


 Cite this: *RSC Adv.*, 2021, 11, 29934

 Received 30th June 2021  
 Accepted 2nd September 2021

DOI: 10.1039/d1ra05070b

[rsc.li/rsc-advances](https://rsc.li/rsc-advances)

# Activator free diastereoselective 1,3-dipolar cycloaddition: a quick access to coumarin based spiro multi heterocyclic adducts†

 Nagender Thadem,<sup>ab</sup> Manda Rajesh <sup>a</sup> and Saibal Das <sup>\*ab</sup>

A formal diastereoselective 1,3-dipolar cycloaddition of azomethine ylide and coumarin derivatives to construct coumarin based spiro multi heterocyclics has been described. The *in situ* generation of azo-ylide was achieved for various heterocyclic carbonyls (indenoquinoxaline and isatin). This transformation is also suitable for maleimide dipolarophiles for the synthesis of hydro-maleimide derivatives. These decarboxylative annulations neither required any catalyst nor any activator. Further the pure products were isolated by filtration from the reaction mixture after the reaction under ambient conditions.

## Introduction

Coumarin is a privileged structural motif; the core skeletons are frequently observed in many natural products and active pharmaceutical ingredients (Fig. 1).<sup>1–3</sup> These scaffolds, possess an ample range of modulatory and cytoprotective functions, which provides therapeutic potentiality in multiple disorders such as anti-inflammatory, anti-cancer, anti-bacterial, anti-coagulant, anti-tumour, anti-HIV therapy, photo-chemotherapy *etc.*<sup>1,2</sup> Therefore, the synthesis and structural modification of this motif have captured huge attention from the synthetic chemist community. Over the past few decades, several remarkable achievements were reported on the various scaffolds of coumarin and its derivatives.<sup>2,3</sup> However, the structural decoration around these scaffolds is still in demand for the construction of multi-functionalized bioactive coumarin adducts.

On the other hand, spiro heterocyclics are proven to be potent pharmacologically active scaffolds (Fig. 1), which are found in a huge range of therapeutics and are also widely available in several natural products.<sup>4–6</sup> These spiro cyclic derivatives are usually fabricated through multicomponent reactions (MCRs). Owing to their bond forming efficiency, MCRs are facile approaches to create diversified complex molecular frameworks from readily available feedstocks in a high atom economy way. In this MCR approach, the 1,3-dipolar cycloaddition path has become an essential tool to

create valuable synthetic methodologies for the synthesis of various natural products and biologically active compounds.<sup>5,6</sup> The usual nitrogen based 1,3-dipoles are azomethine ylides, which are found to be short lived or stable intermediates.<sup>5,6</sup>

Besides, a large spectrum of cycloaddition reactions is reported on these dipoles, by using an array of activated and unactivated dipolarophiles to assemble multicyclics in a stereoselective manner.<sup>5,6</sup> Subsequently, cyclic dipolarophiles (like cyclopropene, maleimides *etc.*) provides these spiro cyclic heterocyclics (Scheme 1a) with an additional ring system.<sup>6</sup> Nevertheless, huge scope in this topic is awaited for the production of new chemical entities using multiple raw materials in one operation. Further, these approaches avoid pre-functionalizations of reactive centres, which is an obvious

