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A facile synthesis of pyrazole derivatives in neat WERSA

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Herein, we report a simple, convenient and green protocol for rapid synthesis of pyrazole derivatives via three-component reaction of hydrazine hydrate, ethyl acetoaetate and β-nitrostyrenes. Biomass-derived catalyst "Water extract of rice straw ash (WERSA)" was used as a catalyst and solvent. This eco-friendly method is easy to operate and yields range from good to excellent. Easy isolation and open air reaction are added advantages of this protocol.

Keywords: WERSA, 3-methylpyrazole-5-one, β-nitrostyrene, 3-methyl-4-nitro-5-styrylisoxazoles, eco-friendly.

Introduction

In recent years, chemical processes conducted in agro-waste extract solvents have become very fascinating area of research in green chemistry[1]. Recent progress on Biomass-derived catalytic processes gives additional imminent into nature's method of chemical synthesis[2]. Certainly, to conserve the environment, it is necessary to reduce the amount of dangerous and poisonous substances evolving from the regular use of solvents in organic synthesis[3]. In consideration of this, agro-waste extract based solvents was a enviable medium for catalysis as it is an eco-friendly, non-hazardous and economically attractive medium. Recently, the utilization of nature-feedstock as a reaction medium is very significant in view of green chemistry[4]. The necessary components of a perfect green synthesis were, replacement of hazardous solvents and toxic metal/non-metal catalysts with an eco-friendly solvents such as agro-waste extracts, high atom economic, and catalyst-free synthesis[5]. Therefore, the development of eco-efficient protocols for the synthesis of biologically and medicinally effective scaffolds, has emerged as a remarkable in synthetic organic chemistry[6].

On the other hand, pyrazole-containing compounds are ubiquitous in several natural products, active pharmaceuticals and agrochemical industries[7]. Remarkably, pyrazoles and their analogues act as antimicrobials, analgesics, anti-inflammatory agents and oncology drugs[8]. Specially, some of the leading commercial drugs based on the pyrazole scaffold include celecoxib[9], lonazolac[10] and rimonabant (Fig. 1)[11]. Synthesis of such pyrazole analogues using Biomass-derived catalyst and medium is always highly significant.

Recently, many methods have been developed for the synthesis of pyrazole derivatives by Michael addition of 2-methylpyrazol-5-one to α,β-unsaturated carbonyls[12], β-nitrostyrenes[13] and 3-methyl-4-nitro-5-styrylisoxazoles[14]. But these protocols frequently suffer from some drawbacks, such as high cost, toxic or air-sensitive catalysts, harmful metals, harsh reaction conditions, necessity to maintain an inert atmosphere, solvents, additives, specialized apparatus, longer reaction times, and tedious workup procedures. Hence, the development of an efficient, general and convenient method for the synthesis of pyrazole derivatives is still immense value. Based on the biological significance of pyrazole derivatives in mind and as a part of our interest in establishing eco-friendly, green and safe protocols, herein we attach a one-pot, three-component method for the synthesis of diverse pyrazole derivatives.

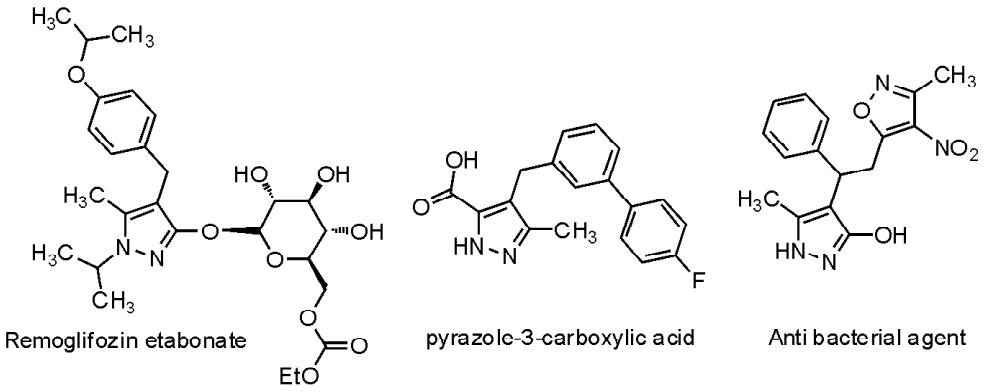


Fig. 1. Some biologically active pyrazole compounds.

