International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.8, No.11 pp 457-465, 2015

Synthesis of Benzimidazole and Benzoxazole Derivatives Catalyzed by Nickel Acetate as Organometallic Catalyst.

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Abstract: Nickel acetate efficiently catalyzed the synthesis of benzimidazole and benzoxazole derivatives. This method has been applied to a variety of substrates including nucleophilic and sterically hindered diamines, aldehyde and phenol with excellent yields of benzimidazole and benzoxazole derivatives. The remarkable selectivity under mild and neutral conditions of this commercially available inexpensive catalyst is an attractive feature of this present protocol.
Key words: Benzimidazoles, Benzoxazoles, Nickel acetate, 2-aminophenol, Aldehydes.

Introduction

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand[1]. Benzimidazole are present in various bioactive compounds possessing antiviral, antihypertension and anticancer properties[2,3]. Compounds possessing the benzimidazole moiety express significant activity against several viruses such as HIV[4], Herpes(HSV-1)[5] and influenza[6]. Bis-benzimidazole is DNA-minor grove binding agents possessing anti-tumour activity[7]. The condensation of o-phenylenediamine with carbonyl compounds in the presence of strong acids such as polyphosphoric acid or mineral acids[8] and other reagents such as I_2/KI/K_2CO_3[9], N-halosuccinamide (X=Cl, Br, I)[10], $Yb(OTf)_3$[11], PEG-100[12], $(NH_4)H_2PW_{12}O_{40}$[13] and palladium as well as microwave irradiation [14] and solid phase reactions [15] are reported in literature. However, many of the synthetic protocols reported so far suffer from disadvantages, such as a requirement for anhydrous conditions, use of organic solvents, harsh reaction conditions, prolonged reaction times, expensive reagents and low to moderate yields. Almost all the reported methods make use of an acid catalyst, giving rise to tedious working procedures. Therefore, the development of a cost-effective, safe and environmentally friendly reagent is still needed.

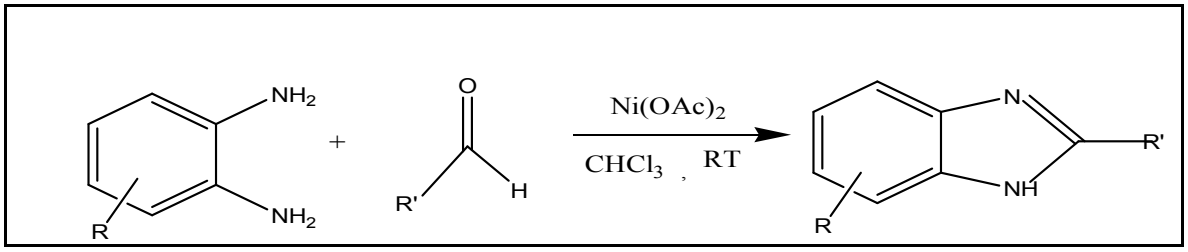
Experimental

All the reagents and reactant were purchased from commercial suppliers and were used without further purification. Melting points were recorded on an Electrothermal digital melting-point apparatus. ^{1}H NMR spectra were recorded on 400MHz Bruker spectrometer using $CDCl_3$ as a solvent and chemical shifts have been expressed in δ ppm using TMS as an internal standard. Infrared spectra were recorded on Jasco-FT/IR 4100 LE ATR PRO450-S spectrometer.

General Experimental Procedure

A mixture of benzaldehyde (1mmol) and O-Phenylene diamine (1mmol) {or benzaldehyde (1.2mmol) and 2-Amino Phenol (1mmol)} with Nickel Acetate (0.1mmol) was stirred magnetically with $CHCl_3$ at room temperature and the progress of reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, the catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4 and then evaporated under a vaccum to afford the crude product, which was further purified by column chromatography. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

Scheme – 1



R': Phenyl, Alkyl

In this communication, we report a simple and efficient method for synthesis of benzimidazole and benzoxazole derivatives using nickel acetate as a catalyst under mild conditions.

