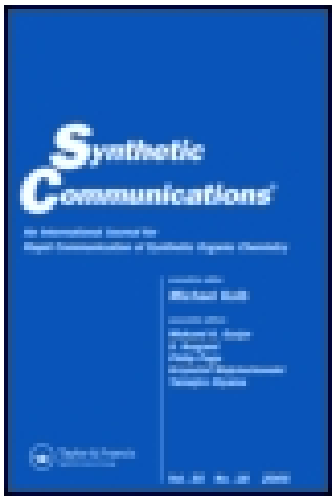


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Simple and Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles from #-Diaminoarene and Aryl Aldehydes

Mohan Lakshmi Punna Rao Alapati[ab], Sridhar Rao Abburi[ab], Saratchandra Babu Mukkamala[a] & M. Krishnaji Rao[b]

[a] Dept of Chemistry, GITAM Institute of Science, GITAM University, Visakhapatnam, India

[b] Quality Control Department, Unit-II, DIVIS Laboratories Ltd., Visakhapatnam, India

Accepted author version posted online: 20 Aug 2015.

A Simple and Efficient One-Pot Synthesis of 2- Substituted Benzimidazoles from θ-Diaminoarene and Aryl Aldehydes

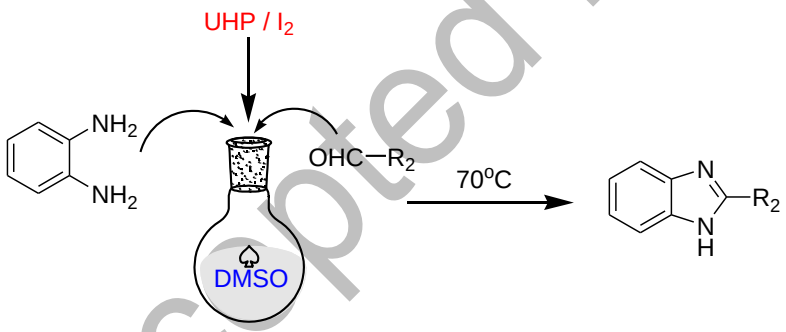
Mohan Lakshmi Punna Rao Alapati[1,2], Sridhar Rao Abburi[1,2], Saratchandra Babu Mukkamala[1], M. Krishnaji Rao[2]

[1]Dept of Chemistry, GITAM Institute of Science, GITAM University, Visakhapatnam, India, [2]Quality Control Department, Unit-II, DIVIS Laboratories Ltd., Visakhapatnam, India

Corresponding author to M. L. P. R. A. Alapati: E-mail: mohan_alapati@yahoo.com

Abstract

An easy and efficient one pot condensation method for the synthesis of substituted benzimidazoles from θ-phenylenediamines with aryl aldehydes using UHP and I_2 in DMSO. This method provides wide substrate scope with good to excellent yields, simple and quick isolation of the products



KEYWORDS: Benzimidazole, θ-diaminoarene, urea hydrogen peroxide, iodine, aldehydes

INTRODUCTION

Benzimidazole and its analogues have gained importance in modern drug discovery[1] (Telmisartan, Dexlansoprazole). In particular, they have been in use as anticancer drug

agents[2], anti-ulcer,[3] anti-HIV,[4] antihypertensive,[5] analgesic,[6] antiviral,[7] anti-inflammatory,[8] and are also very useful intermediates in organic synthesis. Numerous synthetic methods are available for the construction of benzimidazoles on the basis of condensation reaction between Θ-diaminoarene and a carboxylic acids (or) esters (or) β-Diketones (or) weinreb amide (or) aldehydes (or) acid chlorides (or) nitriles (or) aryl alcohols in the presence of different catalysts such as $PhI(OAc)_2$,[9] IBX,[10] silica-sulfuric acid,[11] PEG-mediated catalyst-free condition,[12] $BF_3.OEt_2$,[13] UHP/SiO_2-OPO_3H_2,[14] MgI_2,[15] DABAL-Me_3,[16] HCl/H_2O_2,[17] and CAN/H_2O_2.[18] Further, several transition-metal catalyzed reactions have been reported for the synthesis of 2-substituted benzimidazoles such as CuCl,[19] Cu_2O,[20] $CoCl_2$,[21] $Yb(OTf)_3$,[22] $In(OTf)_3$,[23] and WOx/ZrO_2.[24] However, these methods suffer from several disadvantages like low yield, harsh reaction conditions, use of expensive catalysts, occurrence of side reactions, additional oxidation step, tedious work-up procedure and low reaction rate. The present method aims at overcoming all these problems.

