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Copper nitrate catalyzed synthesis and biological activity evaluation of some naphtho[2,3-d]imidazoles

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A series of naphtho[2,3-d]imidazoles **(2a-l)** were synthesized in good yields by the reaction of 2,3-diaminonaphthalene with aromatic aldehydes in the presence of catalytic amounts of copper nitrate, $Cu(NO_3)_2.6H_2O$. Some features of this practical protocol are: use of catalyst, short reaction times and easy workup. The antibacterial activity of these naphtho[2,3-d]imidazoles was tested against *Staphylococcus aureus* (mm) and *Escherichia coli* (mm) bacterial strains.

Key words: aromatic aldehydes, imidazole, 2,3-diaminonaphthalene, catalyst.

1. INTRODUCTION

Naphtho[2,3-d]imidazoles have received substantial attention because of their broad application for the preparation of biologically active molecules and for the Chichibabin reaction [1,2].

Several methods have been reported for the preparation of benzimidazoles. The general procedure for the synthesis of simple benzimidazoles usually involves the reaction of carboxylic acids or their derivatives (nitriles, orthoesters, imidates) with *o*-phenylenediamines, and the reaction of *o*-phenylenediamines with aldehydes in the presence of an acid catalyst under various reaction conditions [3-11]. In each case, the cyclization involves coupling at the *o*-phenylene nitrogen. However, due to the low basicity of 2,3-diaminonaphthalene compared to 1,2-phenylenediamine, synthesis of simple naphtho[2,3-d]imidazoles is difficult under similar conditions and most of the references in the literature report the synthesis of substituted naphtho[2,3-d]imidazoles under different conditions [12,13]. Because of the increasing importance of naphtho[2,3-d]imidazoles, a simple procedure for the synthesis of these heterocyclic compounds would be of great value.

In view of these points and as a part of our research work on the development of new methods for the synthesis of condensed imidazoles [4,6,11] we are going to report a clean and practical synthetic method for the preparation of naphtho[2,3-d]imidazoles using $Cu(NO_3)_2.6H_2O$ as an efficient catalyst.

2. EXPERIMENTAL

Reagents and methods

All used chemicals were purchased from Merck or Fluka Company. Melting points were determined on an Electrothermal digital melting point apparatus. The IR spectra were recorded on a Unicom Galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referred to the internal standard tetramethylsilane (TMS). Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III). The microanalyses results agreed with the calculated values. Reactions were monitored by thin layer chromatography using silica gel F_{254} aluminum sheets (ethyl acetate/ n-nexane, 3:1). The microbial strains were identified and obtained from the Pasteur Institute of Iran: *Staphylococcus aureus* (RTCC, 1885), and *Escherichia Coli* (ATCC, 35922).

General procedure for the preparation of naphtho[2,3-d]imidazoles

To a solution of 2,3-diaminonapthalene (1 mmol) and the corresponding aromatic aldehyde (1 mmol) in ethanol (15-20 mL) $Cu(NO_3)_2.6H_2O$ (15 mol%) was added. The reaction mixture was stirred at 50°C for desired time (Table 1). The reaction progress was monitored by TLC. After completion of the reaction, water (20-25 mL) was added. The precipitated crystals were filtered, washed with cold water and air dried.

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Table 1. Reaction of 2,3-diaminonaphthalene with aromatic aldehydes catalyzed by 15 mol% $Cu(NO_3)_2.6H_2O$ at 50 °C

Product (**2**)	Ar	Time (min)	Yield (%)	M.P. (°C)
a	2-$NO_2C_6H_4$	20	68	270 (dec)
b	4-$NO_2C_6H_4$	40	78	180 (dec)
c	4-$CH_3C_6H_4$	50	65	241 (dec)
d	3-BrC_6H_4	30	58	240-242
e	4-BrC_6H_4	35	67	270 (dec)
f	2-ClC_6H_4	40	78	274-278
g	3-ClC_6H_4	35	60	212 (dec)
h	4-ClC_6H_4	38	89	220 (dec)
i	4-$CH_3OC_6H_4$	55	60	320 (dec)
j	C_6H_5	45	40	260 (dec)
k	2-Cl-6-F-C_6H_3	30	67	267-268
l	2-OH-5-Br C_6H_3	40	63	312-314

