ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of 2-Substituted-1 *H*-Benzo[*d*]Imidazoles through Oxidative Cyclization of O-Phenylenediamine and Substituted Aldehydes using Dioxane Dibromide.

Satish S Birajdar[1], Girish D Hatnapure[1], Ashish P Keche[1], and Vandana M Kamble[1,2] *

[1] Department of Chemistry, Maharashtra Udaygiri Mahavidyalaya, Udgir- 413517, India.
[2] Department of Chemistry, The Institute of Science, Mumbai-400032, India.

ABSTRACT

Benzimidazole ring is a useful synthon in medicinal chemistry and is a part of many biologically active compounds. This communication reports a mild and efficient approach for the synthesis of benzimidazole ring through oxidative cyclization of o-phenylenediamine and different aldehydes using dioxane dibromide, as a user-friendly reagent. This is a new, convenient and facile methodology for the synthesis of 2-substituted-1*H*-benzo[*d*]imidazoles.

Keywords: Benzimidazole, cyclization, dioxane dibromide, aldehyde, o-Phenylenediamine.

Corresponding author

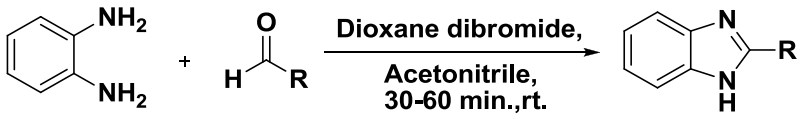
ISSN: 0975-8585

INTRODUCTION

Heterocyclic ring systems are the important class of organic compounds in the current drug discovery research. Among different classes of heterocyclic compounds, benzimidazole is the key scaffold which can be found in many active pharmaceutical ingredients [1]. Benzimidazole ring system is a part of a broad class of therapeutic areas [1, 2] like antiviral, antiulcer, antihypertensive, anticancer, etc., for that reason the synthesis of benzimidazole gained vital importance in organic synthesis in recent years.

Different synthetic approaches for the building of benzimidazole ring are reported in the literature. o-phenylenediamine was condensed with aldehydes using solid-supported catalyst [3], transition metal catalysts like $Sc(OTf)_3$ [4], $Yb(OTf)_3$ [5], $FeCl_3.6H_2O$ [6], $In(OTf)_3$ [7], Cobalt complexes [8] etc. and also in the presence of various oxidizing agents like Air [9], $Pb(OAc)_4$ [10], sulphamic acid [11], MnO_2 [12], Oxone [13], Iodine [14], DIB [15], H_2O_2–HCl [16], DDQ [17] etc. One more approach wherein carboxylic acids were condensed with o-phenylenediamine in the presence acid catalysts [18].

However, many of these methods have a number of drawbacks like high temperature, low yields, hazardous reagents, a special oxidation process, long reaction time and tedious work up with co-occurrence of side reactions. Therefore, the discovery of mild and practicable routes for synthesis of benzimidazole continues to attract the attention of researchers. Dioxane dibromide is a mild and efficient catalyst used in different transformations [19-22]. To avoid the bromine handling because of its corrosive nature, this is one of the best alternative forms of bromine. The good part of this reagent is solid and inexpensive. The reagent can be synthesized by the procedure given in literature [22] wherein bromine was added to cold 1,4-dioxane under stirring to get orange solid, which was filtered and washed with 1,4-dioxane to obtain pure dioxane dibromide.



Scheme 1. Synthesis of 2-substituted-1*H*-benzo[*d*]imidazoles.

MATERIALS AND METHODS

Experimental

The reagents o-phenylenediamine and aldehydes used for reaction were commercially available. Reagent grade solvents were used. Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS and coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were taken by electrospray ionization method (ES-MS). Progress of reaction

was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel MERCK 60 F 254 that were visualized by UV lamp.

