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An efficient, multicomponent, green protocol to access 4, 7-dihydrotetrazolo [1, 5-*a*] pyrimidines and 5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4H)-ones using PEG-400 under microwave irradiation

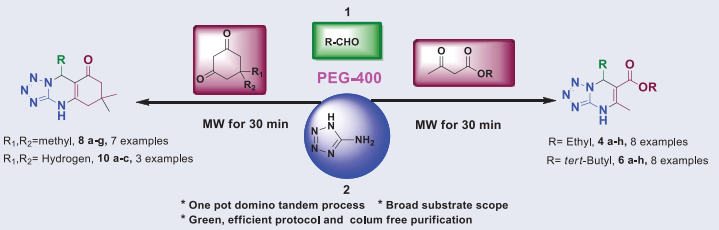
Shaik Firoj Basha, Tangella Nagendra Prasad, Veera Babu Gudise, Vadiga Shanthi Kumar, Naveen Mulakayala, and Shaik Anwar

Division of Chemistry, Department of Sciences and Humanities, Vignan's Foundation for Science, Technology and Research – VFSTR (Deemed to be University), Guntur, India

ABSTRACT

A facile one-pot synthesis of ethyl 5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine, 5-*tert*-butyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine, 6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4H)-one and 5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4H)-one derivatives were described *via* a three-component reaction of aldehyde, 5-aminotetrazole and diketones in PEG-400 under microwave irradiation at 110 °C for 30 min. A wide range of diketones such as ethylacetoacetate, *tert*-butyl acetoacetate, 5,5-dimethylcyclohexane-1,3-dione and 1,3-cyclohexanedione were utilized to carry out the synthesis of different dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones. This method has the advantage of green protocol, operational simplicity, high yields, recyclability of the solvent and involves isolation of the final product without column purification. The scope of this reaction tolerates with aromatic, heteroaromatic and alicyclic aldehydes.

GRAPHICAL ABSTRACT



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Introduction

Multicomponent reactions [MCR][1–7] are those in which two or more reactants react in a reaction vessel to form a single complex structure in which most of the atoms of

CONTACT Shaik Anwar shaikanwarcu@gmail.com, drsa_sh@vignan.ac.in Division of Chemistry, Department of Sciences and Humanities, Vignan's Foundation for Science, Technology and Research – VFSTR (Deemed to be University), Guntur 522213, India. https://www.vignan.ac.in/bshanwar.php

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starting materials are retained. In general, ideal multicomponent reactions are the one which proceeds by simple one reactant addition on another reactant without isolation of intermediate and leads to the formation of a single complex structure (or) cyclic structures.[8] There are several approaches in multicomponent reactions, i.e., transition metal catalyzed MCR, acid catalyzed MCR, non-catalyzed MCR and MCR involving cycloadditions. Among the group of multicomponent reactions, PEG-400[9–11] mediated non-catalyzed multicomponent reactions played a vital role towards the synthesis of a variety of heterocyclic compounds with simple and easy workup procedures as well as high yields of isolated products. Moreover, multicomponent reactions are highly chemoselective, flexible, convergent and atom economy process. Over the decades, there are several reports for the development of multicomponent reactions which explored the fields of pharmaceutical industry, academics, and combinatorial chemistry. In general, the concept of multicomponent reactions is to replace the hazardous and toxic chemical processes by carrying out reactions in neat condition[12] while heating the reactants (or) by using PTC (or) by using ionic liquids (or) usage of eco-friendly solvent, that is, water as a medium. In 1900, Bulow was the first person to describe the formation of ditetrazolopyrimidines from the reaction of cyclic β-diketonoes (or) β-keto esters with 5-aminotetrazole and carboxaldehyde.[13] The synthesis of heterocyclic compounds via MCR strategy is gaining importance in both industrial and academics due to its widespread applications in the development of new drugs.[14] Pyrimidine derivatives are the important class of heterocyclic compounds, present in the wide variety of drugs and is an essential constituent of nucleic acids.[15] Tetrazolopyrimidines are a class of heterocyclic compounds which exhibit the properties of pyrimidine as well as tetrazole skeleton. Several API ingredients contains the pyrimidine as well as tetrazole as their core moiety (Fig. 1).[16,17]