Table 2. Zone inhabitation of naphtho[2,3-d]imidazoles **(2a-l)**

Entry	Compound	*Staphylococcus aureus* (mm)	*Escherichia coli* (mm)
1	2a	9 ± 0.1	18 ± 0.2
2	2b	36 ± 0.1	**—**
3	2c	6 ± 0.2	**—**
4	2d	30 ± 0.1	**—**
5	2e	9 ± 0.1	**—**
6	2f	24 ± 0.2	**—**
7	2g	30 ± 0.1	**—**
8	2h	27 ± 0.2	**—**
9	2i	39 ± 0.2	**—**
10	2j	42 ± 0.2	**—**
11	2k	27 ± 0.1	**—**
12	2l	15 ± 0.2	**—**
13	DMSO	—	**—**
	Standard drugs	Penicillin 33 mm	Gentamicin 18 mm

— indicates resistance of bacteria to compounds

Antibacterial study

The agar disk diffusion technique was used for evaluation of the biological activity. In each test 5 mg of the synthesized naphtho[2,3-d]imidazole **(2a-l)** were dissolved in 250 µl of DMSO and 100 µl of the test compounds of known concentration were introduced onto the disks (0.7 cm) and then allowed to dry. The disk was completely saturated with the test compounds. Then the disk was introduced onto the upper layer of the medium with the bacteria. 100 µl of solvent (DMSO) were added to the blank disk, which was used as a negative control on each plate along with the standard drugs. The plates were incubated overnight at 37°C. The inhibition zones were measured and compared with the controls. The results are given in Table 2.

2-(2-Nitrophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2a)

IR (KBr): ν= 3055 ($CH_{aromatic}$), 1525, 1477 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.47-8.24 (m, 10H, $CH_{aromatic}$), 13.51 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53%. Found: C, 70.68; H, 3.56.; N, 14.45%.

2-(4-Nitrophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2b)

IR (KBr): ν= 3387 (NH), 3079 ($CH_{aromatic}$), 1606 (C=N), 1518 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 8.05-8.55 (m, 10H, $CH_{aromatic}$), 13.34 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}N_2O_3$: C, 70.56; H, 3.83; N, 14.53%. Found: C, 70.44; H, 3.98; N, 14.61%.

2-*p*-Tolyl-1-*H*-naphtho[2,3-*d*]imidazole (2c)

IR (KBr): ν= 3448 (NH), 3049 ($CH_{aromatic}$), 1612 (C=N), 1491 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ=

7.39-8.20 (m, 10H, $CH_{aromatic}$), 13.10 (bs, 1H, NH). Anal. calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84%. Found: C, 83.49; H, 5.59; N, 10.98%.

2-(3-Bromophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2d)
IR (KBr): ν= 3049 ($CH_{aromatic}$), 1541 (C=N), 1471 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.30-8.53 (m, 10H, $CH_{aromatic}$), 13.40 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}BrN_2$: C, 63.18; H, 3.43; N, 8.67%. Found: C, 62.91; H, 3.25; N, 8.96%.

2-(4-Bromophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2e)
IR (KBr): ν= 3049 ($CH_{aromatic}$), 1599 (C=N), 1483 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.40-8.23 (m, 10H, $CH_{aromatic}$), 13.20 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}BrN_2$: C, 63.18; H, 3.43; N, 8.67%. Found: C, 63.01; H, 3.56; N, 8.77%.

2-(2-Chlorophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2f)
IR (KBr): ν= 3047 ($CH_{aromatic}$), 1473 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.49-8.21 (m, 10H, $CH_{aromatic}$), 13.70 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05%. Found: C, 73.32; H, 4.10; N, 10.21%.