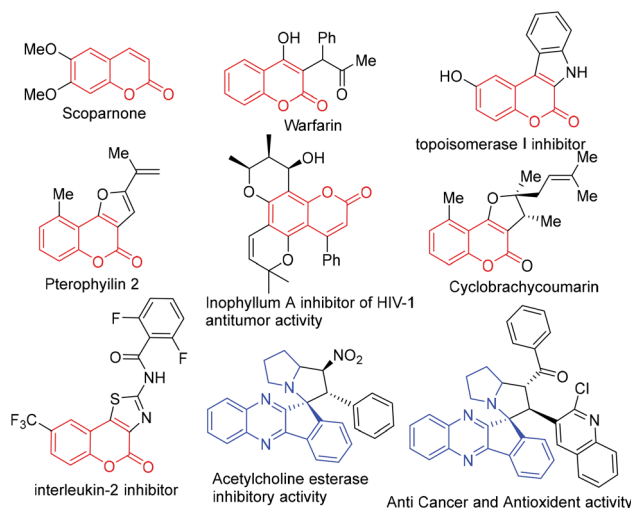


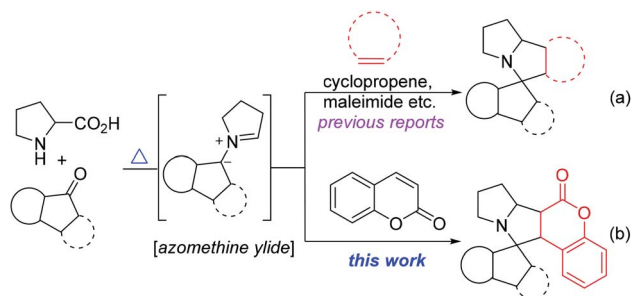
Fig. 1 Some bioactive coumarin and spiro multicyclics.

<sup>a</sup>Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IIT), Hyderabad 500007, India. E-mail: saibal@iict.res.in; Tel: +91 40 2719 1887

<sup>b</sup>Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

† Electronic supplementary information (ESI) available. CCDC 2065302–2065304. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra05070b





Scheme 1 1,3-Dipolar cyclo-addition of azomethine ylide.

demand in the green synthesis<sup>7</sup> research area. In this regard, we herein report, aforementioned coumarin as dipolarophile in azo-ylide (generated from indenoquinoxalines and isatins) cycloaddition arsenal in stereo-selective way. These hybrid (coumarin based spiro multicyclics) structural motifs may also enhance the pharmacological properties of regular spiro cyclic scaffolds<sup>2,4</sup> (Scheme 1b).

## Results and discussion

We have optimized the reaction conditions by using indenoquinoxaline **1a**, proline and coumarin **2a** as reactive partners (Table 1). Initially, as a model reaction, we used catalytic amount of copper iodide (CuI) as an activator in MeCN at 60 °C and isolated the expected **3aa** in 35% yield (entry 1). We further

Table 1 Optimized conditions<sup>a,b</sup>

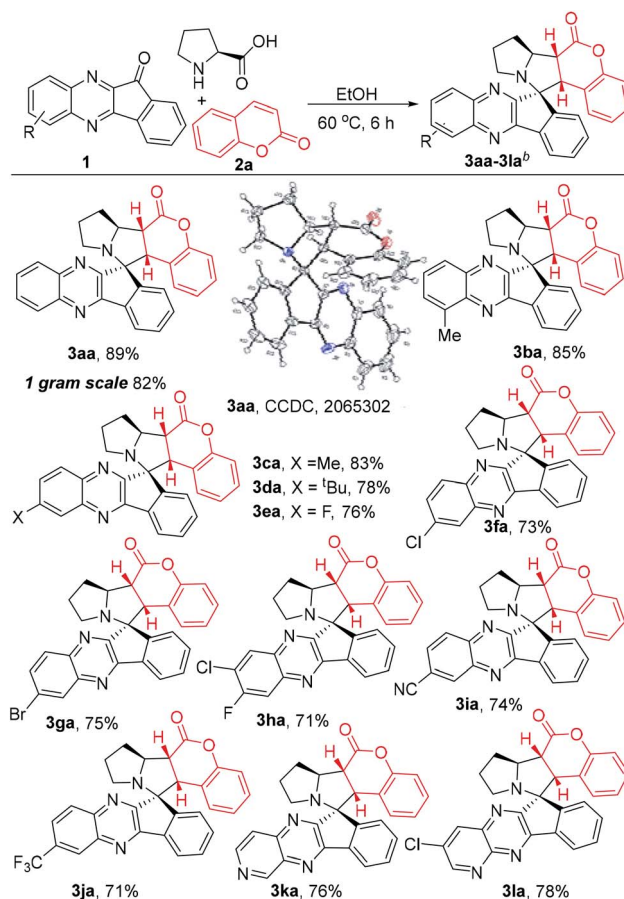
Entry	Activator	Solvent	Time	Temp (°C)	yield <sup>c</sup>
1	CuI (10 mol %)	MeCN	4	60	35
2	CuI (10 mol %)	DMF	4	60	40
3	CuI (10 mol %)	Dioxane	4	80	48
4	CuI (10 mol %)	Toluene	4	90	20
5	CuI (10 mol %)	MeOH	4	60	68
6	-	MeOH	6	60	80
7	-	<b>EtOH</b>	<b>6</b>	<b>60</b>	<b>89</b>
8	-	THF	6	60	65
9	-	IPA	12	60	82
10	-	<sup>i</sup> AmOH	8	70	70
11	-	DCE	12	60	Trace
12	-	EtOH	6	70	88
13	-	EtOH	6	80	85

