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Humic acid as an efficient and reusable catalyst for one pot three-component green synthesis of 5-substituted 1*H*-tetrazoles in water†

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Humic acid is a non toxic, inexpensive, easily available high-molecular weight polymer. A simple and facile one pot three-component synthesis of 5-substituted 1*H*-tetrazoles from aldehydes, hydroxylamine hydrochloride and sodium azide using humic acid as an efficient catalyst in water is described. The method reported has several advantages such as high to excellent yields, easy work-up, mild reaction conditions, use of water as a green solvent, and a commercially available, nontoxic and reusable catalyst.

Introduction

Tetrazoles are synthetic nitrogen-rich compounds with a wide range of applications that are receiving considerable attention among the stable heterocycles.¹ They play important roles in energetic materials,² pharmaceuticals³ and coordination chemistry.⁴ Because of their potent usefulness, various synthetic methods have been developed for the construction of tetrazole frameworks, such as the reactions of aryl halides with potassium ferrocyanide,⁵ primary amides with triazido-chlorosilane,⁶ and oximes with sodium azide⁷ or diphenyl phosphorazidate.⁸ Traditional synthesis of 5-substituted 1*H*-tetrazole has been reported to proceed *via* [3 + 2] cycloaddition of azide ions with expensive and toxic nitrile.⁹ In view of the availability, lower toxicity and ease of handling of aldehydes as compared to nitriles, the application of aldehydes for the synthesis of tetrazole derivatives is a highly attractive and advantageous strategy. From the literature survey, we came to know that some methods were reported for the synthesis of 5-substituted 1*H*-tetrazole from aldehyde and the catalysts used were (NH₄)₄Ce(SO₄)₄·2H₂O,¹⁰ TiCl₃,¹¹ Cu(OAc)₂,¹² PVA@Cu Schiff base complex,¹³ I₂,¹⁴ Cu-MCM-41,¹⁵ [bmim]N₃/Cu(OAc)₂ (ref. 16) and P₂O₅.¹⁷ Although each of the above methods has its own merit, most of these methods are associated with certain disadvantages including the use of commercially unavailable catalysts, toxic organic solvents and high reaction temperatures. To avoid such drawbacks, development of more simple and efficient protocols is still in demand.

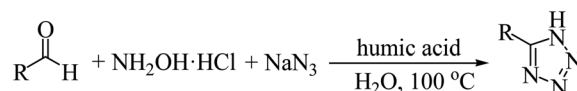
Nowadays, one pot multicomponent reactions (MCRs) have received much attention for the synthesis of diverse compounds and contribute to sustainability by simplifying the synthetic route.¹⁸ MCRs combine three or more starting reagents at a time in the same pot to create the target molecule since there is no need of separating intermediate which help to reduce the energy consumption, solvent waste and reaction time and thus have the advantages of synthetic efficiency, simplicity, atom economy. Compared with the conventional multistep synthetic routes, MCRs are more powerful procedures in the diversity-oriented convergent synthesis of organic heterocycles from simple and easily available substrates.

Humic acid is a high-molecular weight polymer that is primarily derived from biodegradation of dead organic matter and appears mostly in peat, soil, coal, upland streams, dystrophic lakes and well water. Because humic acid is non toxic, inexpensive and easily available, the study of its catalytic activity may be very important. Humic acid is an acidic catalyst owing to the presence of abundant carboxyl and phenolic hydroxyl groups in the structure of it. There are only very few reports in which catalytic activity of humic acid has been described.^{19,20} In view of the efforts toward development of the potential of humic acid as a catalyst, herein, we report an efficient one pot three-component synthesis of 5-substituted 1*H*-tetrazoles from less expensive and easily available starting material aldehydes along with hydroxylamine hydrochloride and sodium azide (Scheme 1).

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Scheme 1 Humic acid catalyzed one pot three-component synthesis of 5-substituted 1*H*-tetrazoles.



Table 1 Effect of solvent on the synthesis of 5-phenyl 1*H*-tetrazole^a

Entry	Solvent	Yield ^c (%)
1 ^b	CH ₃ CN	43
2	DMF	81
3	DMSO	64
4 ^b	EtOH	31
5	Toluene	0
6	H ₂ O	92
7	Solvent-free	0

^a Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol), solvent (2 mL), humic acid (0.1 g) at 100 °C for 4 h. ^b Reaction was performed under reflux condition. ^c Isolated yield.

