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## Synthesis and antimicrobial activity of asymmetrical azines derived from naphtho[2,1-b]furan

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**ABSTRACT**

*2-Hydroxy-1-naphthaldehyde **s**erved as a good starting material for the synthesis of the azines, which was prepared from 2-naphthol by Reimer-Tiemann reaction. The hydroxy aldehyde on treatment with phenacyl bromide, under basic condition, underwent both condensation and cyclization and furnished 2-benzoylnathpho[2,1-b]furan **1**, Nitration of ketone **1,** under mild reaction condition, yielded 2-(3',5'-dinitrobenzoyl)-3-nitronaphtho[2,1-b]furan **2,** as evidenced by its mass spectrum. The reaction of the compound **2**, with hydrazine hydrate, resulted in the formation of corresponding hydrazone **3**. Various azines **4a-g** were obtained when the hydrazone **3** was treated with, appropriate aldehydes by using different reaction condition in absence and in presence of hydrochloric acid as a catalyst. All the newly synthesized compounds have been characterized by analytical and spectral studies and were screened for antibacterial activity against Bacillus subtilus and Alcaligenes fecalies and antifungal activity against Aspergillus nidulans, Aspergillus parasiticus and Aspergillus terius.*

**Keywords:** Naphthofurans, azines, antibacterial activity, antifungal activity.

### INTRODUCTION

Among the wide variety of heterocyclic compounds that have been explored for developing pharmaceutically important molecules, naphtho[2,1-b]furan derivatives play a vital role. Naphthofuran nuclei are key structural moieties found in a large number of biologically important natural products. Therefore synthesis of various derivatives of naphtho[2,1-b]furan was taken up in our laboratory[1-4] in search of new biologically and pharmacologically active heterocyclic compounds. Azines are the organic compounds derived from condensation of an aldehyde or a ketone with hydrazine. Enormous research work has been carried out on different

kinds of azines, both symmetrical and asymmetrical, concerning their application in diverse fields[5-9]. Azines act as biologically and pharmacologically important molecules[10]. In the present work azines are combined with naphtofuran moiety and their antimicrobial activity is evaluated.

Introduction of nitro group in organic molecules, some times, enhances its biological profile mainly due to the electronegative nature of the nitro group. The fact that naphtho [2,1-b]furans associated with wide spectrum of biological[11-14]and pharmacological activities[15-17]and importance of azines has stimulated our interest to synthesize asymmetrical azines involving naphtho[2,1-b]furan, especially with nitro substituent on furan ring of naphthofuran moiety.

## EXPERIMENTAL SECTION

Melting points were recorded in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR Research Spectrophotometer Schimadzu 8201 PC (4000-400 $cm^{-1}$) and NMR on Bruker DRX-300 (300MHz-FT-NMR with low and high temperature facility $-90^0$ to $+80^0$ ). Standard chemical shifts are given in δ ppm values. All the reactions were monitored by thin layer chromatographic method. TLC was run on silica gel using ethyl acetate and petroleum ether (10:90) as eluent. The newly synthesized compounds were purified by column chromatography using silica gel (60-120 mesh).

**Synthesis of 2-benzoylnathpho[2,1-b]furan 1**

2-Hydroxy-1-naphthaldehyde (1.72 g, 0.01 mol), phenacyl bromide (1.99 g, 0.01 mol) and anhydrous potassium carbonate (20.2 g, 0.01 mol) were heated under reflux temperature for 24 hr in dry acetone (25ml). The reaction mixture was filtered and potassium carbonate was washed with acetone. Evaporation of the solvent from the filtrate yielded the product, 2-benzoylnaphtho [2,1-b]furan **1** which was recrystallised from ethanol. Mixed melting point with authentic sample did not show any depression.

**Synthesis of 2-(3', 5'-dinitrobenzoyl)-3-nitronaphtho[2,1-b]furan 2**

A cooled nitrating mixture of concentrated nitric acid and concentrated sulphuric acid in the ratio 1:2 (13 ml : 26 ml) was added very slowly to a cooled solution of 2-benzoylnaphtho[2,1-b]furan (2.72 g, 0.01 mol) in glacial acetic acid (6 ml) and the mixture was stirred for about 30 min at 5-$15^0$C. The stirring was continued for 3 hr at the same temperature and the reaction mixture was poured on to crushed ice. The product which was separated as solid was collected, dried recrystallised from aqueous ethanol.