Experimental

Materials:

All chemicals were of analytical grade and used without any further purification. Ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes, nitromethane, 3,5-dimethylisoxazole, were obtained from Sigma-Aldrich and AVRA Pvt. Ltd. Acetic acid, ethanol, methanol and dichloromethane were purchased from Merck.

Preparation of pyrazole derivatives:

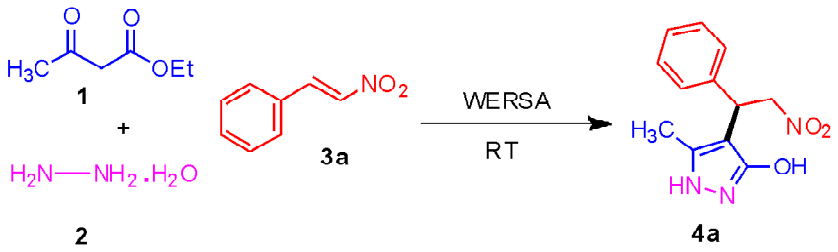
In a typical experiment the ethyl acetoacetate **1** (1 mmol), hydrazine hydrate **2** (1 mmol), β-nitrostyrene **3a-3h**/**6a-6h** (1 mmol) and WERSA (water extract of rice straw ash, pH 12) (3 mL) were placed in a 10 mL round-bottomed flask and stirred at room temperature for 60 min/180 min. After completion of the reaction (monitored by TLC), filtered using sintered glass funnel, and the resulting solid was washed with hot water and diethyl ether and recrystallized from ethanol to give pure compounds. All the synthesized compounds were characterized by (NMR, Mass spectrometry and IR) spectral data.

Characterization methods:

All ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ + DMSO-d_6 (6:4) on Avance 300 or Avance 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual chloroform ($CHCl_3$) (^{1}H: δ 7.26 ppm, ^{13}C: δ 77.00 ppm) as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded on Thermo Nicolet FT/IR-5700 spectrometer. Mass spectra were recorded using Waters mass spectrometer.

Results and discussion

Initially, we employed ethyl acetoacetate (**1**), hydrazide hydrate (**2**) and β-nitrostyrene (**3a**) as model substrates to test the desired three-component reaction in neat WERSA (Scheme 1). We performed a reaction using 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a** and WERSA 3mL (1%) at room temperature. After 60 min, we found 30% product formation (Table 1, entry 1**)**. Later, we carried the reaction with 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a** and WERSA 3 mL with diverse mol percentage i.e. 5, 7, 10 and 20 as de-



Scheme 1

Table 1. Optimization reaction condition for the three-component reaction[a]

Entry	% Concentration of aqueous extract (w/v)	Time (min)[b]	Yield (%)[c]
1	1	60	28
2	5	60	47
3	7	60	69
4	**10**	**60**	**94**
5	20	60	94
6	10	30	68
7	10	90	94
8	10	120	94

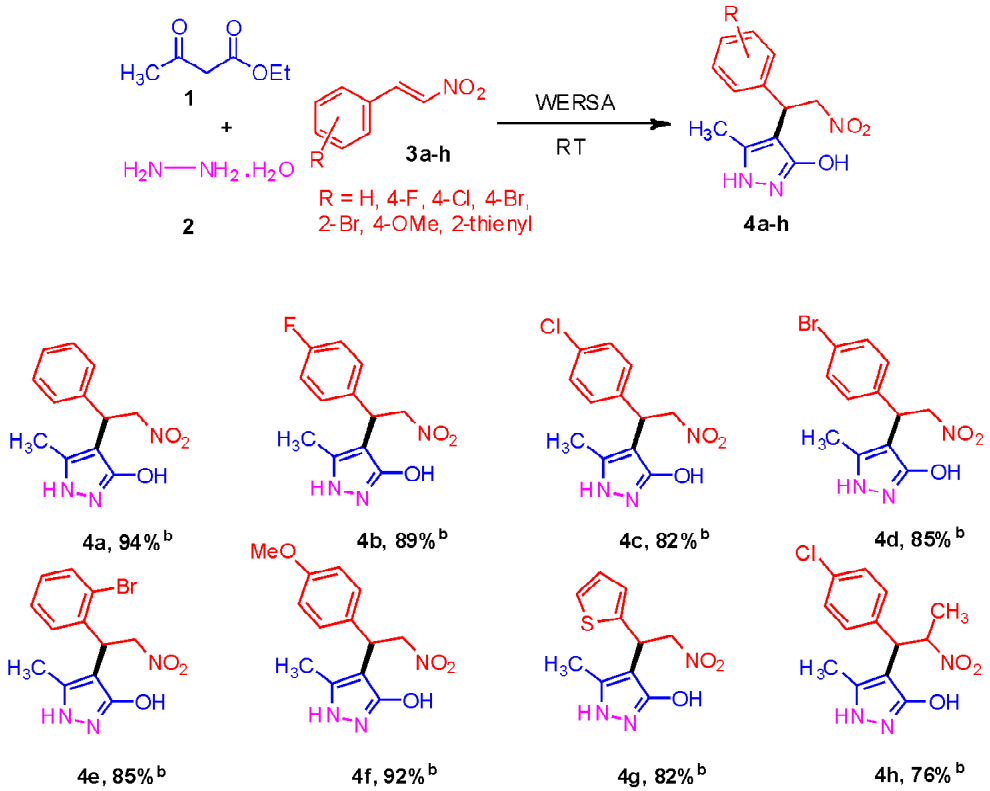
[a]All reactions were carried out with **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and 3 mL WERSA. [b]Reaction time in minutes. [c]Isolated yields of the product.

