RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 24647

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

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Received 6th June 2021
Accepted 5th July 2021

DOI: 10.1039/d1ra04372b

rsc.li/rsc-advances

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,[1] monoamine oxidase (MAO) inhibitors,[2] PDE10A inhibitors,[3] and for the treatment of hepatitis C virus (HCV) infection.[4] 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.[5] The addition of metal catalysts such as $CuSO_4 \cdot 5H_2O$, $Al(OTf)_3$, and $Cu(OAc)_2$ also enhances the transformation of such products.[6] 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).[7] 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).[4] 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).[2]

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.[8] 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_2SO_4 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).

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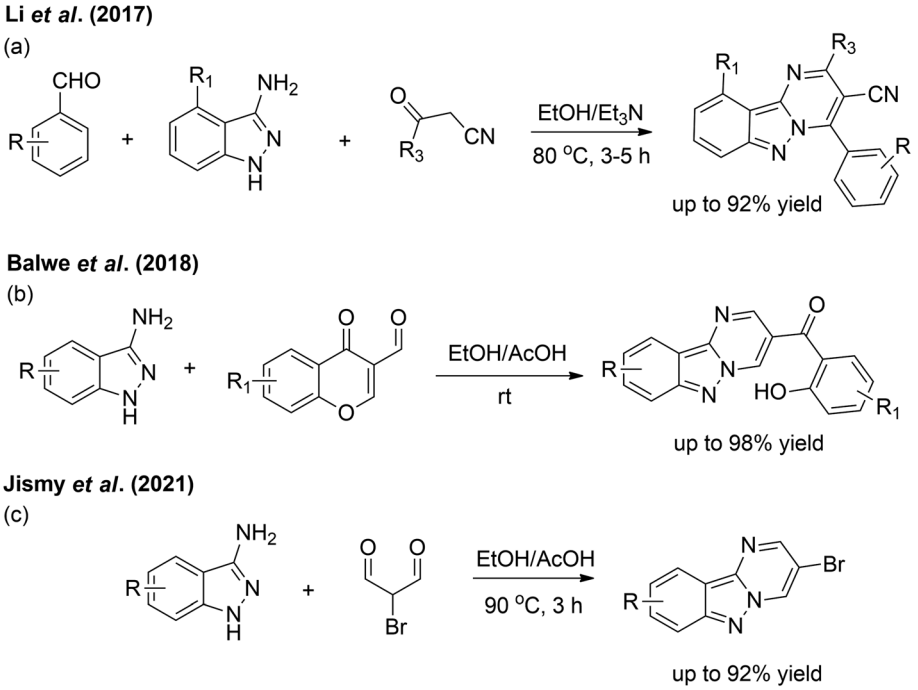
† Electronic supplementary information (ESI) available. CCDC 2082645. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra04372b



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**[a]

