



## A rapid solid supported synthesis of 4-amino-5-(pyridin-4-YL)-4H-1,2,4-triazol-3-thiol and its derivatives

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### ABSTRACT

1,2,4-Triazoles and its substituted derivatives were synthesized since these compounds are known for their excellent antibacterial, antifungal, anti-tubercular, antioxidant, anticancer, anti-inflammatory, analgesic, anticonvulsant and anxiolytic activities. 1,2,4-triazole and substituted derivatives of 1,2,4-triazole were synthesized using solid state microwave irradiation technique and synthesized compounds were characterized by UV-Visible, FTIR and GC-MS techniques and in future study the biological activities of synthesized compounds will be studied.

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**Capsule Summary:** In view of 1,2,4-Triazoles and its substituted derivatives biological activities, 1,2,4-Triazoles and its substituted derivatives were synthesized by solid state microwave irradiation technique and characterized using advanced techniques.

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### INTRODUCTION

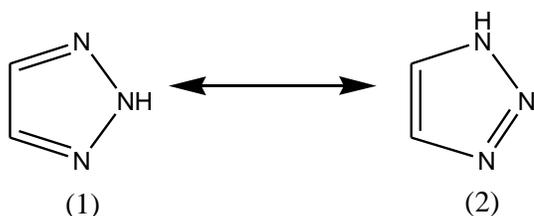
A non-classical heating method "microwave" named as "bunsen burner of the 21<sup>st</sup> century" is strongly decreasing reaction times and gaining publicity. In the progress of man-made processes, green chemistry in which microwave is used have succeeded for example drugs and proper chemical synthetic processes that are rather more practical. This developing microwave-aided chemistry is not producing chemical waste products. In these organic reactions and transformations, time is becoming reduced. Different kind of substitutes such as solid support reagents, green reaction mixture i.e. watery, ionic liquid and solventless are included

in MW-sponsored transformations for the production of various heterocycles, coupling reactions, redox reactions etc (Vivek and Rajender, 2008).

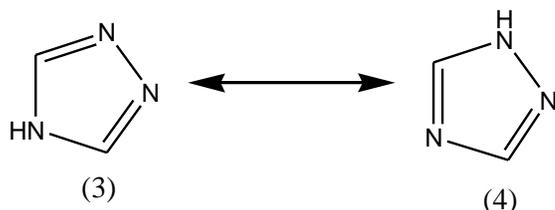
In the mid 1980s, microwave heating was used in organic synthesis. "Usage of microwave in organic reactions" 1<sup>st</sup> news about this case were published by the assemblies of Richard Gedye (1986) and George et al. (1986). Usually domestic microwave ovens are used in many chemical reactions. They are used in many organic chemical reactions because these ovens are freely available and low-cost. Microwave heating is very speedy. Microwave induced organic synthesis techniques has its own significance as compared to usually heating reactions, though they have the same finishing temperature and these both are used for performing

experiments. A huge number of incidents like blasts have actually been reported in microwave assisted organic synthesis. To avoid such kind of problematic conditions, microwaves have to be modernized and solid supports can be used for these reactions such as alumina, silica, celite, bentonite etc. by eliminating the solvents. Majority of the publications are present containing this kind of work (Cotterill et al., 1998; Deshays et al., 1999).

Five membered ring systems "TRIAZOLES" that consist of two carbon and three nitrogen atoms. They occur in two isomeric forms, one is 1,2,3-triazoles which are present as two unlike tautomeric forms i.e. 2H-1,2,3-triazoles (1) and 1H-1,2,3-triazoles (2). It is known as *osotriazole*.



Similarly the second one is 1,2,4-triazoles which are also present as two unrelated tautomeric forms i.e. 4H-1,2,4-triazoles (3) and 1H-1,2,4-triazoles (4). It is recognized as *triazole*.



