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Synthesis and Antitubercular Studies on Pyridine 1, 2, 3-Triazole Derivatives

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A B S T R A C T

Tuberculosis (TB), an infectious disease that usually attacks the lungs, is frighteningly on the rise. Once nearly vanquished by antibiotics, at least in the developed world, TB resurged in the late 1980's, now second only to AIDS among infectious disease. Thirty million people are at risk of dying from TB in the next 10 years, most of them living in Africa. [1] It is a chronic disease caused by mycobacteria of the ''tuberculosis complex'', including primarily *Mycobacterium tuberculosis*, but also *M. bovis* and *M. africanum*. [2,3] The discovery of the causative agent of tuberculosis by Robert Koch in 1882 gave great hope that this 'white plague' would soon be vanquished. During the 20th century new anti-tuberculosis drugs were discovered. In the early 1980's the great majority of patients could be cured by treatment with short-course curative chemotherapy that was possible as a consequence of several newly introduced anti-tuberculosis drugs. Only one decade later, an outbreak of HIV-related multi drug resistant tuberculosis in New York made TB suddenly the centre of attention. In the last decade, TB has re-emerged as one of the leading causes of death worldwide (nearly 3 million deaths annually). [4] The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7,000 each day. [5,6] 1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications including as pharmaceutical agents. Different methods for synthesizing 1, 2, 3-triazole are described in the literature [7]. In this work, the cycloaddition reactions between diazomalonaldehyde (1) and pyridine hydrochlorides in water were effectively used to prepare the pyridine based-1, 2, 3-triazole-4-carbaldehydes in moderate-to-good yields.

Keywords: Tuberculosis, Mycobacterium, Anti-tubercular, Multi drug resistance.

A R T I C L E I N F O

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1. Introduction

Tuberculosis

It was estimated that nearly 1 billion more people will be infected with TB in the next 20 years. About 15% of that group (150 million) will exhibit symptoms of the disease, and about 3.6% (36 million) will die from TB if new disease prevention and treatment measures are not developed.[8] A survey by WHO indicates that 1out of 3 people on earth are infected with TB bacilli however usually this latent infection is not reactivated. [9] The dramatic increase in TB cases observed in the resent years is due to firstly synergy with Human Immunodeficiency Virus (HIV). [10,11] (By destroying the two most important cells to the containment of tubercle bacilli (macrophages and CD4-receptor-bearing lymphocytes), HIV vigorously promotes the progression of recent or remotely acquired TB infection to active disease). [12] At the same time TB bacteria assist in accelerating the progress of HIV infection in the patient. Second is the increase in resistant strains of the disease with some showing cross-resistance to as many as nine drugs.[13,14] Despite the availability of antitubercular agents, tuberculosis remains primary cause of comparatively high mortality worldwide. In HIV infected patients, TB has become the main cause of death. At the moment one out of three HIV infected patients is co-infected with TB and 40% of them develop the active disease, rendering the HIV problem countries (most of them lying in Africa) also the regions with the highest TB incidence in the world. Although it is a leading cause of HIV related destruction, only little attention is paid to TB in HIV/AIDS programs so far. [15] Reactivation of this latent infection can be due to immuno-deficiency, HIV-infection, use of corticosteroids, aging, alcohol and drug abuse.

TB is spread from actively infected individuals through the air along much the same means as the influenza, that is water droplets expelled during coughing, sneezing or talking and is primarily transmitted via the respiratory tract.[16] If there is no proper treatment with an active TB infection the effected person can, infect 10 to 15 people annually.\ Although one possible long term solution to the problem is a better vaccine, in the short term, the major reliance will be on chemotherapy [17] requiring the development of novel, effective and non-toxic antitubercular agents. [18, 19]

The identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of multi-drug resistant strains. To do this, biochemical pathways specific to the mycobacteria and related organisms disease cycle must be better understood. A number of metabolic processes occur during the biosynthesis of mycobacterium cell wall components. [20]

Pathogenesis

The interaction of the human host and *M. tuberculosis* is extremely complex. Partly, it is determined by the virulence of the strain but probably more importantly by the specific and non-specific resistance of the host. Cell-mediated immunity plays an important role in the development of disease symptoms. It is convenient to distinguish between two kinds of human tuberculosis infections:

1. Primary infection
2. Postprimary (or reinfection). [21 22]

(1) The primary infection is the first infection that an individual acquires and usually results from droplets containing viable bacteria from an individual with an active pulmonary infection. The bacteria that reach the lungs are ingested by macrophages but often survive because the fusion between the phagosome and the lysosome is hindered. The bacteria multiplying in macrophages cause a chemotactic response that brings additional macrophages into the area forming aggregates of macrophages, called tubercles in which *M. tuberculosis* continues to multiply intracellularly. After a few weeks many of the macrophages die, releasing TB bacteria and forming a liquid centre in the tubercle, which is surrounded by a mass of macrophages and lymphocytes. The disease may become dormant after this stage. In a few individuals with low resistance, the bacteria are not effectively controlled. The centre of the tubercle enlarges in the process of liquefaction, forming an air-filled tuberculosis cavity in which the bacilli multiply extracellularly. Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into a bronchiole and thus be disseminated throughout the respiratory system to other systems. This causes an acute pulmonary infection which can lead to an extensive destruction of lung tissue, the spread of bacteria to other parts of the body and death. However, in most cases of tuberculosis, acute infection does not occur and the infection remains localised and is usually inapparent.

(2) The postprimary infection occurs when immunity wanes (e.g. HIV-infection, use of corticosteroids, alcoholism, lung emphysema, diabetes, malnutrition and stress etc). The mycobacteria can multiply again in macrophages, the tubercle wall breaks down and the infection spreads to different tissues. This causes symptoms like weight loss, night sweats, feverishness and a cough that produces greenish sputum flecked with blood.

Diagnosis of the Tuberculosis

M. tuberculosis is a slow growing microorganism, thus the diagnosis of TB is difficult. A sputum smear microscopic analysis, typical symptoms, responsiveness to certain antibiotics and X-ray examinations can give an initial idea of *M. tuberculosis* infection. However, it takes weeks to grow it out of sputum, for unambiguous confirmation of *M. tuberculosis* infection. The following tests are used for diagnosis of disease:

Tuberculin skin test

This test measures the hypersensitivity of an individual against the bacteria or their products caused by the primary

infection. When tuberculin, a protein factor extracted from *M. tuberculosis*, is injected intradermally into a hypersensitive individual, it elicits a localized immune reaction (induration and swelling) within 1-3 days at the site of the injection. This test doesn't indicate the active disease but only that the individual has been exposed to the organism at some time. Vaccination with the BCG vaccine can also result in a positive tuberculin skin test. [25]

Culture

Sputum is by far the best material for the diagnosis of pulmonary mycobacterial infections. As most specimens submitted for culture growth contain other bacteria and possibly fungi, which will rapidly overgrow the medium, it is important to treat the specimens with reagents that selectively kill non-acid-fast organisms. Because of the very specific features of their cell wall, mycobacteria are relatively more resistant to acids, alkalis and certain disinfectants than other micro-organisms. Depending on the contamination grade of the specimen, 'hard' or 'soft' decontamination methods are used.

Sputum Smear Microscopy

M. tuberculosis gets visualized with a Zeehl-Neelsen stain. However, there is a 25% chance for a false negative result; 25% of the smear negative patients appear to be culture positive. [26]

Radiometry

So far the only rapid method in routine clinical use is radiometry. In this technique, the bacillus uses [14C]-palmitic acid as a nutrient and consequently releases radioactive labeled carbon dioxide, which can be detected within two or three days. Although this technique is clearly more rapid than conventional methods, the high price restricts the use in many countries.[27]

X-ray

Primary and secondary tuberculosis have distinct radiographic patterns. When renewed pulmonary infection occurs, it is usually a chronic infection that involves destruction of lung tissue, followed by partial healing and slow spread of the lesions within the lungs. Those spots of damaged tissue may be observed by X-ray examination. However, intercurrent pneumonia, pulmonary embolism or supervening carcinoma may be confounding factors.

2. Materials and Methods

General procedure of the synthesis of diazomalonaldehyde (1)

The preparation of diazomalonaldehyde was performed by the procedure described by stojanovic and Arnold. [33]

Preparation of N,N-Dimethyl –N-{2-(dimethyl amino methylene)amino-3-dimethy-aminoprop-2-enylidine ammonium diperchlorate.

Phosphorus oxychloride (33ml) was added dropwise to ice-cooled dimethylformamide (73 ml) under constant stirring, the mixture was stirred for 30 min without cooling, and cooled down again with ice.

Preparation of Glycine hydrochloride

Glycine hydrochloride was prepared by evaporating a mixture of glycine and a slight excess of hydrochloric acid, and crystallizing the residue twice from 80% aqueous acetic acid, about 14 gm of glycine hydrochloride was prepared.