**Synthesis of 2-( 3',5'-dinitrobenzoyl)-3-nitronaphtho[2,1-b]furanhydrazone 3**

A mixture of 2-(3', 5'-dinitrobenzoyl)-3-nitronaphtho[2,1-b]furan (4.07 g, 0.01 mol), hydrazine hydrate (0.5 ml, 0.01 mol), concentrated hydrochloric acid (3-4 drops) in ethanol (30 ml) were heated under reflux for3 hrs,neutralized with aqueous sodium hydroxide(5%) and The product that separated as solid, was collected by filtration, dried and recrystallised from ethanol.

**Synthesis of asymmetrical azines 4a-g**

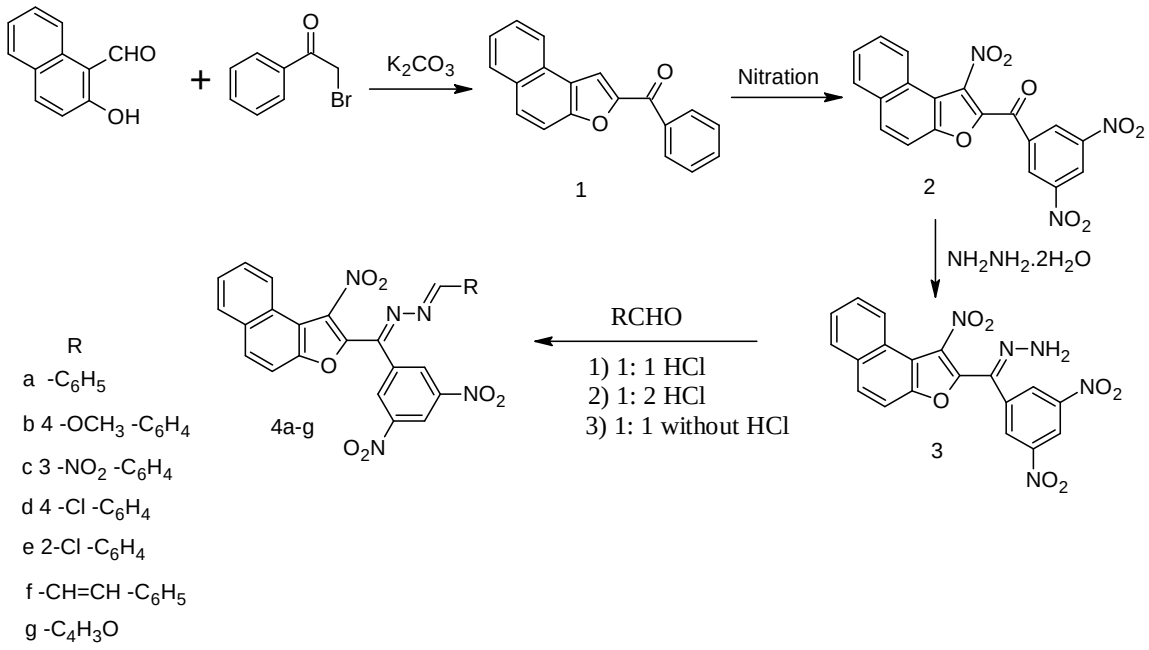
A mixture of 2-(3', 5'dinitro-benzoyl)-3-nitronaphtho[2,1-b]furanhydrazone **3** (2.1 g, 0.005 mol), benzaldehyde (0. 5 ml, 0.005 mol) in ethanol (30 ml) and concentrated hydrochloric acid (3-4 drops) was refluxed on a water bath for 9 hr. The reaction mixture was poured in to ice water and neutralized with aqueous sodium hydroxide (5%), solid thus separated was collected by filtration and dried. The crude product was identified as condensed asymmetric azine **4a.**

Similar reaction in the ratio of 1:2 in presence of catalytic amount of concentrated hydrochloric acid and in absence of concentrated hydrochloric acid also produced only one product i.e. **4a**.

Similarly the various asymmetrical azines **4b-g** were obtained from **3** by reacting it with other aromatic aldehydes such as, 4-methoxybenzaldehyde,3-nitrobenzaldehyde, 4-chlorobenzaldehye, 2-chlorobenzaldehyde, cinnamaldehyde and furfuraldehyde, under identical reaction conditions.

