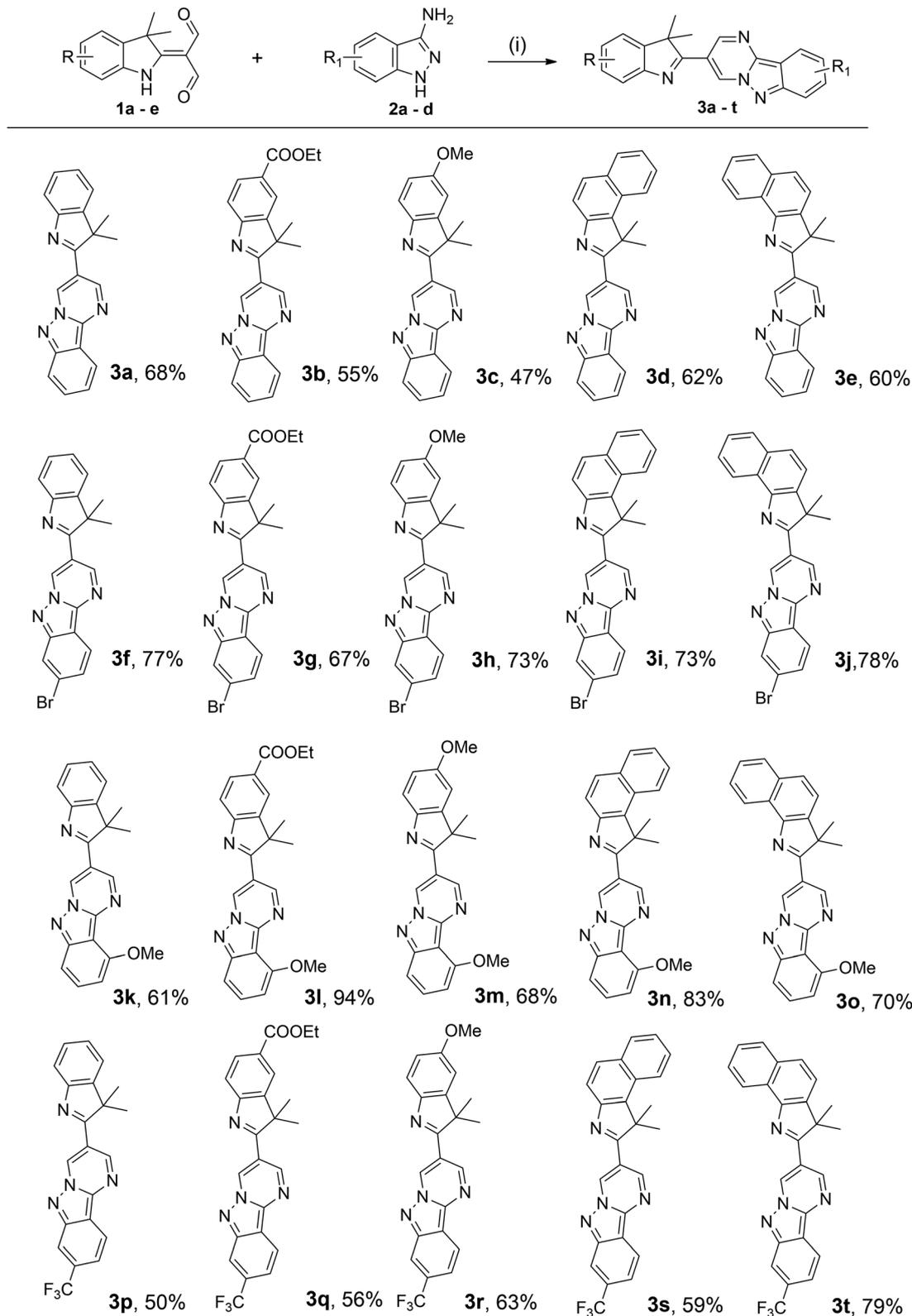
<sup>a</sup> Reaction conditions: **1a** (1 equiv.), **2a** (1.1 equiv.) in 5.0 mL of solvent/acid.

The <sup>1</sup>H NMR spectra reveal two sets of doublets ( $J = 1.2$ – $2.4$  Hz) between  $\delta$  9.50–9.94 ppm which correspond to the two olefinic protons of the pyrimidine ring. The six methyl protons appear as singlets in the range of  $\delta$  1.64–1.96 ppm. The HRMS of the compounds show that the pseudo-molecular ions are in good agreement with the theoretical values.

