

Studies on the Synthesis and Reactivity of Novel Bis(5-(arylo)benzofuran-2-yl) methanone and their Imine and Oxime Derivatives

Naqui Jahan Siddiqui¹, Mohammad Idrees² and Anuradha Korde³

¹ & ²Department of Chemistry,
Government Institute of Science, Nagpur (M.S.), INDIA.

³Department of Chemistry,
Government Science College, Gadchiroli (M.S.), INDIA.
email: naquiphd.2010@gmail.com.

(Received on: November 5, Accepted: November 8, 2017)

ABSTRACT

2-hydroxy-5-(arylo)benzaldehyde (**1a-d**) on reaction with 1,3-dichloro ketones afforded Bis(5-(arylo)benzofuran-2-yl)methanones (**2a-d**) as a starting reagents. A series of Bis(5-(arylo)benzofuran-2-yl) methanone oximes (**3a-d**) was synthesized in moderate to good yields from **2a-d** on reaction with hydroxylamine hydrochloride in pyridine. Extending the reactions of **2b**, **2c** and **2d** with reagents such as phenyl hydrazine, semicarbazide and thiosemicarbazide afforded **4b**, **4c** and **4d** respectively. The structures of this synthesized compound have been satisfactorily confirmed on the basis of chemical transformation reaction, elemental and spectral data came from IR, ¹H NMR and mass spectra.

Keywords: Bis(5-(arylo)benzofuran-2-yl)methanone, semicarbazone, ketoximes, imine, and thiosemicarbazone.

INTRODUCTION

Condensed heterocyclic compounds containing different heteroatoms such as oxygen and nitrogen have attracted significant consideration as a result of their important biological actions and occurrence in a vast array of natural products. The benzofuran ring system is one of an important class of heterocyclic compound that occur in immense number of natural products¹⁻², that can be isolated particularly from *Machilus glaucescens*, *Ophryosporus charua*, *Ophryosporus lorentzii*, *Krameria ramosissima*, and *Zanthoxylum ailanthoidol*³. The most recognized benzofurans are aianthoidol, amiodarone, and bufuralol compounds, which possess broad range of important physiological, pharmacological and toxic properties and

hence there is a continuous interest in their chemical synthesis⁴⁻⁵. Furthermore, benzo[b]furans are also used as building blocks for fluorescent sensors⁶ and are used as optical brighteners. Similarly, numerous bisheterocyclic systems have been synthesized⁷⁻¹⁰ and their structures have also been suggested, but literature survey still indicates that less work is published on bisbenzofuran and its derivatives. On the other hand, biological activity studies on bisbenzofuran containing compounds were also found to be limited¹¹⁻¹². Since the last decade, oxime ethers have found to be used as nonsteroidal antiinflammatory drugs¹³, beta-adrenergic¹⁴, mold inhibitory active compound in poultry science¹⁵, anti-protozoan¹⁶, insect growth regulator¹⁷ and as various materials with steroidal effects¹⁸. Previous studies, have reported the synthesis and antimicrobial activity of some bis-(benzofuran-2-yl) methanone, cyclobutane and mesitilen substituted benzofuran derivatives¹⁹⁻²². Heterocycles like substituted methanone possessing interesting biological activities have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system. Encouraged by the literature survey we planned to prepare bisbenzofuran methanones containing azo linkage and their various imine derivatives by reacting it with different reagents like phenyl hydrazine, semicarbazide and thiosemicarbazide.

MATERIAL AND METHODS

Chemicals used for the synthesis were of AR grade of Merck, S.D.Fine and Aldrich. The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, ν max in cm^{-1}). Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micromass Q-TOF Micro, Mass Spectrophotometer. ¹H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d₆ as solvent. Chemical Shifts are given in parts per million (ppm). Elemental (CHN) analysis was done using Thermo Scientific (Flash-2000), the compounds were analyzed for carbon, hydrogen and nitrogen and the results obtained are in good agreement with the calculated values. The reactions were monitored by E. Merck TLC aluminum sheet silica gel 60 F254 and visualizing the spot in UV Cabinet and iodine chamber.

EXPERIMENTAL

Aryl primary amines such as p-toluidine (**a**), m-anisidine (**b**), p-bromo aniline (**c**), p-anisidine (**d**) as starting material were used for diazotization for the synthesis of 2-hydroxy-5-(aryloxy)benzaldehyde (**1a-d**) following the available literature procedure. The structural identities were confirmed on the basis of physical data as in table 1 and spectral data is given below.

