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Multi-component synthesis of 3-substituted indoles and their cyclisation to α-carbolines *via* I_2-promoted intramolecular C2 oxidative amination/aromatisation at room temperature†

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Condensation of indoles, aldehydes and pyrazol-5-amine in the presence of ceric ammonium nitrate gives 3-substituted indoles. These then cyclise to α-carbolines at room temperature through I_2-promoted intramolecular C2 amination and aromatisation in open air. A plausible mechanism is proposed based on some controlled experiments.

Indoles are one of the most promising structural motifs widely used in pharmaceuticals and, therefore, this structural moiety is important due to its potential in the creation of a new era of drugs.[1] Many derivatives of indoles are used as antihypertensive,[2] antineoplastic,[2] antibacterial,[3] and antimitotic agents,[2] and hypoglycemic,[4] and protein kinase inhibitors.[5] Due to their significant bioactivities, the synthesis of new indole derivatives has become an interesting topic for pharmaceutical industries. Indoles have high affinity to bind with most of the biological targets and because of this, most of the indole derivatives are found in biologically active natural products.[6] The study of α-carbolines, a class of fused indole alkaloids are lagging behind in comparison with well-known β-carbolines. Few α-carboline alkaloids have been isolated to date (Fig. 1). Grossularine-1 and grossularine-2 are derivatives of α-carbolines having an anti-cytotoxic effect and are isolated from the tunicate *Dendrodoa grossularia*.[7] Compound [C] is a GABA modulator used in the treatment of anxiety.[8] Natural α-carboline mescengricin is used as an inhibitor of L-glutamate excitotoxicity in neurons, isolated from *Streptomyces griseoflavus*.[9] Cryptotackieine isolated from *Cryptolepis sanguinolenta* displays a strong antiplasmodial activity.[10]

Strategies for the development of nucleophilic reactions at C3 and C2 positions of indoles have become an interesting and challenging topic for chemists nowadays. Generally, C3 and C2 positions of indoles give electrophilic reactions. There are some reports in which researchers developed a new methodology to synthesize important indole derivatives by converting the nucleophilic centre of the indole to the electrophilic centre.[11] For instances, Batey and coworkers have reported allylation and crotylation reactions of indoles at the C2-position using allylic trifluoroborate salts by an electrophilic addition reaction.[11b] Nishina and coworkers have reported the C2 site-selective intermolecular nucleophilic addition of an electron-rich aromatic compound using $BF_3{\cdot}OEt_2$ in $(CF_3)_2CHOH$.[11a]

In recent years, different methodologies for the formation of C–O,[12] C–S,[13] and C–N[14] bonds at the C2 position of indoles have been applied, which leads to complex molecular structures. We are also interested in the polarity inversion of the C2 carbon of indoles especially through intramolecular cyclisation.[12a] There are a number of reports of intermolecular C–N bond formation at the C2 position of indoles through this process.[14a–g] But intramolecular C–N bond formation at the C2

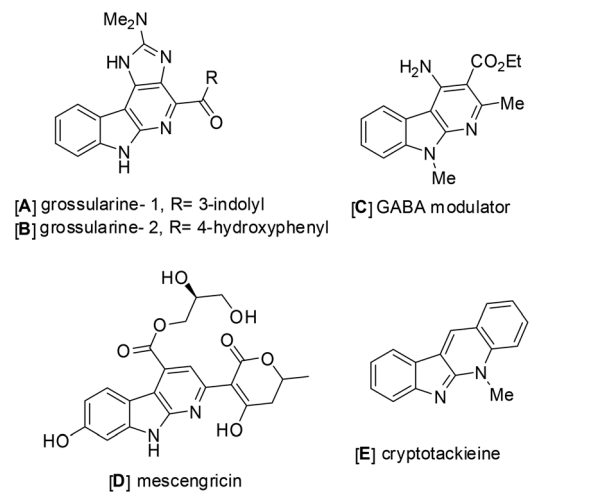

Fig. 1 Few bioactive α-carbolines.