The sequence of the reactions is depicted in scheme

**Scheme**




The characterization data of the synthesized compounds are as shown in **Table 1**.

**Antimicrobial activity:**

The in vitro antimicrobial activity was carried out against 36 hr old culture against two bacteria and three fungi by paper disc diffusion method. Assay were performed according to National committee for Clinical Laboratory Standards[18,19] by employing the paper disc diffusion method All the newly synthesized compounds were tested for antibacterial activity against- *Bacillus subtilus, Alcaligenes fecalies* and antifungal activity against *Aspergillus terius, Aspergillus nidulans, Aspergillus parasiticus.* Nystatin and Gentamycin were used as standards for antifungal and antibacterial activity respectively. The compounds were tested at a concentration of 0.0025 mol/ml. Solvent dimethyl formamide was used as control. The zone of inhibition was compared with the standard drug. The results are tabulated in T**able 2.**

## RESULTS AND DISCUSSION

The starting material 2-benzoylnaphtho[2,1-b]furan **1,** was synthesized in two steps, the first step involved Reimer-Tiemann reaction of 2-naphthol with chloroform and sodium hydroxide, which resulted in the formation of 2-hydroxy-1-naphthaldehyde, and the second step involved conversion of 2-hydroxy-1-naphthaldehyde to 2-benzoylnaphtho[2,1-b]furan **1**, which was accomplished by treatment of 2-hydroxy-1-naphthaldehyde with phenacyl bromide in presence of weak base, potassium carbonate. In the second step condensation and cyclization occurred in

single step and the product was obtained in good yield. It underwent smooth nitration with concentrated nitric acid and concentrated sulphuric acid at low temperature in presence of acetic acid as a solvent and produced 3', 5'-dinitrobenzoyl-3-nitronaphtho[2,1-b]furan. **2.** The structure of compound **1** was established by recording its IR and $^1$H NMR spectra and comparing the same with an authentic sample. The structure of compound **2** was established by recording its IR spectrum which showed strong absorption bands at 1535 cm$^{-1}$ and 1354 cm$^{-1}$ due to $NO_2$ group. The mass spectra of this compound showed a molecular ion peak at m/Z 407 corresponding to its molecular weight, accounting for three nitro groups. Other peaks appearing at m/Z 362, 316, 286 were in accordance with the fragmentation pattern. The reaction of **2** with hydrazine hydrate in ethanol was straight forward and produced corresponding hydrazone **3**, in excellent yield. The IR spectrum of **3** showed strong absorption band at 1622 cm$^{-1}$ due to C=N, and broad band at 3364 cm$^{-1}$due to $NH_2$ group and at 1525 cm$^{-1}$due to $NO_2$ group. The $^1$H NMR of this compound confirmed the assigned structure. The hydrazone **3** served as an excellent intermediate for the synthesis of asymmetrical azines.

**Table 1- Analytical data of the synthesized compounds**

| Compound | R | Molecular formula | Molecular weight | MP(c) | Yield % | C Found (calcd)% | H Found (calcd)% | N Found (calcd)% |
|---|---|---|---|---|---|---|---|---|
| 1 | - | $C_{19}H_{12}O_2$ | 272 | 131 | 93.5 | 15.9(15.85) | 84.0(84.15) | |
| 2 | - | $C_{19}H_9N_3O_8$ | 407 | 126 | 71.81 | 56.0(56.03) | 2.0(2.23) | 10.0(10.32) |
| 3 | - | $C_{19}H_{11}N_5O_7$ | 421 | 152 | 63.1 | 54.0(54.16) | 2.6(2.63) | 16.0(16.62) |
| 4a | -$C_6H_5$ | $C_{26}H_{15}N_5O_7$ | 509 | 190 | 60.0 | 60.0(61.3) | 2.0(2.97) | 13.0(13.75) |
| 4b | 4- OCH3-$C_6H_4$ | $C_{27}H_{17}N_5O_8$ | 539 | 210 | 72.0 | 60.0(60.11) | 3.0(3.18) | 12.0(12.98) |
| 4c | 3-$NO_2$-$C_6H_4$ | $C_{26}H_{14}N_6O_9$ | 554 | >250 | 62.0 | 56.3(56.32) | 2.0(2.55) | 15.0(15.16) |
| 4d | 4-Cl-$C_6H_4$ | $C_{26}H_{14}N_5O_7Cl$ | 543.5 | 165 | 61.0 | 57.0(57.42) | 2.0(2.59) | 12.0(12.88) |
| 4e | 2-Cl-$C_6H_4$ | $C_{26}H_{14}N_5O_7Cl$ | 543.5 | 198 | 61.0 | 57.0(57.42) | 2.0(2.59) | 12.0(12.88) |
| 4f | CH=CH$C_6H_5$ | $C_{28}H_{17}N_5O_7$ | 535 | 120 | 52.0 | 62.0(62.81) | 3.0(3.20) | 13.0(13.08) |
| 4g | $C_4H_3O$ | $C_{24}H_{13}N_5O_8$ | 499 | 230 | 55.0 | 57.0(57.72) | 2.60(2.62) | 14.0(14.02) |