picted in Table 1 (entries 2, 3, 4 and 5**)**. We observed the increase in yield with increase in mol percentage of WERSA. Finally, we identified 1.0 mmol of **1**, 1.0 mmol of **2**, 1.0 mmol of **3a** and WERSA 3 mL (10%) at room temperature in 60 min gave the desired product with 94% of yield (Table 1, entry 4). The structure of the required product was confirmed by using ^{1}H NMR, ^{13}C NMR, infrared spectroscopy and mass spectrometry.

With the observed reaction conditions in hand, we studied substrate scope of this eco-friendly methodology. To our delight, the protocol is proceeded well with diverse β-nitrostyrenes as shown Table 2 (entries **4a-4h**). The reaction gave good yields with β-nitrostyrenes having electron withdrawing as well as donating groups on phenyl ring. We also used heterocyle β-nitrostyrenes **3g** and **3h** fruitfully as substrates.

In order to enhance the advantages of this green protocol, we checked this reaction with 3-methyl-4-nitro-5-

Table 2. Synthesis of 5-methyl-4-(2-nitro-1-arylethyl)-1*H*-pyrazol-3-ol[a]



[a]Reaction conditions: All reactions were carried out with **1** (1 mmol), **2** (1 mmol), **3a-h** (1 mmol) and 3 mL WERSA. [b]Yield of the product.

styrylisoxazoles as substrates instead of β-nitrostyrenes (Scheme 2). To our delight, the protocol is applicable well with variety of 3-methyl-4-nitro-5-styrylisoxazoles in 180 min (Table 4, entries **6a-6h**), which is more reaction time (Table 3, entries 1-5) when compared with Scheme 1. However, the reaction gave the desired products in good yield with eco-friendly catalyst WERSA and it is advantageous when compared with earlier reports.