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position of indoles is not as much reported.[14h–j] Recently, Yao *et al.* reported the formation of the C–N bond at the C2 position of indoles using Pd(II) as a catalyst and a stoichiometric amount of silver salt as an oxidant, which leads to the formation of indolo[1,2-*a*]quinazolinones.[14j] Sekar and coworkers recently disclosed a couple of reports in which they also synthesized indolo[1,2-*a*]-quinazolinones and a variety of fused indole derivatives through intramolecular C2 amidation of indoles.[14h–i] Here we have developed an efficient synthetic method to obtain α-carboline derivatives *via* intramolecular C2 amination of 3-substituted indole, which is formed from the 3-component reaction at room temperature (Scheme 1).

At the beginning, we planned to synthesize **4** by the 3-component reaction of indole **1a**, benzaldehyde **2a** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3a**. The reaction was treated under different conditions by taking 1 equivalent of each starting material. The results are summarized in Table 1. In some cases we observed complete formation of bis(indolyl)methanes (BIMs), *e.g.*, $InCl_3$ and $FeCl_3{\cdot}6H_2O$ gave 47% and 43% of BIM, respectively, with no formation of **4a** (entries 2 and 3, Table 1). After screening different catalysts and solvents, we found maximum yield of **4a** (90%) in 8 h when 10 mol% of ceric ammonium nitrate (CAN) was used as a catalyst at room temperature under neat conditions (entry 9, Table 1). A trace amount of BIM was also formed as a side product. Under heating, the reaction afforded less yield of **4a** while increasing the formation of BIM (entry 11, Table 1).

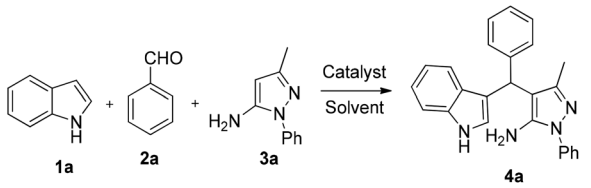
Since we were interested in synthesizing **5** through C2 cyclisation of the indole ring of **4**, we isolated **4a** and attempted to cyclise it into **5a**. We checked the feasibility of the reaction with different catalysts and solvents. Initially we found that molecular I_2 (0.1 eq.) in the presence of TBHP (1.5 eq.) in DCE at room temperature produced good yield of the cyclised product (entry 4, Table 2). We also used different catalysts in the presence of TBHP. However, none of these were as good as I_2. Under reflux conditions the reaction gave poor yield after 1 h, although complete disappearance of **4a** was noticed (entry 9, Table 2). When the reaction was performed in the absence of TBHP using only I_2 (1 eq.) in DCE, we observed that the reaction produced an even better yield of **5a** than the yield obtained using TBHP/I_2 (entry 4 *vs.* 14, Table 2). In both the cases we recovered a minute quantity of unreacted **4a**. To improve the yield further, we used more amount of I_2 (2 eq.) or increased the reaction time, but failed to obtain better yield (entries 15 & 16, Table 2).

We made an attempt to synthesize the cyclised product **5a** through a one-pot process by mixing all the reactants (**1a**, **2a** and **3a**) and adding CAN (10 mol%) and I_2 (1 eq.) in DCE solvent. But the reaction gave only **4a** and no trace of **5a** was observed. We presumed that the reason for no formation of **5** in a one-pot process may be the presence of CAN which interferes in the cyclisation step. Therefore, we performed a reaction to synthesize **4a** first and removed the catalyst CAN after completion of the reaction by washing with water. Crude **4a** was then treated with I_2 in DCE to obtain the cyclised product **5a**. In this process we were able to isolate good yield of **5a** and therefore, we treated it as our optimized reaction condition to synthesize **5** (Scheme 2).

We next screened the substrate scope of the reaction. We noticed that electron-withdrawing groups such as –F, $–NO_2$, –Br and –Cl on the aldehyde ring increased the product yield, whereas electron-donating groups such as $–CH_3$ and $–OCH_3$ decreased the yield of **5**. We obtained a similar yield in *o*-, *m*-, and *p*-substituted aromatic aldehydes (*e.g.*, **5e–5g**, Scheme 2). Heterocyclic aromatic aldehydes also produced good yield (**5k**, Scheme 2).