In pharmaceutical chemistry, 1,2,4-Triazoles have a great contribution from last two decades because of its vast activities, little poisonousness and good pharmacodynamic and pharmacokinetic outlines. Wide variety of biotic actions are permitted by 1,2,4-triazoles like antibacterial (Gokce et al., 2001; Pintilie et al., 2007; Varvarason et al., 2000), antifungal (Chem et al., 2000; Zan et al., 2002), hypoglycaemic (Mullican et al., 1993; Mhasalkar et al., 1971), antidepressant (Kane et al., 1988), analgesic (Shenone et al., 2001), antitumor (Al-Masoudi et al., 2003), antiproliferative (Wong et al., 2011), antitubercular (Husain et al., 1987), anticonvulsant activities (Chimirri et al., 1999). In recent years, the chemistry of triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. For example, a large number of 1,2,4-triazole-containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety, antimicrobial and antimigraine agents (rizatriptan) and antimycotic activity. Antimycotic active compounds inhibit the biosynthesis of ergosterol by blocking 14- $\alpha$ -

demethylation such as fluconazole (**4a**) and voriconazole (**4b**). Letrozole (**4c**) and anastrozole (**4d**) have 1,2,4-triazole nucleus and are very effective as aromatase inhibitors.

In addition, triazoles undergo different types of reactions to yield other heterocyclic compounds e.g., manich bases (Plech et al., 2013), thioureas (Kucukguzel et al., 2001; Kucukguzel et al., 2008; Kucukguzel et al., 1994), thioethers (Kucukguzel et al., 2001; Kucukguzel et al., 2004) schiff bases, triazolothiadiazoles and triazolothiadiazines (Khan et al., 2013) and triazolothiazines and triazolothiazepines (Abd El-Badih et al., 2012). The researchers have been investigated for in vitro and in vivo metabolism of 1,2,4-triazole. 4-Amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiols (**5**) were used for antimicrobial activity against *Yersinia pseudotuberculosis*, *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Bacillus cereus* and *Staphylococcus aureus* and it disclosed good results (Hacer et al., 2009).

## MATERIAL AND METHODS

Analytical grade chemicals, reagents and solvents and pyrex glassware were used in this research work. VELP Scientific hot plate, Gallenkamp melting point apparatus, U-2800 HITACHI UV-Visible spectrophotometer, IR-Prestige 21 FT-IR and GC-MS spectrometer were from schmadzo corporation.

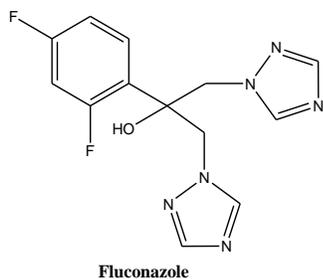
### Step 1 and 2: Synthesis of 4-Amino-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (1)

**Conventional Method:** A mixture of KOH (0.056g), isonicotinic acid hydrazide (0.137g), alumina or bentonite or celite (0.05g) and CS<sub>2</sub> (0.12ml) was stirred in round bottom flask for 5 hours at room temperature. Then, to this mixture, hydrazine hydrate (0.05ml) was added dropwise and refluxed for 5 hours. After reflux, ethanol was added and the reaction mixture was again stirred for 5 mins which was followed by filtration to separate alumina or bentonite or celite. The leftover ethanol was evaporated and 5M HCl was dropwise added to it. The precipitates obtained were filtered, dried and recrystallized with ethanol. Yield: 75%

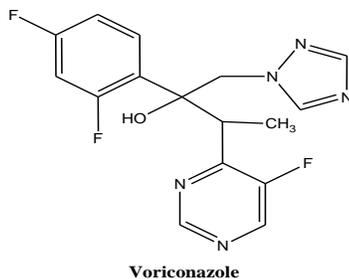
**Microwave Method:** A mixture of KOH (0.056g), isonicotinic acid hydrazide (0.137g), alumina or bentonite or celite (0.05g) and CS<sub>2</sub> (0.12ml) was irradiated for 1 minute of 5 seconds interval. Then, to this mixture, added hydrazine hydrate (0.05ml) and irradiated for 2 minutes of 5 seconds interval. Cooled this mixture to room temperature. Then added ethanol to this mixture and stirred for 5 mins and filtered it to separate alumina or bentonite or celite. The leftover ethanol was evaporated and 5M HCl was dropwise added to it. The precipitates obtained were filtered, dried and recrystallized with ethanol. Yield: 80%

### Step 3: Synthesis of 4-(Alkylidene amino)-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-thiol(6a-f)

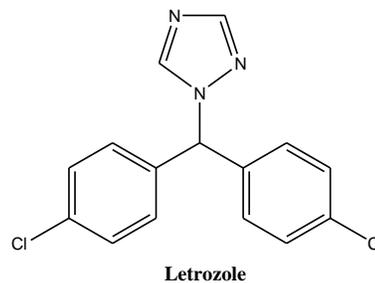
**Conventional Method:** A mixture of 4-Amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol (0.05mmol, 0.01g), few drops of acetic acid, alumina or bentonite or celite (0.005g) and substituted benzaldehyde (0.05mmol) was refluxed for 5