Prepared glycine hydrochloride was added portionwise to the above mixture .The whole mixture was heated at 80 ^{0}C for 4 hours and at 125 ^{0}C for 2 hours, cooled down , and decomposed by pouring into water (60ml), the temperature being maintained at 15-20^{0}C by means of efficient external cooling with dry ice/methnol. Perchloric acid (70% 24ml) was then added at -10 ^{0}C, the mixture cooled down to -35 ^{0}C under continuous stirring (to deposit a crystalline precipitate), and kept at this temperature for 2 hours. The precipitates were rapidly collected with suction on a sintered glass funnel and washed three times with a small amount of precooled ethanol. The analytical sample, m.p 222-228 ^{0}C was obtained by recrystallisation from methnol.

Preparation of N,N-Dimethyl-N-{2-(dimethyl amino methylene)amino-3-dimethyl- amino}prop-2-enylidene-ammonium Perchlorate.

The diperchlorate (24g) was dissolved in a refluxing mixture of ethanol (184ml) and triethylamine (12gm). The solution was filtered through a small amount of active charcoal while hot and the filterate was allowed to crystallize. The yield was 15gm of perchlorate, m.p 143 ^{0}C (139-141 ^{0}C).

Preparation of diazomalonaldehyde (1).

A mixture of N,N-Dimethyl-N-{2-(dimethyl amino methylene)amino-3-dimethylamino} prop-2-enylidene-ammonium Perchlorate (15gm; 0.05 mmol) and 125 ml of 2m-NAOH was heated at 40 ^{0}C under stirring for 20 hours. The solution was filtered with a small amount of charcoal and concentrated on rotary evaporator. The volume was made up to 100 ml and 4g (0.065 mol) of sodium nitrite was added. The mixture was cooled at -10 to -15 ^{0}C and acetic acid (15 ml) was added drop wise to it under stirring (internal temperature not exceeding -5 ^{0}C).

The cooling bath was taken off and the mixture stirred at room temperature for another 2 hours during which the red turbid solution cleared up. The reaction mixture was extracted 6 times with 200 ml of dichloromethane and each extract was washed 3 times with 25 ml of a 10 % potassium hydrogen carbonate solution and 20 ml of water. The combined extract was dried over magnesium sulphate and the solvent distilled of through a column under reduced pressure (distillation temperature about 20 ^{0}C, maximum bath temperature about 45^{0}C).

Yield of diazomalonaldehyde was 1.50 g (30 %).

General procedure for the synthesis of 1-(Pyridin-4-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (compound A).

Preparation of Pyridine Hydrochlorides (step-1)

For the preparation of pyridine hydrochloride, 4-aminopyridine was dissolved in chloroform. Then through this chlorine gas was passed. The chlorine gas was prepared in the Kipp's Apparatus by allowing concentrated sulfuric acid to react with lumps of fused ammonium chloride. The gas may be dried by passage through a drechsel bottle containing concentrated sulphuric acid, the latter should be followed by an empty drechsel bottle as a precaution against 'sucking back' of the contents of the reaction vessel. After about half an hour there was formation of solid part in chloroform liquid. The solid part was collected as the hydrochloride of the pyridine base molecule.

Preparation of the compound A (step-2)

A solution of diazomalonaldehyde (**1**) (5.0mmol) in water (30ml) was added drop wise to stirred solution of pyridine hydrochloride (4.5mmol) in water. The reaction mixture was stirred for 48 hours at room temperature, the liquid solution was then concentrated on rotary evaporator. A yellow colored viscous liquid was obtained as product.

General procedure for the synthesis of 1-(Pyridin-2-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (B).

Preparation of Pyridine Hydrochlorides (step-1)

This was done by dissolving the 2-aminopyridine in chloroform and passing chlorine gas through it. The chlorine gas was prepared by the Kipp's Apparatus.

Preparation of the compound B (step-2)

A solution of diazomalonaldehyde (**1**) (5.0mmol) in water (30ml) was added drop wise to stirred solution of pyridine hydrochloride (4.5mmol) in water. The reaction mixture was stirred for 48 hours at room temperature. The liquid solution was concentrated on rotary evaporator. A yellow colored viscous liquid was obtained as product.

General Procedure for the synthesis of (E)-1-(4-(Phenyl diazenyl) phenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (C).