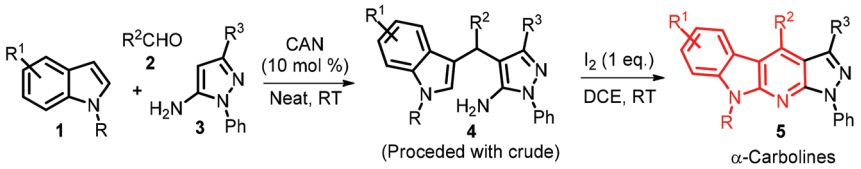
On the other hand, substitution in the indole ring decreased the yield of the product (**5u**, Scheme 2). With

Table 1 Optimization of the synthesis of **4** [a]



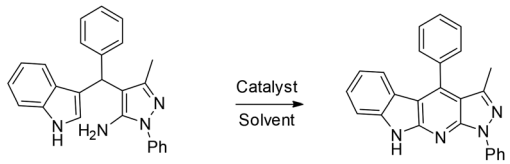
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield of **4a** (%)
1	—	—	18	n.r.[b]
2	$InCl_3$ (10)	CH_3CN	12	n.d.[c]
3	$FeCl_3{\cdot}6H_2O$ (10)	CH_3CN	12	n.d.[c]
4	LiCl (10)	CH_3CN	12	n.r.
5	CAN (10)	CH_3CN	8	80
6	CAN (10)	DCE	8	80
7	CAN (10)	Toluene	12	68
8	CAN(10)	DMF	12	55
9	CAN(10)	—	8	90
10	CAN (20)	—	8	90
11	CAN(10)	—	1	72[d]
12	$(CF_3SO_3)_3Yb$	—	8	60

[a] Unless otherwise mentioned, all reactions were performed using **1a** (1 mmol, 117 mg), **2a** (1 mmol, 106 mg) and **3a** (1 mmol, 173 mg) at room temperature. Products were purified by column chromatography using silica gel (100–200 mesh) and yields are for the isolated products. [b] n.r.: no reaction. [c] n.d.: The desired product **4a** was not detected but obtained only BIM. [d] Reaction was carried out at 80 °C.



Scheme 1 Synthesis of α-carbolines.

Table 2 Optimization of the synthesis of 5 [a]