Spectral analysis of 2-hydroxy-5-(p-tolylazo)benzaldehyde (1a)²³: IR cm^{-1} : 3185(-OH), 3030 (ArH), 2918, 2994 (-CH₃), 1655 (C=O), 1619,1602,1479 (-C=C-), 2742 (C-H str. in -CHO), 1500,1575 (-N=N-) ¹H NMR (DMSO-d₆) δ ppm: 11.41(s, 1H, -OH), 10.37(s, 1H, -

CHO), 2.4(s, 3H, -CH₃), 7.18-8.18 (m, 7H, ArH); MS: 241[M+1]⁺ Elemental analysis Calcd. For C₁₄H₁₂N₂O₂: C, 70.00; H, 5.00; N, 11.76 Found: C, 69.91; H, 4.93; N, 11.82

Table-1: Physical data of the synthesized compounds

Entry	R	Colour	Recry. Solvent	m.pt. °C	% Yield	R _f	m.f.
1a	4-CH ₃	Yellow	Acetic acid	152-154	68.25	0.72	C ₁₄ H ₁₂ O ₂ N ₂
1b	3-OCH ₃	Brown	Acetic acid	98-100	75.58	0.68	C ₁₄ H ₁₂ O ₃ N ₂
1c	4-Br	Yellow	Acetic acid	112-113	69.25	0.64	C ₁₃ H ₉ O ₂ N ₂ Br
1d	4-OCH ₃	Brown	Acetic acid	110-112	82.32	0.71	C ₁₄ H ₁₂ O ₃ N ₂

Procedure for the synthesis of Bis(5-(aryloxy)benzofuran-2-yl)methanones (2a-d): In 100 mL round bottom flask, **1a** (5 mmol) and 30 mL anhydrous acetone were taken. To this solution 1,3-dichloro acetone (5 mmol) and potassium carbonate (5 mmol) was added and refluxed for 6h. Later the reaction mixture was poured in crushed ice, the precipitate so obtained was filtered and washed with water and recrystallized from suitable solvent (Scheme 1). Similarly, **2b-d** were synthesised from **1b-d** by extending the same procedure followed for **2a**, the physical data of all synthesized compounds are furnished in table 2.

Reaction Scheme : 1

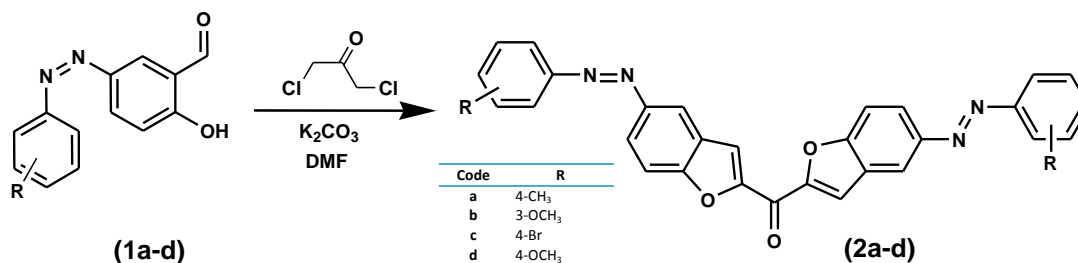


Table-2: Physical data of the synthesized compounds

Entry	R	Colour	Recry. Solvent	m.pt. °C	% Yield	R _f	m.f.
2a	4-CH ₃	Yellow	DMF	285-288	71.47	0.58	C ₃₁ H ₂₂ O ₃ N ₄
2b	3-OCH ₃	Yellow	DMF	238-240	62.90	0.65	C ₃₁ H ₂₂ O ₅ N ₄
2c	4-Br	Yellow	DMF	324-326	56.82	0.64	C ₂₉ H ₁₆ O ₃ N ₂ Br
2d	4-OCH ₃	Yellow	DMF	273-275	52.72	0.62	C ₃₁ H ₂₂ O ₅ N ₄

Procedure for the synthesis of Bis(5-(aryloxy)benzofuran-2-yl)methanone oximes (3a-d): **2a** (3.3 mmol) was dissolved in pyridine (20 mL) in a round bottom flask. Then hydroxylamine hydrochloride (3.33 mmol) was added and the reaction mixture was refluxed for 2h. Afterwards it was poured in crushed ice, the precipitate so obtained was filtered, washed with water and recrystallized from DMF to get **3a** (Scheme 3). Similarly, **3b-d** were synthesised from **2b-d** by extending the same procedure applied for **3a**, the physical data of all synthesized compounds are summarized in table 3.

Spectral analysis of Bis(5-(p-tolylazo)benzofuran-2-yl)methanone oxime (3a): IR cm^{-1} : 3183, 3101(-N-OH), 3025(ArH), 2850,2919 (CH_3), 1649 ($\text{C}=\text{N}$), 1500,1550 (-N=N-), 1602, 1613, 1581,1466 ($\text{C}=\text{C}$ str.), 1279,1265 ($\text{C}-\text{O}-\text{C}$ sym. str.),1022,1098 ($\text{C}-\text{O}-\text{C}$ asym. str.); ^1H NMR ($\text{DMSO}-d_6$) δ ppm: 13.22 (s, 1H, -OH of =N-OH), 2.43 (s, 6H, two $-\text{CH}_3$ group), 7.40-8.36 (m, 16H, ArH,) MS: 514[M] $^+$, 515[M+1] $^+$, Elemental analysis Calcd. For $\text{C}_{31}\text{H}_{23}\text{O}_3\text{N}_5$: C,72.50, H,4.51, N,13.64 Found: C, 72.072, H, 5.171, N, 13.145.