Some of the compounds having pyrimidine and tetrazole moiety exhibit the broad spectrum of biological activity includes antiplatelet and vasodilator[18] (trapidil), anticancer[19] (monastrol), antitumor,[20] inhibitor of Hepatitis B Virus Surface Antigen Secretion,[21] anticonvulsant,[22] antidiabetic,[23] antibacterial,[24] antihypertonic.[25]

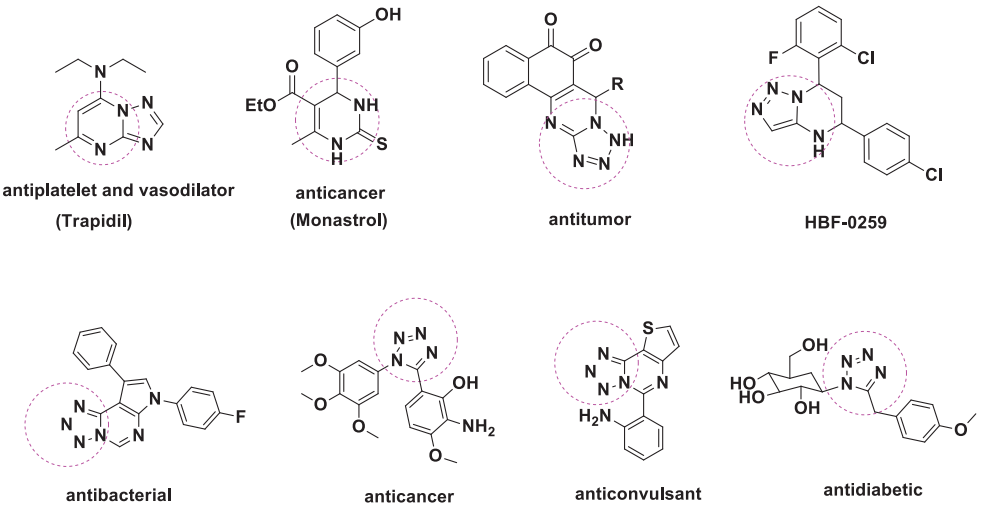
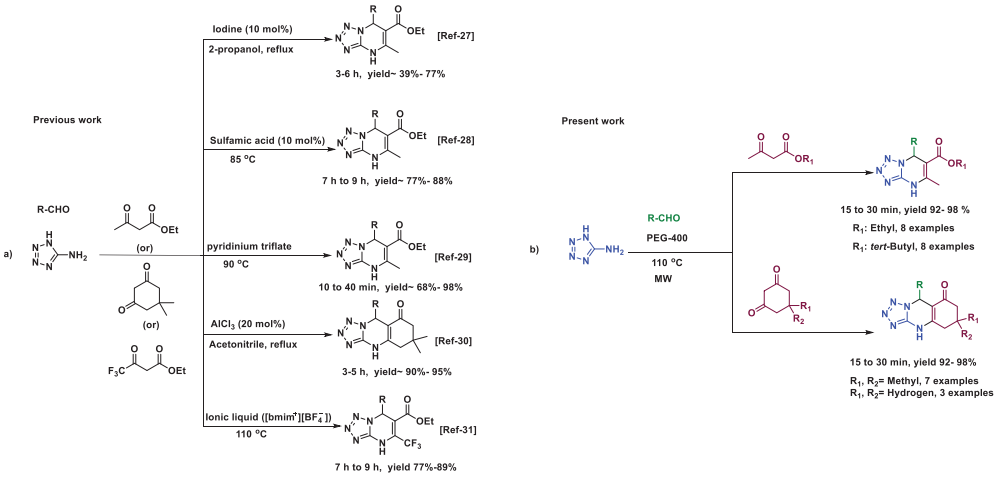


Figure 1. Active drugs containing pyrimidine and tetrazole nucleus as their core unit.



Scheme 1. Previous and present one-pot methods to the synthesis of dihydrotetrazolopyrimidines.

