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Microwave-assisted synthesis of [1,2,4]-triazoles : A short review

Priyanka Rani*, Aastha Pareek and Kishore D.

Department of Chemistry, Banasthali University, Banasthali, Rajasthan, India.

***Corresponding Author:** E-Mail: **priyankapundir0509@gmail.com**

ABSTRACT

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions. Microwave reactions under solvent free conditions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling. The recent introduction of single mode technology assures safe and reproducible experimental procedures and microwave synthesis has gained acceptance and popularity among the synthetic chemist community. By applying the microwave irradiation method, several 1, 2, 4-triazole derivatives were recently reported.

Keywords: Microwave, technique, pollution and reproducible.

1. INTRODUCTION

Triazoles are aromatic five-membered ring systems containing three nitrogen atoms, which can be arranged in two different ways to give either a 1, 2, 3-triazole [1] (1) or a l, 2, 4-triazole (2) (Figure 1). Triazole, has attracted a wide spread attention of the medicinal chemist in search for the new therapeutic agents. Out of its two possible isomers, 1, 2, 4- triazole is a wonder nucleus which possess almost all many types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. In recent years, the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance [2].

1 2

Figure - 1: structures of trizole

1.1 Biological aspects of triazole

The search of new medicinal agents is one of the most challenging tasks to the medicinal chemist. 1,2,4-Triazole nucleus has been incorporated into a wide variety of therapeutically useful materials. A number of biological activity such as antibacterial [3-5], antifungal [6], antimicrobial[7,8] , antimycobacterial[9-11], anti-inflammatory[12,13],analgesic[14],antihypertensive [15], hypolipidemic[16], antitumor[17] and anticancer[18-20] have been associated with N-substituted triazoles attached with different heterocyclic nuclei.

The importance of triazole derivatives in the field of medicinal chemistry owes its origin to the presence of these nitrogen atoms in a five membered ring. These have occupied a unique position in heterocyclic chemistry, due to its various biological activities. Examples of some antifungal drugs are Fluconazole[21] (3), Ravuconazole [22] (4) and Voriconazole [23] (5) (Figure 2). Fluconazole causes second bronchial arch anomalies in mice. Ribose N-glycoside [24] is a broad spectrum antiviral agent containing the 3-aminocarbonyltriazole moiety. It is active against both RNA and DNA viruses and is used in an aerosol for lower respiratory tract viral disease as well as in the treatment of influenza, Lassa fever and Hantaan virus [25]. In addition, it was reported that compounds having triazole moieties, such as vorozole, letrozole and anastrozole appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer [26-28]. 5-HT_1 agonist triptan drugs such as Rizatriptan [29] are prescribed for migraine headaches. A novel and very promising HIV treatment is Pfizer's maraviroc [30] which contain triazole moiety.

1.2. Synthesis of [1,2,4]-triazoles using microwave methods

Cyclization of 1-[(2-methyl-1H-indole)-3-carbonyl]thiosemicarbazides (6) under microwave irradiation using different reaction conditions gave some novel 1,2,4 triazole derivatives [31] (8). (Scheme 1)

Zamani and Bagheri [32] have reported different types of 4,5-disubstituted-1,2,4-triazole-3-thiones (10) by microwave irradiation as well as by a classical method. Microwave irradiation on the reaction resulted in the shortening of reaction times (from 2-9 h to 2-4 min) and a minor decrease (1-4%) in yields. (Scheme 2)

4,5-Disubstituted-1,2,4-triazole-3-thiones (14) have been prepared [33] in one stage from the reaction of acid hydrazide (11) with alkyl or aryl isothiocyanate (12) in the presence of KOH (10%) solution on the surface of silica gel as well as on the surface of montmorrilonite K10 under microwave irradiation. These triazoles (14) have also been prepared from the reaction of 4-substituted-1-aroyl thiosemicarbazides (13), with a KOH (10%) solution on the surface of silica gel under microwave irradiation. (Scheme 3)

