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Synthesis of Isoniazide Series Derivative in Aqueous Medium

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ABSTRACT

Isoniazide isoxazoles derivatives have been prepared from the reaction of one equivalent of aromatic carboxylic acid, one equivalent isoniazide in the presence of environmentally benign medium. Glycerol in water used as a green medium to increase yield and rate of reaction.

Keywords : isoniazide oxazole, carboxylic acid, glycerol-water, green chemistry

Introduction

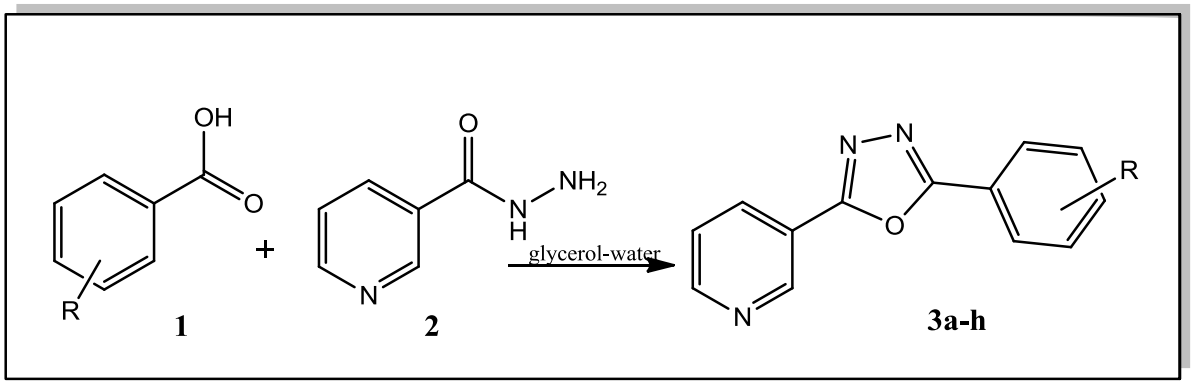
Literature survey reveals that, the synthesis of a diverse range of functionalized heterocyclic moiety are significant to the medicinal chemists as they provide the ability to expand the available drug-like chemical space, which bind to the biological targets based on their chemical diversity[1-3]. They exhibit a robust nature in cell metabolism and are essential components in the pharmaceutical industry [4-5]. To expedite the drug discovery program, it is highly prudent to develop reliable synthetic methods for the generation of a diverse collection of heterocyclic molecules. Over the last few decades, new methods for synthesizing heterocycles have revolutionized. A five membered heterocyclic molecular scaffold i.e. Isoxazole, is broadly used as important compound in the research of drug discovery[6-7]. The versatility of substituted isoxazole in undergoing chemical transformations to produce valuable synthetic intermediates makes them significant synthons as well. Organic compounds consuming the oxazole moiety revealed potent therapeutic efficacy in the field of agriculture and medicine. The isoxazole derivatives have long been used in organic synthesis due to the broad range of biological and pharmaceutical[8-10] activities such as antifungal, antiviral[12], antibacterial[13] antihelmintic[14], hypolipemic[15], anti-allergic[16] emits as characteristics of an agent that blocks histamine.

Pharmacologically important isoxazole[17] are semisynthetic penicillin's, semisynthetic lephalosporins, antibacterial sulfonamides, anabolic steroids, monoamine oxidase inhibitor which is used in the psychotherapy etc. in addition, isoxazole derivatives also used in the treatment of leprosy[18].

Isoniazide is a isonicotic acid hydrazide (INH) is an antibiotic used for the treatment of tuberculosis. For active tuberculosis,it is often used together with rifampin, pyrazinamide and either streptomycin or ethambutol. Isoniazide and a related drug, iproniazid, were among the first drugs to be referred to as antidepressants. Use against tuberculosis continued as isoniazide effectiveness against the disease outweighs its risk. [19] Isonazide is a prodrug that inhibit the formation of the mycobacterial cell wall. The development of isoniazid derivatives has been a focus of pharmaceutical research to address challenges such as drug resistance, side effects, and limited spectrum of activity associated with isoniazid, a widely used first-line antitubercular agent. [20] As a hydrazide derivative of isonicotinic acid, isoniazid possesses a versatile chemical structure that can be modified to create new compounds with enhanced pharmacological properties.

Many researchers worked on the synthesis of isoxazole and screened for the various microbial activity.

Herein, we have developed new environmentally friendly protocol for the synthesis of isoniazid isooxazoles in glycerol medium under microwave.



Scheme 1: Synthesis of isoniazid iso-oxazoles in glycerol-water

Experimental

Material and method

All the chemicals and solvents used were of AR grade and were utilized without additional purification. Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR measurements were taken on a Bruker AC–400F, are presented in parts per million (PPM).

General procedure for the synthesis of isoniazid isooxazole

To a solution of glycerol-water (2:1), aromatic carboxylic acid (1–mmol) and isoniazide (1–mmol) was added. The reaction mixture was irradiated at 400 watt power under microwave at $120^{0}C$. After the completion of reaction, the reaction mixture was poured into ice water. The Solid obtained was filtered, dried and recrystallized from ethanol.