It was observed that the reaction of 2-acetyl-3-nitronaphtho[2,1-b]furanhydrozone resulted in the formation of different products i.e. symmetrical azines, asymmetrical azines and starting material 2-acetyl-3-nitronaphtho[2,1-b]furan, under different reaction conditions, when reacted various aromatic aldehydes. However in this case the reaction of 2-(3', 5'-dinitrobenzoyl)-3-nitronaphtho[2,1-b]furanhydrazone **3** with various aldehydes such as benzaldehyde, 4-methoxybenzaldehyde, 3-nitrobenzaldehyde, 4-chlorobenzaldehye and 2-chlorobenzaldehyde, cinnamaldehyde and furfuraldehyde in 1:1 mol ratio, 1:2 mol ratio at reflux temperature in ethanol, in the presence of acid and 1:1 mol ratio in the absence of acid produced only asymmetric azines and not symmetrical azines. It could be attributed the presence of bulky nitro groups on benzene ring as well as on furan moiety of naphthofuran ring system.

The IR spectrum of **4b** exhibited the absorption band at 1601cm$^{-1}$due to C=N. Additional support for the structure **4b** was obtained by recording its $^1$H NMR spectrum in $CDCl_3$ which showed a singlet at 3.9 δ due to –$OCH_3$ protons, singlet at 9.9 δ due to methine proton and multiplet at 7.0-8.8 δ for aromatic protons. The mass spectra of **4b** showed a molecular ion peak at 506. The $^1$H NMR spectra of compounds **4a-g** were consistent with their structures.

The antimicrobial activity of the compounds are evaluated by the disc diffusion method and shown in Table 2. Among the series of compounds tested **4c** and **4e** showed better inhibition

with both *Bacillus subtilus* and *Alcaligenes fecalies*. 4**b** and **4g** showed moderate inhibition to *Alcaligenes fecalies.* The compounds **4c** and 4**d** showed promising activity against *Aspergillus nidulans*. The better inhibition is due to the presence of the chloro, and nitro groups [20]. The compounds **4a-g** did not exhibit antifungal activity against *Aspergillus parasiticus* and *Aspergillus terrus*

**Table 2- Antimicrobial activity of the synthesized compounds**

| | Antibacterial | | Antifungal | | |
|---|---|---|---|---|---|
| | MIC in mm | | MIC in mm | | |
| **Compound** | ***Bacillus subtilus*** | ***Alcaligenes fecalies*** | ***Aspergillus nidulans*** | ***Aspergillus parasiticus*** | ***Aspergillus terrus*** |
| 4a | - | - | - | - | - |
| 4b | - | 15 | - | - | - |
| 4c | 16 | 10 | 11 | - | - |
| 4d | - | - | 18 | - | - |
| 4e | 15 | 10 | - | - | - |
| 4f | 12 | - | - | - | - |
| 4g | - | 12 | - | - | - |
| **Standard** | 40 | 23 | 18 | 15 | 12 |

## CONCLUSION

The present work describes a novel and simple approach for synthesis of asymmetrical azines. Some of the compounds exhibited good antibacterial and antifungal activity. Among the series of compounds screened for antibacterial activity **4c** and **4e** showed maximum inhibition against both *Bacillus subtilus* and *Alcaligenes fecalies*. **4b** and **4g** showed moderate inhibition against *Alcaligenes fecalies.*

The compounds **4c** and **4d** exhibited significant antifungal activity against *Aspergillus nidulans*

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