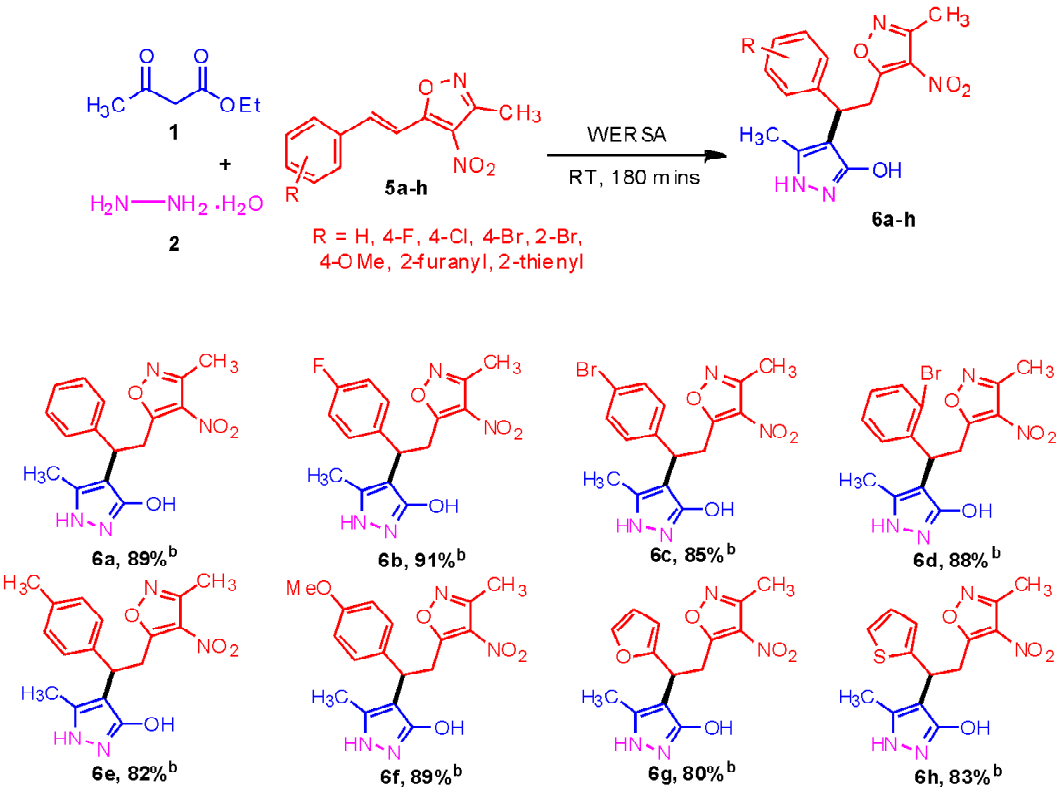
Based on the above studies and earlier reports, a plausible mechanism was suggested as shown in Scheme 3. Initially, ethyl acetoacetate **1** and hydrazine hydrate **2** reacts to form 3-methyl-pyrazol-5-one (**A**). WERSA contains alkali metal ions like K, Na along with CO_3 anions and its pH is around 12 which makes to behave as a base; it helps to remove proton from the 3-methyl-pyrazol-5-one (**A**). Which further undergo conjugate addition with β-nitrostyrene (**4**)/3-methyl-4-nitro-5-styryl-isoxazole (**5**) followed by rearrangement to give the corresponding product **3/6** as depicted in Scheme 2/Scheme 3.

Table 3. Optimization reaction condition for the three-component reaction

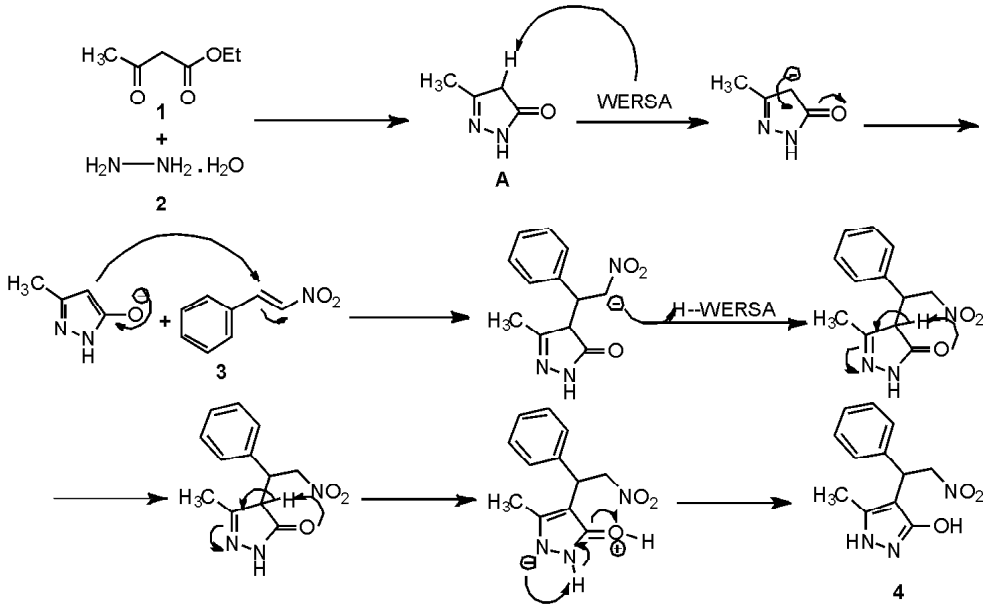
Entry	% Concentration of aqueous extract (w/v)	Time (min)[b]	Yield (%)[c]
1	10	60	42
2	10	90	55
3	10	120	67
4	10	150	82
5	**10**	**180**	**86**
6	10	360	85
7	20	180	86

[a]All reactions were carried out with **1** (1 mmol), **2** (1 mmol), **5a** (1 mmol) and 3 mL WERSA. [b]Reaction time in minutes. [c]Isolated yields of the product.