A typical procedure for the preparation of benzimidazoles

To a pre-cooled (0-5°C) solution of o-phenylenediamine (9.3 mmol) in acetonitrile (20 ml), a solution of aldehyde (9.3 mmol) in acetonitrile (5 ml) was added slowly. Reaction mixture was allowed to room temperature. The formation of imine was monitored by ES-MS. After complete formation of imine, reaction mixture was again cooled to 0-5°C. The dioxane dibromide (9.3 mmol) was added to reaction mixture. Reaction mixture was allowed to room temperature. Completion of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and the residue was dissolved in ethyl acetate. Organic layer was washed with saturated $NaHCO_3$, water and brine solution. Organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product. The crude material was then subjected to column chromatography (silica gel, 35-40% ethyl acetate in hexane) to get pure compound. The spectroscopic data are in good agreement with those reported for the authentic sample. This procedure was followed for the synthesis of all the products listed in Table 2. The physical and spectral data of some representative compounds are given below,

2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole (entry 3)

Brownish solid, mp 280-283°C. IR (KBr, cm^{-1}): 3053 (NH), 2918, 1682 (C=N); ^{1}HNMR (400 MHz, DMSO-d6-δ ppm): δ 12.98 (br s, -NH), 8.19-8.18 (d, 2H, *J*=7.2 Hz), 7.63-7.61 (m, 4H), 7.21 (m, 2H); ES-MS *m/z* 229 [M+1].

2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole (entry 5)

Off white solid, mp 222-224°C. IR (KBr, cm^{-1}): 3350 (NH), 2949, 1671 (C=N); ^{1}HNMR (400 MHz, DMSO-d6-δ ppm): δ 12.96 (br s, -NH), 8.17-8.16 (d, 2H, *J*=7.2 Hz), 7.62-7.60 (m, 4H), 7.21 (m, 2H), 3.57 (s, 3H); ES-MS *m/z* 225 [M+1].

2-(pyridin-3-yl)-1H-benzo[d]imidazole (entry 9):

Off white solid, mp 246-248°C. IR (KBr, cm^{-1}): 3445 (NH), 3054, 2431, 1618 (C=N); ^{1}HNMR (400 MHz, $CDCl_3$-δ ppm): δ 12.8 (br s, 1H, NH), 9.27 (s, 1H), 8.67-8.66 (d, 1H), 8.45-8.42 (m, 1H), 7.43-7.40 (m, 1H), 7.30-7.25 (m, 4H); ES-MS *m/z* 196 [M+1].

2-methyl-1*H*-benzo[*d*]imidazole (entry 13):

Grayish solid, mp 172-175°C. IR (KBr, cm^{-1}): 3450 (NH), 3030, 1632 (C=N), 928; ^{1}HNMR (400 MHz, DMSO-d6-δ ppm): δ 12.7 (s, 1H, NH), 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 2.51 (s, 3H); ES-MS *m/z* 133 [M+1].

ISSN: 0975-8585

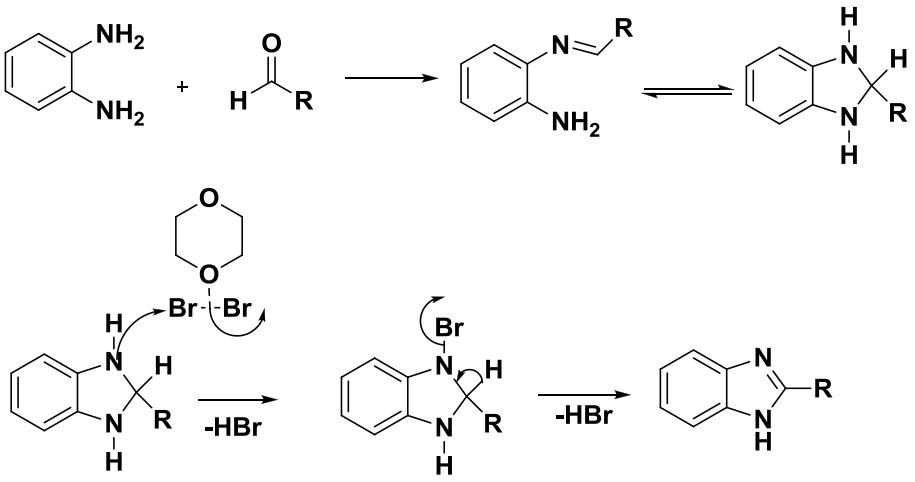
2-cyclohexyl-1*H*-benzo[*d*]imidazole (entry 14):

