A Mild, One-Pot Preparation of 2-Substituted Benzimidazoles from Organic Halides

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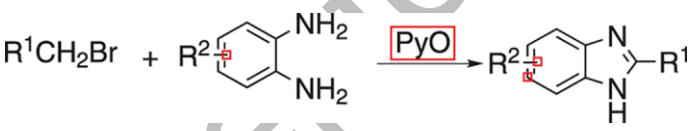
Abstract

Alkyl halides are feasibly transformed into benzimidazoles by an domino reaction under solvent-free conditions. The organic halides react with orthophenylenediamines in stoichiometric amounts in the presence of pyridine-N-oxide to produce the desired substituted benzimidazoles. This domino synthesis does not requires catalysts. The synthesis occurs in dry medium and the environmental impact is minimal. The method provides products without intermediate separation. A mechanism of benzimidazole synthesis is also proposed.

Graphical Abstract



KEYWORDS: benzimidazoles, domino reaction, oxidation, dry medium

INTRODUCTION

The benzimidazole ring is one of the most important pharmacophores in the design of modern synthetic drugs. [1] The biological activity of benzimidazole compounds is quite

diverse, and many benzimidazole derivatives are used in various active pharmaceutical ingredients for human and veterinary use. [2]

Benzimidazoles and their derivatives exhibit important pharmacological properties; for example, they act as histamine H(4) receptor binders,[4] anti-ulcer agents, [4] anti-hypertensive agents, [5] anti-cancer agents, [6] poly(ADP-ribose) phosphorylase inhibitors, [7] anti-viral agents, [8] anti-tumour agents, [9] anti-microbial and antifungal agents, [10] anti-parasitic agents, [11] anti-inflammatory agents [12] and HIV inhibitors. [13] Benzimidazole ligands are also found in biological molecules forming complexes with transition metal ions. [14] From the medicinal chemistry point of view, only compounds substituted in positions 1, 2 and 5 exhibit a wide range of pharmacological activities. [15] Typically, several different approaches have been used to synthesize substituted-1*H*-benzo [d]imidazoles. [16]

Traditional methods of synthesizing benzimidazoles consist of the reaction between orthophenylenediamines and carboxylic acids [17] or their functional derivatives (nitriles, imidates, orthoesters) [18] or cascade reactions of o-aminoanilines or naphthalene-1,8-diamines with terminal alkynes and p-tolylsulfonyl azide.[19] However, these methods have many disadvantages, such as a strong acidic medium, harsh dehydrating reaction conditions, high temperatures and long reaction times (from 3 h to 23 h).

The catalytic intramolecular *N*-arylation of *N*-(2-haloaryl) alkylimidamides, [20] the condensation between arylamino oximes and dichloromethane [21] and the cascade intermolecular addition/intramolecular C-N coupling process of o-haloarylcarbodiimides with *N*- or *O*-nucleophiles produce benzimidazoles. [22] Nevertheless, many of the protocols used to prepare substituted benzimidazoles require hazardous solvents (tertiary amines, DMSO, DCM, DMEDA), expensive catalysts (e.g. palladium) and very long reaction times (from 6 h to 30 h).

Oxidative procedures were developed by replacing the carboxylic acids with aldehydes or alcohols in the synthesis of benzimidazoles from o-aminoanilines in the presence of an oxidant. [23-30] The oxidant performs cyclodehydrogenation of the corresponding aromatic amine Shiff bases intermediate. Such oxidants are H_2O_2, [23] hypervalent iodine reagents, [24] potassium peroxymonosulfate, [25] MnO_2, [26] $Pb(OAc)_4$, [27] NH_4VO_3, [28] nitrogen dioxide and ozone (Kyodai nitration), [29] air and green catalysts. [30] These methods are not straightforward and require laborious workup and purification procedures. The malign oxidants containing heavy metals generate toxic byproducts and low isolation yields.

Recently, [31] a synthetic way to obtain substituted benzimidazoles has been reported. The procedure uses 2-nitroanilines and aldehydes and involves a reductive cyclization strategy. The protocol requires sodium dithionite ($Na_2S_2O_4$), formic acid, iron powder and NH_4Cl as additives to reduce the nitro group and accomplish the imidazole

cyclization. However, this protocol consumes a very large amount of iron, with the excess turning into waste iron oxides at the end of the reaction.