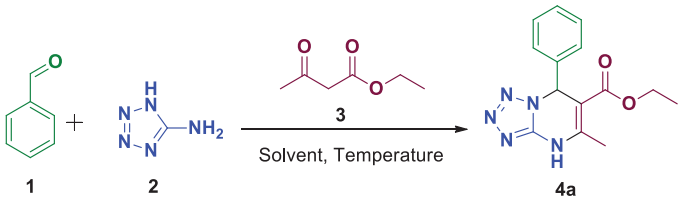
Along with the different biological activities, macrocyclictetrazole moiety[26] serves as a basis for medical diagnostic composite in MRI scan. The previous methods[27–34] for the synthesis of heterocyclic tetrazolopyrimidines involves the use of toxic reagents, tedious workup, laborious isolation of products from the reaction mixture.[35–37] Therefore, the approach towards an environmentally benign, simple and convenient, protocol for the synthesis of 4,7-tetazolopyrimidines is still in demand. Here, we have carried out an efficient one-pot three-component synthesis of tetrazolopyrimidines under microwave irradiation in moderate-to-high yields using polyethylene glycol-400(PEG-400) as eco-friendly reaction medium (Scheme 1).

PEG-400 was utilized in our multicomponent reaction is to serve as catalyst and solvent simultaneously. The microwave irradiation reaction promotes the formation of tetrazolopyrimidine is a simple, an effective and gave the promising yields within a short duration of time. This method avoids the usage of metal halides, carcinogenic solvents and longer reaction time. In addition to simple operation, the method of purification is also simple, it involves the treatment of reaction mixture with cold water, the precipitate formed was filtered, air dried to afford the desired products.

Results and discussion

At first, we have carried out the reaction of benzaldehyde **1**, 5-amino tetrazole **2** and diketoester such as ethyl 3-oxobutanoate **3** (Scheme 2). The effect of solvent on the rate of reaction was studied with different solvent systems as summarized in Table 1.

The desired products 7-substituted-ethyl 5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate **4a** was obtained in 43% yield for ethylacetate (entry 1, Table 1). Use of acetonitrile as solvent gave promising results for the formation of product **4a** (entry 2–3, Table 1). Further improvement in the yield for product formation was observed for ethanol as solvent (entry 4–5, Table 1). Increasing the polarity of solvents, that is, acetic acid and DMF could not improve the yield of the reaction (entry 6–9, Table 1).



Scheme 2. Synthesis of ethyl 5-methyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate **4a**.

Table 1. Optimization of reaction condition for synthesis of **4a**[a].

S. No.	Solvent	Temperature	% of Yield[b]	Time in MW
1	EtOAc	80 °C	43%	30 min
2	ACN	80 °C	74%	30 min
3	ACN	110 °C	75%	30 min
4	Ethanol	80 °C	82%	30 min
5	Ethanol	110 °C	84%	30 min
6	Acetic acid	80 °C	71%	30 min
7	Acetic acid	110 °C	74%	30 min
8	DMF	80 °C	75%	30 min
9	DMF	110 °C	79%	30 min
10	PEG-400	80 °C	81%	30 min
11	PEG-400	110 °C	92%	15 min
12	PEG-400	110 °C	93%	30 min

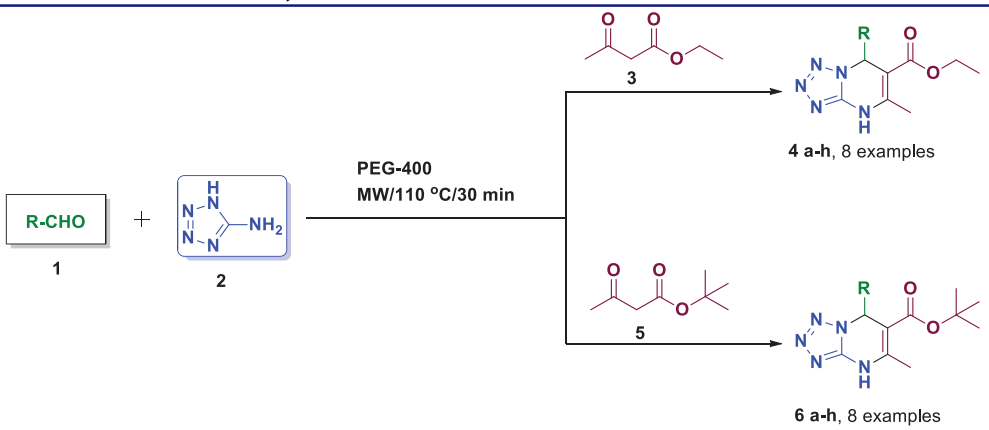
[a]Experimental conditions: aldehyde **1** (4.71 mmol), 1-H-5-aminotetrazole **2** (4.71 mmol), ethyl acetoacetate **3** (4.71 mmol), PEG-400 (5 mL).
[b]Yields of isolated products.