<sup>a</sup> IPA, isopropanol, <sup>i</sup>AmOH, isoamyl alcohol. <sup>b</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol) and proline (0.6 mmol) in 3 mL solvent. <sup>c</sup> Isolated yields.

screened various solvents on this model reaction such as DMF, dioxane, toluene, methanol and the yields were observed to be improving up to 68% (entries 2–5). When we exclude the CuI in methanol, to our delight the same product was obtained in 80% yield (entry 6). Then, we have screened various solvents and temperature in absence of an activator. The best result was found in the case of the reaction in EtOH at 60 °C which provided **3aa** in 89% yield (entry 7). Other solvents such as THF, IPA, <sup>i</sup>AmOH and DCE were not that effective as in the case of EtOH (entries 8–11).

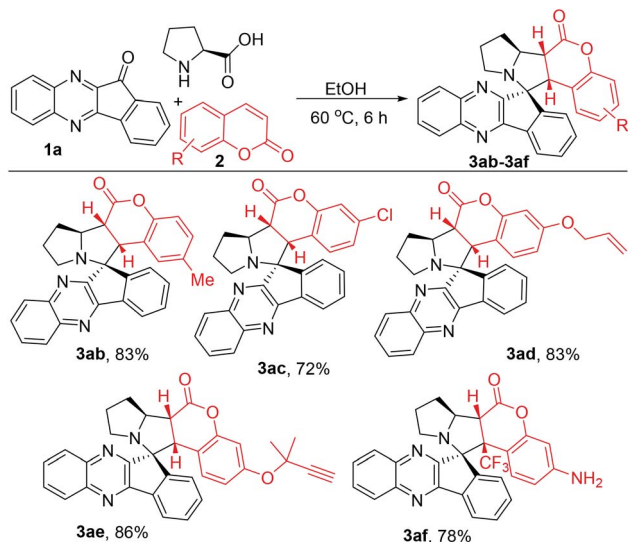
It is noteworthy to mention that no remarkable improvement was observed in the yield when elevated temperatures were conditioned (entries 12–13). The structure and stereochemistry of **3aa** was confirmed and assigned by <sup>1</sup>H NMR, <sup>13</sup>C NMR and X-ray crystallography analysis (Scheme 2). Based on previous reports<sup>6</sup> and X-ray crystal analysis, the dipole configured aza-ylide interacts with coumarin dipolarophile in *endo*-mode. This *endo*-mode approach led to a single diastereomer product in cycloaddition reaction.<sup>6b,c</sup>

With the optimized reaction conditions in hand, we have first taken up the study to generalize the substrate scope of indenoquinoxaline derivatives **1** as depicted in Scheme 2. Initially, we screened alkylated adducts **1b–d** to provide the



<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol) and Proline (0.6 mmol) in 3 mL solvent. <sup>b</sup>Isolated yields.

Scheme 2 Scope of indenoquinoxalines.