Unconventional methods involving microwaves [32] and ultrasounds [33] have also been used to obtain substituted benzimidazoles.

RESULTS AND DISCUSSION

Given the great medicinal and pharmaceutical importance of benzimidazole derivatives, we developed a method that transforms organic halides and orthophenylenediamines into substituted benzimidazoles. From what we know so far, this is the first direct synthesis of benzimidazoles from halocarbons by domino reaction with the help of pyridine-*N*-oxide in absence of catalysts and solvents (Scheme 1).

The pattern reaction between benzyl bromide, o-phenylenediamine and pyridine-*N*-oxide in which the 2-phenylbenzimidazole product is obtained was used as a starting point in our study. The reaction mixture was heated at different temperatures for varying periods of time. Benzimidazole production depends strongly on the molar ratio of reactants, temperature and time (Table 1). Thus, an excess of 25% pyridine-*N*-oxide gives a better result compared to the stoichiometric molar ratio of the reaction. The reaction temperature of 105 °C provided a good yield of 80% after 2 h (Table 1, entry 7).

We think that in the first stage, the halide is oxidized to aldehyde by pyridin-N-oxide (Scheme 2). This transformation is very similar to that of the Kornblum reaction [34] but

with the advantage of mild reaction conditions. Next, o-phenylenediamine gives a condensation reaction with benzaldehyde to form the Schiff base N^1-benzylidene benzene-1,2-diamine (II). The Schiff base turns into 2,3-dihydro-1*H*-benzoimidazole (III) by an intramolecular cycloaddition, followed by oxidation with pyridin-*N*-oxide to 2-phenylbenzimidazole (IV).

With this set of reaction conditions, a series of benzimidazoles derivatives was obtained (Table 2). The synthesis of the products performs in high yields. The amount of benzimidazole derivative depends on the experimental conditions, such as the work reaction temperature, the molar ratio of reactants, the reaction time and the nature of the halide and amine used.

Toxic by-products such as hydrogen bromide does not release from the synthesis because results the salt of pyridinium bromide, $[PyH]^+Br^-$. Further, pyridine was fully recovered from the filtrate (99.5%) using the well-known method of azeotropic distillation and separation of sodium hydroxide. Pyridine was recycled in the synthesis of benzimidazole derivatives by conversion into pyridine-*N*-oxide. Pyridine oxidation was achieved with peracetic acid using the existing protocol. [35]

Although the carboxylic acids, aldehydes and alcohols are more affordable than organic bromine compounds used in our protocol, the negative impact of the environment constitute a strong drawback. The synthesis of benzimidazoles from aromatic amines and aldehydes in excess is performed using harmful organic solvents (acetonitrile, DMSO,

DMF, dioxane) with large amounts of concentrated acid catalysts (350% excess of HCl 37% and 600% excess of H_2O_2 30%), [23] heavy metal salts (CuCl), [47] IBX (in excess of 50%), [24] H_2O_2 37% (300% excess) coupled with ceric ammonium nitrate [48]. The synthesis of benzimidazoles from amines and carboxylic acids requires a large amount of carboxylic acid (200% excess), [49] organic solvents (DCM) and Lewis acids. [50] The excess of aldehyde or carboxylic acid along with the catalysts and organic solvents generate significant harmful wastes at the end of the synthesis.

Recently, a patent [51] and a paper [52] published by the same authors describe the same method of synthesis of benzimidazoles from organic halides, *o*-phenylenediamines and DMSO with the help of copper halide and sodium bicarbonate as catalysts at temperature of 120°C. This method requires 24 h reaction time and very large amount of hazardous organic solvents.

All these known methods involve either hazardous catalysts or toxic organic solvents as reaction medium. Moreover, the separation of benzimidazoles is carried out by chromatographic techniques and require huge amounts of toxic organic solvents. Also, chemistry metrics have strong drawbacks, as they have a high environmental E-factor and low mass efficiency.

CONCLUSION

A rapid work-up and high-yielding benign protocol that uses organohalide and amine in stoichiometric amounts without solvents and catalysts was developed for the domino

synthesis of benzimidazoles. The reaction occurs in dry heterogeneous medium without separation of the intermediates and their purification. The method is an alternative to the expensive and poisonous catalysts, hazardous solvents, and strong acids usually used in all current protocols for the preparation of benzimidazoles. The benefits of domino sequences cover reduction of waste generated and atom economy.

