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# Synthesis and Antimicrobial Activity of 4-aryl furo Pyridazines

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## Abstract

*Benzoyl hydrazides (**1a-b**) was condensed with furan-2-aldehyde (**2**) in the presence of sodium hydroxide and dry ethanol, furan-2-yl-benzoyl hydrazone (**3a-b**) was achieved. Intramolecular cyclization of compound **3a-b** with PPE afforded 4-aryl furo pyridazines (**4a-b**)*

***Keywords**: Furan aldehyde, furo pyridazines, hydrazides, hydrazones.*

## Introduction

Many pyridazine and related analogue were found to possess valuable properties such as antiangiogenic, anticancer, antineuroinflammatory , antimicrobial and anticonvulsant activities. Besides they exhibit antiviral activity against the replication of human immunodeficiency virus, inhibit human picornaviruses, protein kinase and acyl coenzyme A: cholesterol acyltransferase.[1-9]

In recent years , a substantial number of pyridazines have been reported to possess antimicrobial, antitubercular, antifungal, potent analgesic and anti-inflammatory .phosphodiesterase 4 (PDE4) inhibitors are effective anti-inflammatory drugs as potent and selective COX-2 inhibitors , antipyretic activities ,antidiabetic, antifeedant , insecticidal activities , antihypertensive and antiplatelet activities[10] .

Pyridazine derivatives are found in skeleton of some commercially available drugs. For instance, Apresoline contains hydralazine **(4)** as a pyridazine derivative that is used to treat hypertension for pregnant[11]

Previously aryl-thieno[2,3-d]–pyridazine was synthesized by a different route to study the pentobarbital sleep in mice[12]. Further pyridazine analogues are synthesized and investigated as modulators of unwinding reaction mediated by west nile virus[13]. Based on these findings it was considered valuable to incorporate furan ring in pyridazine framework as in **4a-b**, which might enhance the biological activity. Herein we are reporting the conversion of 1-aroyl-hydrazones **3a-b** to the corresponding pyridazines **4a-b** using PPE in good yield.

## Experimental

Melting points were determined in open capillary tube on the Buchi oil bath melting point apparatus. Infrared (IR) absorption spectra were recorded on FT-IR Shimadzu 8300 spectrometer using nujol mull. Proton nuclear magnetic resonance ($^1$H NMR) spectra were routinely recorded either on a Hitachi R-600 (60 MHz) spectrophotometer or on a Bruker 300 MHz spectrophotometer in $CDCl_3$ or DMSO-$d_6$ and

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absorptions are given in parts per million (δ) downfield using tetramethylsilane (TMS) as an internal standard.

***Furan-2-yl-2-methy21lbenzoyl hydrazone (3a)***

A mixture of acid hydrazide **1a** (4.45 g, 0.036 mol) and 2-furan aldehyde (**2**, 4.0g, 0.035 mol)[33] and sodium hydroxide (0.3 g) was refluxed in dry ethanol (30 ml) in round bottom flask for 5h. The reaction mixture was reduced to a small volume (15 ml) by distilling off the ethanol. The pale yellow solid obtained was filtered washed with water to neutral $^{pH}$, dried and on recrystallization from ethanol gave yellow solid **3a** 73% (5.55g) yield.

**M.P.** 170-172°C

**IR (Nujol):** 1645 (C=N), 1650 (amide C=O), 3218-3320 $cm^{-1}$ (NH stretch)

**$^1$H NMR (DMSO-$d_6$):** δ 2.2 (s, 3H, $CH_3$), 6.8-7.8 (m, 4H, Ar-H), 8.5 (s, 1H, NH)

***Furan-2-yl-2-chlorobenzoyl hydrazone (3b):***

Obtained from **2** (3.47 g, 0.031 mol),2-chlorobenzoyl hydrazide **(1b** ,5 g, 0.029 mol) and sodium hydroxide (0.3 g) in ethanol (30 ml) as a pale yellow solid in 64% (4.85 g) yield.

**M.P.**180-192$^0$C

**IR (Nujol):** 1645 (C=N), 1650 (amide C=O), 3220-3360 $cm^{-1}$ (NH stretch)

**$^1$H NMR (DMSO-$d_6$):** 7.0-7.8 (m, 4H, Ar-H), 8.4 (s, 1H, NH)

***General procedure for the synthesis of 4-Aryl furo pyridazines (4a-B)***

A typical procedure is described for the preparation of:

***4-(2-Methylphenyl) furo[2,3-d]pyridazine (4a)***

Compound **3a** (3.0 g, 0.012 mol) was added to a solution of PPE[34]. [prepared by refluxing phosphorous pentoxide (50 g), dry diethyl ether (50 ml) and dry chloroform (150 ml) for 26h.] and refluxed for 8h. The cooled reaction mixture was poured into ice (250 g), basified by adding 10% ammonium hydroxide (100 ml) and stirred for 15 min. The organic layer separated was washed with 5% sodium hydroxide solution (3x30 ml) and then with water (3x50 ml). After evaporating the solvent, the solid was recrystallized from benzene to give pale yellow crystalline solid in 64% (1.80 g) yield.

