

Synthesis and Structural characterization of New Type of Thio-benzimidazole Compound and Study Fluorescence Properties.

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Abstract

The functions of biological compounds present in our body are mimicked by several heteroaromatic compounds and benzimidazolic compounds are one of them. The synthesized benzimidazoles compounds were prepared from the condensation reaction between diamine and thio-benzaldehyde in the presence of formic acid and oxygen as a catalyst. The purity of the compounds was ascertained and characterized by single crystal X-ray diffraction, IR, ¹H-NMR and TLC. X-ray crystal structure analysis shows that 2-[2-(*t*-butylthio) phenyl]-1*H*-phenanthro [9,10-*d*]imidazole crystallizes in monoclinic system with $P2_{1/n}$ space group. The newly synthesized benzimidazole compounds were screened for fluorescence studies and compounds showed strong emission band at 360 nm.

Keywords: Benzimidazole, Single Crystal X-ray Diffraction, Fluorescence property.

1. Introduction

Heteroaromatic rings are important because of their similarities to the biologically significant compounds present in our body[1]. Nitrogen containing heterocyclic compounds are present in numerous natural products, pharmaceuticals and organic materials. Mainly, imidazole based compounds are studied more thoroughly because of their prevalence in biomolecules viz. proteins, histamine, purines, and biotin[2]. Transition metal coordination compounds which contain imidazole ligands are predominant class of organic compounds involved in coordination chemistry, photochemistry, photophysics, bioinorganic chemistry and bioorganic chemistry[3]. Benzimidazole is considered to be an important class of imidazole ring systems in which the 4th and 5th position of the imidazole ring is substituted with benzene[4]. They have become significant intermediates in synthetic organic chemistry due to their tremendous applications. Benzimidazole derivatives are reported with a vast range of pharmaceutical and biochemical activities such as antiviral[5], antifungal[6], anti-allergic[7], anti-inflammatory[8], antitumor[9], antiulcer, anticancer[10], anti-helminthic [11], and many more. Most common pharmaceutical drugs which involve benzimidazole scaffold include albendazole, omeprazole, mebendazole and bendamustine[12]. Benzimidazole moieties have wide range of applications in the materials used as membranes for fuel cells, organic light emitting diodes, pigments, optical brighteners for coatings, chemical UVB filters[13]. The ongoing investigations mainly focus on synthesis of transition metal complexes with benzimidazole, benzoate ion for further physicochemical, spectral and biological activities. A significant amount of interest has been shown towards the development of efficient synthesis methods for benzimidazole and thio-benzimidazole compounds due to their various biological, and pharmaceutical applications. Thio-benzimidazole is type of heterocyclic compounds contains nitrogen and sulfur atom which induce changes in their properties. Benzimidazole was synthesized firstly by Hoebreckner through reduction and dehydration of 2-nitro-4-methylacetanilide[14]. In literature reports, it shows that synthesis of benzimidazole was done with the use of different types of catalysts like bioinspired orthoquinone catalyst[15], phosphine-free tridentate NNS ligand-derived manganese(I) complex[16], NHCPd(II)-Im complex[17], Oxone mediated synthesis[18] and many more. Herein, we report a synthesis of thiobenzimidazole compounds 2-[2-(*t*-butylthio) phenyl]-1*H*-phenanthro [9, 10-*d*]imidazole (**1**) without the use of metal catalyst. Introducing thio-*t*-butyl group to these benzimidazole introduce some changes the properties of these ligands. These compounds form better metal complexes, because of sulfur atoms which enable sulfur-metal interactions. There are numerous metal sulfur interactions are known in biomolecules, Hence these compounds can be explored in many ways.

2. Experimental Section

2.1. Preparation of the compound

2.1.1. Chemicals, solvents and starting materials

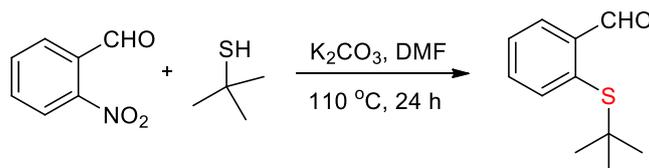
All the starting compounds employed in this study were procured from Sigma-Aldrich and TCI were used without further purification. For thin layer chromatography (TLC), silica



aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light. Column chromatography was performed using FINAR silica gel 100-200 mesh. All the other reagents and solvents were used of Analytical grade (A.R. grade).

