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An Efficient and Green Method for The Preparation of 2,3 – Dihydro-2-Phenyl-1 H-Naphtho-[1,2-E] [1,3] Oxazine by Using Tannic Acid

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ABSTRACT

A Novel route one-pot three-component reaction was developed for the synthesis of 2,3-Dihydro-2-phenyl-1-H-Naphtho-[1,2-e] [1,3] Oxazine by using Substituted Aniline, Formalin & β-Naphthol in the presence of Tannic acid (10 Mol %) as catalyst. The reaction is observed by using TLC, after completion of reaction product is characterized by 1H, NMR, 13C NMR, IR and Mass Spectra.

Keywords: Substituted Aniline, β-Naphthol, Formalin and Tannic acid.

I. INTRODUCTION

Derivative of oxazine are among the most important heterocyclic chemicals that have attracted substantial attention in synthetic chemistry because of wide array of pharmaceutical effects [1].

Oxazine is a compound that may be synthesized by the substitution of carbon (C) atoms with nitrogen (N_2) & oxygen (O_2) in benzene and its reduction products [2]. Oxazines are a class of heterocyclic compounds characterized by the presence of single nitrogen and a single oxygen atom [3]. Three isomers exist based on the respective positioning of heteroatom & relative positioning of double bonds [4]. The synthesis of oxazines (aromatic) was firstly accomplished in 1944 by Holly & Cope using Mannich processes. There has been a limited amount of research conducted on basic derivatives of these ring systems, with the majority of studies focusing on the reduced 1, 3 and 1, 4 molecules. One of the most significant examples of a simple 1,4-oxazine compound morpholine, also known as tetrahydro-1,4-oxazine. Morpholine the white liquid that exhibits miscibility with water [5].

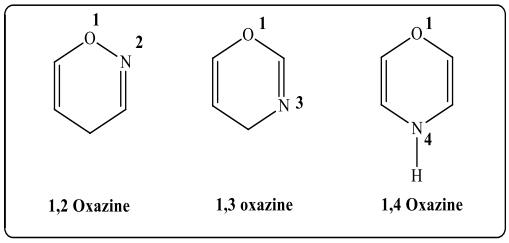
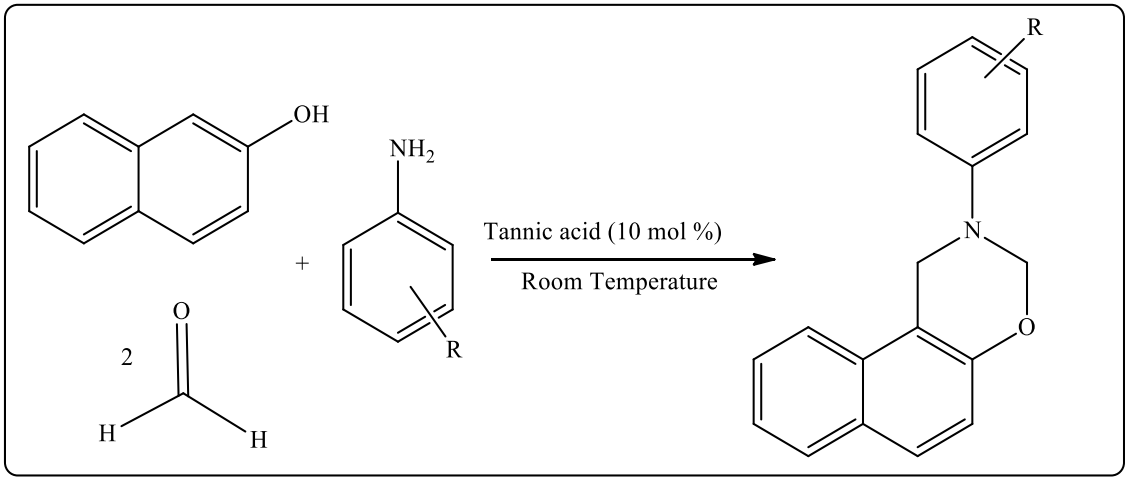