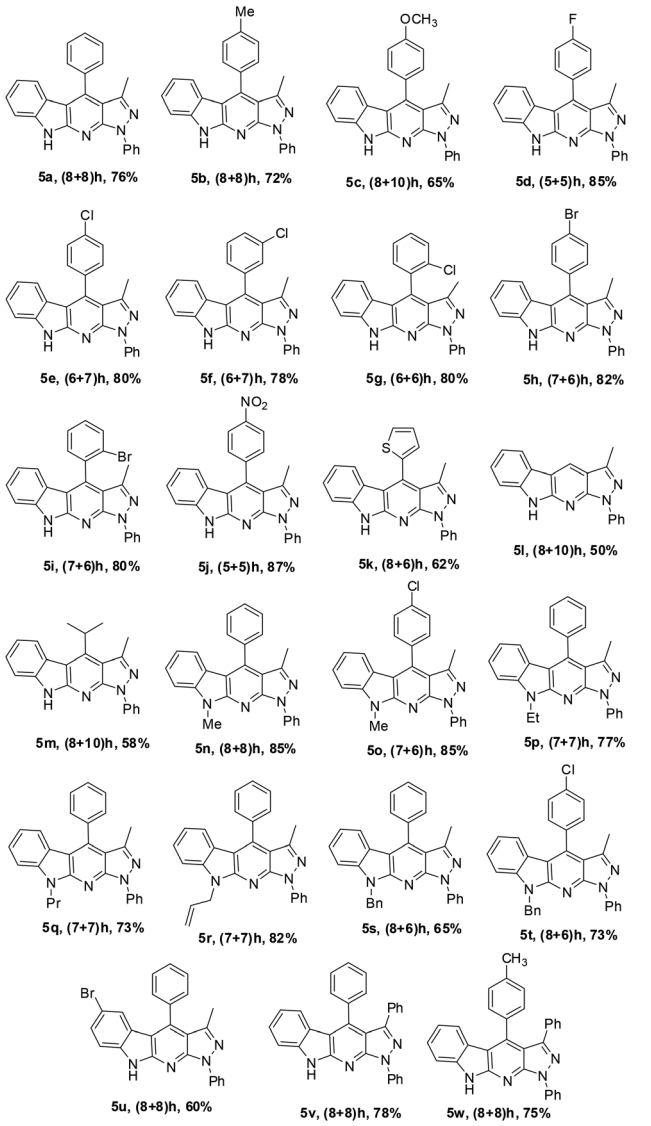


Entry	Catalyst (equiv.)	Oxidant (equiv.)	Solvent	Time [h]	Yield [%]
1	I_2 (0.1)	TBHP (1.5)	DCM	10	36
2	I_2 (0.1)	TBHP (1.5)	$CHCl_3$	10	30
3	I_2 (0.1)	TBHP (1.5)	CH_3CN	10	70
4	I_2 (0.1)	TBHP (1.5)	DCE	10	78
5	I_2 (0.1)	TBHP (1.5)	Toluene	10	50
6	I_2 (0.1)	TBHP (1.5)	MeOH	10	20
7	I_2 (0.1)	TBHP (2)	DCE	10	78
8	I_2 (0.1)	TBHP (1.5)	—	10	20
9	I_2 (0.1)	TBHP (1.5)	DCE	1	25 [b]
10	KI (0.1)	TBHP (1.5)	DCE	8	60
11	NBS (0.1)	TBHP (1.5)	DCE	8	62
12	NIS (0.1)	TBHP (1.5)	DCE	8	67
13	NCS (0.1)	TBHP (1.5)	DCE	8	n.d. [c]
14	I_2 (1.0)	Open air	DCE	8	87
15	I_2 (1.0)	Open air	DCE	12	86
16	I_2 (2.0)	Open air	DCE	8	87

[a] Unless otherwise mentioned, all reactions were performed with **4a** (0.5 mmol, 189 mg) at room temperature. The product **5a** was purified by column chromatography using silica gel (100–200 mesh) and yields are for the isolated products. [b] Reaction was carried out at reflux. [c] n.d.: not detected.

N-substituted indoles we also obtained very good yield of the product (**5n–5t**, Scheme 2). We also investigated the scope of the reaction by changing the aromatic aldehyde to aliphatic aldehyde. The reaction gave us moderate yield (**5l–5m**, Scheme 2). 3-Phenyl substituted pyrazol-5-amines were also used and a very good yield of **5** was isolated in all cases (**5v–5w**, Scheme 2). The single crystal X-ray structures of **5a** and **5u** established the structure of the cyclised product (Fig. 2).

The mechanism for the formation of **4** is usual.[15] Indole reacts with an aldehyde in the presence of catalyst and gives an intermediate alkylideneindolenine, which is then attacked by pyrazol-5-amine to form **4**. To establish the mechanism for the conversion of **4** to **5**, we performed a number of control experiments (a–e, Scheme 3). Radical scavengers such as butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) were used under the optimum reaction conditions along with I_2 (1 eq.) to check the probability of the radical pathway for the reaction (Scheme 3a). Both the scavengers inhibited the cyclisation reaction indicating the radical route. As I_2 cannot be a free radical at room temperature in the absence of any radical initiator, we thought light may be the source of the initiators. And therefore, we performed a reaction under dark conditions. However, darkness could not stop the reaction from occurring and we isolated 79% of **5a** (Scheme 3b). From previous reports it is obvious that one equivalent of I_2 is the minimum requirement for C–C or C–X bond



Scheme 2 Synthesis of α-carbolines from the 3-component reaction without isolating the uncyclised compound **4**. Time in the parentheses indicates the reaction time for the synthesis of **4** and its conversion to **5**. Products were purified using column chromatography and yields are for the isolated products.