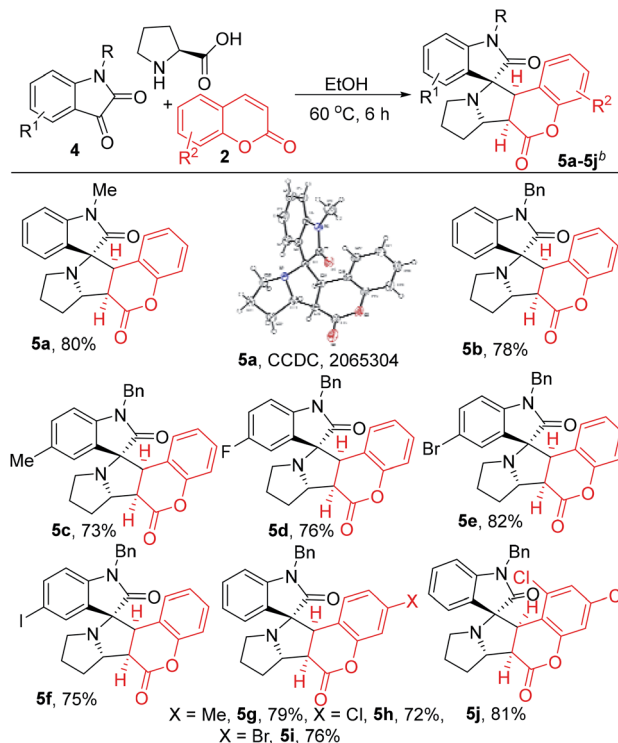


Scheme 3 Scope of coumarins.

corresponding products **3ba–3da** in excellent yields (78–85%). In addition, the halo substituted substrates, fluoro **1e**, chloro **1f**, bromo **1g** and dihalo substituted substrates **1h** (F and Cl) smoothly underwent the title transformation and furnished **3ea–3ha** (71–76%). Also, the electron withdrawing groups, like cyano, trifluoromethyl (**1i–j**) substrates comfortably produced **3ia–3ja** in good yields. Likewise, heterocyclic skeletons **1k** and **1l** showed equal ease in the reaction for the synthesis of **3ka** and **3la** in good yields.

Thereafter, we have investigated the substrate scope of coumarin derivatives **2** (Scheme 3). As usual, methyl **2b** and chloro **2c** coumarins gave corresponding adducts **3ab** and **3ac** in 83% and 72% yields respectively. Gratifyingly, reactive functional groups such as allyloxy- and propargyl coumarins **2d–2e** were efficiently converted to expected products **3ad** and **3ae** in 83% and 86% yields. Worth mentioning that the other possibility of 1,3-dipolar cyclo addition (with allyloxy- and propargyl groups), indeed didn't hamper the anticipated conversion. This might be attributed to the electronic richness on these groups, which did not allow the cycloaddition with azomethine ylide. Furthermore, electron withdrawing substitutions on the 4th position of coumarin increases the reactive ability. As expected, 4-CF<sub>3</sub> motif **2f** gave final product **3af** in good yield.

After establishing the applicability of coumarins as 1,3-dipolar cycloaddition partners on quinoxaline derivatives, we then quested to extend the same on the other potential heterocyclics to deliver a new class of spiro heterocyclics. At this point, we choose isatins as suitable adducts in the above discussed cycloaddition transformation due to their wide applicability in drug discovery<sup>8</sup> applications and comparable reactivity as indenoquinoxalines. At first, we conducted the reaction of *N*-methyl **4a** and *N*-benzyl **4b** isatins in optimized conditions and we have isolated **5a** and **5b** in 80% and 78% yield respectively (Scheme 4). The structure and stereochemistry of **5a** was confirmed by X-ray analysis. Further, methyl and halo variants (F, Br and I) **4c–4f** provides analogue products **5c–5f** in



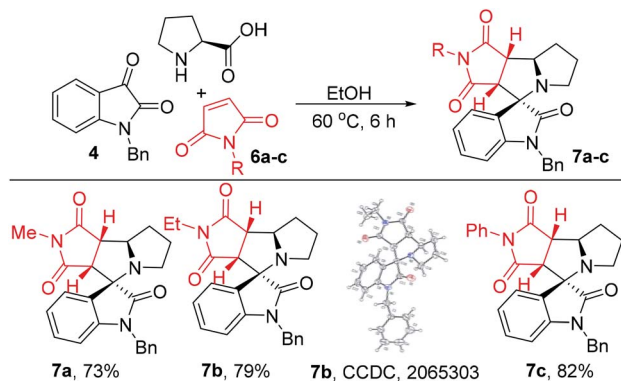
<sup>a</sup>Reaction conditions: **4** (0.5 mmol), **2** (0.75 mmol) and Proline (0.6 mmol) in 3 mL solvent. <sup>b</sup>Isolated yields.