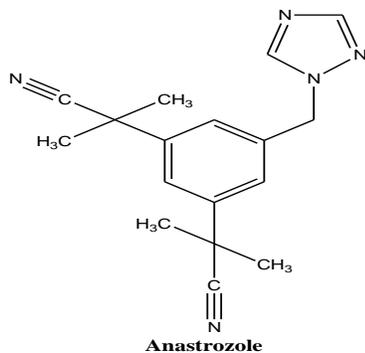
(4a)



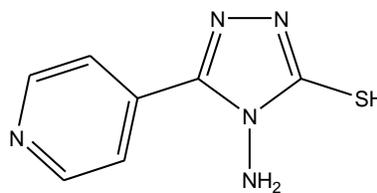
(4b)



(4c)



(4d)



(5)

hours. After reflux, ethanol was added and the reaction mixture was stirred for 5 mins which was followed by filtration to separate alumina or bentonite or celite. Ethanol was evaporated and product was obtained.

**Microwave Method:** A mixture of 4-Amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol (0.05mmol, 0.01g), few drops of acetic acid, alumina or bentonite or celite (0.005g) and substituted benzaldehyde (0.05mmol) was irradiated for 1 minute. Cooled it to room temperature. Ethanol was added and the reaction mixture was stirred for 5 mins which was followed by filtration to separate alumina or bentonite or celite. Ethanol was evaporated and product was obtained.

**4-(p-Methoxyphenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol (6a)**

Yellow solid, mp: 172C<sup>0</sup>,  $\lambda_{\max}$ : 319nm, IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup>: 1512, 1639, 2358, 3431, MS (m/z): 313 [M+H]<sup>+</sup>.

**4-(m-Hydroxyphenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (6b)**

Yellow solid, mp: 215C<sup>0</sup>,  $\lambda_{\max}$  : 310nm, IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1514, 1695, 2312, 3738, MS (m/z): 297 [M+H]<sup>+</sup>.

**4-(m-Chlorophenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (6c)**

Yellow solid, mp: 298C<sup>0</sup>,  $\lambda_{\max}$  : 320nm, IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1417, 1514, 2312, 3442

**4-(p-Chlorophenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (6d)**

Yellow solid, mp: 278C<sup>0</sup>,  $\lambda_{\max}$  : 326nm, IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1512, 1695, 2312, 3489, MS (m/z): 313 [M+H]<sup>+</sup>.