2.1.2. Synthesis procedure of 2-(*t*-butylthio) benzaldehyde

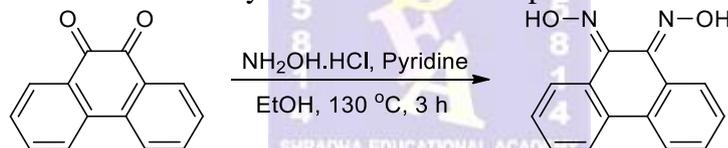
An oven dried round bottom flask was charged with 2-nitrobenzaldehyde (10mmol), 2-methyl-2-propanethiol (10mmol), potassium carbonate (11mmol) and dimethyl formamide (15mL) and kept for stirring at 110°C for 24 hrs. After the complete consumption of starting materials as monitored by TLC, the reaction mixture was cooled down to room temperature and poured into ice-cold water. The organic product was extracted with diethylether (3*10mL), dried over magnesium sulfate and concentrated. The crude was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to obtain 2-(*t*-butylthio) benzaldehyde as yellow oil.



Scheme 1: Synthesis of 2-(*t*-butylthio)benzaldehyde

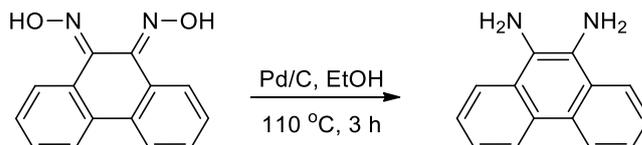
2.1.3. Synthesis procedure of 2-[2-(*t*-butylthio)phenyl]-1*H*-phenanthro[9,10-*d*]imidazole (**1**)

An oven-dried double-necked round bottom flask fitted with condenser was charged phenanthroquinone (14.4mmol), hydroxylamine hydrochloride (72mmol) and pyridine (9mL) in ethanol (150mL). The resulting reaction mixture was refluxed at 90°C for 3 hrs. After the complete consumption of starting materials as monitored by TLC, the reaction mixture was cooled down to room temperature and poured into methanol: water (1:10 v/v) system. The obtained residue was filtered, vacuum dried to get 9,10-*N,N'*-dihydroxyphenanthrene-9,10-diimine (P1) as crude and directly used for the next step without further purification.



Scheme 2: Synthesis of 9,10-*N,N'*-dihydroxyphenanthrene-9,10-diimine

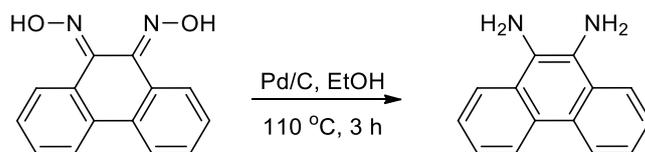
50mL of ethanol was added into the double necked reaction flask and backfilled with argon gas for 30 mins. After 30 mins P1(4.2mmol) was added to the flask and heated to 90°C to completely dissolve P1. Then Palladium on activated charcoal (Pd/C) (0.5g) was added followed by slow addition of hydrazine hydrate (10mL) in ethanol (10mL) over 10 mins. After 24 hrs, the reaction was terminated and Pd/C was filtered through celite. The filtrate was evaporated under vacuum and poured into ice-cold water (300mL) to observe precipitation. The precipitated product was filtered and washed with water. The product Phenanthrene-9,10-diamine (P2) was dried in the vacuum oven and used in the next step without further purifications.



Scheme 3: Synthesis of Phenanthrene-9,10-diamine.