Results and discussion

In order to determine the best reaction conditions, the effect of solvent (Table 1), catalyst loading (Table 2) and temperature (Table 3) were examined in the reaction of benzaldehyde, hydroxylamine hydrochloride and sodium azide. This reaction was very dependent on the nature of the solvent utilized. It was observed that the use of high boiling point polar solvents such as DMF and DMSO resulted in moderate conversion to the cycloaddition product (Table 1, entries 2 and 3). But no product was formed with weak polar solvent toluene (Table 1, entry 5), it may be due to the poor solubility of hydroxylamine hydrochloride and sodium azide in toluene. An additional disadvantage of DMF and DMSO is their solubility in both organic solvents and water, thus removing DMF and DMSO from tetrazole is difficult. Water was the best solvent for this protocol in terms of yield (Table 1, entry 6). However, no reaction was observed under solvent-free conditions (Table 1, entry 7). The reaction did not proceed with no catalyst (Table 2, entry 1). Decreasing the catalyst concentration resulted in lower yields under the same conditions (Table 2, entries 2 and 3). The best result was achieved by carrying out the reaction with 0.1 g of humic acid (Table 2, entry 4). Further increase in catalyst concentration did not show any significant effect on yields (Table 2, entries 5 and 6). At room temperature a useful conversion was not observed

Table 2 Effect of catalyst loading on the synthesis of 5-phenyl 1*H*-tetrazole^a

Entry	Catalyst loading (g)	Yield ^b (%)
1	None	0
2	0.04	48
3	0.07	76
4	0.10	92
5	0.13	92
6	0.16	93

^a Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol), H₂O (2 mL), catalyst humic acid at 100 °C for 4 h. ^b Isolated yield.

(Table 3, entry 1). However, the productivity increased on raising the temperature. The increase of reaction temperature will accelerate the thermal movement of molecules and increase the probability of intermolecular collision, thus, the rate of the reaction is improved. Different research groups established that using high temperature is necessary for cycloaddition reactions,^{10–12} so it seems reasonable to think that increasing the reaction temperature would be a good choice for improvement in the yield. The best result for this reaction was obtained at 100 °C (Table 3, entry 5).

After optimization of the reaction conditions, to expand the efficiency and generality of this methodology, aldehydes were treated with hydroxylamine hydrochloride and sodium azide in the presence of 0.1 g of humic acid in water at 100 °C and a large variety of tetrazole derivatives were formed. The results are summarized in Table 4. This strategy applies to all types of aldehydes (aromatic, heterocyclic and aliphatic). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups reacted successfully to give the corresponding tetrazoles in good to excellent yields irrespective of the electronic nature and substituent position on the aromatic ring (Table 4, **2a–2r**). Heterocyclic aldehydes also reacted well to give corresponding products in high yields (Table 4, **2s** and **2t**). In addition, good results were also obtained with aliphatic aldehydes (Table 4, **2u–2w**). From the above results, it is concluded that humic acid is an excellent catalyst for the synthesis of 5-substituted 1*H*-tetrazoles which tolerate a wide range of substituents.

One of the most significant features of a catalyst is its ability for reusability. Thus, we studied the reusability of the catalyst humic acid for the synthesis of 5-phenyl 1*H*-tetrazole (**2a**) under the optimized reaction conditions. The catalyst was separated from the reaction mixture by convenient filtration. According to the data presented in Table 5, the catalyst was reusable for five consecutive runs without any significant reactivity loss.

A comparison among humic acid and other catalysts reported in the literature for the preparation of 5-phenyl 1*H*-tetrazole reveals the advantages of humic acid over most of the other catalysts in terms of higher yield and shorter reaction time (Table 6).

