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Alkyl-1*H*-benzo[d]imidazole synthesis from alkyl bromides and 1,2-benzenediamines by a mild domino reaction

Research article

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Abstract
A method was implemented for synthesis of 2-alkyl-*1*H-benzo[d]imidazole derivatives in dry medium. Starting reagents, 1,2-diaminobenzene derivatives and primary alkyl halides using pyridine *N*-oxide is converted into benzimidazoles. The protocol does not use catalyst and solvent. Simplicity and easy work-up are the important advantages of the method.

Keywords: heterogeneous medium; benzimidazole; alkyl halides; pyridine *N*-oxide; domino reaction.

1. INTRODUCTION

The benzimidazole core can be designated ”Master Key” as it is an essential skeleton in many natural and synthetic compounds used by pharmaceutical and medicinal chemistry [1, 2].

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Biological activity exhibits only benzimidazoles substituted in 1, 2 and/or 5(or 6) nucleus positions [3].

Benzimidazole derivatives are considered an important heterocyclic motif that features a wide range of applications as therapeutic agents including antitumors [4], antifungals [5], antivirals [6], antidepressants [7], antihypertensives [8], anti-convulsants [9], anti-HIVs [10], antibacterials [11], proton pump inhibitors [12, 13], antidiabetics and antiasthmatics [14].

The most commonly used method of synthesizing 2-substituded benzimidazoles involves the condensation reaction of 1,4-benzenediamines and carboxylic acids or their derivatives with the help of strong inorganic acid catalysts [15, 16]. 2-Alkylbenzimidazoles can be prepared via condensation reaction of o-phenylenediamines with aromatic aldehydes over nano-Ni(II)/Y zeolite as a heterogeneous catalyst [17].

The reduction of 2-nitroanilines with sodium hydride followed by alkylation with organic halides [18] or reduction with stannous chloride followed by reaction with an organic acid anhydride [19] also provides 2-alkylbenzimidazoles. Thermal decomposition of 2-azidobenzenamines in the presence of an aldehyde produces 2-alkyl-substituted benzimidazoles [20]. Green methods involving microwaves have also been used to synthesize 2-alkylbenzimidazole derivatives [21, 22].

Previously, we developed a proceeding for obtaining 2-arylbenzimidazoles in heterogeneous medium from benzylic halides and o-phenylenediamines [23, 24]. In this line, starting from primary alkyl halides and 1,2-benzenediamine derivatives, we have extended the new method to obtain 2-alkyl-substituted benzimidazoles as well.

2. MATERIALS AND METHODS

2.1. Materials

All reagents, 1, 2-benzenediamines, alkyl bromides, and pyridine-*N*-oxide are commercial compounds from Fluka or Aldrich.

The reagents used in the synthesis have analytical purity and are used as such.

2.2. Apparatus

Infrared spectra were recorded using an Alpha Bruker Optics spectrometer in the range of 600-4000 cm^{-1} at ambient temperature. The melting points were determined on a Gallenkamp digital melting point apparatus. The purity of the compounds and their characterization was done by thin layer chromatography on silica gel glass plates (TLC, MeOH-DCM). The structure of the products was confirmed by comparing their physical properties (melting temperatures, IR absorption bands) with those of the known compounds from the literature.

2.3. Methods

General procedure for the synthesis of 2-alkyl-substituted-1*H*-benzo [d] imidazole derivatives (1-5)

In a round bottom flask fitted with a reflux bulb condenser were added alkyl bromide (6 mmol), 1,2-benzenediamines derivative (6 mmol), and pyridine-*N*-oxide (21 mmol). The mixture of reactants was heated to selected temperature for required time. After completion of reaction (TLC, MeOH-DCM) the resulting mixture was washed with dilute NaOH and filtered off. The obtained precipitate was recrystallized from EtOH-H_2O to isolate 2-alkyl-substituted-1*H*-benzo[d]imidazole compound (Table II).

2-Methyl-1*H*-benzo[d]imidazole (1) [25]. Yield: 72%; mp. 172-173°C; Molecular formula $C_8H_8N_2$; IR: 3178s, 2544s, 1668m, 1570m, 1490vs, 1464m, 1440m, 1362vs, 1220m, 1044vs, 1004s, 897vs cm^{-1};

2-Ethyl-1*H*-benzo[d]midazole (2) [26]. Yield: 70%; mp.174-175°C; Molecular formula $C_9H_{10}N_2$; IR: 3085s, 2640s, 1550m, 1460vs, 1410vs, 1271vs, 1043s, 966m, 748vs cm^{-1};

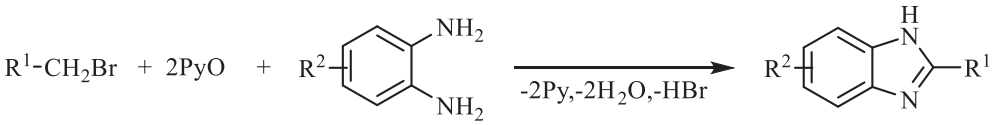
2-Vinyl-1*H*-benzo[d]imidazole (3) [27]. Yield: 84%; mp. 152-153 °C; Molecular formula $C_9H_8N_2$; IR: 3221s, 2945s, 2631m, 1649m, 1450vs, 1262vs, 1037m, 768 vs cm^{-1};

