

Synthesis and Characterization of Substituted 1,2,4-Triazole and Its Derivatives

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Isoniazid was agitated with potassium hydroxide and carbon disulphide to yield sulphur-potassium salt which on refluxed with hydrazine hydrate/ammonia to give substituted 1,2,4-triazoles. The synthesized compounds have been characterized by spectral and elemental analysis.

Key Words: Triazole, Amines, Isoniazid, Anti- TB activity.

INTRODUCTION

Heterocyclic compounds promote the formation of life on earth¹. They are widely distributed in nature and essential to life as they play vital role in the metabolism of living cells. Heterocyclic ring system containing hydrogen and nitrogen-sulphur heteroatom exhibited chemotherapeutic² and other medicinal uses.

1,2,4-Triazole are ubiquitous features of many pharmaceutical and agrochemicals products^{3,4}. Triazole nucleus is associated with various pharmacological activities like antimicrobial, antibacterial, antiviral, antifungal effects⁵. Dendrobine a cytotoxic substance from marine tunicate is an example has medicinal value⁶.

Now-a-days substituted 1,2,4-triazole nucleus is commonly example found in various marketed drugs such as flucanazole⁷, tercanazole, rizatriptan, triazole, *etc.* which act as antifungal agent⁸.

There are some other substituted 1,2,4-triazole entities which are very interesting components in terms of their biological properties, such as antibacterial antitubercular, herbicidal and plant growth regular activities have been reported⁹.

Due to these valuable findings and its need, present work has been carried out in the precipitation of substituted 1,2,4-triazole and their derivatives. These compounds were subjected to *in vitro* anti-TB activity against *Mycobacterium tuberculosis* H₃₇ RV. Some of these compounds exhibited good profile of activity.

EXPERIMENTAL

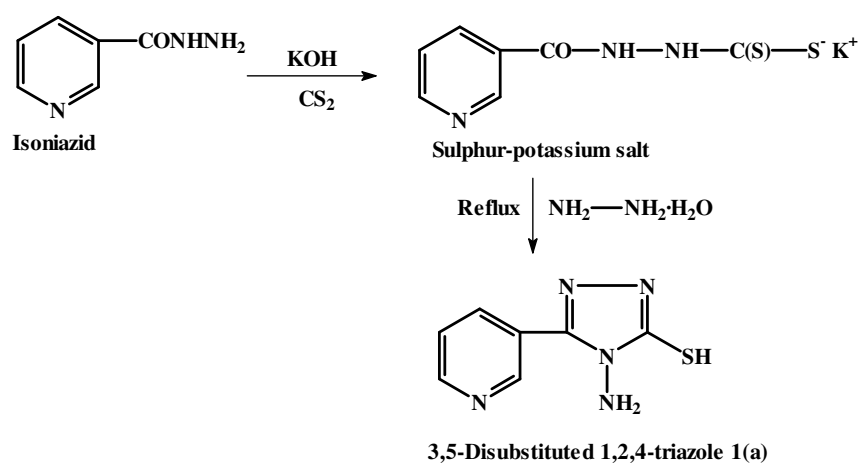
Synthesis of 3-(3-pyridyl)-4-amino-1,2,4-triazole-5-thiol (Ia): Isoniazid (0.01 mol, 1.38 g) was dissolved in absolute ethanol (20 mL). Stirred it for 2 h at room temperature. Meanwhile strong base like potassium hydroxide (0.1 mol, 5.6 g) was separately dissolved in absolute ethanol (20 mL) and carbon disulphide (0.1 mol, 6.28 g) with constant stirring at 25-30 °C, and refluxed for 5 h. The completion of

reaction checked by thin layer chromatography. The paste of sulphur-potassium salt was formed which was added to the isoniazid solution and refluxed for 4 h with continuous stirring. It was then cooled at room temperature to yield the yellow crystals and finally washed by ethanol (25 mL). It was recrystallized in ethanol:water (80:20) to obtain the yellow shiny crystals.