Results and Discussion

In order to find out the most effective catalyst for synthesis of benzimidazole, we employed various organometallic catalyst with o-phenylenediamine and benzaldehyde (1:1 equimolar) at room temperature. According to the results obtained, Nickel acetate was found to be the most efficient catalyst (Table 1, Entry 6). However, other organometallic catalyst such as $Zn(OAc)_2$, $Mg(OAc)_3$, $Cu(OAc)_2$, $Pb(OAc)_2$ and $Pd(OAc)_2$ exhibit less significant catalytic properties in the synthesis of benzimidazole by o-phenyl diamine and benzaldehyde (Table 1, Entry 1-5).

Table- 1. **Reaction of o-phenyldiamine and benzaldehyde in the presence of different organometallic catalysts with Chloroform at room temperature**

Entry	Organometallic catalyst	Time (min)	Yield [a] (%)
1	$Zn(OAc)_2$	30	92
2	$Cu(OAc)_2$	180	72
3	$Mg(OAc)_3$	90	74
4	$Pd(OAc)_3$	810	65
5	$Pb(OAc)_2$	120	78
6	$Ni(OAc)_2$	10	96

[a] Isolated yield

In order to find out the most effective solvent for benzimidazole derivative, benzaldehyde was chosen as a model substrate. It was treated with 1 mmol of o-phenylene diamine in presence of 0.1 mmol of $Ni(OAc)_2$ in various solvents at room temperature (Table 2). The reaction in DCM, MeOH, EtOH, THF, Toluene (Table 2, entries1- 7) were found to be less effective. Since then we, have carried out the reaction in the presence of $CHCl_3$ solvent to get an excellent yield (96% entry 8).

Table- 2. Optimization of reaction conditions

Entry	Solvent	Time (hrs)	Temp (^oC)	$Ni(OAc)_2$ (mol%)	Yield [a] (%)
1	DCM	10	40	0.2	45
2	MeOH	08	65	0.2	70
3	EtOH	05	80	0.1	86
4	EtOH	05	80	0.2	91
5	THF	12	65	0.2	55
6	Toluene	15	100	0.2	30
7	Solvent free	12	100	0.1	70
8	$CHCl_3$	10 min	RT	0.1	96

[a] Isolated yield

The Catalytic activity of $Ni(OAc)_2$ was investigated with respect to loadings. It was observed that when less than 0.1 mmole % $Ni(OAc)_2$ was used, more time was required to get corresponding products with considerable yield(Table 3, entries 1 and 2). On the other hand a catalyst more than 0.1mmol% gives excellent yields and require less time (Table 3, entries 3 and 4).

Table- 3. Catalytic effect of $Ni(OAc)_2$ with o-phenyldiamine and benzaldehyde with Chloroform at room temperature

Entry	$Ni(OAc)_2$ (mmol%)	Time (min)	Yield [a] (%)
1	0.01	30	55
2	0.05	30	65
3	0.10	10	96
4	0.15	10	96
5	0.20	10	96

[a] Isolated yield of corresponding product

Table-4. Variety of aldehydes, aliphatic, heterocyclic and aromatic possessing both electron- donating and electron withdrawing groups were employed for benzimidazole formation and in all cases, the yields were excellent. (Table-4, entries 1-18). Four different types of o-phenylenediamines were employed and all of them reacted smoothly under the reaction conditions. The Aromatic aldehydes reacted under same conditions gave considerable yields (Table-4, entries 1-11,15-18). Aldehyde with an electron-donating group showed moderate yields (Table 4, entries 3,4, 6-11). Aldehyde with an electron-withdrawing group showed excellent yields (Table 4, entries 2,5,16,17,18). Substituted o-phenylene diamine (Table 4, entries 15-18) and aliphatic aldehydes showed considerable yield (Table 4, entries 12-13).

Table- 4. Synthesis of benzimidazole in presence of $Ni(OAc)_2$ with Chloroform at room temperature