Preparation of Pyridine Hydrochlorides (step-1)

A solution of 4-aminoazobenzene in chloroform was prepared. Then through this chlorine gas was passed.

Preparation of the compound C (step-2)

A solution of diazomalonaldehyde (**1**) (5.0mmol) in water (30ml) was added drop wise to stirred solution of hydrochloride (4.5mmol) in water. The reaction mixture was stirred for 24 hours at room temperature. The solid was collected washed with cold water, and recrystallized from ethanol. The product was obtained as yellow solid.

3. Results and Discussion

Synthesis of Diazomalonaldehyde (1)

The preparation of diazomalonaldehyde (1) was performed by the procedure described by Stojanovic and Arnold (Scheme 2). [34]

Preparation of N,N-Dimethyl –N-{2-(dimethyl amino methylene) amino-3-dimethy-amino}prop-2-enylidine ammonium diperchlorate.

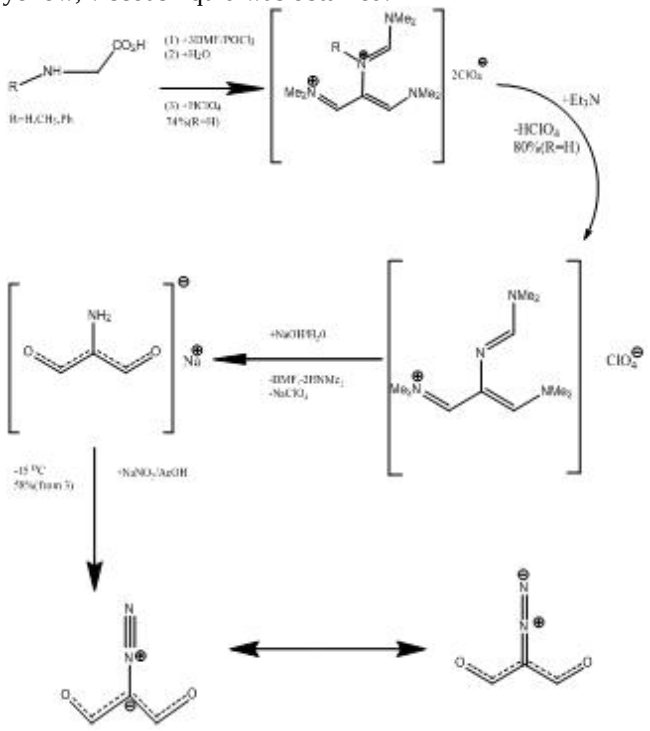
Phosphorus oxychloride was added drop wise into dimethyl formamide. Freshly prepared glycine hydrochloride was added portion wise to the mixture. Perchloric acid (70%) was then added at -10 ^{0}C, the mixture cooled down to -35 ^{0}C under continuous stirring (to deposit a crystalline precipitate), and kept at this temperature for 2 hours.

Preparation of N, N-Dimethyl-N-{2-(dimethyl amino methylene) amino-3-methylamino}-prop-2-enylidene ammonium perchlorate.

The diperchlorate was dissolved in a refluxing mixture of ethanol and triethyl amine. The solution was filtered with a small amount of active charcoal while hot and the filtrate was allowed to crystallize.

Preparation of Diazomalonaldehyde (1)

A mixture of N, N-dimethyl-N-{2-(dimethyl amino methylene) amino-3-dimethylamino}-prop-2-enylidene ammonium perchlorate and NAOH (2M) was heated. The solution was filtered with a small amount of charcoal and concentrated on rotary evaporator followed by addition of 0.065 mol sodium nitrite. After extraction and washing, a yellow, viscous liquid was obtained.



Scheme 1: General scheme for synthesis of compound (1)

Synthesis of Pyridine Based Triazole Derivatives by Reaction of Diazomalonaldehyde (1) with Amino Substituted Pyridine Hydrochlorides.

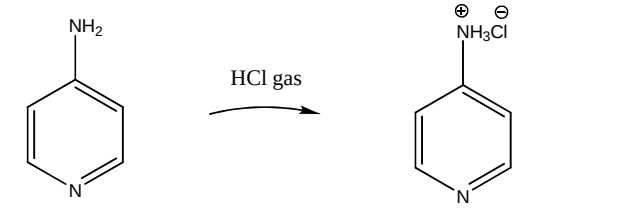
A. Synthesis of 1-(Pyridin-4-yl)-1*H*-1,2,3-triazole-4-carbaldehyde

For this step firstly the pyridine base molecules available were converted to their hydrochlorides.