Bentiss et. al. [34] have synthesized 3,5-disubstituted-4-amino-1,2,4-triazoles (16) from the reaction of aromatic nitriles (15) with $NH_2NH_2.2HCl$ in the presence of $NH_2NH_2.2H_2O$ in ethylene glycol under microwave irradiation. (Scheme 4)

Yeung et. Al [35] described a convenient and efficient one-step, base-catalyzed synthesis of 3,5-disubstituted-1,2,4-triazoles (19) by the condensation of nitriles (17) and hydrazides (18) under microwave irradiation. (Scheme 5)

Kidwai et. al. [36] have synthesized new antifungal azoles including 1,2,4-triazole derivatives from substituted hydrazide using various solid supports under microwave irradiation, as shown in (Scheme 6).

Condensation of acid hydrazide (22) with S-methylisothioamide hydroiodide (23) and ammonium acetate on the surface of silica gel under microwave irradiation afforded 1,2,4-triazoles [35] (24). (Scheme 7)

Dandia et. Al. [37] have investigated a microwave-assisted cost effective synthesis of 3-substituted-4 amino-5-mercapto-1,2,4-triazole derivatives by condensation of different alkanoic acids (27) and thiocarbohydrazide (25). The use of microwave irradiation allowed a rapid (4-8 min) and high-yielding (90-93%) reaction. (Scheme 8)

Joshi et. al. [38,39] applied microwave methodology for the synthesis of 1,2,4-triazole derivatives 30 starting from aryl potassium dithiocarbazinate (28) and hydrazine hydrate. Hydrazine hydrate itself is quite polar and it was thought that the reactions would precede best in slight excess of hydrazine hydrate, in the absence of any additional solvent. Reactions of 2-mercapto-5-substituted-1,3,4-oxadiazoles (29) with excess of hydrazine hydrate also gave 1,2,4-triazole derivatives 30. (Scheme 9)

Lee et. al.[40] synthesized 3-methyl-1,5-diphenyl-1H-1,2,4-triazole (33) under various reaction conditions by microwave irradiation. (Scheme 10)

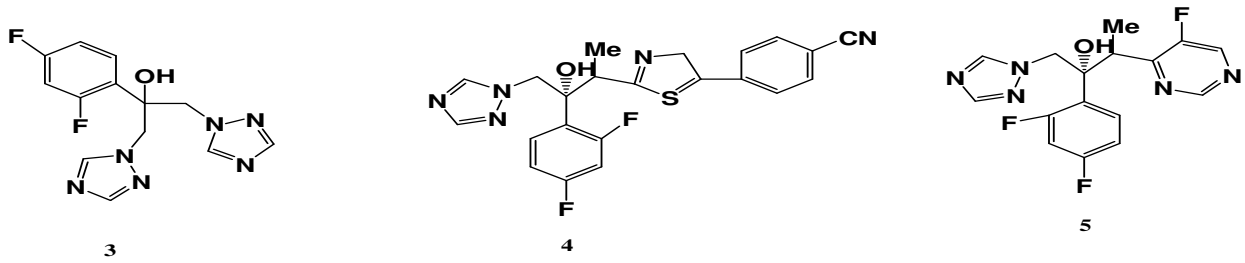
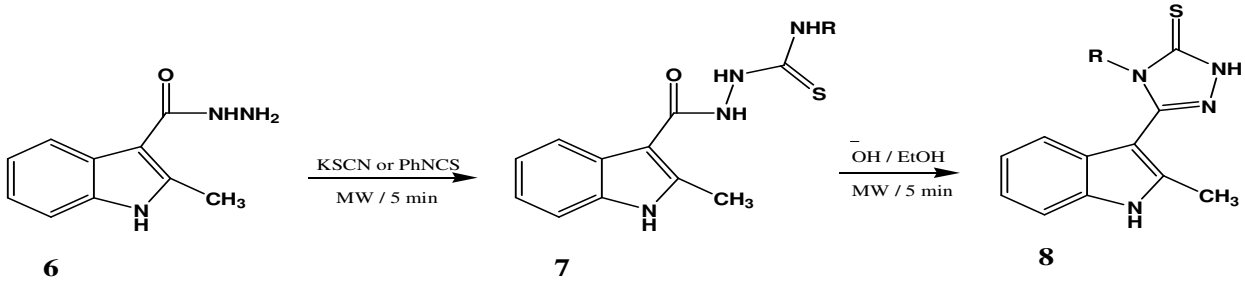
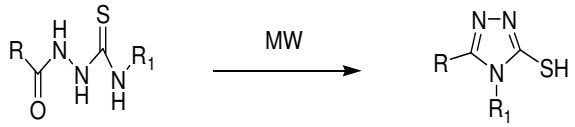