2-(3-Chlorophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2g)
IR (KBr): ν= 3474 (NH), 3049 ($CH_{aromatic}$), 1543 (C=N), 1473 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.45-8.41 (m, 10H, $CH_{aromatic}$), 13.40 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05%. Found: C, 73.41; H, 3.84; N, 10.12%.

2-(4-Chlorophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2h)
IR (KBr): ν= 3036 ($CH_{aromatic}$), 1618 (C=N), 1483 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.40-8.32 (m, 10H, $CH_{aromatic}$), 12.90 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05%. Found: C, 73.10; H, 4.23; N, 9.92%.

2-(4-Methoxyphenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2i)
IR (KBr): ν= 3053 ($CH_{aromatic}$), 2939 ($CH_{aliphatic}$), 1608 (C=N), 1499, 1450 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 3.86 (s, 3H CH_3), 7.16-8.29 (m, 10H, $CH_{aromatic}$), 13.00 (bs, 1H, NH). Anal. calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21%. Found: C, 78.58; H, 5.21, N, 10.29%.

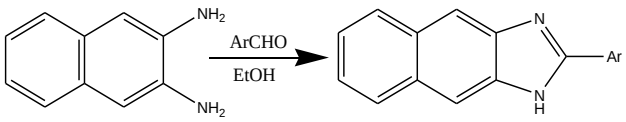
2-Phenyl-1-*H*-naphtho[2,3-*d*]imidazole (2j)
IR (KBr): ν= 3300 (NH), 3047 ($CH_{aromatic}$), 1545 (C=N), 1471 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.46-8.35 (m, 11H, $CH_{aromatic}$), 13.40 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47%. Found: C, 83.69; H, 5.09 N, 11.69%.

2-(2-Chloro-6-fluorophenyl)-1-*H*-naphtho[2,3-*d*]imidazole (2k)
IR (KBr): ν= 3148 (NH), 3051 ($CH_{aromatic}$) 1525, 1475 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 7.55-8.28 (m, 9H, $CH_{aromatic}$) 13.80 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{10}ClFN_2$: C, 68.81; H, 3.40; N, 9.44%. Found: C, 68.56; H, 3.53, N, 9.62%.

4-Bromo-2-(1H-naphtho[2,3-d]imidazol-2-yl)phenol (2l)
IR (KBr): ν= 3284 (NH), 3045 ($CH_{aromatic}$), 1606 (C=N), 1510, 1456 cm^{-1}. ^{1}HNMR (300 MHz, DMSO): δ= 6.81-8.41 (m, 9H, $CH_{aromatic}$), 13.43 (bs, 1H, NH). Anal. calcd. for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.72; N, 8.26%. Found: C, 60.28; H, 3.55; N, 8.39%.

3. RESULTS AND DISCUSSION

During our recent research directed toward the development of simple and practical procedures for the synthesis of some condensed imidazoles,[4,6,11] we have succeeded in preparing the naphtho[2,3-d]imidazoles **(2a-l)**, by condensation reaction of the appropriate aromatic aldehyde with 2,3-diaminonaphthalene in the presence of $Cu(NO_3)_2.6H_2O$ in good yields. No byproducts were observed in this reaction (Scheme 1).



1 **Scheme 1** **2**

For the primary study and optimization of the reaction conditions, we investigated the reaction of equimolar amounts of *p*-nitrobenzaldehyde and 2,3-diaminonaphthalene in the presence of copper nitrate. After many examinations, we found that the best conditions for this reaction were: 15 mol% of catalyst at 50 °C using ethanol as a solvent. The results are presented in Table 3.

To explore the validity of this procedure, we extended our study using 15 mol% copper nitrate as a catalyst at 50 °C with different aromatic aldehydes to prepare a series of naphtho[2,3-d]imidazoles.