Scheme 4 Scope of isatins.

73–82% yields. In addition, methyl, chloro, bromo and dichloro substituted coumarins provided the corresponding products **5h–5k** in good yields (72–81%).

Conversely, the synthesis of such 3D frame works was quite challenging in MCRs. The main drawback in these transformations is multiple reaction possibilities within the reactive partners. Therefore, tuning of the single reactive centered substrates is somewhat difficult.<sup>7</sup> However, we have successfully utilized the dipolarophile behaviour of coumarins in azomethine ylide cycloaddition reactions.

Despite the dipolarophile skeleton, we further focus on the synthesis of complex spirocycles using other cyclic



Scheme 5 Scope of maleimides.

dipolarophiles. Therefore, we selected maleimide as cyclic dipolarophile in azomethine ylide cycloaddition. Thus, the reaction of maleimide **6a** with isatin **4a** offers dihydromaleimide derivative **7a** in 73% (Scheme 5). We further synthesized two more derivatives **7b** and **7c** in good productive yields (79–82%). The structure and stereochemistry of **7b** was confirmed by X-ray crystallographic analysis.

## Conclusions

In conclusion, we have demonstrated, a formal 1,3-dipolar cycloaddition reaction of coumarins and *in situ* generated azomethine ylides which offers coumarin based spiro cyclic adducts in a diastereoselective manner. *In situ* ylides formation was achieved with indenoquinoline and isatin derivatives using proline. This transformation is also equally viable to maleimides for the synthesis of hydro-maleimide derivatives. This strategy delivers biologically intriguing spirocyclics in environmentally benign conditions without the addition of any activator and products were isolated by simple filtration.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

N. T. thanks CSIR for the fellowships MR thanks CSIR-IICT for facilities. We thank the Department of Analytical and Structural Chemistry at CSIR-IICT for all the analytical support and especially Dr Sridhar Balasubramanian for X-ray data. We gratefully acknowledge the overall support by CSIR-IICT [IICT/Pubs./2021/075].