Fig. 2

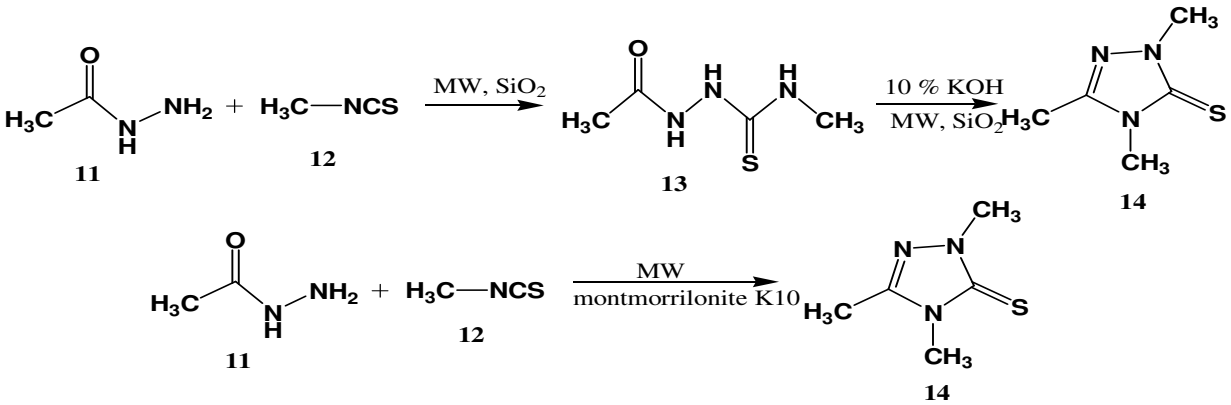


Scheme 1



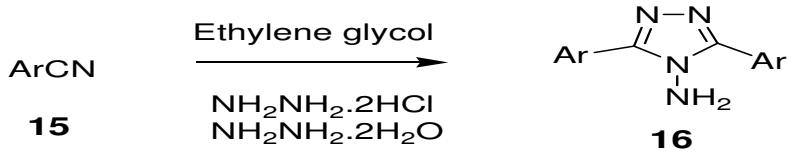
9 **10**

Scheme 2



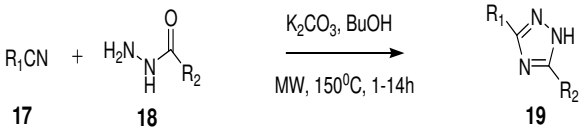
11 **12** **13** **14**

Scheme 3



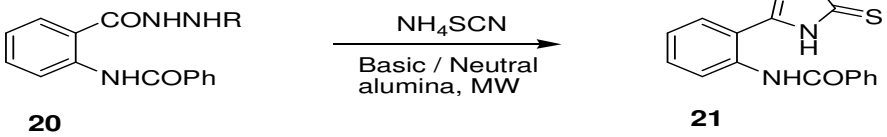
15 **16**

Scheme 4



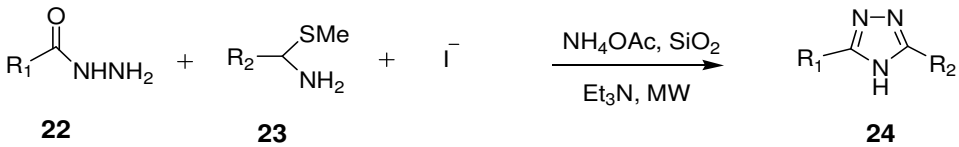
17 **18** **19**

Scheme 5



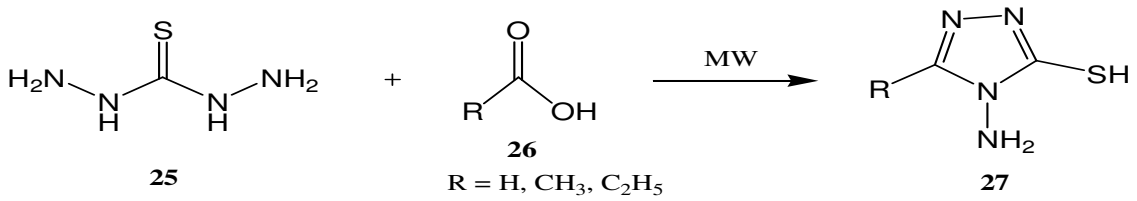