white solid, mp 281-284. IR (KBr, cm^{-1}): 3420 (NH), 1630 (C=N); ^{1}HNMR (400MHz, DMSO-d6-δ ppm): δ 12.35 (br s, -NH), 7.53-7.59 (m, 2H), 7.15-7.20 (m, 2H), 2.89-2.99 (m, 2H), 2.05-2.15 (m, 3H), 1.83-1.87 (m, 2H), 1.66-1.77 (m, 2H), 1.30-1.51 (m, 2H); ES-MS *m/z* 201 (M+1).

RESULTS AND DISCUSSION

In continuation of our research work [23] on the development of useful synthetic methodologies, we have observed that benzimidazole can be synthesized efficiently by treatment of o-phenylenediamine with aldehyde using dioxane dibromide at room temperature (Scheme 1). The methodology was found to be a new, facile and efficient for the synthesis of 2-substituted-1*H*-benzo[*d*]imidazole.

In order to establish the optimum condition for the reaction, various mole ratio of dioxane dibromide were examined by using o-phenylenediamine and *p*-chlorobenzaldehyde as a simple model substrate, dioxane dibromide was added in various ratios in different solvents as shown in Table 1. Very little amount of the desired product was obtained in the absence of dioxane dibromide (Entry 6) even after longer reaction period, while the best result was obtained with 100 mole % of dioxane dibromide. It was observed that when we had used 50 mole % (Entry 7) of dioxane dibromide for longer period, the yield was less; it could be due to the degradation of reaction mass. Based upon these results, we have proposed a plausible reaction mechanism (Scheme 2) where we propose the role of dioxane dibromide as a oxidative reagent.



Scheme 2. Plausible reaction mechanism

Next the effect of solvent was examined. Different solvents namely, 1,4-dioxane, THF, acetonitrile, chloroform, ethanol, water were used. The results are shown in Table 1. It was found that the acetonitrile (Entry 8) was the solvent of choice for the reaction and the desired product was obtained in excellent yield (87%). While in other solvents, the reaction had taken long time for completion along with lesser yield as compare to acetonitrile.

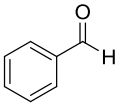
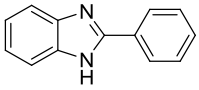
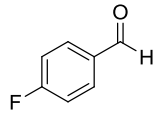
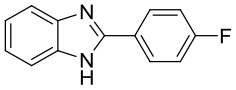
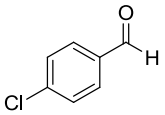
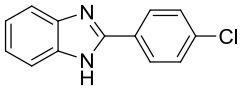
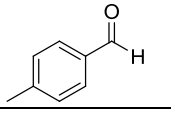
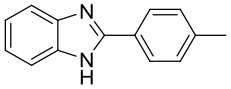
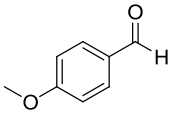
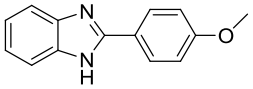
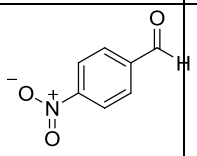
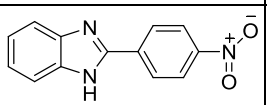
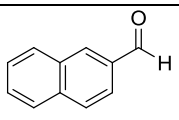
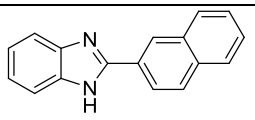
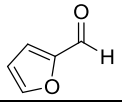
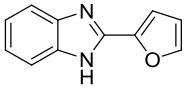
ISSN: 0975-8585

Table 1: Optimization of reaction conditions.