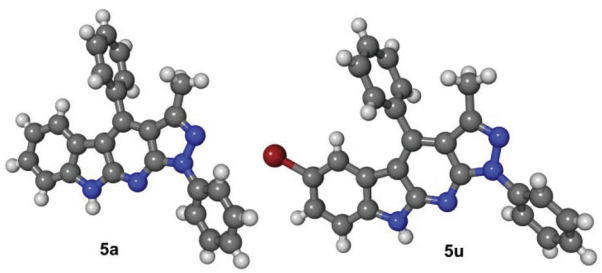
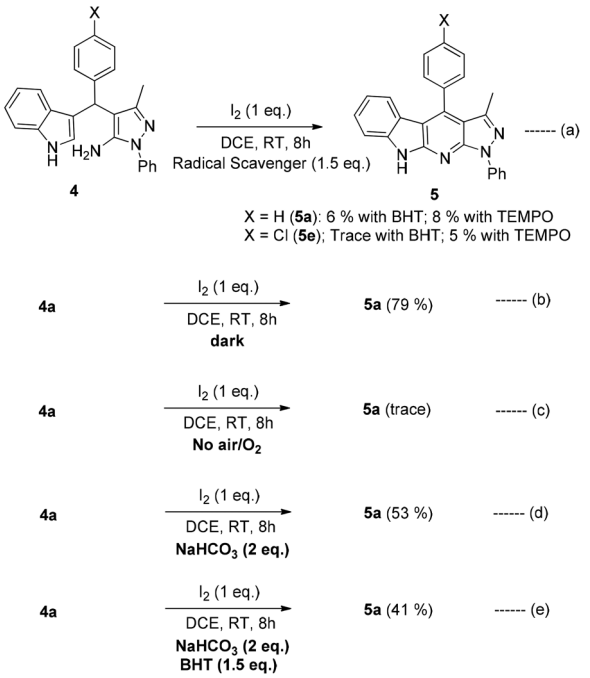
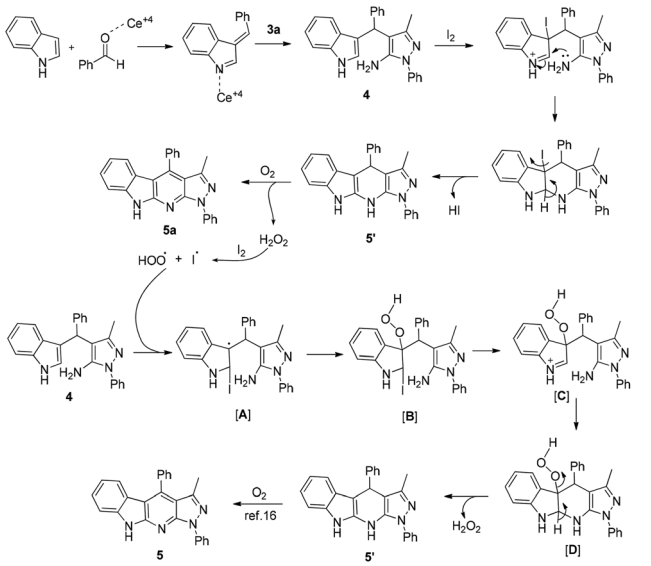


Fig. 2 X-ray structure of **5a** (CCDC 1867796†) & **5u** (CCDC 1867797†).



Scheme 3 Controlled experiments (a–e) to establish the mechanism.