20 **21**

Scheme 6

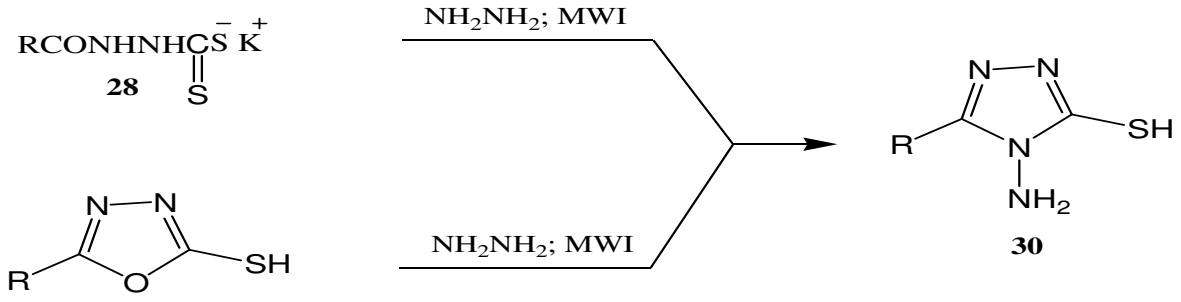


22 **23** **24**

Scheme 7

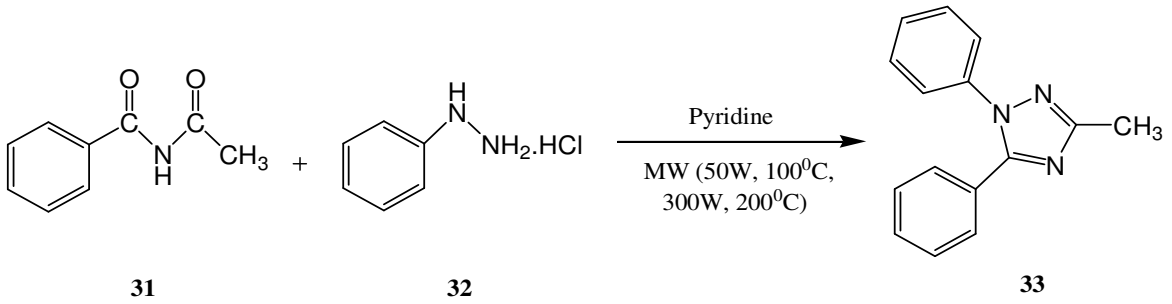


Scheme 8



R = Phenyl
R = 4-chlorophenyl
R = 2-chlorophenyl
R = 4-methylphenyl
R = 4-methoxyphenyl
R = 3-methylphenyl
R = 4' pyridyl

Scheme 9



Scheme 10

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