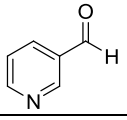
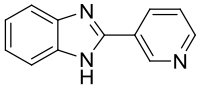
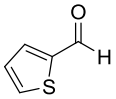
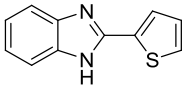
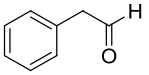
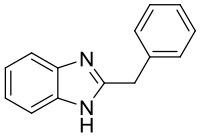
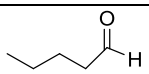
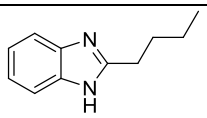
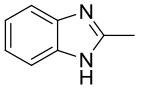
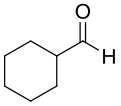
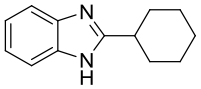
Entry	Solvents	Dioxane dibromide (mol %)	Time (min)	Yields [a] (%)
1.	1,4-Dioxane	100	120	70
2.	THF	100	80	75
3.	Chloroform	100	90	63
4.	Ethanol	100	80	78
5.	Water	100	160	45
6.	Acetonitrile	0	160	20
7.	Acetonitrile	50	90	45
8.	Acetonitrile	100	35	87

[a] Isolated yields after column purification.

Table 2: Synthesis of 2-substituted-1*H*-benzo[*d*]imidazoles[#]

Entry	Substrate	Product	Time (min)	Yields (%)	MP (Observed) °C	MP (Literature) °C
1			30	90	286-287	286-288 [24]
2			40	84	241-243	245-246 [25]
3			35	87	280-283	284-286 [24]
4			45	78	261-264	261-263 [26]
5			40	85	222-224	223-226 [27]
6			30	86	306-308	308-310 [26]
7			50	78	215-217	217 [24]
8			55	73	288-289	287-288 [28]

ISSN: 0975-8585

9			50	80	246-248	248 [25]
10			50	70	331-334	330 [27]
11			60	82	184-186	184-186 [29]
12			60	73	147-149	148-149 [30]
13			60	70	172-175	175 [31]
14			60	76	281-284	282-283 [32]

[#]Aldehyde (1 mol.), o-phenylenediamine (1 mol.), dioxane dibromide (1 mol.), room temperature, [%]Isolated yields after column purification.

We were pleased to find that, several aldehydes (aromatic, hetero-aromatic and aliphatic) underwent the above conversion to form a series of benzimidazoles (Table 2). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked very well. Hetero-aryl aldehyde (Table 2, entry 8-10) gave acceptable yields. Aliphatic aldehydes (Table 2, entry 11-14) also afforded the desired products in good yields. The method is also suitable for the preparation of benzimidazole from an acid sensitive aldehyde such as furfuraldehyde (Table 2, entry 8) and the sterically hindered aldehyde 2-naphthaldehyde (Table 2, entry 7). The reaction conditions are mild and the experimental procedure is simple. The products were formed in high yields (70–90%). The structures of the products were determined from their spectral (IR, ^{1}H NMR and ES-MS) data along with their melting point. The observed data then compared with reported values.

CONCLUSION

We have developed a new, facile and efficient methodology for preparation of 2-substituted-1*H*-benzo[*d*]imidazoles through oxidative cyclization of o-phenylenediamine and substituted aldehydes using dioxane dibromide. We have also shown the versatility of this methodology by applying it to wide variety of aldehyde substrates. To the best of our knowledge, this is the first report on the synthesis of benzimidazole derivatives using dioxane dibromide.

ACKNOWLEDGEMENTS

The authors are thankful to The Department of Chemistry, Maharashtra Udaygiri Mahavidyalaya, Udgir for resourceful laboratory facility for conducting this research.