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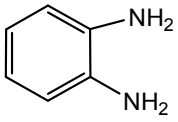
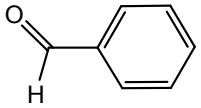
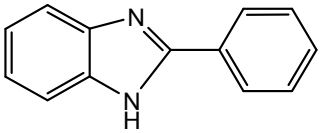
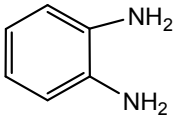
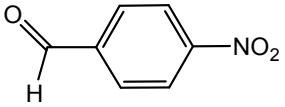
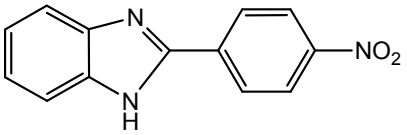
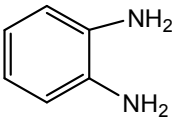
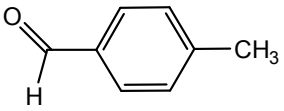
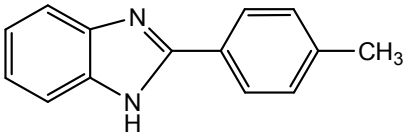
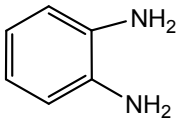
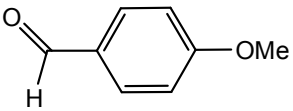
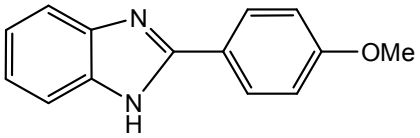
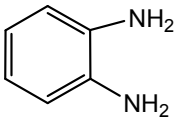
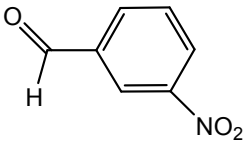
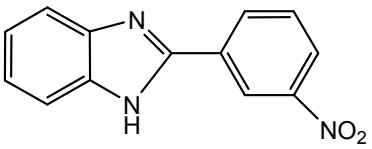
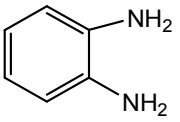
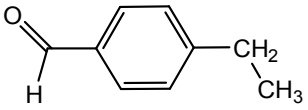
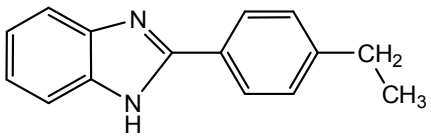
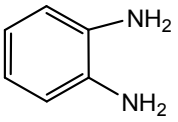
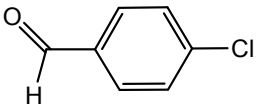
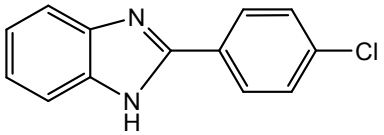
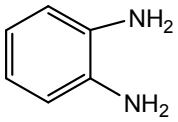
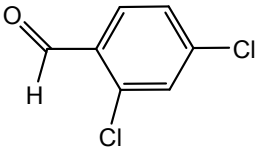
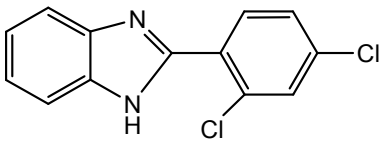
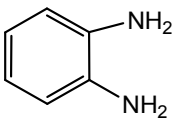
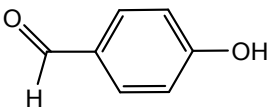
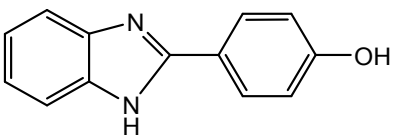
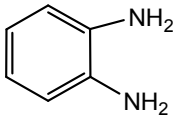
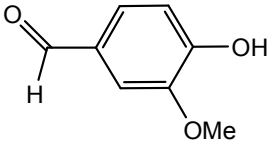
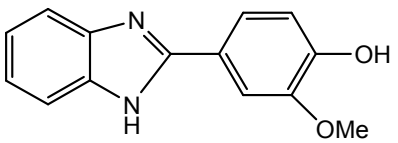
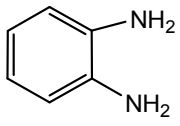
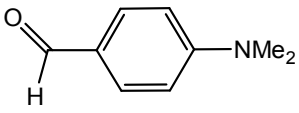
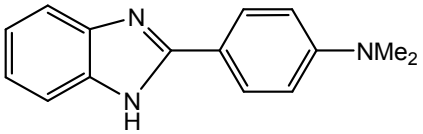
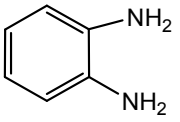
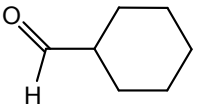
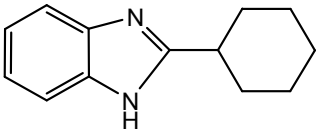
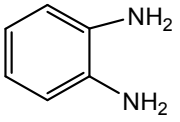
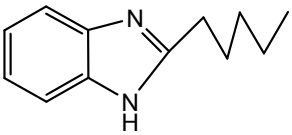
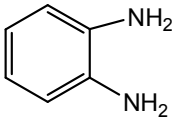
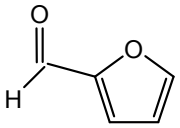
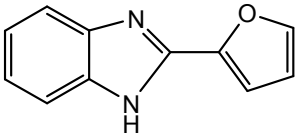
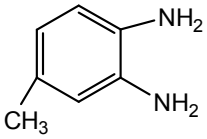
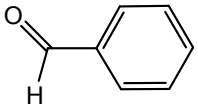
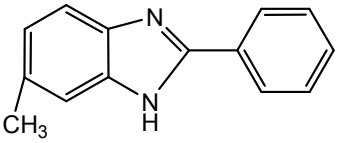
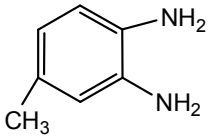
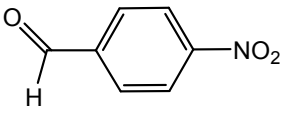
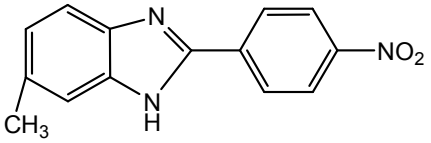
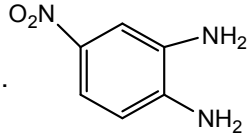
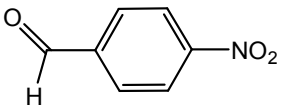
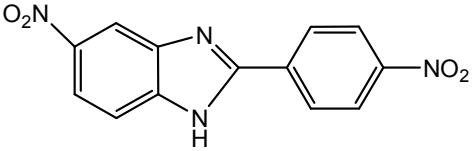
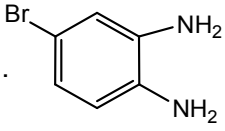
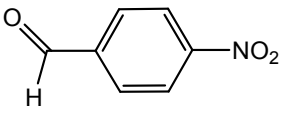
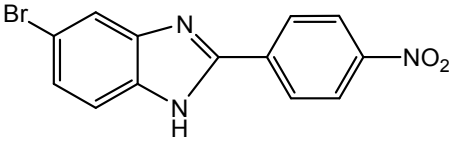
1.				10	96
2.				10	96
3.				10	89
4.				15	88
5.				20	95
6.				15	87
7.				10	90
8.				20	90
9.				25	88
10.				40	85