The representative molecular structure, namely **3a**, was elucidated by X-ray crystallography. The structure crystallises in the monoclinic space group  $P2_1/m$  with half a molecule comprising the crystallographic asymmetric unit. With the exception of the methyl substituents, the molecule lies on a crystallographic mirror plane, as illustrated in Fig. 1. The X-ray analysis indicates that the heteroatoms of the five-membered rings are *syn*. There is substantial delocalisation of the  $\pi$ -electron density in the pyrimido[1,2-*b*]indazole ring. Thus, there is evidence for the lengthening of the formally double bond lengths of C19–N4 [1.373(3) Å], C12–C14 [1.428(4) Å], C15–C16 [1.365(5) Å] and C17–C18 [1.356(4) Å]. Furthermore, the C11–N2 [1.319(4) Å] and C12–N2 [1.312(4) Å] bonds are experimentally equivalent to the pair of C13–N3 [1.364(4) Å] and C10–C13 [1.359(4) Å] bonds; the N3–N4 bond length is 1.341(3) Å. The details of the molecular packing are given in the ESI (Fig. S2 and S3<sup>†</sup>).

A plausible mechanism for the reaction is proposed in Scheme 3. The first step involves the formation of intermediate **I** through the mono-condensation reaction between derivatives **1** and **2**. The protonation at the aldehyde-oxygen atom produces intermediate **II**. Next, the donation of a lone-pair of electrons from the pyrazole–nitrogen atom to the carbocation centre generates a fused pyrimidine ring of intermediate **III**. The deprotonation of the pyrazole ring gives rise to intermediate **IV**. The protonation of





Scheme 2 Substrate scope for the synthesis of 3. Reaction conditions: (i) 1a–e (1.0 equiv.) and 2a–d (1.1 equiv.) in ethanol/acetic acid (v/v = 4 : 1) at 78 °C for 5 h. Isolated yield.

the hydroxyl group produces intermediate **V**. The removal of a water molecule gives intermediate **VI**. Finally, the deprotonation of the indole generates the corresponding product **3**.

The UV-Vis absorption spectra of **3a** in chloroform and **3d** in other solvents are shown in Fig. 2. Compound **3a** shows an intense absorption band at 328 nm, which is assigned to the  $\pi$ -



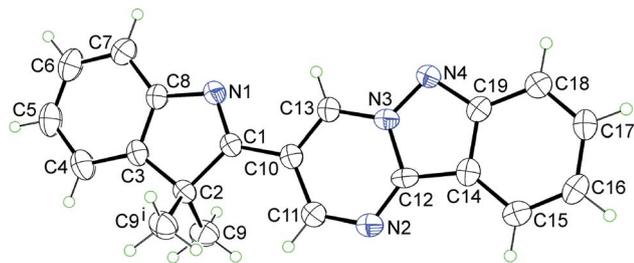


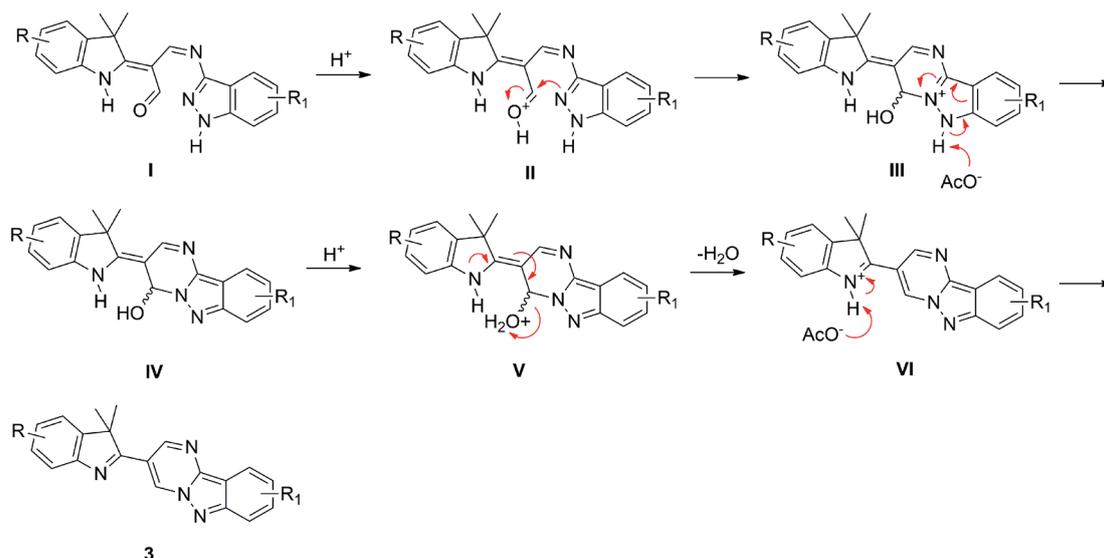
Fig. 1 Molecular structure of **3a** showing atom labelling scheme and displacement ellipsoids at the 35% probability level. The molecule, save the methyl groups, lies on a mirror plane; symmetry operation  $i: x, \frac{1}{2} - y, z$ .