Reaction Scheme : 2

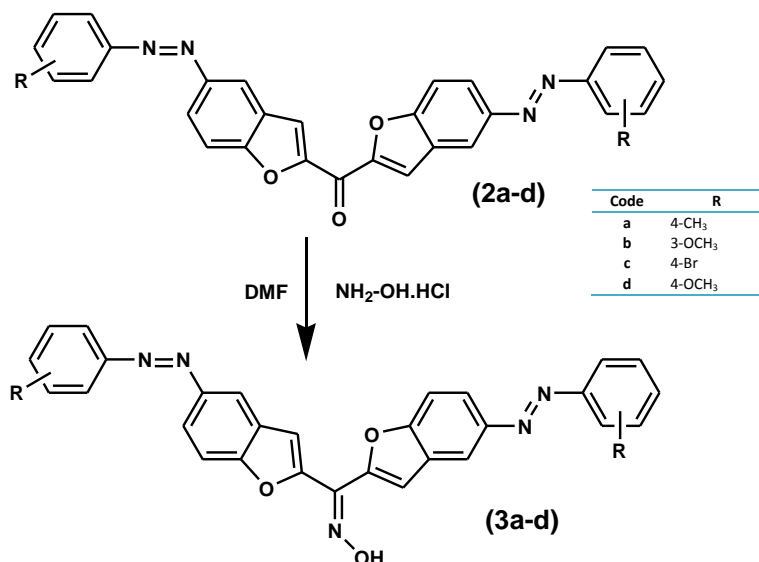


Table-3: Physical data of the synthesized compounds

Entry	R	Colour	Recry. Solvent	m.pt. $^{\circ}\text{C}$	% Yield	R _f	m.f.
3a	4- CH_3	Yellow	DMF	310-312	61.73	0.46	$\text{C}_{31}\text{H}_{23}\text{O}_3\text{N}_5$
3b	3- OCH_3	Yellow	DMF	222-224	76.14	0.51	$\text{C}_{31}\text{H}_{23}\text{O}_5\text{N}_5$
3c	4-Br	Yellow	DMF	270-272	72.09	0.65	$\text{C}_{29}\text{H}_{17}\text{O}_3\text{N}_5\text{Br}$
3d	4- OCH_3	Yellow	DMF	286-288	54.95	0.59	$\text{C}_{31}\text{H}_{23}\text{O}_5\text{N}_5$

Procedure for the synthesis of Bis(5-(m-methoxyphenylazo)benzofuran-2-ylmethylene)-2-phenylhydrazine (4b): **2b** (1.43 mmol) was dissolved in DMF (20 mL) in a round bottom flask. Then phenyl hydrazine (1.43 mmol) and few drops of acetic acid were added and the reaction mixture was refluxed for 2h. Then it was poured in crushed ice, the precipitate so obtained was filtered, washed with water and recrystallized from suitable solvent (Scheme 3).

Procedure for the synthesis of Bis(5-(p-bromophenylazo)benzofuran-2-ylmethylene) semicarbazide (4c): **3c** (3.27 mmol) was dissolved in DMF (20 mL) in a round bottom flask. Then semicarbazide (3.27 mmol) and pyridine in (25 mL) were added and the reaction mixture was refluxed for 2h. Then it was poured in crushed ice, the precipitate so obtained was filtered,

washed with water and recrystallized from suitable solvent (Scheme 3). **Procedure for the synthesis of Bis(5-(p-methoxyphenylazo)benzofuran-2-ylmethylene) thiosemicarbazide (4d) :** **2d** (3.27 mmol) was dissolved in pyridine (20 mL) in a round bottom flask. Then thiosemicarbazide (3.27 mmol) and reaction mixture was refluxed for 2h. Then it was poured in crushed ice, the precipitate so obtained was filtered, washed with water and recrystallized from suitable solvent (Scheme 3). The physical data of all synthesized compounds are summarized in table 4.