## Notes and references

- (a) F. Rodriguez-Enriquez, D. Vina, E. Uriarte, R. Laguna and M. J. Matos, *ChemMedChem*, 2021, **16**, 179–186; (b) A. Szappanos, A. Mandi, K. Gulacsi, E. Lisztes, B. I. Toth, T. Biro, A. Konya-Abraham, A. Kiss-Szikszai, A. Benyei, S. Antus and T. Kurtan, *Biomolecules*, 2020, **10**, 1462–1504; (c) D. Cao, Z. Liu, P. Verwilst, S. Koo, P. Jangjili, J. S. Kim and W. Lin, *Chem. Rev.*, 2019, **119**, 10403–10519; (d) M. B. Majnooni, S. Fakhri, A. Smeriglio, D. Trombetta, C. R. Croley, P. Bhattacharyya, E. Sobarzo-Sanchez, M. H. Farzaei and A. Bishayee, *Molecules*, 2019, **24**, 4278–4297; (e) E. Jameel, T. Umar, J. Kumar and N. Hoda, *Chem. Biol. Drug Des.*, 2016, **87**, 21–38; (f) E. Jameel, T. Umar, J. Kumar and N. Hoda, *Chem. Biol. Drug Des.*, 2016, **87**, 21–38; (g) C. Kontogiorgis, A. Detsi and D. Hadjipavlou-Litina, *Expert Opin. Ther. Pat.*, 2012, **22**, 437–454; (h) M. A. Musa, J. S. Cooperwood, M. Omar and F. Khan, *Curr. Med. Chem.*, 2008, **15**, 2664–2679.
- (a) S.-M. Yang, C.-Y. Wang, C.-K. Lin, P. Karanam, G. M. Reddy, Y.-L. Tsai and W. Lin, *Angew. Chem. Int. Ed.*, 2018, **57**, 1668–1672; (b) J. Zhang and C. -S. Jiang, *Med. Chem. Res.*, 2018, **27**, 1717–1727; (c) L. Chen, L. Wu, W. Duan, T. Wang, L. Li, K. Zhang, J. Zhu, Z. Peng and F. Xiong, *J. Org. Chem.*, 2018, **83**, 8607–8614; (d) S. Emami and S. Dadashpour, *Eur. J. Med. Chem.*, 2015, **102**, 611–630; (e) S. S. Sahoo, S. Shukla, S. Nandy and H. B. Sahoo, *Eur. J. Exp. Biol.*, 2012, **2**, 899–908; (f) F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.*, 2005, **12**, 887–916.
- (a) B. Zhao and B. Xu, *Org. Biomol. Chem.*, 2021, **19**, 568–573; (b) Y.-J. Wang, T.-T. Wang, L. Yao, Q.-L. Wang and L.-M. Zhao, *J. Org. Chem.*, 2020, **85**, 9514–9524; (c) I. Cortes, L. J. Cala, A. B. J. Bracca and T. S. Kaufman, *RSC Adv.*, 2020, **10**, 33344–33377; (d) H. J. Yoo and S. W. Youn, *Org. Lett.*, 2019, **21**, 3422–3426; (e) J. Hou, A. Ee, W. Feng, J. -H. Xu, Y. Zhao and J. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 5257–5263; (f) Y. Li, Z. Qi, H. Wang, X. Fu and C. Duan, *J. Org. Chem.*, 2012, **77**, 2053–2057; (g) M. S. Reddy, N. Thirupathi, M. H. Babu and S. Puri, *J. Org. Chem.*, 2013, **78**, 5878–5888, and references therein.
- (a) W.-F. Zuo, J. Zhou, Y.-L. Wu, H.-Y. Fang, X.-J. Lang, Y. Li, G. Zhan and B. Han, *Org. Chem. Front.*, 2021, **8**, 922–927; (b) N. S. Zimnitskiy, A. D. Denikaev, A. Y. Barkov, I. B. Kutyashev, V. Y. Korotaev and V. Y. Sosnovskikh, *J. Org. Chem.*, 2020, **85**, 8683–8694; (c) Y. Ji, X. He, C. Peng and W. Huang, *Org. Biomol. Chem.*, 2019, **17**, 2850–2864; (d) Y.-L. Ji, H.-P. Li, Y.-Y. Ai, G. Li, X.-H. He, W. Huang, R.-Z. Huang and B. Han, *Org. Biomol. Chem.*, 2019, **17**, 9217–9225; (e) A. A. Raj, R. Raghunathan, M. R. SrideviKumari and N. Raman, *Bioorg. Med. Chem.*, 2003, **11**, 407–419.
- (a) Y. Ling, Y. Huang and X. Li, *Chem. Heterocycl. Compd.*, 2021, **57**, 181–186; (b) S. S. Shinde, S. Laha, D. T. Tiwari, B. Sridhar and P. R. Likhar, *Org. Biomol. Chem.*, 2019, **17**, 4121–4128; (c) K. S. Mani, W. Kaminsky and S. P. Rajendran, *New J. Chem.*, 2018, **42**, 301–310; (d) A. Yu. Barkov, N. S. Zimnitskiy, I. B. Kutyashev, V. Yu. Korotaev and V. Ya. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2018, **54**, 43–50; (e) M. S. Reddy, N. S. Kumar and L. R. Chowhan, *RSC Adv.*, 2018, **8**, 35587–35593; (f) A. Yu. Barkov, N. S. Zimnitskiy, I. B. Kutyashev, V. Yu. Korotaev and V. Ya. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2017, **53**, 1315–1323; (g) A. M. Akondi, S. Mekala, M. L. Kantam, R. Trivedi, L. R. Chowhan and A. Das, *New J. Chem.*, 2017, **41**, 873–878; (h) N. Shahrestani, F. Salahi, N. Tavakoli, K. Jadidi, M. Hamzehloueian and B. Notash, *Tetrahedron: Asymmetry*, 2015, **26**, 1117–1129; (i) S. Lanka, S. Thennarasu and P. T. Perumal, *RSC Adv.*, 2014, **4**, 2263–2266; (j) V. S. Moshkin, V. Ya. Sosnovskikh and G.-V. Roschenthaler, *Tetrahedron*, 2013, **69**, 5884–5892; (k) A. A. Karsalary, M. R. Mohammadzadeh, A. R. Hasaninejad, A. A. Mohammadi and A. R. Karimi, *J. Iran. Chem. Soc.*, 2010, **7**, 45–50, and references therein.
- (a) A. S. Filatov, S. Wang, O. V. Khoroshilova, S. V. Lozovskiy, A. G. Larina, V. M. Boitsov and A. V. Stepanov, *J. Org. Chem.*, 2019, **84**, 7017–7036; (b) S. Nayak, P. Pattanaik, S. Mohapatraa, D. R. Mishra, P. Panda, B. Raiguru, N. P. Mishra, S. Jena and H. S. Biswal, *Synth. Commun.*, 2019, **49**, 1823–1835; (c) P. R. Mali, N. B. Khomane,