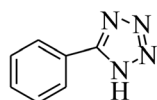
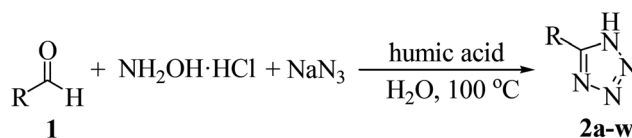
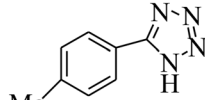
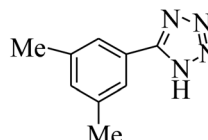
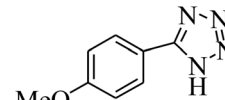
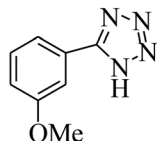
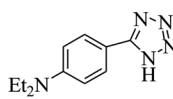
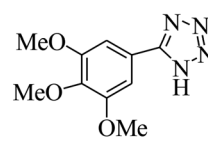
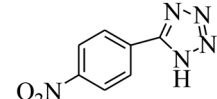
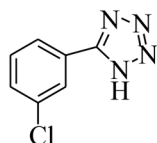
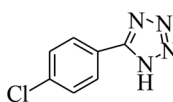
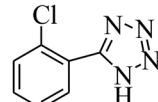
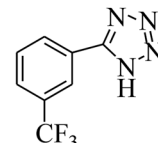
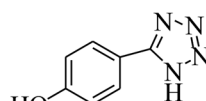
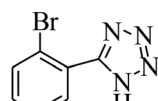
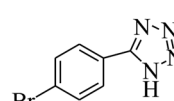
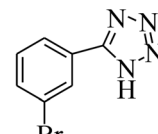
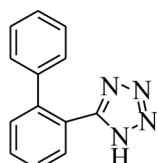
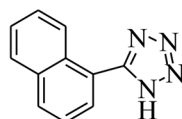
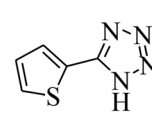
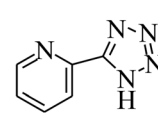
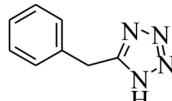
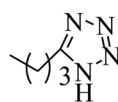
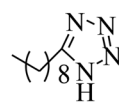
A plausible mechanism for the synthesis of 5-substituted 1*H*-tetrazole is represented in Scheme 2. After the activation of the

Table 3 Effect of temperature on the synthesis of 5-phenyl 1*H*-tetrazole^a

Entry	Temp. (°C)	Yield ^b (%)
1	Room temp.	19
2	40	22
3	55	43
4	70	55
5	85	79
6	100	92

^a Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol), H₂O (2 mL), humic acid (0.1 g) at different temperature for 4 h. ^b Isolated yield.



Table 4 Synthesis of 5-substituted 1*H*-tetrazoles catalysed by humic acid^{a,b}**2a** (92%, 4 h)**2b** (92%, 4 h)**2c** (89%, 4 h)**2d** (90%, 5 h)**2e** (86%, 5 h)**2f** (85%, 6 h)**2g** (84%, 6 h)**2h** (96%, 3 h)**2i** (94%, 3 h)**2j** (95%, 3 h)**2k** (92%, 3 h)**2l** (94%, 4 h)**2m** (87%, 4 h)**2n** (90%, 3 h)**2o** (96%, 3 h)**2p** (93%, 3 h)**2q** (85%, 6 h)**2r** (91%, 4 h)**2s** (93%, 4 h)**2t** (90%, 4 h)**2u** (87%, 6 h)**2v** (83%, 8 h)**2w** (81%, 8 h)

^a Reaction conditions: aldehydes (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol), humic acid (0.1 g), 100 °C, H₂O (2 mL). ^b Isolated yields.

carbonyl group of aldehyde catalyzed by protic acids on the humic acid surface and the nucleophilic attack of the nitrogen atom of hydroxylamine to the active carbonyl group, aldehyde oxime is obtained. The coordination of the protic acids with

oxygen atom of aldehyde oxime assists to activate C=N bond to form intermediate for nucleophilic addition of NaN₃. The reaction proceeds *via* [3 + 2] cycloaddition pattern. Finally, the elimination of water and acidic hydrolysis give the



Table 5 Reusability of the catalyst humic acid^a

Run	1	2	3	4	5
Yield ^b (%)	92	92	92	91	90

^a Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol), H₂O (2 mL), humic acid (0.1 g) at 100 °C for 4 h. ^b Isolated yield.

corresponding 5-substituted 1*H*-tetrazole. The active site on the humic acid represented as -COOH is considered in the mechanism.