ISSN: 0975-8585

REFERENCES

[1] O`Neil MJ The Merck Index. 14th ed. Merck and Co., Inc, New Jersey, 2006.
[2] Gravatt GL, Baguley BC, Wilson WR, Denny WA. J Med Chem 1994; 37: 4338-4345; (b) Kim JS, Gatto B, Yu C, Liu A, Liu LF, Lavoie EJ. J Med Chem 1996; 39: 992-998; (c) Horton DA, Bourne GT, Smythe ML Chem Rev 2003; 103: 893-930.
[3] Srinivas U, Srinivas Ch, Narender P, Rao J, Palaniappan S Catal Commun 2007; 8: 107-110; (b) Kumar A, Maurya RA, Ahmad P. J Comb Chem 2009; 11: 198-201.
[4] Itoh T, Nagata K, Ishikawa H, Ohsawa A. Heterocycles 2004; 63: 2769-2783.
[5] Massimo C, Francesco E, Francesca M. Synlett 2004; 10: 1832-1834.
[6] Singh MP, Sasmal S, Lu W, Chatterjee MN. Synthesis 2000; 10: 1380-1390.
[7] Trivedi R, De SK, Gibbs RA. J Mol Cat A: Chem 2005; 245: 8-11.
[8] Chari MA, Shobha D, Sesaki T. Tetrahedron Lett 2011; 52: 5575-5580.
[9] Lin S, Yang L. Tetrahedron Lett 2005; 46: 4315-4319.
[10] Stephens FF, Bower JD. J Chem Soc 1949; 2971-2972.
[11] Chakrabarty M, Karmakar S, Mukherji A, Arima S, Harigaya Y. Heterocycles 2006; 68: 967-974.
[12] Bhatnagar I, George MV. Tetrahedron 1968; 24: 1293-1298.
[13] Beaulieu PL, Hache B, Von Moos E. Synthesis 2003; 11: 1683-1692.
[14] Gogoi P, Konwar D. Tetrahedron Lett 2006; 47: 79-82.
[15] Du LH, Wang YG. Synthesis 2007; 5: 675-678.
[16] Bahrami K, Khodaei MM, Kavianinia I. Synthesis 2007; 4: 547-550.
[17] Vanden Eynde JJ, Delfosse F, Lor P, Haverbeke YV. Tetrahedron 1995; 51: 5813-5818.
[18] (a) Wright, JB Chem Rev 1951; 48: 397-541; (b) Middleton RW; Wibberley DG. J Heterocycl Chem 1980; 17: 1757-1760.
[19] Kutschy P, Suchy M, Monde K, Harada N, Maruskova R, Curillova Z, Dzurilla M, Miklosova M, Mezencev R, Mojzis J. Tetrahedron Lett 2002; 43: 9489-9492.
[20] Hino T, Nakagawa M. Tetrahedron 1967; 23: 1441-1450.
[21] Paul S, Gupta V, Gupta R, Loupy A. Tetrahedron Lett 2003; 44: 439-442.
[22] Chaudhuri S, Roy S, Bhar S, Beilstein. J Org Chem 2012; 8: 323-329.
[23] Keche AP, Hatnapure GD, Tale RH, Rodge AH, Birajdar SS, Tale RH, Kamble VM. Bioorg Med Chem Lett 2012; 22: 3445-3448; (b) Hatnapure GD, Keche AP, Rodge AH, Birajdar SS, Tale RH, Kamble VM. Bioorg Med Chem Lett 2012; 22: 6385-6390.
[24] Mobinikhaledi A, Forughifar N, Zendehdel M, Jabbarpour M. Synth React Inorg Metal-Org Nano-Metal Chem 2008; 38: 390-393.
[25] Joshi RS, Mandhane PG, Dabhade SK, Gill CH. J Chin Chem Soc 2010; 57: 1227-1231.
[26] Shingalapur RV, Hosamani KM. Catal Lett 2010; 137: 63-68.
[27] Gogoi P, Konwar D. Tetrahedron Lett 2006; 47: 79-82.
[28] Sharghi H, Beyzavi MH. Eur J Org Chem 2008; 24: 4126-4138.
[29] Chari MA, Shobha D, Kenawy ER, Al-deyab SS, Subba Reddy BV, Vinu A. Tetrahedron Lett 2010; 51: 5195-5199.
[30] Zhang ZH, Yin L, Wang YM. Catal Commun 2007; 8: 1126-1131.
[31] Vogel AI. A Textbook of Practical Organic Chemistry, 3rd ed. Longman Group Ltd: London 1956; pp. 853.
[32] Nagawade RR, Shinde DB. Chin Chem Lett 2006; 17: 453-456.