$\pi^*$  transition. The optical band gap of the compound is 3.24 eV, which is determined from the absorption edge of the spectrum.<sup>9</sup>

In comparison, the spectrum **3d** in chloroform displays a bathochromic shift to 350 nm due to the extension of the  $\pi$ -conjugation system. This results in the reduction of the optical band gap of **3d** by 0.36 eV. Furthermore, the absorption spectra of **3d** in other solvents such as acetic acid, dimethylformamide, methanol and tetrahydrofuran media are not significantly solvent-dependent, implying that the effect of solvent polarity is indistinguishable in the ground state. Details of the spectroscopic parameters for both compounds are summarized in ESI (Table S2†).

## Conclusions

In summary, a new series of indoleninyl-substituted pyrimido [1,2-*b*]indazoles was successfully synthesised in good to high yields. The main advantages of this synthetic method are the



Scheme 3 Plausible mechanism for the formation of **3**.

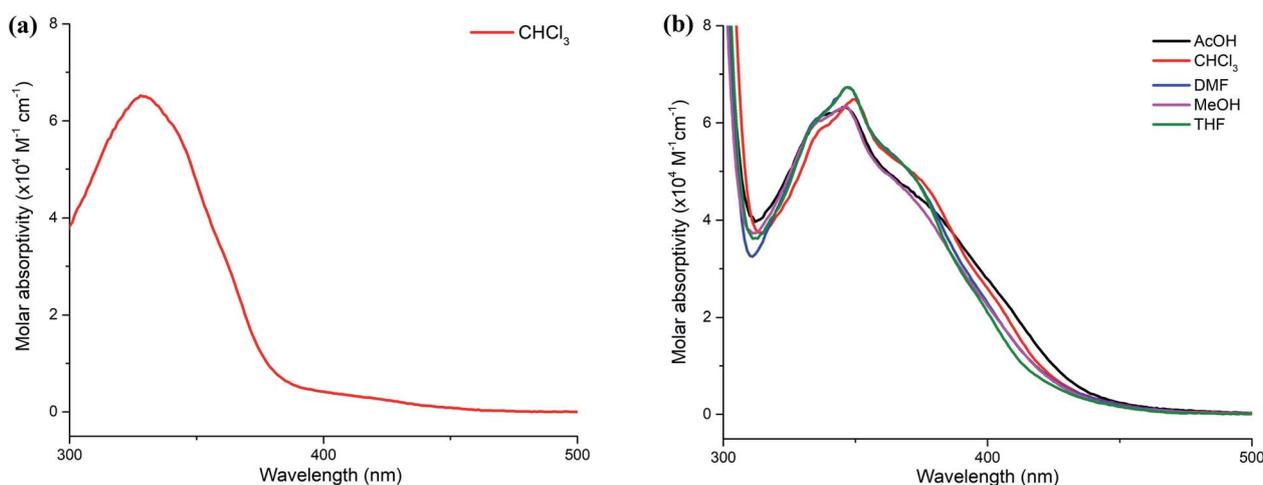


Fig. 2 UV-Vis absorption spectra of (a) **3a** in chloroform and (b) **3d** in various solvents at a concentration of 14  $\mu$ M.



simple operation, free from chromatographic purification and the ability to diversify the substituents on both the indolenine and indazole rings for the formation of the pyrimido[1,2-*b*]indazole scaffolds. The nitrogen-rich products are potent candidates for drug screening and biological studies. Further efforts to expand the synthetic scope of fused nitrogen tricyclic heterocycles are currently under investigation.

## Conflicts of interest

The authors declare no conflict of interest.

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