Micellar catalysis provides a means for synthesizing novel and conventional materials in aqueous media, resulting in improved reaction rates and eliminating the need for organic solvents. Humic acid generally forms micelle-like structure in aqueous environment, which is an effective way to realize [3 + 2] cycloaddition of aldehydes, hydroxylamine hydrochloride and sodium azide, and the addition of inorganic electrolyte (hydroxylamine hydrochloride and sodium azide) into the aqueous phase can markedly promote the catalysis effect.²¹ The critical micelle concentration (CMC) value of the humic acid used in this study was 5.11 ± 0.10 g L⁻¹.

Conclusions

In conclusion, we have disclosed that humic acid works as a non toxic, inexpensive and efficient catalyst for one pot three-component synthesis of 5-substituted 1*H*-tetrazoles from aldehydes, hydroxylamine hydrochloride and sodium azide in water. Advantages of this methodology are use of commercially available and reusable catalyst and water as a green solvent, simple experimental and work-up procedure, high yields and environment friendly. This environmentally friendly method to synthesizing 5-substituted 1*H*-tetrazoles holds promising potential for future applications in both academic and industrial research.

Experimental

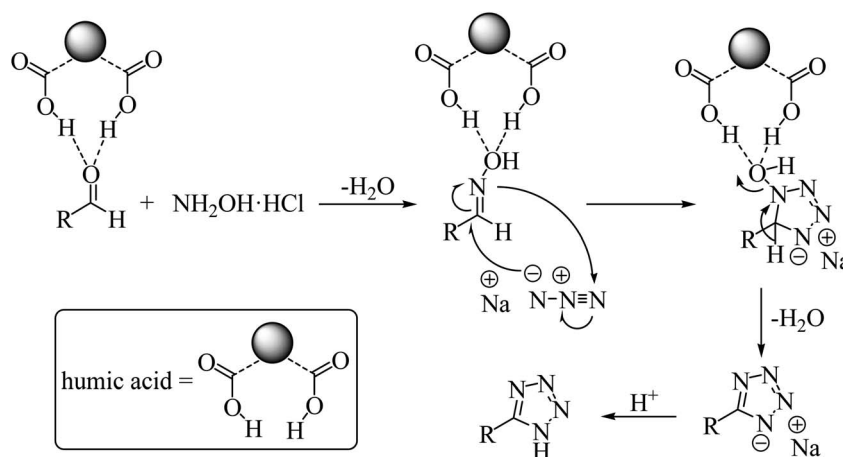
Materials and instrumentation

Humic acid and other chemicals were all purchased from Aladdin Reagent Company and used as received unless mentioned otherwise. Melting points were determined on an XT4A electrothermal apparatus equipped with a microscope and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-d₆. Elemental analyses were performed on a PerkinElmer 240-C instrument.

Table 6 Comparison of various catalysts used in synthesis of 5-phenyl 1*H*-tetrazole from benzaldehyde, hydroxylamine hydrochloride and sodium azide

Entry	Conditions	Yield (%)	Ref.
1 ^a	(NH ₄) ₄ Ce(SO ₄) ₄ ·2H ₂ O (20 mol%), DMF, reflux, 5 h	72	10
2 ^a	TiCl ₃ (20 mol%), DMF, reflux, 4 h	86	11
3 ^a	Cu(OAc) ₂ (20 mol%), choline chloride-urea, 100 °C, 12 h	90	12
4 ^b	PVA@Cu Schiff base complex (0.43 mol%), H ₂ O, r.t., 7 min	98	13
5 ^b	Cu-MCM-41 (30 mg mmol ⁻¹), DMF, 140 °C, 12 h	90	15
6 ^a	P ₂ O ₅ (200 mol%), DMF, reflux, 9 h	90	17
7 ^a	Humic acid (0.1 g mmol ⁻¹), H ₂ O, 100 °C, 4 h	92	This work

^a Commercially available catalyst. ^b Commercially unavailable catalyst.

Scheme 2 Plausible mechanism for the synthesis of 5-substituted 1*H*-tetrazoles.