11.				40	90
12.				35	85
13.				45	83
14.				45	91
15.				10	95
16.				10	94
17.				10	94
18.				20	93

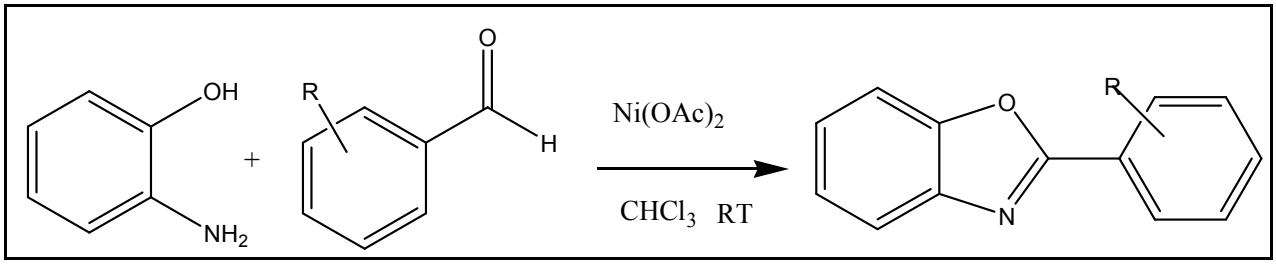
[a] The substrate was treated with benzaldehyde (1 mmol) by using 0.1 mmol of $Ni(OAc)_2$ with Chloroform at room temperature.
[b] All products were identified by their IR and ^1H NMR spectra
[c] Isolated yields.