Finally, the use of PEG-400 as solvent resulted in complete conversion with gradually increase in the rate reaction at a higher temperature of 110 °C (entry 10–11, Table 1).

In addition to polarity of the solvent, there is a slight increase in the rate of reaction with the increase in time from 15 to 30 min under microwave irradiation (entry 12, Table 1). A range of 4, 7-dihydrotetrazolo [1,5-*a*]pyrimidines **4** and **6** were synthesized in good to excellent yields using this protocol. The scope of current protocol was applicable to wide range of aromatic aldehydes containing electron withdrawing and donating groups with >90% yield (entries 2–4, 8–9, 11–12 and entry 16, Table 2). Even heteroaromatic aldehydes and alicyclic carboxyaldehydes like cyclopropane aldehyde gave commendable results when compared to the previous methods of synthesis (entries 5–7, 10 and entries 13–15, Table 2). This method is simple and more convenient to synthesis of tetrazolpyrimidine with different carboxyaldehydes. The presence of multiple electron withdrawing and donating substituents did not affect the yield as compared to previous methods of synthesis.

Using the optimized conditions, we further explored the scope of current protocol using cyclic diketones such as dimedone **7** and 1,3-cyclohexanedione **9** (Table 3). Aromatic aldehydes containing electron withdrawing and donating groups gave excellent yield for product formation (entries 1–5, Table 3). Heteroaromatic aldehydes also retained maximum yield without any drop toward product formation (entry 7 & 10, Table 3). Even alicyclic carboxyaldehydes like cyclohexane and cyclopropane aldehyde

Table 2. Microwave assisted synthesis of **4a–h** and **6a–h** in PEG-400.[a]



S. No	Product	R	Yield[b]
1	**4a**	C_6H_5	93%
2	**4b**	3-Br C_6H_4	94%
3	**4c**	4-F C_6H_4	92%
4	**4d**	3,5-F_2 C_6H_3	93%
5	**4e**	2-C_4H_3S	92%
6	**4f**	4-C_5H_4N	92%
7	**4g**	2-C_4H_3O	93%
8	**4h**	3,4,5-$(OCH_3)_3C_6H_2$	92%
9	**6a**	3,5-F_2 C_6H_3	92%
10	**6b**	4-C_5H_4N	94%
11	**6c**	4-CH_3-S-C_6H_4	91%
12	**6d**	4-F C_6H_4	96%
13	**6e**	2-C_4H_3O	92%
14	**6f**	2-Cl-3C_5H_3N	93%
15	**6g**	C_3H_5	91%
16	**6h**	4-CN C_6H_4	93%