General procedure for the synthesis of 5-substituted 1*H*-tetrazoles

Aldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol) and humic acid (0.1 g) were added to water (2 mL) and the mixture was heated at 100 °C for requisite time. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was filtered to separate out the catalyst. The filtrate was treated with HCl (4 N, 10 mL), extracted with ethylacetate, and washed by water a few times. The extract was dried over anhydrous Na₂SO₄, purified by column chromatography on silica-gel (60–120 mesh) using petroleum ether/ethyl acetate (75 : 25) as eluent to give the corresponding pure product. All the products were characterized by ¹H NMR and ¹³C NMR spectroscopy.

A gram scale synthesis of 5-phenyl 1*H*-tetrazole (2a)

To a 200 mL round-bottomed flask equipped with a magnetic stirrer was added benzaldehyde (10.6 g, 0.1 mol), hydroxylamine hydrochloride (4.2 g, 0.1 mol), NaN₃ (0.5 g, 0.11 mol), humic acid (10.0 g) and water (100 mL). Then the reaction mixture was heated to 100 °C with vigorous stirring. After completion of reaction (4 h), as detected by TLC, the mixture was cooled to room temperature and filtered to separate out the catalyst. The filtrate was adjusted pH to 1.0 with concentrated HCl and extracted with ethylacetate (3 × 50 mL). The combined organic phases were washed with water (2 × 100 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give the pure product 5-phenyl 1*H*-tetrazole as a white solid (13.2 g, 90% yield).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) L. Lang, B. Li, W. Liu, L. Jiang, Z. Xu and G. Yin, *Chem. Commun.*, 2010, **46**, 448; (b) F. Ling, Z. Xie, J. Chen, C. Ai, H. Shen, Z. Wang, X. Yi and W. Zhong, *Adv. Synth. Catal.*, 2019, **361**, 3094; (c) F. Verma, A. Sahu, P. K. Singh, A. Rai, M. Singh and V. K. Rai, *Green Chem.*, 2018, **20**, 3783; (d) B. Gutmann, J. P. Roduit, D. Roberge and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2010, **49**, 7101; (e) W. Luo, B. Shao, J. Li, D. Song, X. Yi, F. Ling and W. Zhong, *Tetrahedron Lett.*, 2019, **60**, 151206.
- (a) G. Steinhäuser and T. M. Klapotke, *Angew. Chem., Int. Ed.*, 2008, **47**, 3330; (b) R. P. Singh, R. D. Verma, D. T. Meshri and J. M. Shreeve, *Angew. Chem., Int. Ed.*, 2006, **45**, 3584.
- P. Srihari, P. Dutta, R. S. Rao, J. S. Yadav, S. Chandrasekhar, P. Thombare, J. Mohapatra, A. Chatterjee and M. R. Jain, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5569.
- V. Pimenta, J. Lhoste, A. Hemon-Ribaud, M. Leblanc, J. M. Greneche, L. Jouffret, A. Martel, G. Dujardin and V. Maisonneuve, *Cryst. Growth Des.*, 2015, **15**, 4248.
- M. Nasrollahzadeh, M. Maryami, M. Sajjadi and E. Mehdipour, *Appl. Organomet. Chem.*, 2019, **33**, 4730.
- A. A. S. Elahl, S. S. Elmorsy, A. H. Elbeheery and F. A. Amer, *Tetrahedron Lett.*, 1997, **38**, 1257.
- S. D. Guggilapu, S. K. Prajapati, A. Nagarsenkar, K. K. Gupta and B. N. Babu, *Synlett*, 2016, **27**, 1241.
- M. Halder, M. M. Islam, P. Singh, A. S. Roy, S. M. Islam and K. Sen, *ACS Omega*, 2018, **3**, 8169.
- (a) N. Kaur, *Synth. Commun.*, 2019, **49**, 1633; (b) R. Mittal and S. K. Awasthi, *Synthesis*, 2019, **51**, 3765; (c) H. Fatahi, M. Jafarzadeh and Z. Pourmanouchehri, *J. Heterocycl. Chem.*, 2019, **56**, 2090; (d) M. A. E. A. A. El-Remaily and O. A. Elhady, *Appl. Organomet. Chem.*, 2019, **33**, 4989; (e) S. Molaei and M. Ghadermazi, *Appl. Organomet. Chem.*, 2019, **33**, 4854; (f) S. B. Bhagat and V. N. Telvekar, *Synlett*, 2018, **29**, 874; (g) B. Yakambram, A. J. Shree, L. S. Reddy, T. Satyanarayana, P. Naveen and R. Bandichhor, *Tetrahedron Lett.*, 2018, **59**, 445; (h) J. M. Chretien, G. Kerrie, F. Zammattio, N. Galland, M. Paris, J. P. Quintard and E. L. Grogneq, *Adv. Synth. Catal.*, 2019, **361**, 747; (i) D. Cantillo, B. Gutmann and C. O. Kappe, *J. Am. Chem. Soc.*, 2011, **133**, 4465; (j) Z. P. Demko and K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945.
- B. Mitra, S. Mukherjee, G. C. Pariyar and P. Ghosh, *Tetrahedron Lett.*, 2018, **59**, 1385.
- R. R. Chakraborty and P. Ghosh, *Tetrahedron Lett.*, 2018, **59**, 3616.
- X. Xiong, C. Yi, X. Liao and S. Lai, *Tetrahedron Lett.*, 2019, **60**, 402.
- M. Kazemnejadi and A. R. Sardarian, *RSC Adv.*, 2016, **6**, 91999.
- M. B. M. Reddy and M. A. Pasha, *Synth. Commun.*, 2011, **41**, 2081.
- M. Abdollahi-Alibeik and A. Moaddeli, *New J. Chem.*, 2015, **39**, 2116.
- M. M. Hevari, A. Fazeli, H. A. Oskooie, Y. S. Beheshtiha and H. Valizadeh, *Synlett*, 2012, **23**, 2927.
- K. M. Khan, I. Fatima, S. M. Saad, M. Taha and W. Voelter, *Tetrahedron Lett.*, 2016, **57**, 523.
- (a) P. Bao, H. Yue, N. Meng, X. Zhao, J. Li and W. Wei, *Org. Lett.*, 2019, **21**, 7218; (b) L. Y. Xie, Y. L. Chen, L. Qin, Y. Wen, J. W. Xie, J. X. Tan, Y. Huang, Z. Cao and W. M. He, *Org. Chem. Front.*, 2019, **6**, 3950; (c) X. Geng, C. Wang, C. Huang, P. Zhao, Y. Zhou, Y. D. Wu and A. X. Wu, *Org. Lett.*, 2019, **21**, 7504; (d) Y. Xia, H. Huang, F. Zhang and G. J. Deng, *Org. Lett.*, 2019, **21**, 7489; (e) X. Li, T. Feng, D. Li, H. Chang, W. Gao and W. Wei, *J. Org. Chem.*, 2019, **84**, 4402; (f) S. W. Tao, J. Y. Zhou, R. Q. Liu and Y. M. Zhu, *J. Org. Chem.*, 2019, **84**, 8121; (g) L. H. Lu, Z. Wang, W. Xia, P. Cheng, B. Zhang, Z. Cao and W. M. He, *Chin. Chem. Lett.*, 2019, **30**, 1237; (h) F. Ling,