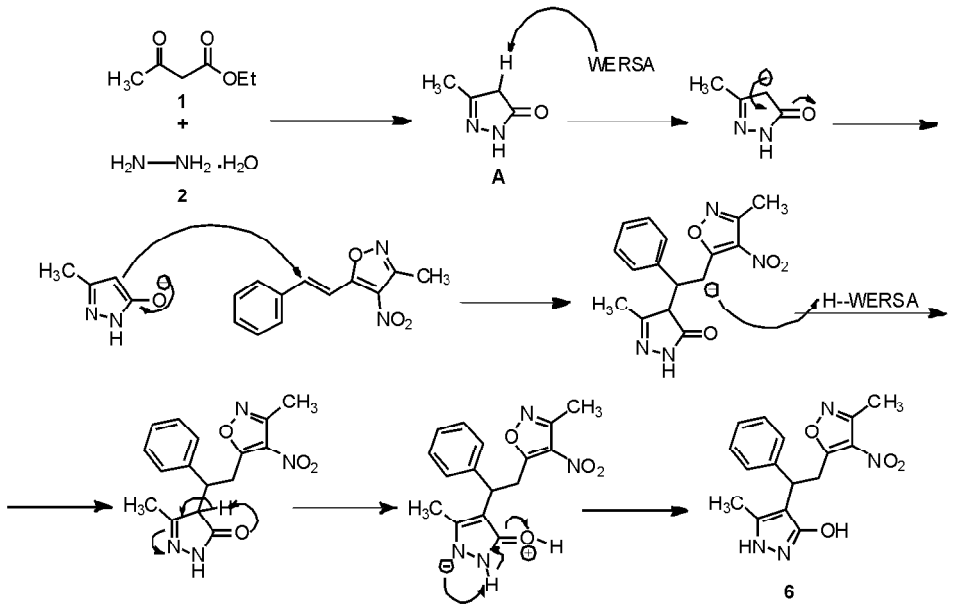
Table 4. Synthesis of 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-arylethyl)-1*H*-pyrazol-3-ol[a]



[a]Reaction conditions: All reactions were carried out with **1** (1 mmol), **2** (1 mmol), **5a-h** (1 mmol) and 3 mL WERSA. [b]Yield of the product.



Scheme 2: Plausible mechanism.



Scheme 3. Plausible mechanism.

Conclusions

In summary, an efficient and environmentally benign method has been developed for the synthesis of diverse pyrazole derivatives via cyclization followed by Michael addition in neat WERSA. The method has an excellent tolerance for various electron-withdrawing and electron-donating substituted reactants. It is important to note that the protocol does not require any catalyst and promoter. Pure form of product was isolated without using column chromatography are the added advantageous of this green protocol.