An oven-dried round bottom flask fitted with condenser was charged with 2-(*t*-butylthio)benzaldehyde (10mmol) and phenanthrene-9,10-diamine(**P2**)(10mmol) in ethanol (40mL). The resulting mixture was refluxed for 24 hrs. After the complete consumption of starting materials as monitored by TLC, the reaction mixture was cooled down to room temperature. The compound was concentrated and kept for crystallization in ethanol solvent. After 10 days, the yellowish colored crystals of 2-[2-(*t*-butylthio) phenyl]-1*H*-phenanthro [9, 10-*d*]imidazole were obtained. The compound was washed with hexane and dried in vacuo

over silica gel indicator. Yield of **1**: 0.374 g (81.3% based on OPD) Spectroscopic results for C₃₂H₃₉N₅O₁₉Fe₄ (**1**): IR (KBr pellet, cm⁻¹): 3365(vNH), 1634.56 (vCN); UV-Vis (1 x 10⁻⁴ M, lmax(abs), nm, MeCN): 246(0.53), 297(0.96), 350(0.33), 523(0.26).



Scheme 4: Synthesis of 2-[2-(*t*-butylthio) phenyl]-1*H*-phenanthro [9, 10-*d*]imidazole

2.2. Physical measurements

Infrared spectrum (KBr) was recorded with a FTIR-8400S SHIMADZU spectrophotometer in the range 4000 to 400 cm⁻¹ with KBr pellet. ¹H NMR spectrum in CDCl₃ was obtained on a Bruker Advance 400 MHz spectrometer at 25°C and was recorded at 400 MHz. Ground state absorption and all spectrophotometric analysis were recorded with a LABINDIA ANALYTICAL, UV 3000+ UV-Vis spectrophotometer. Electrospray ionization (ESI) mass spectrum was recorded using a Q-tof-micro quadrupole mass spectrometer magnetometer in the. X-ray diffraction study Single crystal X-ray diffraction data of the thio-benzimidazole.

2.3. Single Crystal X-ray Diffraction (SCXRD):

Single crystal X-ray diffraction data were collected using a Rigaku XtaLABmini X-ray diffractometer equipped with Mercury CCD detector with graphite monochromatic Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) at 298.0 (2) K using ω scans. The data were reduced using CrysAlisPro 1.171.38.46 and the space group determination was done using Olex2. The crystal structures were solved by using ShelXT and were refined using ShelXL through Olex2 suite. All the hydrogen atoms were geometrically fixed and refined using the riding model. Absorption correction was done by multi-scan method. All the packing and interaction diagrams have been generated using Mercury 3.9.

3. Results and Discussion:

3.1. Synthesis and formulation of the thio-benzimidazole **1**:

2-[2-(*t*-butylthio) phenyl]-1*H*-phenanthro [9, 10-*d*]imidazole were synthesized according to the procedure as discussed above. Along with single crystal X-ray diffraction study, several differentspectroscopic and analytical techniques were used for structural and geometrical determination of **1**.

3.3. Experimental spectroscopic data of **1**:

The synthesized compounds are soluble in common organic solvents such as methanol, acetonitrile, and dichloromethane. UV-Vis spectra of **1** and derivatives shows high intensity band 248nm to 275 nm. The band at 275 nm corresponds to π - π^* chromophore. The nm corresponds to transfer transition excitation at 290 solution, a strong 360 nm at room fluorescence spectra

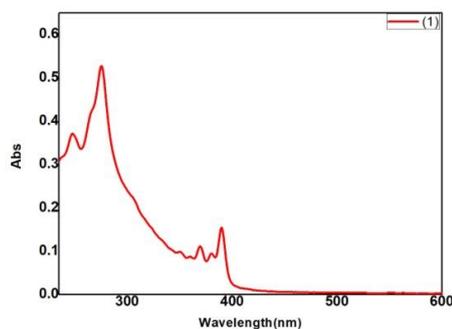
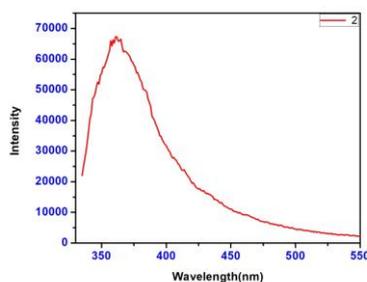


Figure 1: UV-Vis spectra of **1** in acetonitrile.