EXPERIMENTAL

Organic bromide, orthophenylenediamine, pyridine-N-oxide are commercial compounds. The synthesized products were identified by TLC (EtOAc-petroleum ether), elemental analysis, ^{1}H-NMR, ^{13}C-NMR, and IR spectra. The NMR spectra were recorded on a BRUKER ARX instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C). DMSO-d_6 was used as the solvent and tetramethylsilane as an internal standard. The infrared spectra were recorded using an Alpha Bruker Optics spectrometer. Microanalyses were carried out on a Carlo Erba CHN analyzer, model 1106. The melting points were determined on a Gallenkamp digital melting point apparatus.

General Procedure For The Synthesis Of 2-Substituted Benzimidazoles

Primary alkyl bromide derivative (5 mmol), pyridine-*N*-oxide (12.5 mmol) and orthophenylenediamine derivative (5 mmol) are well mixed in a 25 mL round bottomed flask and placed in an oil bath on a magnetic stirrer hot plate at required temperature. The mixture was heated to selected temperature for required time (Table 2). After completion of the reaction (TLC, AcOEt-petroleum ether), the organic mixture was washed with dilute NaOH and filtered off. The filtrate was collected for recovery of pyridine. The

resulting residue was recrystallized from EtOH-H_2O to give the desired benzimidazole products. Pyridine was recovered from the filtrate (99.5%) by azeotropic distillation (bp. 92.6°C) and separation on sodium hydroxide. Resulting pyridine was oxidized with peracetic acid to the pyridine-*N*-oxide [35] which was then reused in reaction. All of the products are known compounds [36-46] and their identity was easily confirmed by comparison with authentic samples (mp, ^{1}H-NMR, ^{13}C-NMR).

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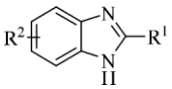
Table 1. Screening of reaction conditions for 2-phenylbenzimidazole synthesis.

Entry	Molar ratio			Time [min.]	T [°C]	Yield [%]
	$PhCH_2Br$	Pyridine-*N*-oxide	o-Phenylenediamine			
1	1	1	1	160	100	34
2	1	1	2	130	110	78
3	1	1.5	1	120	105	56
4	1.5	1	1	140	110	59
5	1	2	1	120	105	76
6	1	2.5	1	130	100	73
7	1	2.5	1	120	105	80
8	1	2.5	1	130	105	80
9	1	2.5	1.5	120	105	79
10	1.5	2.5	1	140	110	70
11	1	2.5	2	150	110	80

Table 2 Synthesis of benzimidazole derivatives in dry heterogeneous medium. [a]



No	Product	Time [min]	T [°C]	Yield [b] [%]
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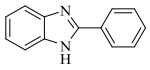
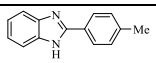
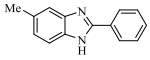
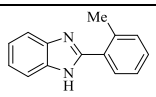
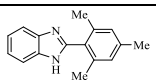
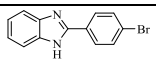
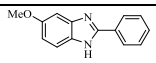
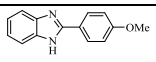
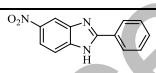
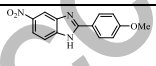
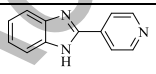
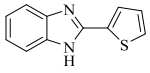
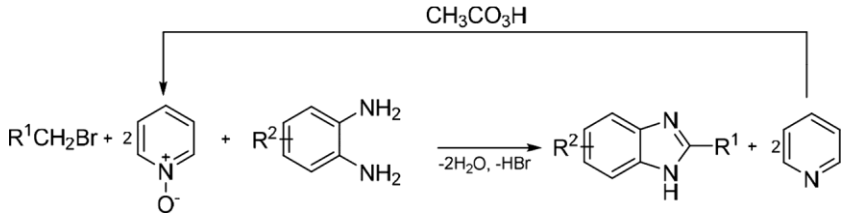
1		120	105	80
2		120	105	78
3		120	110	83
4		130	105	73
5		190	110	62
6		120	110	76
7		120	105	85
8		120	110	77
9		120	110	74
10		120	110	64
11		120	110	79
12		120	105	76

a -The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

b - Isolated and unoptimized yields.

Scheme 1. Conversion of primary alkyl halides to benzimidazoles.



Scheme 2. Presumed reaction mechanism of formation of 2-phenyl benzimidazole.