2-Ethynyl-1*H*-benzo[d]imidazole (4) [28]. Yield: 86%; mp. 183-184°C; Molecular formula $C_9H_6N_2$; IR: 3198m, 2910s, 2050w, 1580m, 1442 vs, 1245vs, 752s cm^{-1};

2-(1-Propen-1-yl)-1*H*-benzo[d]imidazole (5) [29]. Yield: 88%; mp. 192-193°C; Molecular formula $C_{10}H_{10}N_2$; IR: 3219s, 2939s, 2627w, 1640m, 1447s, 1258vs, 1031w, 780 vs cm^{-1};

3. RESULTS AND DISCUSSION

We developed a protocol to obtain benzimidazoles by a one-pot two-component domino reaction. An initiator as pyridine *N*-oxide was used. The synthesis of 2-alky-1*H*-benzo[d]imidazoles occurs in dry medium without any catalyst (Scheme 1).



1-10

R^1: Me, Et, vinyl, ethynyl, 1-propenyl, tert-Bu; R^2: H, Me, NO_2

Scheme 1. 2-Alkyl- 1*H*-benzo [d] imidazole synthesis initiated by pyridine *N*-oxide

Optimal conditions of synthesis were determined to obtain 2-(1-propen-1-yl)-1*H*-benzo[d]imidazole from crotyl bromide and 1,2-benzenediamine. For this, several determinations were made by modifying the reaction parameters such as the molar ratio of reactants, temperature and time (Table 1).

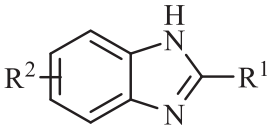
Table 1. Finding of the optimal conditions for the synthesis of 2-(1-propen-1-yl)-1*H*-benzo[d]imidazole.

Entry	Molar ratio			Time	T	Yield
	$H_3CCH=CHCH_2Br$	$1,2-(NH_2)_2C_6H_4$	PyO	(h)	(°C)	(%)
1	1	1	1	3	90	38
2	1	2	1	4	90	46
3	1	1	1.5	2	95	60
4	1	1	2.5	4	95	85
5	1.5	1	1	3.5	95	65
6	1	1	2	4	95	81
7	1	1	2	2.5	100	62
8	1	1	3	3	95	86
9	1	1	3.5	4	95	88
10	1	1	4	4	95	88
11	1.5	1	2.5	4.5	100	71

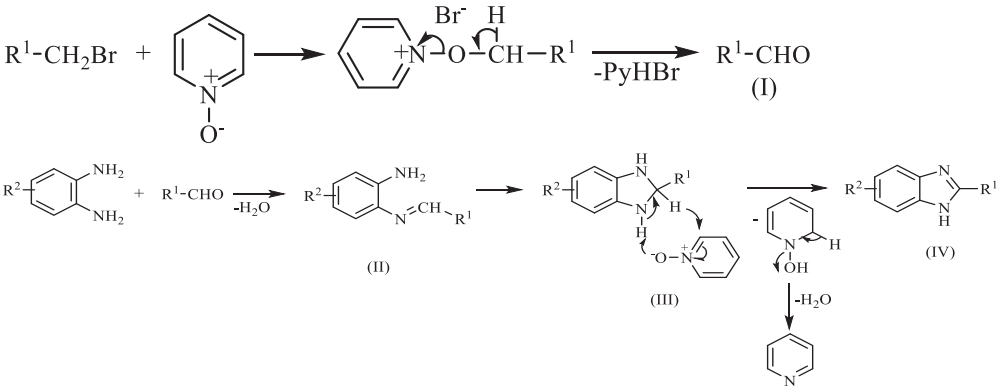
The halogenated compound and the aromatic amine are in equimolar amount, but an excess of 75% pyridine *N*-oxide is required. The synthesis occurs at 95°C for 4 h. Under these conditions, 2-(1-propen-1-yl)-1*H*-benzo[d]imidazole is obtained in a yield of 88%. With this set of reaction conditions, a series of 2-alkylbenzimidazoles were synthesized (Table 2).

We suppose that pyridine-*N*-oxide transforms alkyl halide into aldehyde (I) by Kornblum oxidation (Scheme 2) [23]. The resulting aliphatic aldehyde (I) forms a Schiff base (II) with the 1,2-benzenediamine derivative. An intramolecular cycloaddition of Schiff (II) base generates 2-alkyl-2,3-dihydro-1*H*-benzo[d]imidazole (III) which was oxidized to 2-alkyl-1*H*-benzo[d]imidazole (IV) by another pyridine *N*-oxide molecule.

Table 2. Synthesis of 2-alkyl-1*H*-benzo[d]imidazoles by a domino reaction.