Table 3. Optimization of the reaction conditions of *p*-nitrobenzaldehyde with 2,3-diaminonaphthalene in the presence of copper nitrate

Entry	Solvent	$Cu(NO_3)_2.6H_2O$ (mol%)	Temperature (°C)	Time (min)	Yield (%)[a]
1	CH_3CN	15	50	40	74
2	DMF	15	50	40	62
3	DMSO	15	50	40	58
4	CH_3OH	15	50	40	67
5	C_2H_5OH	15	50	40	78
6	C_2H_5OH	5	50	70	65
7	C_2H_5OH	10	50	55	70
8	C_2H_5OH	20	50	40	77
9	C_2H_5OH	-	Reflux	45	<5

[a] Isolated yields

The results are summarized in Table 1. Various aromatic aldehydes bearing electron-withdrawing groups (such as nitro, halide) and electron-releasing groups (such as methyl and methoxy) show almost equal ability of product formation in reasonable yields. Aliphatic aldehydes such as formaldehyde or acetaldehyde were also examined under the same conditions, but the corresponding products were isolated in low yields (< 5%). The procedure is simple and more convenient than other reported methods in the literature, which were carried out under forced reaction conditions or using special starting materials [12,13].

The structure of the synthesized compounds was confirmed by IR and NMR spectral data. The chemical shifts in the ^{1}H NMR spectra of the compounds were related to the substituted Ar group. The Ar group with an electron donor substituent (e. g. CH_3, OCH_3) produces a lower shift. The ^{1}H NMR spectra of (**2a-h)** display a multiplet at 7.30-8.55 ppm and a broad singlet at 12.90-13.70 ppm attributed to the resonance of 10 aromatic protons and the NH group, respectively. The ^{1}H NMR spectra of (**2k-l)** are very similar to those of (**2a-h)** and have a multiplet with integration of 9 due to the resonance of 9 aromatic protons. The broad singlet of the NH group appeared at 13.40-13.80 ppm. The appearance of one NH proton signal in the ^{1}H NMR spectra of **2a-l** in high field compared to the spectra of the starting materials is a good support of the observed reactions**.** This broad signal for compounds **2a** and **2f** appeared at a lower shift compared to that of other compounds containing an electron withdrawing group, probably due to the interaction between the NH group and the Cl or NO_2 group at the ortho position. The IR spectra of the compounds revealed the presence of absorption bands in the range from 3284 to 3448 cm^{-1} for the NH group, from 3036 to 3079 cm^{-1} for C-H and from 1450 to 1518 cm^{-1} for C=C aromatic stretching vibrations.

The antibacterial study (Table 2) shows that all naphtho[2,3-d]imidazoles **(2a-l)** exert antibacterial activity against *Staphylococcus aureus* as gram positive and only compound **2a** has antibacterial activity against *Escherichia coli* as gram negative bacteria. The maximum and minimum antibacterial activities against *Staphylococcus aureus* were related to compounds **2j** and **2c**, respectively**.** The biological activity did not give a reasonable relationship with the electronic effects of the substituents and was comparable with that of imidazole or benzimidazole derivatives [14,15].

6. CONCLUSIONS

In summary, we have developed a simple and efficient methodology for the synthesis of various biologically active naphtho[2,3-d]imidazoles in the presence of copper nitrate as a catalyst without using drastic conditions. In addition to the efficiency and simplicity provided by this procedure, ease of workup and short reaction time make the method advantageous**.** Further investigations with appropriate structural modifications of title compounds may improve their biological activities.

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СИНТЕЗА НА НЯКОИ НАФТО[2,3-d] ИМИДАЗОЛИ ПРИ КАТАЛИЗАТОР ОТ МЕДЕН НИТРАТ И ОЦЕНЯВАНЕ НА БИОЛОГИЧНАТА ИМ АКТИВНОСТ

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(Резюме)

Синтезирани са група от нафто[2,3-d] имидазоли с добър добив чрез реакцията между 2,3-диаминонафтален и ароматни алдехиди в присъствие на $Cu(NO_3)_2.6H_2O$ като катализатор. Следствия от протокола на изследванията е кратки времена на реакцията в присъствие на катализатор и лесно изолиране на продукта. Изследвана е антибактериалната активност върху *Staphylococcus aureus* и *Escherichia coli*.