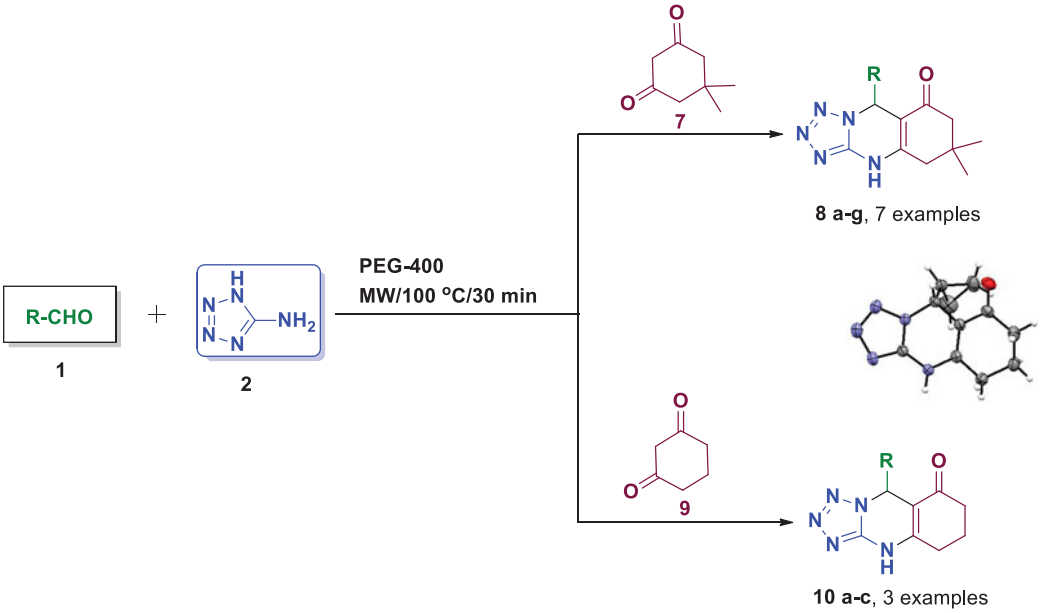
[a]Experimental conditions: carboxyaldehyde **1** (4.71 mmol), 1-H-5-aminotetrazole **2** (4.71 mmol), ethyl acetoacetate **3** (4.71 mmol) or *tert*-Butyl acetoacetate **5** (4.71 mmol), PEG-400 (5 mL).
[b]Isolated yield.

gave encouraging results when compared to the previous methods of synthesis (entry 6, 8–9, Table 3). The structure of 10b was further confirmed by single crystal XRD.[38]1

It is significantly noted that the current protocol was successfully applied for the preparation of tetrahydrotetrazolo [1,5-*a*]quinazolinone derivatives **8** and **10** with the readily available starting materials. The more advantage of this method involves the simple workup procedure without using solvents for purification technique. The simple workup procedure involves the cooling of reaction mixture to room temperature followed by dilution with cold water (10 mL). Further stirring for about 10–15 min resulted in the formation of solid precipitate which was eventually filtered and dried under vacuum to obtain the desired products. Hence, the optimized protocol avoids the use of column purification and recrystallization techniques to reduce the usage of organic solvents while purification.

From the experimental results, the plausible mechanism proceeds in three steps (Scheme 3). Step 1, involves the formation of Knoevenagel condensation product **A** when aldehyde **1** reacts with ethylacetoacetate **3**. In step 2, 5-aminotetrazole **2** attacks the electrophilic benzylic carbon atom to give **B** by simple hydroamination reaction. The final step involves the

Table 3. Microwave assisted synthesis of **8a–g** and **10a–c** in PEG-400.[a]



S. No	Product	R	Yield[b] (%)
1.	**8a**	4-F C_6H_4	92%
2.	**8b**	3-CF_3 C_6H_4	93%
3.	**8c**	4-CH_3-S-C_6H_4	91%
4.	**8d**	4-NO_2 C_6H_4	96%
5.	**8e**	4-CN C_6H_4	95%
6.	**8f**	C_3H_5	93%
7.	**8g**	2-OH-3C_5H_3N	95%
8.	**10a**	C_6H_{11}	97%
9.	**10b**	C_3H_5	94%
10.	**10c**	2-OH-3C_5H_3N	97%