In the recent years, the versatility of urea hydrogen peroxide(UHP) reagent has been disclosed in organic synthesis for instance, in the oxidation of aryl aldehydes to acids,[25] sulfides to sulfoxides,[26] imines to nitrones,[27] preparation of heterocyclic *N*-oxides,[28] solid-state oxidation,[29] and conversion of pyridines to *N*-oxides.[30]

In continuation of our studies in developing inexpensive and environmentally benign methodologies for the synthesis of bioactive molecules, herein, we report UHP mediated

synthesis of 2-substuted bezimidazoles via oxidative condensation of θ-diaminoarene and substituted aldehydes followed by cyclization reaction.

RESULTS AND DISCUSSION

First, we investigated the reaction conditions for the synthesis of benzimidazole (3a), as shown in Table-1. We choose the reaction of θ-diaminoarene (1a) (1.0 mmol) was treated with benzaldehyde (2a) (1.1 mmol) and I_2 (0.1 mmol) in DMSO (5 mL) at 70 ^{0}C as a model reaction to optimize the reaction conditions.

In the absence of oxidant the product was obtained in 25% yield (Table 1, entry 1). Therefore, our efforts were focused on the search for a suitable oxidant. Initially, trifluoroperacetic acid (TFPA) (20 mol%) was utilized as an oxidant to carry out this reaction, it gave 29% yield at 1h (Table 1, entry 2). Then, cumene hydroperoxide (CHP) (20 mol%) was used as an oxidant in DMSO at 70 ^{0}C and it gave 54% yield in 56 minute (Table 1, entry 3). Next, we turned our attention to various inorganic peroxides, these were screened in our model reaction (Table 1). Finally, we found that Urea Hydrogen Peroxide (UHP) showed high catalytic activity in terms of reaction time as well as yield of the product (Table 1, entry 9). Once we established the suitable catalyst for the synthesis of 2-substituted benzimidazoles, we then focused on the quantity of UHP. It was found that 20 mol% is sufficient for the reaction (Table 1, entry 6). The product was obtained in very low yield without iodine (Table 1, entry 7). It was found that 20 mol% of UHP and Iodine (0.1 mmol) were significant to carry out the reaction smoothly. The effect of temperature on reaction rate as well as on yields of products was also

investigated. Increasing the temperature yields of the reaction was not satisfactory (Table 1, entries 10, 11).

In the process of reaction optimization, we investigated the effect of various solvents on the model reaction (Table 2, entries 1-6). Among the tested solvents DMSO and CH_3CN gave excellent results. However, DMSO was preferred over CH_3CN because it provided better solubility for polar reactants. From process of optimization studies, UHP/I_2 and DMSO witnessed as the efficient catalyst and solvent respectively.

With this optimized reaction conditions in hand, the scope of cyclization reaction was examined between variety aryl aldehydes and θ-diaminoarene, the results are presented in Table 3.

It was found that various substrates were converted into the corresponding products with good yields under the optimized conditions. Hetero aromatic aldehydes gave slightly lower yields (Table 3, entries 3m, 3n, 3o and 3p) when compared to general substituted aromatic aldehydes (Table 3, entries 3a-3l). We also investigated the aldehydes with electron withdrawing as well as with electron donating groups participated in the reaction uniformly and gave better yields of the target products. Similarly, no steric effect was observed (Table 3 entries 3d & 3i).

General Procedure For Synthesis Of 2-Substituted Benzimidazoles (3a-P):

A stirred solution of θ-diaminoarene (1.0 mmol), aryl aldehyde (1.1 mmol), iodine (0.1 mmol), 20 mol% UHP and DMSO (5 mL) was heated to 70 ^{0}C for specified time. After completion of the reaction as indicated by TLC, it was cooled to room temperature, aqueous sodium carbonate solution was added and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine solution (2 × 25 mL), dried over anhy. Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using etyl acetate: hexane (3:7) to afford the pure product.

CONCLUSION:

In conclusion, we have developed a new, one-pot synthetic method for the preparation of substituted benzimidazoles from different aryl aldehydes and θ-diaminoarene using UHP/I_2 as a catalyst. This method shows several advantages such as experimental simplicity, readily available starting material, simple purification procedure and therefore, the present protocol will be of wide application in medicinal chemistry and organic chemistry.

ACKNOWLEDGEMENT

We thank the DIVIS LOBORATERIES for financial support for this work. We are grateful to the Academic Paper Editing Saratchandra Babu and at GITAM Unevarsity.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

[1] (a) Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; Mckinney, E.; Tang,C. J. Article Title. *Antirhino/Enteroviral Vinylacetylene Benzimidazoles: A Study of Their Activity and Oral Plasma Levels in Mice*, *J. Med. Chem.* **1997**, *40*, 3937-3946; (b) Ries, U. J.; Mihm, G.; Narr, B.; Hasselbach, K. M.; Wittneben, H.; Entzeroth, M.; van Meel, J. C. A.; Wienen, W.; Hauel, N. H. 6-Substituted benzimidazoles as new nonpeptide angiotensin II receptor antagonists: synthesis, biological activity, and structure-activity relationships. *J. Med. Chem*. **1993**, *36*, 4040-4051; (c) Valerie, E. F.; Xi, W.; Beth, P.; Jing-Yuan, L.; Jian-Ting, Z. Repositioning Proton Pump Inhibitors as Anticancer Drugs by Targeting the Thioesterase Domain of Human Fatty Acid Synthase. *J. Med. Chem*. **2015**, *58*, 778-784.