formation at the C2 carbon of the indole.[13a,14b,d] Conversion of **4** to **5** involves C–N bond formation (cyclisation) and then aromatisation. Our reaction requires one equivalent of I_2 which we believe is consumed for C–N bond formation. Moreover, we have already seen in Table 2 (entry 16) that the increased amount of I_2 did not improve the yield of **5**, which indicates that I_2 is not involved in the aromatisation. To check the role of aerial O_2, we performed a reaction in the absence of air which gave us a trace amount of **5** (Scheme 3c). Therefore, we come to a conclusion that aerial O_2 is responsible for the aromatization. During the aromatisation by oxygen, H_2O_2 is formed as the by-product.[16] Therefore, we believe that this H_2O_2 might function as the radical initiator in the reaction. In acidic medium H_2O_2 reacts with I_2 to generate iodine free radicals.[17] To prevent free radical generation, we neutralized the acidic medium of the reaction (which is formed due to the elimination of HI in the reaction) by adding $NaHCO_3$ (2 eq.) under the optimal condition. To our surprise, the reaction still produced a moderate yield of product **5** (Scheme 3d). To explain the paradox, we performed a reaction again in the presence of $NaHCO_3$ (2 eq.) but along with BHT (1.5 eq.) under the optimal condition (Scheme 3e). This time we observed that there was a little inhibition of the reaction by BHT unlike earlier. This means that in the presence of $NaHCO_3$ (under neutral conditions) the reaction is not a free radical process. From the above controlled experiments we concluded that the reaction could be a free radical or non-free radical process. But under our optimized reaction conditions, it preferably follows a free radical pathway as the free radical reacts faster with the substrate.



Scheme 4 Tentative mechanism for the reaction.

Based on these experiments we here propose a tentative mechanism (Scheme 4). Compound **4** first reacts with I_2 in a non-free radical process and is cyclised to **5′**, which is subsequently aromatized to **5** by O_2 and generates H_2O_2. Once a small amount of H_2O_2 is generated, it reacts with I_2 forming an iodine radical and hydroperoxyl radical. This initiates the radical chain and compound **4** converts to **5′** *via* [**A**] to [**D**] and is finally aromatized to **5**.

Conclusions

In summary, we have successfully developed an efficient methodology to synthesise α-carboline derivatives. The reaction of indoles, aldehydes and pyrazol-5-amine first gives 3-substituted indoles which undergo intramolecular oxidative amination at the C2 carbon of the indole ring and aromatisation giving the desired product. All the reagents and substrates are very cheap and environmentally benign. The reaction is mild, and has a broad substrate scope. A tentative mechanism is proposed based on several controlled experiments.

Experimental

General procedure for the synthesis of 5

Compounds **1** (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) were stirred in the presence of CAN (10 mol%) at room temperature for mentioned hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in EtOAc and washed with H_2O (2 × 25 mL). The organic layer was separated and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator which gave **4** as the crude product. The crude **4** was then dissolved in DCE and I_2 (1 eq.) was added. Then the reaction

mixture was stirred at room temperature for the appropriate time. The solvent was removed using a rotary evaporator and the crude product was purified using column chromatography (silica gel, 100–200 mesh; ethyl acetate/hexane).

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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Notes and references

1 (*a*) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235; (*b*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

2 (*a*) M. A. Metwally, S. Shaaban, B. F. Abdel-Wahab and G. A. El-Hiti, *Curr. Org. Chem.*, 2009, **13**, 1475; (*b*) J. Hajicek, *Collect. Czech. Chem. Commun.*, 2007, **72**, 821; (*c*) S. Agarwal, S. Cammerer, S. Filali, W. Frohner, J. Knoll, M. P. Krahl, K. R. Reddy and H. J. Knolker, *Curr. Org. Chem.*, 2005, **9**, 1601.

3 J. Ford and R. J. Capon, *J. Nat. Prod.*, 2000, **63**, 1527.

4 K. Nikoofar, D. Kadivar and S. Shirzadnia, *Iran. Chem. Commun.*, 2014, **2**, 300.

5 S. Olgen, E. Akaho and D. Nebioglu, *J. Enzyme Inhib. Med. Chem.*, 2003, **18**, 485.

6 (*a*) F. R. de Sá Alves, E. J. Barreiro and C. A. M. Fraga, *Mini-Rev. Med. Chem.*, 2009, **9**, 782; (*b*) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 1.