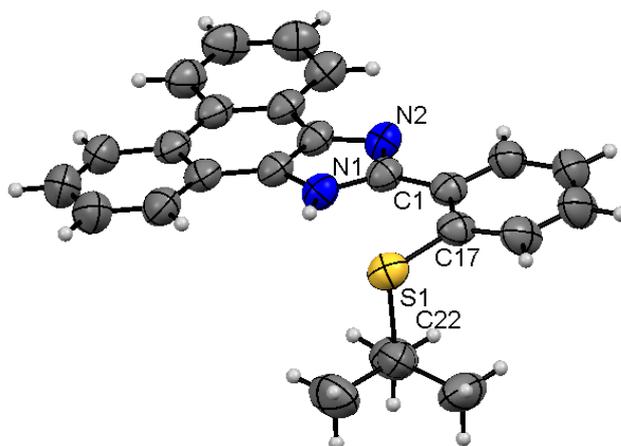
Figure 2: Fluorescence spectra of **1**. The plot shows Intensity on the y-axis (0 to 70000) versus Wavelength (nm) on the x-axis (350 to 550). The spectrum shows a strong emission band with a peak around 360 nm.



emission spectra of **1**. structure butylthio)phenyl]-1*H*-*d*]imidazole(**2**) crystallizes in

monoclinic $P2_1/n$ space group (Table 1). The ORTEP diagram of **1** is shown in Fig.3. Intramolecular H-bonding is forming between S1...H2 and this bond distance is 2.488Å. These are interacting through pi-pi interactions, weak vanderwaal interactions.

Figure 3:
representations
Table 1:
of **1**



ORTEP
of compound **1**
Crystallographic data

Data	2-[2-(<i>t</i> -butylthio)phenyl]-1 <i>H</i> -phenanthro[9,10- <i>d</i>]imidazole
Empirical formula	C ₂₅ H ₂₂ N ₂ S
CCDC number	1940307
Formula weight	382.50
Crystal system	monoclinic
Space group	$P2_1/n$
a(Å)	11.6498 (5)
b(Å)	12.2944(6)
c(Å)	14.0170(7)
α (°)	90
β (°)	94.434(4)
γ (°)	90
V(Å ³)	2001.61(16)
Z	4
ρ_{calc} (g/cm ⁻³)	1.269
Temperature (K)	290.0(2)
μ /mm ⁻¹	0.174
2 $\theta_{\text{min, max}}$ (°)	5.496, 65.396
F (000)	808.0
$h_{\text{min, max}}$; $k_{\text{min, max}}$; $l_{\text{min, max}}$	-13,17; -17,10; -16,21
Total no. of reflections	10941
R_{int}	0.0276
No. of unique reflections	6553
R_1 [$I > 2\sigma(I)$]	0.0621
w R_2 (all data)	0.1685
GoF on F ²	1.035
$\Delta\rho_{\text{max, min}}$ /eÅ ⁻³	0.47, -0.40

4. Conclusion

In conclusion, we have reported new types of thiobenzimidazole compounds **1** derived from *t*-butyl thiobenzaldehyde. The compounds were synthesized without any metal catalyst but the use of catalytic amount of formic acid in aerobic conditions. Notably, the desired starting materials have been synthesized followed by known procedures. Structure of the compound **1** was determined by single-crystal X-ray diffraction studies. We are currently exploring the

use of the reported compound 1 as an organic ligand for preparing transition metal (especially for iron and copper) complexes and bio-mimicking chemistry (S-protein, anti-fungal).