Preparation of Pyridine Hydrochlorides

The hydrochlorides were prepared by passing freshly prepared chlorine gas through a solution of commercially available pyridine-4-amine in chloroform. Firstly, a solution of 4-aminopyridine was prepared by dissolving it in sufficient amount of chloroform. Through this solution chlorine gas prepared by using apparatus was passed (using concentrated sulphuric acid and fused ammonium chloride) (scheme 3).

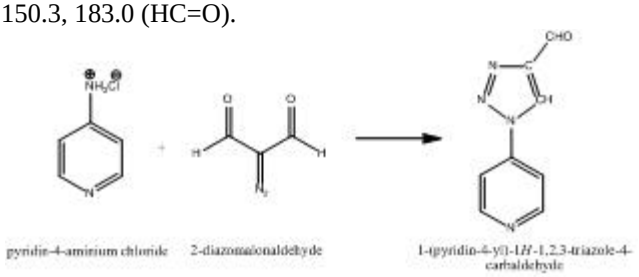
Figure 1: Kipp's Apparatus for generating HCl gas



pyridin-4-amine pyridin-4-ammonium chloride(1a)

Scheme 2

Solution of diazomalonaldehyde **(1)** in water was added drop wise to stirred solution of pyridine hydrochloride (1a) in water. The reaction mixture was stirred for 48 hours at room temperature. The liquid solution was concentrated. The product was obtained as yellow semisolid (scheme 4).[102] This compound was characterized by spectroscopic techniques, IR which shows C-N stretching at peak 1645 cm^{-1}. It represents presence of triazole and pyridine ring and C=O stretching gave a at peak 2970 cm^{-1}. It indicates the presence of CHO group and C-C streching peak shown at 1531 cm^{-1}. Further the structure was confirmed by ^{1}H NMR and ^{13}C NMR. **^{1}H NMR ($CDCl_3$) δ** (ppm)**:** 6.82 (d, 2H, Ar-H), 7.85 (s, IH, C_5-H), 8.01 (d, 2H, Ar-H), 8.5 (s, 1H,CHO), **^{13}C NMR ($CDCl_3$) δ** (ppm): 120.0, 124.0, 146.0, 147.2, 150.3, 183.0 (HC=O).



(1a) **(1)** **(A)**

Scheme 3

B. Synthesis of 1-(Pyridin-2-yl)-1*H*-1,2,3 triazole-4-carbaldehyde.

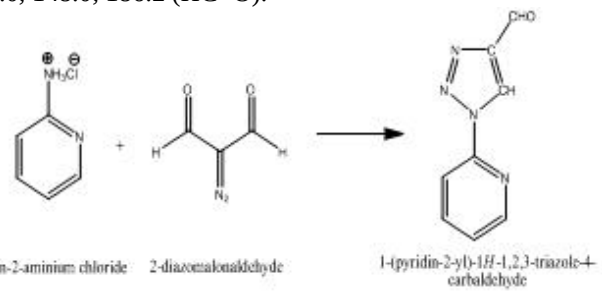
Again the commercially available pyridine base molecule was converted to its hydrochloride (Scheme 5).

pyridin-2-amine pyridin-2-aminium chloride(1b)

Scheme 4

The solution of diazomalonaldehyde (1) in water was added drop wise to stirred solution of pyridine hydrochloride (1b) in water. The reaction mixture was stirred for 48 hours at room temperature. The liquid solution was concentrated. The product was obtained as yellow semisolid (Scheme 6). The compound was characterized by spectroscopic techniques, IR revealed C-N stretching at 1629 cm^{-1}. It represents the presence of triazole and pyridine ring and C=O stretching was shown at 2928 cm^{-1} which represents the presence of CHO group. Further, C-C streching peak was observed at 1466 cm^{-1}. Further structure is confirmed by ^{1}H NMR and ^{13}C NMR. **^{1}H NMR (DMSO-d_6) δ** (ppm): 7.50, 7.90 (m, Ar-H), 8.01, 8.41 (m, Ar-H), 8.08 (s, 1H, C_5-H), 9.65 (s, 1H, CHO)

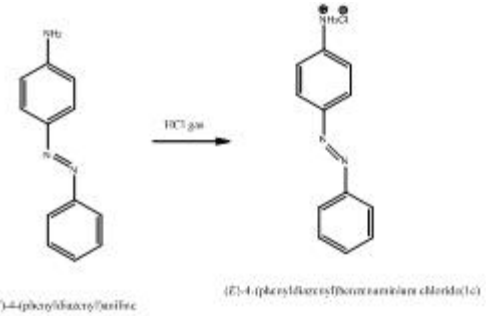
^{13}C NMR (DMSO-d_6) δ (ppm): 120.6, 125.0, 140.0, 143.0, 146.0, 148.0, 186.2 (HC=O).