Result and discussion

Isoniazid bearing isoxazole attracted great attention of organic researchers because of their versatile biological important. It promoted our interest to synthesize new compound bearing isoniazid and isoxazole nucleus. Iso-oxazole also important moiety widely used in pharmaceutical chemistry. Initially, we have tried the reaction of

aromatic carboxylic acid (benzoin acid) with isoniazide in green medium. various green medium and catalyst were used for the present reaction such as PEG, cyclodextrin, water, glycerol and ethanol. It was observed that reaction could takes place in all these selected solvents but combination of glycerol and water acts as good solvent for present protocol. This reaction show excited result such as high atom economy and rapid rate of reaction in glycerol-water under microwave irradiation. (**Table 01**).

Table 1 Choice of solvent for present protocol

Solvent	Proportion	Time in (min)	Yield[a]
PEG	--	20	67-69
glycerol	-	10	78-81
Cyclodextrin	-	23	56-67
water	1	12	76-79
Glycerol-water	2:1	5	84-86

[a] isolated yield

To generalize the scope of present protocol we have selected differently substituted aromatic acid and results are detected in **table 2** all the synthesized compounds were well characterized by IR, NMR and Mass spectral analysis.

Table 2 Synthesis of isoniazid-oxazoles

Compounds	Time (min.)[b]	Yield[a]
3a	**5**	**86**
3b	**6**	**82**
3c	**5**	**83**
3d	**6**	**87**
3e	**4**	**85**
3f	**5**	**87**
3g	**6**	**83**
3h	**5**	**82**

[a] isolated yield

[b] time for overall reaction

Spectral data of synthesized compounds

Spectral data *. 2-(pyridin-3-yl)-5-(p-tolyl)-1,3,4-oxadiazole (**3a**).* ***Mass:*** *[ES]⁻: Calculated – 430.21, Found – 429.77.* ***^{1}H NMR*** *(400 MHz, DMSO, δ ppm): 2.34 (s, 3H, -CH_3), 7.29 (d, 1H, Ar-H), 7.57 (dd, 1H, Ar-H), 7.95 (dd, 1H, Ar-H), 8.42 (d, 1H, Ar-H) 8.70 (d, 1H, Ar-H) 9.24 (d, 1H, pyridinyl-H).* ***^{13}C NMR*** *(400 MHz, DMSO, δ ppm): 21.54, 33.58, 35.61, 41.90, 50.71, 73.65, 81.32, 103.31, 109.56, 110.42, 117.26, 127.73, 132.80, 133.41, 141.33, 144.34, 147.85, 150.81, 153.05, 155.74.*

*7-But-2-ynyl-1-(3-methoxy-benzyl)-3-methyl-8-(4-methylene-piperidin-1-yl)-3,4,5,7-tetrahydro-purine-2,6-dione (**5b**).*

Melting point: *178 - 180 ^{o}C.* ***Mass:*** *[ES]⁻: Calculated – 435.23, Found – 434.70.* ***^{1}H NMR*** *(400 MHz, DMSO, δ ppm): 1.78 (s, 3H, -CH_3), 2.35 (d, 1H, -CH), 2.36 (t, 4H, -CH_2), 3.37 (s, 3H, -CH_3), 3.40 (d, 1H, -CH_2), 3.41 (t, 4H, -CH_2), 3.71 (s, 3H, -OCH_3), 4.80 (s, 2H, -CH_2), 4.91 (d, 2H, =CH), 5.00 (s, 2H, -CH_2), 6.79 – 7.22 (m, 4H, Ar-H).*

^{13}C NMR (400 MHz, DMSO, δ ppm): 3.047, 29.49, 33.56, 35.53, 40.12, 50.77, 54.94, 73.73, 81.19, 103.32, 109.54, 111.99, 113.43, 119.46, 129.30, 139.40, 144.39, 147.55, 150.81, 153.21, 155.69, 159.59.

*1-Benzyl-7-but-2-ynyl-3-methyl-8-(4-methylene-piperidin-1-yl)-3,4,5,7-tetrahydro-purine-2,6-dione (**5c**).*

***Melting point:** 215 ^{O}C. **Mass:** [ES]: Calculated – 405.22, Found – 404.77. ^{1}**H NMR** (400 MHz, DMSO, δ ppm): 1.79 (s, 3H, -CH$_3$), 2.34 (d, 1H, -CH), 2.36 (t, 4H, -CH$_2$), 3.37 (s, 3H, -CH$_3$), 3.38 (d, 1H, -CH$_2$), 3.41 (t, 4H, -CH$_2$), 4.80 (s, 2H, -CH$_2$), 4.91 (d, 2H, =CH), 5.03 (s, 2H, -CH$_2$), 7.22 – 7.31 (m, 5H, Ar-H). ^{13}**C NMR** (400 MHz, DMSO, δ ppm): 3.04, 29.45, 33.56, 35.52, 43.34, 50.76, 73.71, 81.19, 103.32, 109.50, 126.91, 127.44, 128.19, 137.84, 144.37, 147.50, 150.79, 153.21, 155.64.*

Conclusion

In this investigation, new series of isoniazide-isooxazole have been successfully synthesized from the reaction of aromatic carboxylic acid and isoniazid in presence of glycerol-water as an environmental friendly, reusable green medium. The most remarkable features of present investigations are cost effective, high atom and step economy, use of green and non-toxic medium and required minimum reaction time.

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