**4-(p-Bromophenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (6e)**

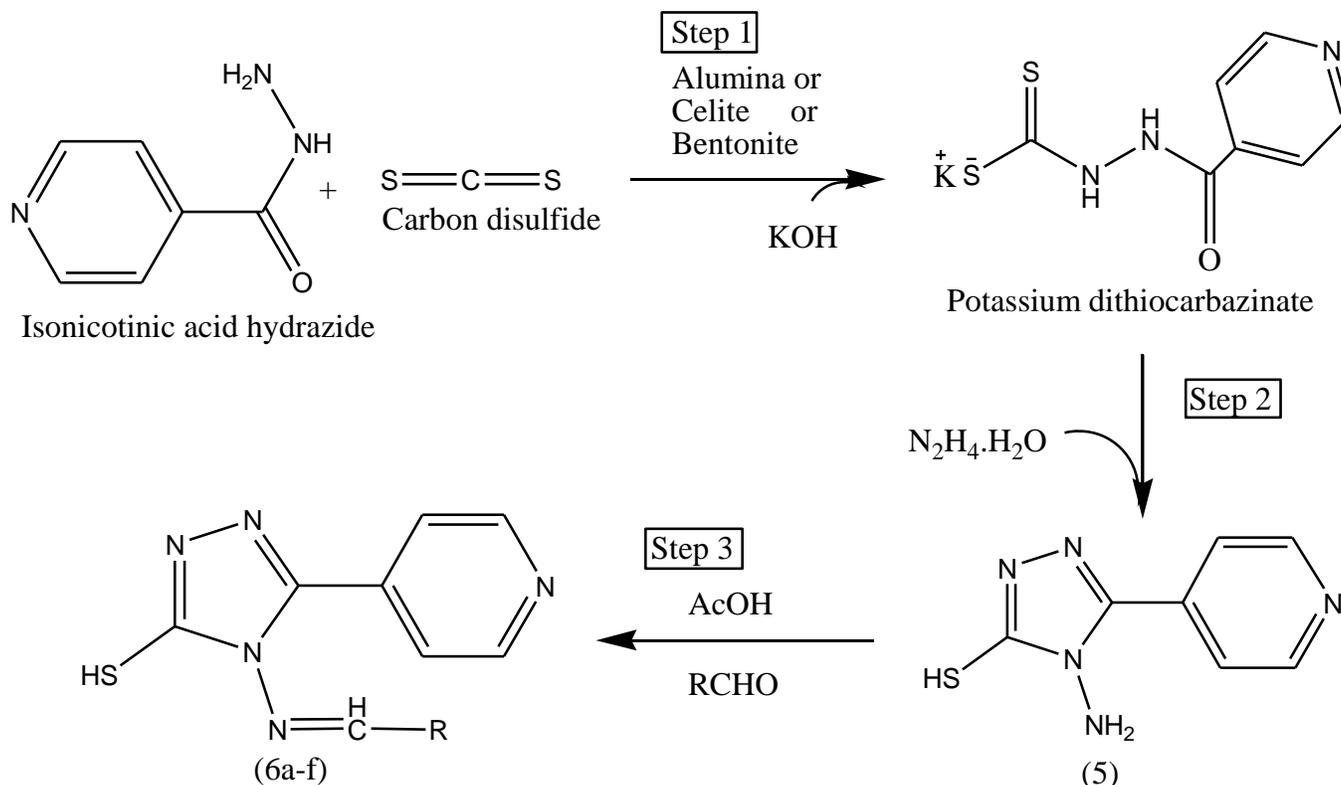
Yellow solid, mp: 256C<sup>0</sup>,  $\lambda_{\max}$  : 318nm, IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1516, 1695, 2358

**4-(p-Fluorophenylmethylidene amino)-5-(pyridine-4-yl)-4H-1,2,4-Triazole-3-Thiol (6f)**

Yellow solid, mp: 245C<sup>0</sup>,  $\lambda_{\max}$  : 320nm, IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 1514, 2358

## RESULTS AND DISCUSSION

Firstly, compound (5) was prepared by the reaction of hydrazine hydrate with potassium dithiocarbazine which was initially prepared when isonicitinic acid hydrazide reacted with CS<sub>2</sub> in the presence of KOH. Then compound (5) was reacted with different aldehydes in the presence of acetic acid to get its derivatives (6a-f). All these three steps were carried out in the presence of solid support. (Scheme 1). After usual workup and purification, the compounds were analysed by UV-Visible, IR and mass spectrometry. Compound (5) showed  $\lambda_{\max}$  of longer wavelength at 320 nm in UV-Visible spectrum. In IR spectrum, compound (5) showed strong absorption at 2358 cm<sup>-1</sup> due to S-H bond.



**Scheme 1:** Synthesis of 4-Amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiols (5) and its derivatives (6a-f)

**Key:** Compound R: 6a = *p*-methoxyphenyl, 6b = *m*-hydroxyphenyl, 6c = *m*-chlorophenyl, 6d = *p*-chlorophenyl, 6e = *p*-bromophenyl and 6f = *p*-florophenyl

Similarly compounds (6a-f) absorbs radiation of longer wavelength above 300 nm in UV-visible region which indicates the presence of C=N, C=C and C–N bonds in these derivatives. These derivatives (6a-f) showed strong absorption at 1695 cm<sup>-1</sup> in IR spectrum due to the presence of C=N bond. It is evident that the Schiff base formation takes place by the nucleophilic attack of amino group of compound (5) on the carbonyl group of aldehydes followed by the elimination of water molecule in step 3. The structure of derivatives (6a-f) were elucidated from MS spectra. Base peak of derivatives was 28 due to the presence of nitrogen or protonated HCN.

## CONCLUSIONS

Solid support microwave technology is particularly attractive where fast, high-yielding procedures and the avoidance or facilitation of purification are highly desirable. Heterocycles have constituted one of the largest areas of research in organic chemistry. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences etc is very well known. Among them, sulfur and nitrogen-containing heterocyclic

compounds have maintained the interest of researchers and their unique structures led to several applications in different areas. 1,2,4-triazoles are important from medicinal, industrial and agricultural point of view. Future studies should be focused on evaluation of biological activities of 1,2,4-triazoles and its derivatives.

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