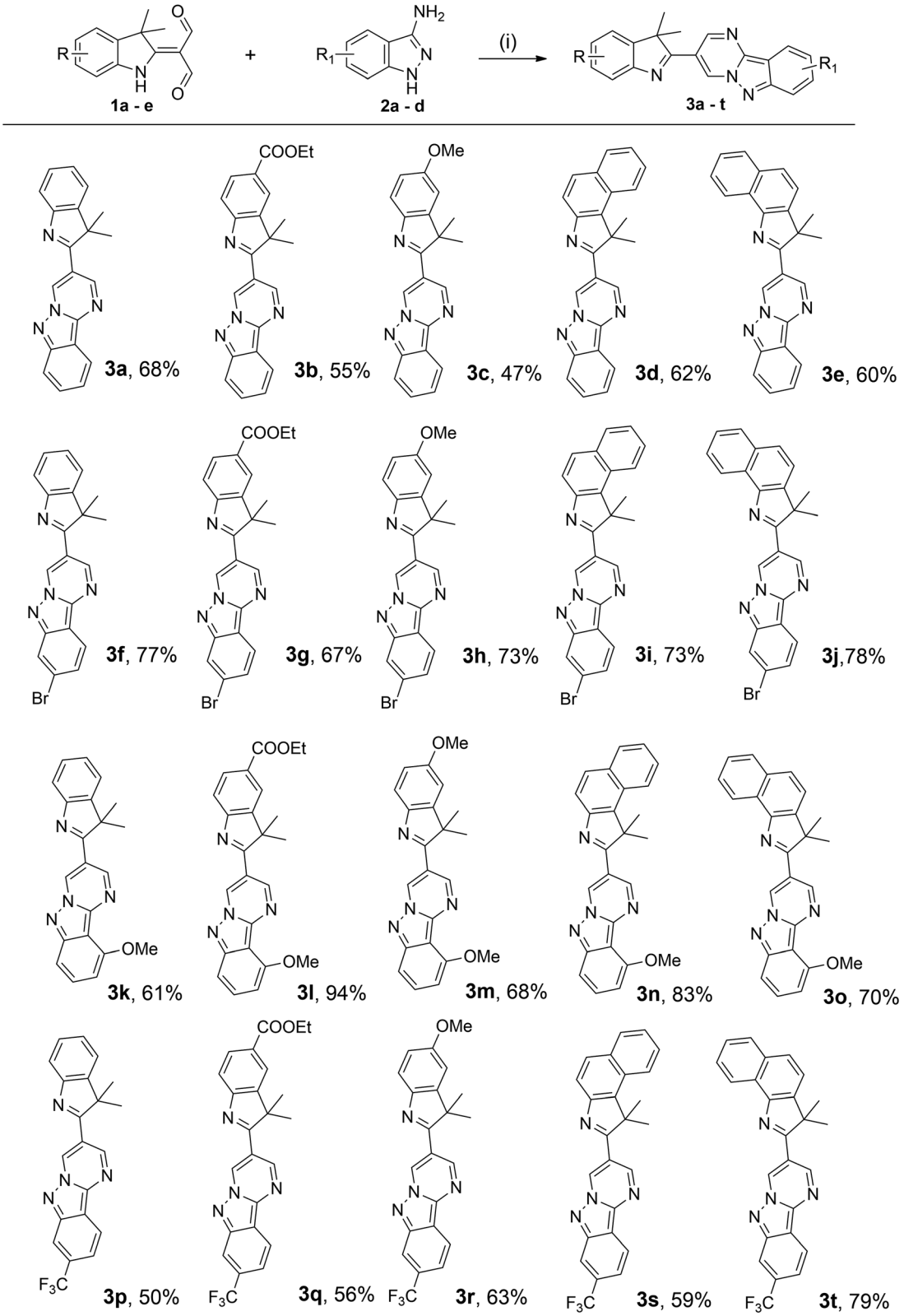
Entry	Solvent/acid	Time (h)	Temperature (°C)	Yield (%)
1	EtOH	5	78	44
2	EtOH/AcOH (99 : 1)	72	25	18
3	EtOH/AcOH (99 : 1)	5	78	61
4	EtOH/37% HCl (99 : 1)	5	78	12
5	EtOH/H_2SO_4 (99 : 1)	5	78	—
6	EtOH/AcOH (4 : 1)	5	78	68
7	MeCN/AcOH (4 : 1)	5	82	5
8	Dioxane/AcOH (4 : 1)	5	101	16
9	MeOH/AcOH (4 : 1)	5	65	5

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

The ^{1}H NMR spectra reveal two sets of doublets (J = 1.2–2.4 Hz) between δ 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 δ 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 π-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†).