**M.P.** 129-131°C

**IR (Nujol):** 1630 $cm^{-1}$ (C=N)

**$^1$H NMR ($CDCl_3$):** δ 2.2 (s, 3H, $CH_3$), 7.0-7.5 (m, 6H, Ar-H), 9.2 (s, 1H, $C_7$-H)

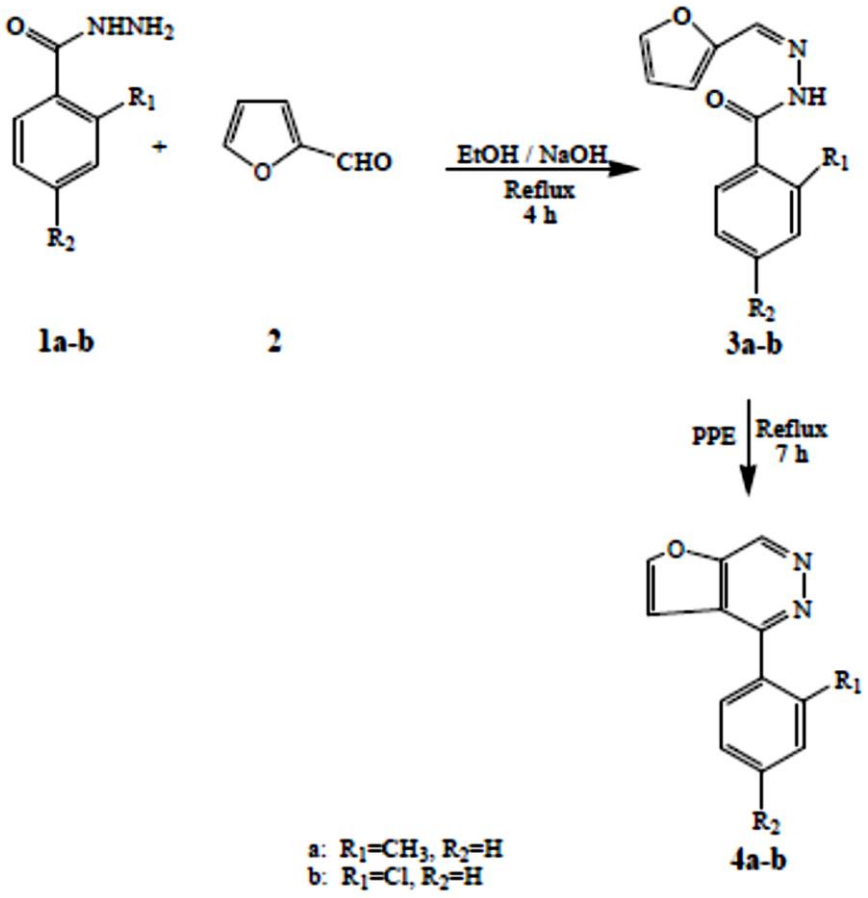
***4-(2-Chlorophenyl) furo[2,3-d]pyridazine, (4b)***

Obtained from **3b** (3.44 g, 0.013 mol), PPE (30 ml) as pale yellow crystalline solid in 59% (1.9 g) yield.

**M.P.** 168-170°C

**IR (Nujol):** 1630 $cm^{-1}$ (C=N)

**$^1$HNMR (DMSO-$d_6$):** δ 7.0-7.5 (m, 6H, Ar-H), 9.3 (bs, 1H, $C_7$-H)




**SCHEME-1**

## Results and Discussion

The structure of synthesized compounds was elucidated by IR, NMR and microanalyses. The IR spectrum of **3a-b** showed stretching absorption bands at 1645, 1650 and 3218-3320 $cm^{-1}$assigned to C=N, C=O and N-H stretching respectively. In $^1$H NMR spectrum, all protons were seen according to expected chemical shifts and integral values. The aromatic protons and amide proton of **3a-b** were observed at δ 6.8-7.8 and 8.5 respectively.

Similarly the IR spectra of **4a-b** showed absorptions at 1615-1630 $cm^{-1}$ assigned to C=N as a shoulder. The $^1$H NMR spectra of **4a-b** showed multiplet in the range δ 7.0-7.5 for six aromatic protons. Further, compounds **4a-b** showed broad singlet at δ 9.1-9.3 due to $C_7$-H and this down field absorption might be due to the presence of electronegative adjacent nitrogen atom.

Antimicrobial activity screening results are qualitative in nature (Table 1,2). The antibacterial screening results have shown that chloro substituted compounds 4b exhibit, growth inhibitory activity

more relevant than that of the reference compound. Even in case of antifungal activity chloro substituted compounds showed growth inhibitory activity more relevant than that of the reference drug.

***Antimicrobial activity***

The compound **4a-b** was screened for antimicrobial activity using cup plate method. The activity was carried out against three pathogenic bacteria, *B. Cereus*, *S. Aureus* and *E. Soli* and two fungal culture, *F. Solani*, *A. Favus*. The standard drugs used were Chloromycetin and Griseofulvin. The compound was tested in dimethyl formaide. The zone of incubation was compared with standard drug after 43 hr of incubation at 370 for antibacterial activity and 36 hr at 370 antifungal activity. Antimicrobial activity screening results are summarized in Table 1 and 2.

***Table 1:*** *Antibacterial activity*

| | ***B. cereus*** | | ***S. aureus*** | | ***E. coli*** | |
|---|---|---|---|---|---|---|
| Compound. | Area of inhibition $mm^2$ | Relative % of inhibition | Area of inhibition $mm^2$ | Relative % of inhibition | Area of inhibition $mm^2$ | Relative% of inhibition |
| **4a** | 287 | 80 | 420 | 91 | 188 | 88 |
| **4b** | 298 | 83 | 431 | 95 | 181 | 85 |

***Table-2:*** *Antifungal activity*

| | ***F. Solani*** | | ***A. Flavus*** | |
|---|---|---|---|---|
| Compound | Area of inhibition $mm^2$ | Relative % of inhibition | Area of inhibition $mm^2$ | Relative % of inhibition |
| **4a** | 133 | 28 | 172 | 50 |
| **4b** | 211 | 59 | 234 | 78 |

## Conclusion

The present work provides a useful method for the preparation of 4-aryl-furo[2,3-d]–pyridazines with moderate yields, as well as easily accessible starting materials. Further compounds with chloro group have shown more antibacterial, antifungal activities.

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