- B. Sridhar, H. M. Meshram and P. R. Likhar, *New J. Chem.*, 2018, **42**, 13819–13827; (d) A. S. Filatov, N. A. Knyazev, M. N. Ryazantsev, V. V. Suslonov, A. G. Larina, A. P. Molchanov, R. R. Kostikov, V. M. Boitsov and A. V. Stepanov, *Org. Chem. Front.*, 2018, **5**, 595–605; (e) P. Pattanaik, S. Nayak, D. R. Mishra, P. panda, B. P. Raiguru, N. P. Mishra, S. Mohapatra, N. A. Mallampudi and C. S. Purohit, *Tetrahedron Lett.*, 2018, **59**, 2688–2694; (f) S. Kanchithalavivan, R. V. Sumesh and R. R. Kumar, *ACS Comb. Sci.*, 2014, **16**, 566–572.
- 7 (a) Y. Wu, J.-Y. Chen, J. Ning, X. Jiang, Y. Deng, R. Xu and W.-M. He, *Green Chem.*, 2021, **23**, 3950–3954; (b) Q.-W. Gui, B.-B. Wang, S. Zhu, F.-L. Li, M.-X. Zhu, M. Yi, J.-L. Yu, Z.-L. Wu and W.-M. He, *Green Chem.*, 2021, **23**, 4430–4434; (c) N. Meng, Y. Lv, Q. Liu, R. Liu, X. Zhao and W. Wei, *Chin. Chem. Lett.*, 2021, **32**, 258–262; (d) R. O. Rocha, M. O. Rodrigues and B. A. D. Neto, *ACS Omega*, 2020, **5**, 972–979; (e) X. Zhang, S. Zhi, W. Wang, S. Liu, J. P. Jasinski and W. Zhang, *Green Chem.*, 2016, **18**, 2642–2646; (f) H. C. Malinakova, *Rep. Org. Chem.*, 2015, **5**, 75–90; (g) R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958–2975; (h) P. Slobbe, E. Ruijter and R. V. A. Orru, *MedChemComm*, 2012, **3**, 1189–1218; (i) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486.
- 8 (a) A. N. Izmestev, G. A. Gazieva, V. A. Karnoukhova and A. N. Kravchenko, *Org. Biomol. Chem.*, 2020, **18**, 6905–6911; (b) Y.-C. Wang, J.-L. Wang, K. S. Burgess, J.-W. Zhang, Q.-M. Zheng, Y. D. Pu, L.-J. Yan and X.-B. Chen, *RSC Adv.*, 2018, **8**, 5702–5713; (c) P. Ramesh, K. S. Rao, R. Trivedi, B. S. Kumar, R. S. Prakasham and B. Sridhar, *RSC Adv.*, 2016, **6**, 26546–26552; (d) R. Sakhuja, S. S. Panda, L. Khanna, S. Khurana and S. C. Jain, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5465–5469; (e) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, **18**, 3003–3025.