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 π–

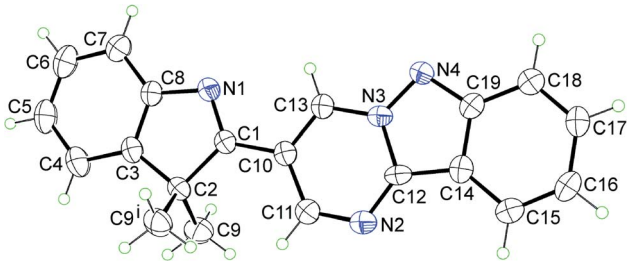


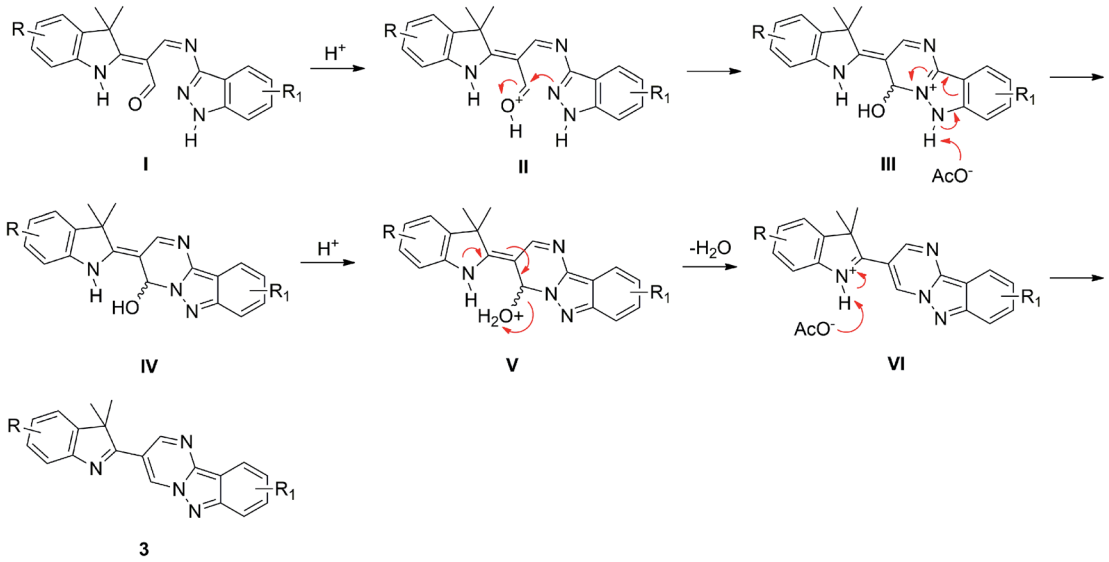
Fig. 1 Molecular structure of **3a** showing atom labelling scheme and displacement ellipsoids at the 35% probability level. The molecule, save the methyl groups, lies on a mirror plane; symmetry operation *i*: $x, 1\frac{1}{2} - y, z$.

π* transition. The optical band gap of the compound is 3.24 eV, which is determined from the absorption edge of the spectrum.[9]

In comparison, the spectrum **3d** in chloroform displays a bathochromic shift to 350 nm due to the extension of the π-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**.

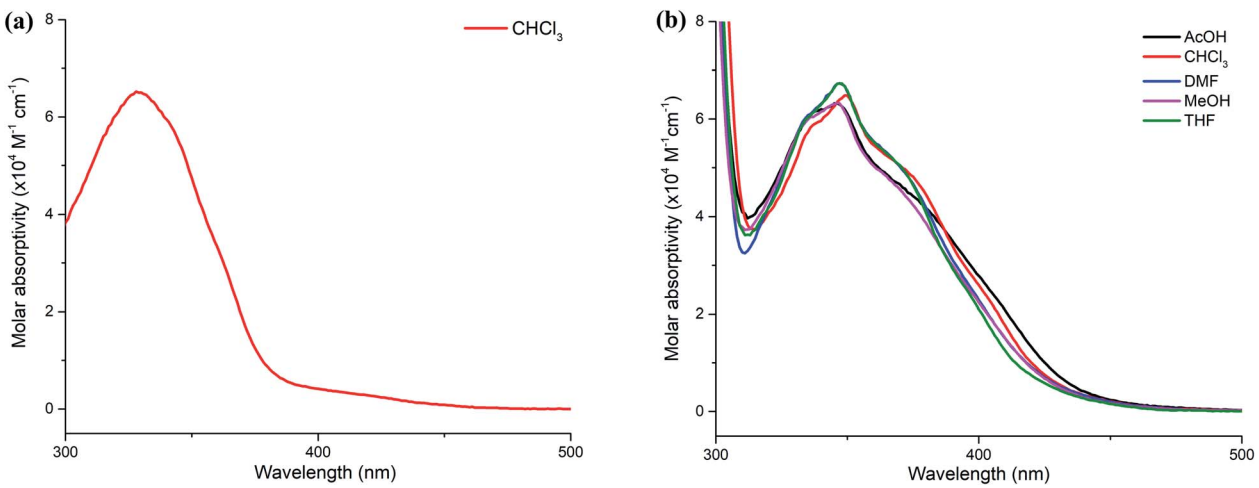


Fig. 2 UV-Vis absorption spectra of (a) **3a** in chloroform and (b) **3d** in various solvents at a concentration of 14 μM.