Fig 1. Isomers of Oxazine

The field of Oxazine chemistry has been the subject of much scientific research worldwide. Oxazines are a class of heterocyclic compounds characterized by a six-membered ring structure consisting of one nitrogen atom, one oxygen atom (O_2), that possess significant biological activity [6].The significance of oxazine derivatives has seen a recent surge of attention due to the diverse range of pharmacological effects demonstrated by molecules containing the dihydro [1,3]Oxazine ring system, as well as their use as synthetic intermediates [7].Furthermore, it has been shown that naphthoxazine derivatives have promising therapeutic properties that might be used in management of Parkinson's bug [8]. "Trifluoromethyl-1,3-oxazine-2-one", a chemical molecule, has been recognized as a very effective non-nucleoside reverse transcriptase inhibitor. It has notable efficiency against several mutant strains of the HIV-1 virus. Consequently, extensive research has been carried out to examine the features and characteristics of 1,3-oxazine derivatives by means of synthesizing these compounds by a three-component cyclo condensation technique. The documented biological actions of the subject include anti-inflammatory, anti-tubercular, anti-diabetic, anticancer, antioxidant, diuretic, and antiviral activities, among others. In addition to their biological activities, benzo-1,3-oxazines possess pharmacological properties and are considered a significant class of chemical pigments. Several techniques are available for production of several oxazines, although necessitating the use of costly and hazardous materials, as well as specific reaction conditions [9]. Boeini and Co-worker did a work whereby they synthesized novel "naphtho [1, 2-e] [1,3] Oxazines" including an aryl sulfonamide moiety. The synthesis was achieved using a one-pot technique, employing an ecologically benign reaction medium. The characterization of the "naphtho [1,2- e] [1,3] Oxazine" derivative was performed by utilization of ^{1}H NMR, ^{13}C NMR, and LC-MS techniques. The in vitro effectiveness of the newly synthesized compounds in inhibiting cancer growth was assessed using breast, colon, & BCLL cancer cell lines [10]. Botla et al. investigated on a wide range of "2,3-dihydro-1H-benzo [2,3] benzofuran [4,5-e] [1,3] Oxazine" derivatives. These compounds were synthesized by a Mannich type condensation chemical reaction of dibenzofuran-2-ol with different amines, utilizing water as the solvent. The ortho-amino methylation process of dibenzo furanols was seen to proceed smoothly in presence of various "aromatic/aliphatic amines & para formaldehyde", resulting in subsequent cyclization [11]. In current times, there has been a rising interest in the investigation to the 1,3-oxazine heterocycles due to their diverse biological features. These qualities include analgesic, anti-convulsant, anti-tubercular, anti-bacterial, & anti-cancer activities [12]. Significance of "1,3-oxazine" derivatives has been recognized in their role as intermediates and their utility in the synthesis of diverse pharmaceutical compounds .Several established methodologies have been documented for their preparation, including the utilization of dehydrated alc. ammonia, ammonium acetate, copper acetate/ zinc chloride, Au(I) complexes, 2-azadienes in combination with alkynes, Bu_4NF/ethyl iodide, & p-TsCl, DMAP/DCM, operating under basic conditions. This study focuses on the production of "2, 3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] Oxazine" derivatives by the utilization of tannic acid [13].



Scheme 1: Preparation of 2, 3-Dihydro-2-Phenyl-1*H*-Naphtho [1,2-e] [1,3] Oxazine

II. RESULT & DISCUSSION

Here, we hope to introduce the use of tannic acid as a catalyst to promote the synthesis of 3,4-dihydro-3-substituted-2H-naphtho[2,1-e][1,3] oxazine derivatives (Scheme 5.3.3). We use the reaction of 2-naphthol (1 mmol), formalin (2 mmol), and 4-methoxy aniline (1 mmol) stirred at room temperature as the reaction model. To determine the suitable concentration of the catalyst Tannic acid, it has been investigate the model reaction first with no catalyst and a smaller amount product is obtained at various concentrations of catalyst like 2.5 , 5 , 7.5, 10 & 12.5 mol % the product produced in 58 , 71 , 82 , 92 and 92 % yields, correspondingly (Table 1). This shows that 10 mol % tannic acid is sufficient to obtain good results in terms of reaction time and product yield. To study the catalyst loading concentration of the reaction model, the procedure was optimized using various molar concentrations of Tannic acid under RT stirring condition. Excellent yield of product was observed by using 10 mol% of catalyst. From that result, it can be seen that the catalyst concentration plays an important role in improving the results to a greater extent. It was also observed that, there is no larger change in yields of product more than 10 mol % of catalysts.