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References

1. (a) R. A. Sheldon, *J. Chem. Technol. Biotechnol*., 1997, **68**, 381; (b) C. Okerse and H. Bekkun, *Green Chem*., 1999, **1**, 107; (c) P. R. Boruah, A. A. Ali, B. Saikia and D. Sarma, *Green Chem.*, 2015, **17**, 1442; (d) P. R. Boruah, A. A. Ali, M. Chetia, B. Saikia and D. Sarma, *Chem. Commun*., 2015, **51**, 11489; (e) A. Mahanta, M. Mondal, A. J. Thakur and U. Bora, *Tetrahedron Lett*., 2016, **57**, 3091; (f) K. J. Tamuli, D. Dutta, S. Nath and M. Bordoloi, *ChemistrySelect*, 2017, **2**, 7787; (g) N. S. Kumar, V. R. Bheeram, S. B. Mukkamala, L. C. Rao and R. Vasantha, *ChemistrySelect,* 2018, **3**, 1915.
2. (a) L. H. Andrade, *J. Mol. Catal. B: Enzyme*, 2006, **38**, 84; (b) R. Pal, *Open J. Org. Chem*., 2013, **1**, 47; (c) A. Mironowicz, *Phytochemistry*, 1998, **47**, 1531; (d) G. M. Silver, *Plant Physiol*., 1991, **97**, 1588.
3. "Clean Solvents: Alternative Media for Chemical Reactions and Processing", eds. M. A. Abraham and L. Moens, D. C. Washington, ACS Symposium Series, 2002, 819.
4. Manashi Sarmah, *ChemistrySelect*, 2017, **2**, 5180.
5. B. M. Trost, *Angew. Chem. Int. Ed*., 1995, **34**, 259.
6. (a) A. Domling, *Chem. Rev*., 2006, **17**, 106; (b) D. J. Raman and M. Yus, *Angew. Chem. Int. Ed*., 2005, **44**, 1602.
7. H. Junek and H. Aigner, *Chem. Ber.,* 1973, **106**, 914.
8. (a) H. Shiohara, H. Fujikura, N. Fushimi, F. Ito and M. Isaji, *PCT Int. Appl. WO,* 2002, **09**, 8893; *Chem. Abstr.,* 2003, **138**, 24917; (b) N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. S. Robertson and A. E. Surgenor, *Bioorg. Med. Chem*., 2006, **14**, 4792; (c) D. A. Barawkar, A. Meru, A. Bandyopadhyay, A. Banerjee, A. M. Deshpande, C. Athare, C. Kodurum, G. Khose, J. Gundu, K. Mahajan, P. Patil, S. R. Kandalkar, S. Niranjan, S. Bhosale, S. De, S. Mukhopadhyay, S. Chaudhary, S. Koul, U. Singh, A. Chugh, V. P. Palle, K. A. Mookhtiar, J. Vacca, P. K. Chakravarty, R. P. Nargund, S. D. Wright, S. Roy, M. P. Graziano, S. B. Singh, D. Cully and T.-Q. Cai, *ACS Med. Chem. Lett.,* 2011, **2**, 919; (d) D. A. Barawkar, A. Bandyopadhyay, A. Deshpande, S. Koul, S. Kandalkar, P. Patil, G. Khose, S. Vyas, M. Mone, S. Bhosale, U. Singh, S. De, A. Meru, J. Gundu, A. Chugh, V. P. Palle, K. A. Mookhtiar, J. P. Vacca, P. K. Chakravarty, R. P. Nargund, S. D. Wright, S. Roy, M. P. Graziano, D. Cully, S. B. Singh and T.-Q. Cai, *Bioorg. Med. Chem. Lett*., 2012, **22**, 4341.
9. T. D. Penning, *J. Med. Chem*., 1997, **40**, 1347.
10. R. Riedel, *Arzneimittelforschung*., 1981, **31**, 655; D. Penning, *J. Med. Chem*., 1997, **40**, 1347.
11. M. Isidro and F. Cordido, *Mini Rev. Med. Chem*., 2009, **9**, 664.
12. (a) H. A. Etman, A. S. El-Ahl and M. A. Metwally, *Arch. Pharm. Res.,* 1994, **17**, 278; (b) S. Gogoi and C. G. Zhao, *Tetrahedron Lett.,* 2009, **50**, 2252; (d) A. N. Alba, A. Zea, Valero, G. Calbet, M. T. Font-Bardia, A. Mazzanti, A. Moyano and R. Rios, *Eur. J. Org. Chem.,* 2011, 1318; (e) Z. Wang, Z. Yang, D. Chen, X. Liu, L. Lin and X. Feng, *Angew. Chem*., 2011, **123**, 5030; (f) H. Mecadon, M. R. Rohman, L. Kharbangar, B. M. Laloo, L. Kharkongor, M. Rajbangshi and B. Myrboh, *Tetrahedron Lett.,* 2011, **52**, 3228.
13. (a) H. M. Meshram, N. Satish Kumar, N. Jagadeesh Babu, L. Chandrasekhara Rao and N. Nageswara Rao, *Tetrahedron Lett.,* 2013, **54**, 5941; (b) K. S. Rao, P. Ramesh, R. Trivedi and M. L. Kantam, *Tetrahedron Lett.,* 2016, **57**, 1227.
14. N. Muthineni, N. Satish Kumar, L. Chandrasekhara Rao, V. Dileep Kumar, M. Misra, L. Raju Chowhan and H. M. Meshram, *ChemistrySelect,* 2016, **1**, 4197.