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.

Acknowledgements

All authors wish to thank the University of Malaya (ST027-2019) and Sunway University Sdn. Bhd. (GRTIN-IRG-01-2021) for their financial support in this work.

References

1 T. Yakaiah, B. P. V. Lingaiah, B. Narsaiah, B. Shireesha, B. Ashok Kumar, S. Gururaj, T. Parthasarathy and B. Sridhar, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3445.
2 B. Jismy, A. El Qami, A. Pišlar, R. Frlan, J. Kos, S. Gobec, D. Knez and M. Abarbri, *Eur. J. Med. Chem.*, 2021, **209**, 112911.
3 A. Chino, R. Seo, Y. Amano, I. Namatame, W. Hamaguchi, K. Honbou, T. Mihara, M. Yamazaki, M. Tomishima and N. Masuda, *Chem. Pharm. Bull.*, 2018, **66**, 286.
4 S. G. Balwe and Y. T. Jeong, *Org. Biomol. Chem.*, 2018, **16**, 1287.
5 (*a*) S. Annareddygari, V. R. Kasireddy and J. Reddy, *J. Heterocycl. Chem.*, 2019, **56**, 3267; (*b*) W. Kong, Y. Zhou and Q. Song, *Adv. Synth. Catal.*, 2018, **360**, 1943; (*c*) J. Palaniraja, S. Mohana Roopan, G. Mokesh Rayalu, N. Abdullah Al-Dhabi and M. Valan Arasu, *Molecules*, 2016, **21**, 1571; (*d*) Y. M. Volovenko and V. A. Chuiguk, *Chem. Heterocycl. Compd.*, 1974, **10**, 859; (*e*) Q. Gao, X. Han, P. Tong, Z. Zhang, H. Shen, Y. Guo and S. Bai, *Org. Lett.*, 2019, **21**, 6074; (*f*) A. M. Jadhav, S. G. Balwe, K. T. Lim and Y. T. Jeong, *Tetrahedron*, 2017, **73**, 2806; (*g*) S. G. Balwe, V. V. Shinde, A. A. Rokade, S. S. Park and Y. T. Jeong, *Catal. Commun.*, 2017, **99**, 121.
6 (*a*) J. Palaniraja, S. M. Roopan and G. M. Rayalu, *RSC Adv.*, 2016, **6**, 24610; (*b*) Y. Gu, F. Wu and J. Yang, *Adv. Synth. Catal.*, 2018, **360**, 2727; (*c*) Y. Zhou, Y. Lou, Y. Wang and Q. Song, *Org. Chem. Front.*, 2019, **6**, 3355.
7 L. Li, H. Xu, L. Dai, J. Xi, L. Gao and L. Rong, *Tetrahedron*, 2017, **73**, 5358.
8 (*a*) A. Rashidi, A. Afghan, M. M. Baradarani and J. A. Joule, *J. Heterocycl. Chem.*, 2009, **46**, 428; (*b*) A. Q. Ramle, H. Khaledi, A. H. Hashim, M. A. Mingsukang, A. K. Mohd Arof, H. M. Ali and W. J. Basirun, *Dyes Pigm.*, 2019, **164**, 112; (*c*) H. A. Rothan, E. Amini, F. L. Faraj, M. Golpich, T. C. Teoh, K. Gholami and R. Yusof, *Sci. Rep.*, 2017, **7**, 45540.
9 A. Q. Ramle, E. R. T. Tiekink, C. C. Fei, N. M. Julkapli and W. J. Basirun, *New J. Chem.*, 2021, **45**, 1221.