In order to expand the scope of new protocol to synthesize of benzoxazole from 2-Amino Phenol with Chloroform, we investigated the reaction of benzoxazole in presence of Nickel acetate.

Benzoxazoles are an important class of heterocyclic compounds that have many applications in medicinal chemistry. Benzoxazole derivatives have been characterized as melatonin receptor agonists[16], amyloidogenesis inhibitors[17], Rho kinase inhibitors[18], and antitumor agents[19]

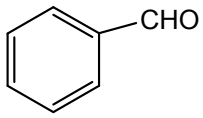
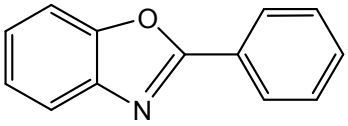
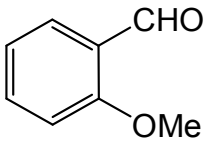
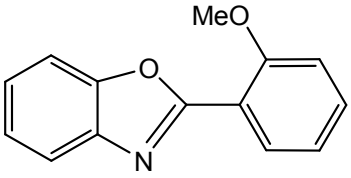
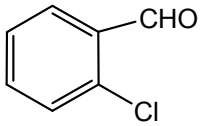
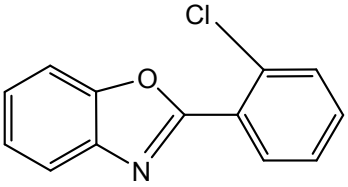
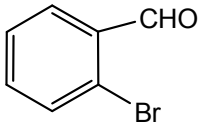
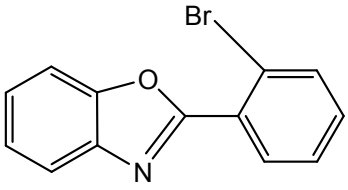
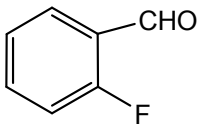
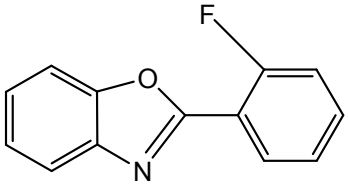
It is interesting to note that when 2-Amino phenol was allowed to react with benzaldehyde in presence of $Ni(OAc)_2$ with Chloroform at room temperature, excellent yield of corresponding Benzoxazole was obtained (Table 5). Amino phenol and substituted aldehydes was employed in order to investigate the scope of reaction. Aldehydes were readily cyclized with 2-amino phenol and these preliminary results indicates that benzoxazole yield is affected by position of substitutent on aromatic ring of the aldehydes. Ortho-substituted aryl aldehyde (Entry2-6), the yield was lower than that when meta-and para-substituted aryl aldehydes were used.

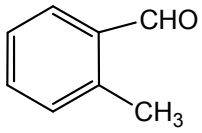
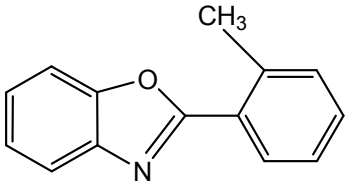
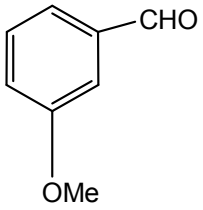
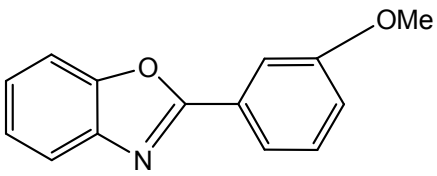
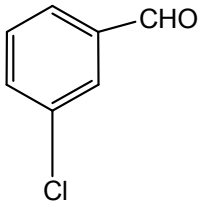
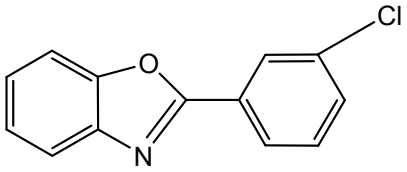
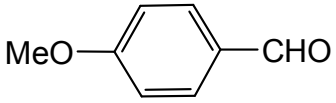
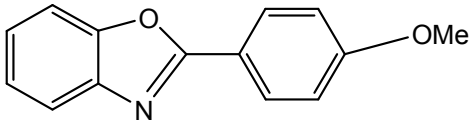
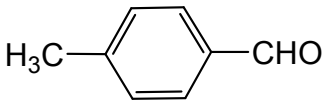
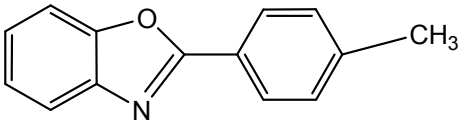
Scheme 2:



R: Phenyl, Alkyl

Table- 5. Synthesis of benzoxazole in presence of $Ni(OAc)_2$ with Chloroform at room temperature

Entry	Aldehyde[a]	benzoxazole[b]	Time (min)	Yield[c] (%)
1.			40	95
2.			40	81
3.			45	70
4.			45	65
5			45	75

6.			45	85
7.			40	92
8.			40	90
9.			40	95
10.			40	95

[a] 2-Amino phenol (1mmol) was treated with benzaldehyde (1.2 mmol) by using 0.1 mmol of $Ni(OAc)_2$ with Chloroform at room temperature.
[b] All products were identified by their IR and ^1H NMR spectra
[c] Isolated yields

In conclusion, this manuscript describes a method in which $Ni(OAc)_2$ is a highly efficient catalyst for the synthesis of benzimidazole and benzoxazole derivatives by using various substrates. The advantages include low cost, ease of catalyst handling, requirement of a very small amount of catalyst as 0.1mmol, mild reaction conditions and reactions carried out at room temperature with excellent yields. The remarkable selectivity under mild and neutral conditions of this commercially available inexpensive catalyst is an attractive features of this method.

Spectral Data for selected Compounds

Benzimidazole:

Entry 2: IR (KBr): 840, 1342, 1525, 1619, 2987, 3474 cm^{-1}

H^1NMR (300MHz, $CDCl_3$): δ = 6.9 (m, 2H, J=7.2Hz), 7.3 (d, 2H, J=7.2Hz) ; 8.2 (d, 2H, J=7.2Hz); 8.4((d, 2H, J=7.8Hz); 8.6 (s, br, 1H, NH)

Entry 4: IR (KBr): 833, 1035, 1125, 1342, 1536, 1628, 2988, 3478 cm^{-1}

H^1NMR (300MHz, DMSO): δ = 3.25 (s, 3H), 7.52(s, broad, 2H), 7.68 (d, 2H, J=7.6Hz, 2H) ; 7.93 (m, 2H); 8.12(d, J=7.6Hz, 2H); 11.92 (s, 1H)

Entry 5: IR (KBr): 837, 925, 1045, 1109, 1129, 1355, 1544, 1629, 2988, 3479 cm^{-1}

H^1NMR (300MHz, DMSO): δ = 7.2(m, 2H), 7.55 (d, broad, J=7.5Hz, 1H) ; 7.62 (d, broad, J= 7.5Hz, 1H); 8.21(d, J= 6.8Hz, 1H); 8.55(d, J= 7.8Hz, 1H); 9.12 (s, 1H), 12.5 (s, 1H)

Benzoxazole:

Entry 1: ^{1}H NMR ($CDCl_3$): δ 8.27–8.24 (m, 2H), 7.79– 7.76 (m, 1H), 7.60–7.57 (m, 1H), 7.54–7.51 (m, 3H), 7.38–7.32 (m, 2H).

Entry 2: ^{1}H NMR ($CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 1H), 7.83–7.80 (m, 1H), 7.60–7.57 (m, 1H), 7.51– 7.47 (m, 1H), 7.35–7.32 (m, 2H), 7.13–7.07 (m, 2H), 4.02 (s, 3H)

Entry 4: ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J = 8 Hz, 1H), 7.86–7.83 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63–7.60 (m, 1H), 7.48–7.32 (m, 4H)

Acknowledgement

The authors acknowledged the partial support of this work by Prof. B.P. Bandgar , Ex.Vice Chancellor, University of Solapur, India and Dr. G. A. Meshram, Associate Professor, Department of Chemistry, University of Mumbai, India.

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