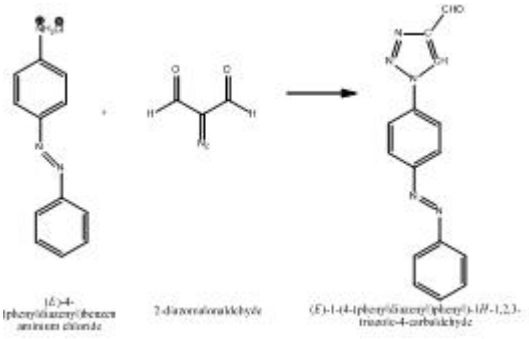
(1b) **(1)** **(B)**

Scheme 5

C. Synthesis of (E)-1-(4-(Phenyldiazenyl)phenyl)-1*H*-1,2,3-triazole-4-carbaldehyde: As above the commercially available base molecule was converted to its hydrochloride. This was done by dissolving the 4-aminoazobenzene in chloroform. The chlorine gas was prepared by the kipp's apparatus (Scheme 7).



Scheme 6



(1c) **(1)** **(C)**

Scheme 7

The solution of diazomalonaldehyde (1) in water was added dropwise to stirred solution of hydrochloride (1c) in water. The reaction mixture was stirred for 24 h at room temperature; the yellow solid was collected, washed with cold water, and recrystallized from ethanol/water (Scheme 8). The compound was characterized by spectroscopic methods, IR shows C-N stretching at peak 1695 cm^{-1}. It indicates the presence of triazole and pyridine ring and

C=O stretching appeared at peak 2922cm^{-1} which represents the presence of CHO group. C-C streching peak was shown at 1589 cm^{-1}. Further, the structure was confirmed by ^{1}H NMR and ^{13}C NMR. **^{1}H NMR (DMSO-d_6) δ** (ppm): 7.26-8.08 (m, 8H-Ar), 8.08 (s, 1H, C_5–H), 9.40 (s, 1H, CHO). **^{13}C NMR (DMSO-d_6) δ** (ppm): 120.1, 122.1125.2, 130.4, 132.0, 138.3, 150.0, 154.7, 186.8 (HC=O).

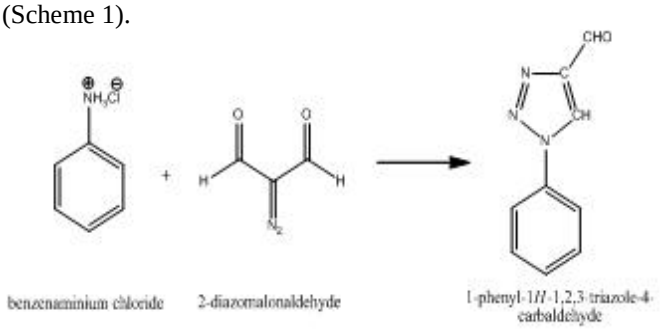
Table 1: Reaction time and percentage yield of the synthesized compounds.

Compound	Reaction time	% yield
A.	48 Hours	54%
B.	48 Hours	56%
C.	24 Hours	60%

4. Conclusion

1,2,3-triazole is one of the important heterocyclic compounds which constitute an important class of organic compound with diverse biological activities, including anti-parasitic, analgesic, antibacterial and anti-inflammatory activities. Considerable efforts have been made in recent years to further develop the synthesis of these molecules which are frequently used in medicinal, agricultural and industrial field. In light of the above facts and with a view to obtain new biologically active agents I was encouraged to synthesize a new series of 1, 2, 3-triazole derivatives.

Recently, the compounds N-subtituted phenyl-1, 2, 3-triazole-carbaldehyde has been synthesized through reactions of amine hydrochlorides with diazo malonaldehyde. These compounds have been screened for inhibitory activity against mycobacterium tuberculosis (Scheme 1).



Scheme 8

Due to high pharmacological activity of 1, 2, 3-triazole systems it was planed to synthesize pyridine based 1,2,3-triazole derivatives and evaluate their anti-tuberculosis activity.

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