Table 1: Effects of Catalyst Concentrations [a]

Sr. No.	Conc. (mol %)	Yield (%) [b]
1	2.5	58
2	5	71
3	7.5	82
4	10	92
5	12.5	92
[a]Reaction conditions: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), Tannic acid (10 mol %) at room temp. [b]Isolated yield		

To evaluate the solvent effect, various solvents such as tetrahydrofuran, acetonitrile, dichloromethane, water, water: ethanol (1:1), methyl alcohol, ethyl alcohol and H_2O: ethyl alcohol (1:9) was used for the model reactions. The preferred product was obtained in 33, 62 54, 50, 60, 84, 86 , and 90 % yields correspondingly after respective time at room temperature conditions. Ethyl alcohol: Water: (1:9) stand out as the solvent of

selection amongst the solvents tested. Because of the speedy conversion & desired product obtained higher yield (Table 2, Sr.No. 8), whereas the product formed in lesser yield (30-85%) in longer time by using varies ratio of water & ethyl alcohol solvents.

Table 2: Screening of solvents

Sr.No.	Solvent	Yield (%)
1	Tetrahydrofuran	33
2	Acetonitrile	62
3	Dichloromethane	54
4	Water	50
5	Water: ethanol (1:1)	60
6	Methyl alcohol	84
7	Ethyl alcohol	86
8	Water: Ethyl alcohol (1:9)	90

To extend this method, we also treated various other amines of the reaction with electron donating group and electron withdrawing group to obtain the corresponding [1, 3] Oxazine derivative. As shown in (Table 3) in most cases the yields were good to excellent.

Table 3: Preparation of 2, 3-Dihydro-2-Phenyl-1*H*-Naphtho-[1, 2-E] [1, 3] Oxazine by use of Tannic Acid.

Sr. No.	Ar-NH_2	Product	Time (min)	Yield (%)	M. P °C
1	4-OCH_3-C_6H_4-NH_2	4a	07	92	88-90
2	3-NO2-C_6H_4-NH_2	4b	10	89	132-134
3	4-NO2-C_6H_4-NH_2	4c	12	83	168-170
4	4-Br-C_6H_4-NH_2	4d	10	89	114-116
5	2-NO2-C_6H_4-NH_2	4e	15	84	109-110
6	3-OCH3-C_6H_4-NH_2	4f	09	90	46-48
7	C_6H_5-NH_2	4g	10	89	48-50
8	3-CH3-C_6H_4-NH_2	4h	10	90	70-72
9	2-CH_3-C_6H_4-NH_2	4i	12	87	58-60
10	4-F-C_6H_4-NH_2	4j	11	86	136-138
11	4-OC_2H_5-C_6H_4-NH_2	4k	07	91	69-71
12	4-OCH_3-C_6H_4-NH_2	4l	05	94	78-80
13	3-OCH_3-C_6H_4-NH_2	4m	07	91	76-78

[a]Reaction conditions: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), tannic acid (10 mol%) at room temperature. [b]Isolated yield.

III.EXPERIMENTAL

Method & Material:

All amines were obtained from freshly opened containers and used without further filtration. The melting point is determined in an open capillary tube in a paraffin bath. The progress of the reaction was observed by TLC (thin layer chromatography). IR spectra were recorded on a Bruker spectrometer on KBr disks. ^{1}H NMR

spectra were recorded on Bruker spectrometer (400 MHz). NMR spectrometer with chemical shift values in units of δ (ppm) with respect to DMSO as solvent and TMS as internal standard.^{13}C NMR also recorded on Bruker spectrometer & Mass spectra recorded on LCMS Water's Synapt-XS Maldi TOF HDMS spectrometer.

General Procedure

A mixture of β-naphthol (1 mmol), formalin (2 mmol), aryl amine (1 mmol) and Tannic acid (10 mol %) as catalyst was stirred at reflux temperature for 90-180 minutes. The development of the reaction was observed by TLC. After completion of reaction transformation, the reaction mixture was pour on crushed ice. The obtained crude product was filtered, dried and recrystallized in ethyl alcohol.

IV.CONCLUSION

In this Work we have developed the new methodology for the simple and efficient preparation of [1, 3] Oxazine derivatives by use of Tannic acid Catalyst. The protocol followed was simple and easy associated with good yield of the product generated 83 to 94% of the product. The major benefit of this method was easy setup, easy workup and less time required to complete the reaction.

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