7 C. Moquin-Pattey and M. Guyot, *Tetrahedron*, 1989, **45**, 3445.

8 T. C. Barden, *Top. Heterocycl. Chem.*, 2010, **26**, 31.

9 J.-S. Kim, K. Shin-ya, K. Furihata, Y. Hayakawa and H. Seto, *Tetrahedron Lett.*, 1997, **38**, 3431.

10 K. Cimanga, T. De Bruyne, L. Pieters and A. J. Vlietinck, *J. Nat. Prod.*, 1997, **60**, 688.

11 (*a*) N. Morimoto, K. Morioku, H. Suzuki, Y. Takeuchi and Y. Nishina, *Org. Lett.*, 2016, **18**, 2020; (*b*) F. Nowrouzi and R. A. Batey, *Angew. Chem., Int. Ed.*, 2013, **52**, 892; (*c*) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354; (*d*) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8358; (*e*) B. Deka, M. L. Deb, R. Thakuria and P. K. Baruah, *Catal. Commun.*, 2018, **106**, 68.

12 (*a*) M. L. Deb, C. D. Pegu, B. Deka, P. Dutta, A. S. Kotmale and P. K. Baruah, *Eur. J. Org. Chem.*, 2016, 3441; (*b*) A. K. Goash and Z.-H. Chen, *Org. Biomol. Chem.*, 2014, **12**, 3567; (*c*) T. P. Pathak, K. M. Gligorich, B. E. Welm and M. S. Sigman, *J. Am. Chem. Soc.*, 2010, **132**, 7870.

13 (*a*) P. Katrun, C. Mueangkaew, M. Pohmakotr, V. Reutrakul, T. Jaipetch, D. Soorukram and C. Kuhakarn, *J. Org. Chem.*, 2014, **79**, 1778; (*b*) T. Hostier, V. Ferey, G. Ricci, D. G. Pardo and J. Cossy, *Chem. Commun.*, 2015, **51**, 13898; (*c*) F. Xiao, H. Chen, H. Xie, S. Chen, L. Yang and G.-J. Deng, *Org. Lett.*, 2014, **16**, 50.

14 (*a*) Q. Shuai, G. Deng, Z. Chua, D. S. Bohle and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 632; (*b*) Y.-X. Li, K.-G. Ji, H.-X. Wang, S. Ali and Y.-M. Liang, *J. Org. Chem.*, 2011, **76**, 744; (*c*) Y.-X. Li, H.-X. Wang, S. Ali, X.-F. Xia and Y.-M. Liang, *Chem. Commun.*, 2012, **48**, 2343; (*d*) W.-B. Wu and J.-M. Huang, *Org. Lett.*, 2012, **14**, 5832; (*e*) D. Beukeaw, K. Udomsasporn and S. Yotphan, *J. Org. Chem.*, 2015, **80**, 3447; (*f*) Z.-J. Cai, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2013, **15**, 5226; (*g*) S. K. Ghosh and R. Nagarajan, *RSC Adv.*, 2014, **4**, 20136; (*h*) S. Badigenchala and G. Sekar, *J. Org. Chem.*, 2017, **82**, 7657; (*i*) S. Badigenchala, V. Rajeshkumar and G. Sekar, *Org. Biomol. Chem.*, 2016, **14**, 2297; (*j*) T. Kotipalli, V. Kavala, D. Janreddy, C. Kuo, T. Kuo, H. N. Huang, C. H. He and C. F. Yao, *RSC Adv.*, 2014, **4**, 2274.

15 (*a*) M. L. Deb, P. J. Borpatra, P. J. Saikia and P. K. Baruah, *Synthesis*, 2017, **49**, 1401; (*b*) M. L. Deb and P. J. Bhuyan, *Tetrahedron Lett.*, 2006, **47**, 1441; (*c*) M. L. Deb, B. Deka, P. J. Saikia and P. K. Baruah, *Tetrahedron Lett.*, 2017, **58**, 1999.

16 M. Asikainen, O. Jauhiainen, O. Aaltonen and A. Harlin, *Green Chem.*, 2013, **15**, 3230.

17 (*a*) M. C. Milenkovićand and D. R. Stanisavljev, *J. Phys. Chem. A*, 2012, **116**, 554; (*b*) G. Schmitz, *Phys. Chem. Chem. Phys.*, 2010, **12**, 6605.