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6. References

- [1] L.V.G. and C.H.G. Gurumeet C. Wadhawa, Vitthal S. Shivankar, Dinanath D. Patil, Yashwant A.Gaikwad, Review on synthesis of benzinimidazharaole using green protocol, *World J. Pharm.Pharm. Sci.* 5 (2016) 624–656. <https://doi.org/10.20959/wjpps20169-7568>.
- [2] S. Sundar, R. Rengan, Direct synthesis of 2,4,5-trisubstituted imidazoles from primary alcohols by diruthenium(ii) catalysts under aerobic conditions, *Org. Biomol. Chem.* 17 (2019) 1402–1409. <https://doi.org/10.1039/C8OB02785D>.
- [3] P.K. Dutta, S. Panda, S.S. Zade, Synthesis, characterization and coordination properties of 2-(2'-(methylseleno)phenyl)benzimidazole, *Inorganica Chim. Acta.* 411 (2014) 83–89. <https://doi.org/10.1016/j.ica.2013.11.030>.
- [4] L.B. Townsend, D.S. Wise, The synthesis and chemistry of certain anthelmintic benzimidazoles, *Parasitol. Today.* 6 (1990) 107–112. [https://doi.org/10.1016/0169-4758\(90\)90226-T](https://doi.org/10.1016/0169-4758(90)90226-T).
- [5] R.T. Benzimidazoles, T. Roth, M.L. Morningstar, P.L. Boyer, S.H. Hughes, R.W. Buckheit, C.J. Michejda, Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles, *J. Med. Chem.* 40 (1997) 4199–4207.
- [6] B. Fang, C.H. Zhou, X.C. Rao, Synthesis and biological activities of novel amine-derived bisazoles as potential antibacterial and antifungal agents, *Eur. J. Med. Chem.* 45 (2010) 4388–4398. <https://doi.org/10.1016/j.ejmech.2010.06.012>.
- [7] M.C. Perault, L. Bergougnan, A. Paillat, I. Zieleniuk, P. Rosenzweig, B. Vandel, Lack of interaction between amisulpride and lorazepam on psychomotor performance and memory in healthy volunteers, *Hum. Psychopharmacol.* 13 (1998) 493–500. [https://doi.org/10.1002/\(SICI\)1099-1077\(1998100\)13:7<493::AID-HUP25>3.0.CO;2-A](https://doi.org/10.1002/(SICI)1099-1077(1998100)13:7<493::AID-HUP25>3.0.CO;2-A).
- [8] B. Agrahari, S. Layek, R. Ganguly, N. Dege, D.D. Pathak, Synthesis, characterization and single crystal X-ray studies of pincer type Ni(II)-Schiff base complexes: Application in synthesis of 2-substituted benzimidazoles, *J. Organomet. Chem.* (2019) 13–20. <https://doi.org/10.1016/j.jorganchem.2019.03.018>.
- [9] A.W. White, N.J. Curtin, B.W. Eastman, B.T. Golding, Z. Hostomsky, S. Kyle, J. Li, K.A. Maegley, D.J. Skalitzky, S.E. Webber, X.H. Yu, R.J. Griffin, Potentiation of cytotoxic drug activity in human tumour cell lines, by amine-substituted 2-arylbenzimidazole-4-carboxamide PARP-1 inhibitors, *Bioorganic Med. Chem. Lett.* 14 (2004) 2433–2437. <https://doi.org/10.1016/j.bmcl.2004.03.017>.
- [10] G. Yadav, S. Ganguly, Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review, *Eur. J. Med. Chem.* 97 (2015) 419–443. <https://doi.org/10.1016/j.ejmech.2014.11.053>.
- [11] S. Sharma, S. Abuzar, The benzimidazole anthelmintics--chemistry and biological activity., *Prog. Drug Res.* 27 (1983) 85–161. https://doi.org/10.1007/978-3-0348-7115-0_3.
- [12] H.J. Lim, D. Myung, I.Y.C. Lee, H.J. Myung, Microwave-assisted synthesis of benzimidazoles, benzoxazoles, and benzothiazoles from resin-bound esters, *J. Comb. Chem.* 10 (2008) 501–503. <https://doi.org/10.1021/cc800053p>.
- [13] B. Agrahari, S. Layek, R. Ganguly, N. Dege, D.D. Pathak, Synthesis, characterization and single crystal X-ray studies of pincer type Ni(II)-Schiff base complexes: Application in synthesis of 2-substituted benzimidazoles, *J. Organomet. Chem.* 890 (2019) 13–20. <https://doi.org/10.1016/j.jorganchem.2019.03.018>.
- [14] S.I. Alaqeel, Synthetic approaches to benzimidazoles from o-phenylenediamine: A literature review, *J. Saudi Chem. Soc.* 21 (2017) 229–237. <https://doi.org/10.1016/j.jscs.2016.08.001>.