- J. Chen, Z. Xie, H. Hou, Z. Pan, C. Feng, H. Shen and W. Zhong, *J. Heterocycl. Chem.*, 2019, **56**, 3333; (i) C. Wu, L. H. Lu, A. Z. Peng, G. K. Jia, C. Peng, Z. Cao, Z. Tang, W. M. He and X. Xu, *Green Chem.*, 2018, **20**, 3683; (j) Z. Cao, Q. Zhu, Y. W. Lin and W. M. He, *Chin. Chem. Lett.*, 2019, **30**, 2132; (k) M. Sun, J. Jiang, J. Chen, Q. Yang and X. Yu, *Tetrahedron*, 2019, **75**, 130456.
- 19 Z. Wei, J. Li, Z. Wang, P. Li and Y. Wang, *Chin. J. Org. Chem.*, 2017, **37**, 1835.
- 20 M. Klavins, J. Dipane and K. Babre, *Chemosphere*, 2001, **44**, 737.
- 21 (a) M. K. Skopic, K. Gotte, C. Gramse, M. Dieter, S. Pospich, S. Raunser, R. Weberskirch and A. Brunschweiler, *J. Am. Chem. Soc.*, 2019, **141**, 10546; (b) Q. Liu, M. Lu and W. Wei, *Sci. China, Ser. B*, 2009, **39**, 440.