Reaction Scheme : 3

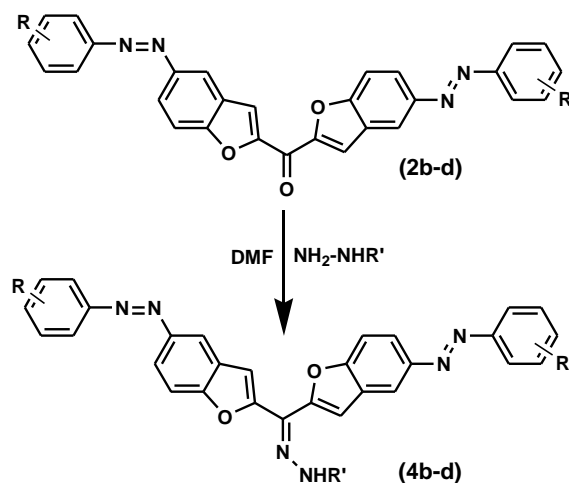


Table-4: Physical data of the synthesized compounds

Entry	R	R'	Colour	Recry. Solvent	m.pt. °C	% Yield	Rf	m.f.
4b	3-OCH ₃	-C ₆ H ₅	Yellow	DMF	<280°C	77.87	0.54	C ₃₇ H ₂₈ O ₄ N ₆
4c	4-Br	-CONH ₂	Yellow	DMF	275-277	80	0.41	C ₃₀ H ₁₉ O ₃ N ₇
4d	4-OCH ₃	-CSNH ₂	Yellow	DMF	278-280	67.21	0.43	C ₃₂ H ₂₅ O ₄ N ₇

RESULT AND DISCUSSIONS

The synthesis of the novel compounds (**2a-d** and **3a-d**) is described in the above reaction schemes. The identities of the newly synthesized compounds have been established on the basis of their elemental analysis and IR, ¹H NMR and Mass spectral data²⁴. Diazotization of four aryl primary amines (**a-d**) afforded (**1a-d**). The significant bands in the FT-IR spectra are those due to the azo chromophore (-N=N-), C-N stretching and strong bands due to the aromatic region in the range of 1400-1600 cm⁻¹ are also significant as azo bond stretching appears between the bands of the aromatic region. The IR spectra of the dye **1a** showed prominent azo bond (-N=N-) vibrations which are identifiable between 1500 cm⁻¹ and 1575 cm⁻¹. The absorption band of the azo chromophore is clearly distinct from the C=C

absorption bands. Due to aromatic region, the higher energy bands appeared from 1407 cm^{-1} to 1479 cm^{-1} while the lower energy bands ranged from 1500 cm^{-1} to 1619 cm^{-1} . The absorption of C-N is also observed as supporting evidence and its frequency ranges from 1206 cm^{-1} to 1353 cm^{-1} . Similarly, the ^1H NMR spectrum showed multiplet in the range of δ 7.18 to 8.18 ppm due to seven protons confirms the formation of **1a** which was further confirmed by mass spectrum with a molecular ion peak at m/z 241 $[\text{M}+1]^+$, is in agreement with the molecular formula $\text{C}_{14}\text{H}_{12}\text{O}_2$ (Scheme1).

Refluxing 2-hydroxy-5-(aryloxy)benzaldehydes (**1a-d**) with 1,3-dichloroacetone in presence of potassium carbonate afforded substituted (**2a-d**). Formation of (**2a-d**) was proved by the FeCl_3 test that was found to be negative and this was also proved by the DNP test that was found to be positive. Refluxing (**2a-d**) with hydroxylamine hydrochloride afforded (**3a-d**). The formation of (**3a-d**) was confirmed by the DNP test that was found to be negative. IR spectra of **3a** showed absorption bands at 3183 cm^{-1} for -OH of (-NOH) group and 1649 cm^{-1} for (C=N). The ^1H NMR spectra of **3a** showed a characteristic peak at δ 13.22 (s, 1H, -OH), 2.41 (s, 6H, two - CH_3 group), δ 7.40-8.36 (m, 16H, Ar-H) and $[\text{M}]^+$ in mass spectra at 514 $[\text{M}]^+$ and 515 $[\text{M}+1]^+$ confirms the formation of **3a** having the molecular formula $\text{C}_{31}\text{H}_{23}\text{O}_3\text{N}$. The percentage of elements corresponding to C, H and N, were found to be in good agreement with the calculated values for **3a**. On the basis of chemical transformation reaction and physical data the synthesized compounds **4b**, **4c** and **4d**, were confirmed.

CONCLUSION

Arylazosalicylaldehydes (**1a-d**), four novel bisketones (**2a-d**) and their imine derivatives (**3a-d**, **4b**, **4c**, and **4d**) containing azo linkage were prepared in the moderate to good yield. The structures of the compounds were confirmed on the basis of physicochemical, spectral and the elemental analysis data.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, Institute of Science, Nagpur, Principal, Government Science College, Gadchiroli, research scholars Mr. Roshan Nasare and Mr. Satish Kola for their support and cooperation. The authors are also thankful to the Director, SAIF, Punjab University, Chandigarh for providing CHN analysis, IR, ^1H NMR and Mass Spectra.

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