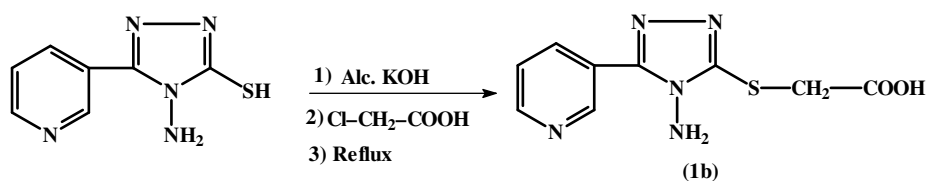
Preparation of derivatives

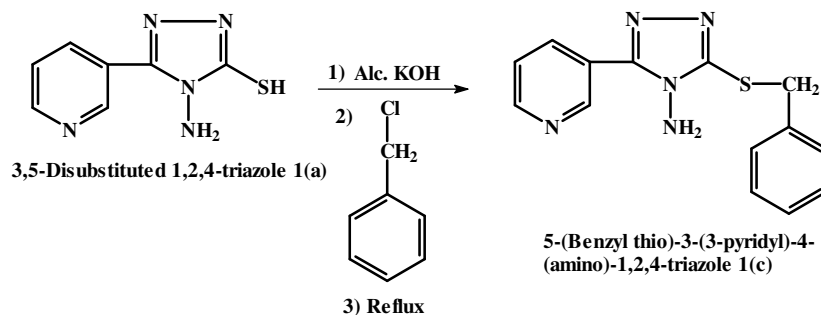
Synthesis of 5-(benzylthio)-3-(3-pyridyl)-4-(amino)-1,2,4-triazole (Ib): An equimolar mixture of 3,5-disubstituted 1,2,4-triazole (1.48×10^3 mol, 0.4 g) and benzyl chloride (1.48×10^3 mol, 1 g) in ethanolic KOH [*i.e.* 0.08 g KOH pellets in 20 mL ethanol] was refluxed for 2 h with continuous stirring which on cooling at 20-25° C yielded a solid mass. The obtained solid was finally recrystallized with water: ethanol (20:80) to give brownish yellow shiny crystals.

Synthesis of 5-(monochlorothio)-3-(3-pyridyl)-4-(amino)-1,2,4-triazole (Ic): A equimolar mixture of 3-disubstituted 1,2,4-triazole (1.48×10^3 mol, 0.4 g) and monochloro acetic acid 1 g and 20 mL alcoholic KOH was refluxed for 3 h with continuous stirring. The hot mixture was filtered and filtrate was acidified with 2 M HCl. The product was dried and recrystallized in ethanol.



Scheme for formation of 3,5-disubstituted 1,2,4-triazole from isoniazid





Scheme for derivatives

Melting point were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on Fourier transform IR spectrophotometer (Shimadzu) using KBr disc method.

The purity of test compounds was determined by thin layer chromatography. A single spot is obtained on TLC side confirm the completion of reaction and R_f value confirms the purity of 3,5-disubstituted 1,2,4-triazole. Physical data of the compounds are recorded in Table-1.

TABLE-1
PHYSICAL DATA OF 1,2,4-TRIAZOLE AND DERIVATIVES

Compd.	Structure	m.f.	Solvent	Yield (%)	m.p. (°C)
1(a)		C ₇ H ₈ N ₅ S	Methanol	72	89
1(b)		C ₁₄ H ₁₅ N ₅ S	Methanol	66	112
1(c)		C ₉ H ₁₀ N ₅ O ₂ S	Methanol	69	104

The compound were analyzed for C, H, N analysis and the values were found to be ± 6.4 % of calculated values. Percentage of elements are recorded by elemental analysis at Wockhardt Ltd. and presented in Table-2.

TABLE-2

Compd.	m.f.	m.w.	Elemental analysis (%)			
			C	H	N	S
1(a)	C ₇ H ₈ N ₅ S	194	43.29	4.12	36.08	16.49
2(b)	C ₁₄ H ₁₅ N ₅ S	285	58.94	5.260	24.56	11.22
3(c)	C ₉ H ₁₀ N ₅ O ₂ S	252	42.85	3.960	27.77	12.69

RESULTS AND DISCUSSION

In the present work, isoniazid were used as the key intermediate for the synthesis of the 3,5-disubstituted 1,2,4-triazole. The base catalyzed intermolecular dehydrate cyclization of the sulphur potassium salt furnished substituted 1,2,4-triazole. The IR spectra of 3,5-disubstituted 1,2,4-triazole gives the significant peak in the region of 2557 cm⁻¹ attributed to S-H stretching C=N stretching at 1665 cm⁻¹, C-N stretching at 1185 cm⁻¹ the absence of C=S, N-H and presence of S-H absorption established that the isolated triazole are in thiol form.

Conclusion

3,5-Disubstituted 1,2,4-triazole and their derivatives are an important class of organic compounds with an diverse agricultural, industrial ant tubercular, antiviral and antifungal effect, *etc.*

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