Entry	R^1	R^2	Time (h)	Yield (%)
1	Me	H	5	72
2	Et	H	5.5	70
3	C_2H_3	H	4	84
4	C_2H	H	4.5	86
5	1-Propen-1-yl	H	4	88



Scheme 2. Presumed reaction mechanism for obtaining 2-alkyl-1*H*-benzo[d]imidazoles

4. CONCLUSIONS

A smooth procedure that allows easy synthesis of 2-alkyl-substituted-1*H*-benzo[d]imidazoles from 1,2-benzenediamines, pyridine-*N*-oxide and a variety of alkyl bromides was developed. The novel one-pot domino sequence uses thermal heating conditions and does not require catalyst and solvent. The method allows the obtaining of the alkyl benzimidazoles in good yields, but the reaction time is longer than in the case of obtaining the aryl benzimidazoles [23, 24]. The main advantages of the procedure are mild conditions, the operational simplicity, easy isolation of alkyl benzimidazole derivatives from reaction medium, and also simple work-up.

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Using Python multi-paradigm programming language in evaluating the antibacterial activity of a Ni(II) complex compound compared to that of its free organic ligand

Research article

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Abstract
As antibiotics are indispensable in treating infections caused by bacteria, there has been much research done within this field, in order to identify new solutions against this kind of pathogen agents. The paper aims to provide information about the antibacterial activity exhibited by a Ni(II) complex compound in comparison with that shown by its free organic bidentate ligand (namely, the bidentate (N, S) heterocyclic ligand is 2-mercapto-3-niacinamido-1,4-naphthalenedione). As it refers to substances that have been described previously from other points of view, the current paper is intended to be the final part of their presentation. More precisely, to complete the description table by evaluating the antibacterial activity, Kirby-Bauer disk diffusion method has been used. The microbiological tests have been conducted against eight kinds of microorganisms: four gram-positive and four gram-negative bacteria. These tests were followed by a thorough statistical analysis of their results, performed within Python multi-paradigm programming language.

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Keywords: Python programming language, Kirby-Bauer disk diffusion method, antibacterial activity, square-planar Ni(II) complex compounds, naphthalenedionic ligands

1. INTRODUCTION

At the beginning of the third millennium, because of the changes in different human habits and also due to the climate changes, bacterial infections have become a main cause of disease and even death. As to overcome this grave medical issues, studying drugs able to treat them is a very significant and challenging matter. Though, drug overuse and/or misuse by people have been resulted in increased bacteria resistance, which is a major public health threat [1].

Consequently, during the current years, much research is concentrated on identifying paths to obtain new drugs, which may be active despides bacteria structural changes, solving the problem of increasing bacterial resistance [1-7].

Coordination chemistry represents a field of major interest, which can play a crucial role in developing new compounds with significant antibacterial activities and, therefore, with potential pharmaceutical applications [1-6].

The present paper reports the results of such a study, performed on a heterocyclic bidentate ligand and its Ni(II) complex compound, which have been tested as potential drugs against eight kinds of microorganisms: four gram-positive and four gram-negative bacteria.

2. MATERIALS AND METHODS

2.1. Materials for obtaining the free ligand and its Ni(II) complex compound

As previously presented [8], so as to synthesize the organic ligand, we have used the following Sigma-Aldrich reagents: 2,3-dichloro-1,4-naphthalenedione, niacinamide, thiourea, NaOH pellets, CH_3COOH and ethyl alcohol and then, with the aim of synthesizing the complex compound, we have also used Sigma-Aldrich reagents, namely:

tetrabutylammonium hydroxide solution, 40 wt. % in H_2O, nickel (II) chloride hexahydrate, diethyl ether and once again ethyl alcohol.

To obtain the solutions for the experimental investigation, we have used Sigma-Aldrich DMF as a solvent.

Furthermore, for the experimental study we have also used Sigma-Aldrich tetrabutylammonium perchlorate, as well as acetone and potassium bromide.

The synthesis paths, for both the free ligand and its Ni(II) complex compound, were already described elsewhere [8].

The ligand appears as a microcrystalline yellowish-orange air-stable powder, whereas its complex with Ni(II) appears as a micro-crystalline orange-red air-stable powder [8, 9].

2.2. Kirby-Bauer disk diffusion method

The Kirby-Bauer diffusion method has several variants, and the standardized technique of antibiotic-impregnated discs in Petri plates is currently used [10].

A number of factors, such as: the strain studied, the culture medium (such as: pH, density and thickness of the medium), the technique used and even the interpretation of the results can influence an antibiogram.

Therefore, all antibiograms must be performed in reproducible conditions, according to relevant standards.

The principle of the method is as follows: on the surface of an agar medium seeded with a standardized inoculum obtained from the strain under test, discs impregnated with antibiotic solutions of a certain concentration are placed at quite equal distances.

If the strain is sensitive to a particular antibiotic, growth will be inhibited on a certain surface around the antibiotic-containing disc, this area being called „the growth inhibition zone".

The procedure is the following: in the first stage, the culture medium is inoculated by sowing in a cloth with a sterile cotton swab that is initially soaked in the inoculum or by flooding with a pipette, a sufficient volume of the inoculum being distributed for obtaining an uniform coverage of the entire surface of the plate.