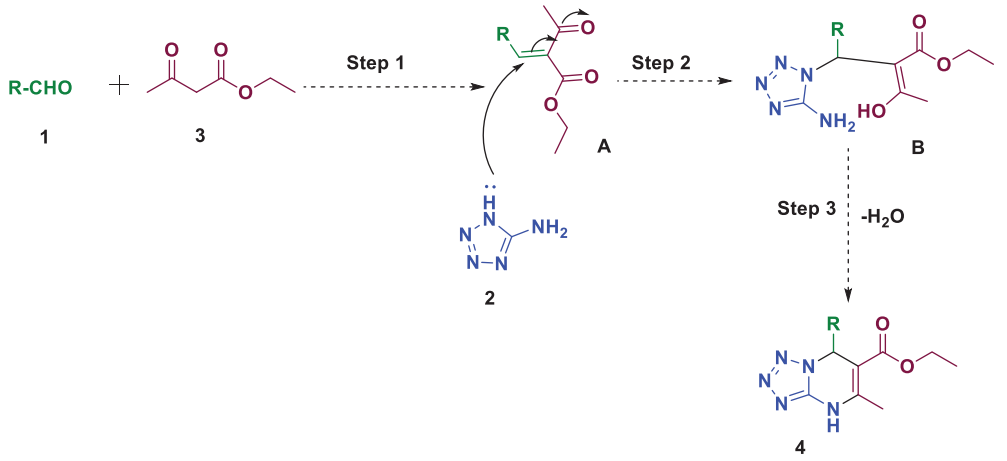
[a]Experimental conditions: aldehyde **1** (4.71 mmol), 1-H-5-aminotetrazole **2** (4.71 mmol), dimedone 7 (4.71 mmol) or 1,3-cyclohexanedione **9** (4.71 mmol), PEG-400 (5 mL).
[b]Isolated Yield.

dehydration followed by cyclization to give the product dihydrotetrazolopyrimidine **4**. In the overall reaction mechanism, PEG-400 acts as catalyst and solvent simultaneously.

Experimental

Materials and methods

Starting materials 5-Aminotetrazole, ethyl acetoacetate, *tert*-butyl acetoacetate, dimedone, 1,3-cyclohexanedione was obtained from commercial suppliers and carboxaldehydes are used in the reaction are freshly distilled at the time of reaction to avoid the presence of corresponding acid byproduct in aldehyde. Microwave reaction performed in CEM microwave apparatus at 110 °C for 15–30 min. Analytical thin-layer chromatography was performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates were visualized by exposure to ultraviolet light. All melting points are uncorrected. Mass and LC-MS spectra were taken on Agilent LC-MS 1100 series



Scheme 3 Plausible mechanism for the formation of product **4.**

instrument in the electrospray ionization (positive ESI) mode. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively in DMSO-d_6. Chemical shifts were reported in ppm from internal TMS (δ). FT-IR was done on solid-phase KBr pellets.

General procedure for the synthesis of 4, 7-dihydrotetrazolo [1,5-a]pyrimidine 4 in PEG-400

To a stirred solution of aldehyde **1** (4.71 mmol), 5-aminotetrazole **2** (4.71 mmol) and ethyl acetoacetate **3** (4.71 mmol) in polyethylene glycol (PEG)-400 (5 mL) and the mixture was heated at 110 °C for 30 min under microwave irradiation. The progress of the reaction was monitored by TLC. After completion of reaction, cooled to RT, diluted with cold water (20 mL), solid precipitated was filtered, washed with diethyl ether (20 mL), and dried under vacuum.

Conclusion

In conclusion, we report an inexpensive, fast and efficient synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones from active methylene groups containing substrates like ethyl acetoacetate **3**, *tert*-butylacetoacetate **5**, dimedone **7**, 1,3-cyclohexanedione **9** with diverse carboxyaldehydes and 5-aminotetrazole in PEG-400 at 110 °C for 30 min under microwave irradiation. This green protocol was applied to alicyclic carboxyaldeydes along with aromatic aldehyde containing electron withdrawing groups as well as donating groups with good yields compared to the previous methods of synthesis. The method of synthesis showed great tolerance towards diverse substrates containing acid and base sensitive functional groups. The great advantage of this method of synthesis involves the simple workup procedure and the isolation products with excellent yields. In addition to simple operation, purification of products involves treating the reaction mixture with cold water resulting in precipitate formation to afford desired products.

Full experimental detail containing IR, ^{1}H, ^{13}C NMR spectra, Mass and Elemental analysis. This material can be found via the "Supplementary Content" section

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Note

1. The deposition number for **10b** CCDC 1948865.

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ORCID

Shaik Firoj Basha http://orcid.org/0000-0002-8700-9336
Veera Babu Gudise http://orcid.org/0000-0002-6368-0256
Vadiga Shanthi Kumar http://orcid.org/0000-0003-4909-8531
Naveen Mulakayala http://orcid.org/0000-0002-5621-6455
Shaik Anwar http://orcid.org/0000-0001-9383-2882

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