[2] Denny, W. A.; Rewcastle, G. W.; Bauley, B. C.; Potential antitumor agents. 59. Structure-activity relationships for 2-phenylbenzimidazole-4-carboxamides, a new class of minimal DNA-intercalating agents which may not act via topoisomerase II. *J. Med. Chem.* **1990**, *33*, 814-819.

[3] Gungor, T.; Fouquet, A.; Eulon, J.-M.; Provost, D.; Cazes, M.; Cloarec, A. Cardiotonic agents. Synthesis and cardiovascular properties of novel 2-arylbenzimidazoles and azabenzimidazoles. *J. Med. Chem*. **1992**, *35*, 4455-4463.

[4] Gardiner, J. M.; Loyns, C. R.; Burke, A.; Khan, A.; Mahmood, N. Synthesis and HIV-1 inhibition of novel benzimidazole derivatives. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1251-1254.

[5] Alonen, A.; Jansson, J.; Kallonen, S.; Kiriazis, A.; Aitio, O.; Finel, M.; Kostiainen, R. Enzyme-assisted synthesis and structure characterization of glucuronic

acid conjugates of losartan, candesartan, and zolarsartan. *Bioorg. Chem*. **2008**, *36*, 148-155.

[6] Elmer, G. I.; Pieper, J. O.; Goldberg, S. R.; George, F. R. Opioid operant self-administration, analgesia, stimulation and respiratory depression inμ-deficient mice. *Psychopharmacology (Berl.)* **1995**, *117*, 23-31.

[7] Gualtieri, F.; Brody, G.; Fieldsteel, A. H.; Skinner, W. A. Antiviral Agents. *2*. Analogs of 2-(a-Hydroxybenzyl)benzimidazole. *J. Med. Chem*. **1972**, *15*, 420-422.

[8] Mader, M.; De Dios, A.; Shih, C.; Anderson, B. D.; Imidazolyl benzimidazoles and imidazo[4,5-b]pyridines as potent p38a MAP kinase inhibitors with excellent in vivo antiinflammatory properties. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 179-183.

[9] Du, L.-H.; Y.-G.Wang, Y.-G. A Rapid and Efficient Synthesis of Benzimidazoles Using Hypervalent Iodine as Oxidant. *Synthesis*, **2007**, *5*, 675-678.

[10] Moorthy, J. N.; Neogi, I. IBX-mediated one-pot synthesis of benzimidazoles from primary alcohols and arylmethyl bromides. *Tetrahedron Lett*, **2011**, *52*, 3868-3871.

[11] Patil, D. R.; Salunkhe, S. M.; Sambavekar, P. P.; Deshmukh, M. B.; Kolekar, G. B.; Der Anbhule, P. V. Silica sulfuric acid: Recyclable and efficient catalyst for the 2-aryl benzothiazoles. *Pharma Chemica*, **2011**, *3*, 189-193.

[12] Chhanda, M.; Pradip Kumar, T. PEG-mediated catalyst-free expeditious synthesis of 2-substituted benzimidazoles and bis-benzimidazoles under solvent-less conditions. *Tetrahedron Lett*. **2008**, *49*, 6237-6240.

[13] (a) Bommegowda, Y. K.; Lingaraju, G. S.; Thamas, S.; Vinay Kumar, K. S.; Pradeepa Kumara, C. S.; Rangappa, K. S.; Sadashiva, M. P. Weinreb amide as an efficient reagent in the one pot synthesis of benzimidazoles and benzothiazoles.

Tetrahedron Lett. **2013**, *54*, 2693-2695; (b) Bastug, G.; Eviolitte, C.; Markó, I. E. Functionalized Orthoesters as Powerful Building Blocks for the Efficient Preparation of Heteroaromatic Bicycles. *Org. Lett.*, **2012**, *14*, 3502-3505.

[14] Momeni, A. R.; Samimi, H. A.; Jahanian, R. Urea-hydrogen peroxide/silica phosphoric acid-catalyzed oxidation-condensation Tandem reaction: One-pot synthesis of 2-substituted benzimidazoles from alcohols. *Iranian Journal of Catalysis*, **2012**, *2*, 141-145.

[15] Nagasawa, Y.; Matsusaki, Y.; Hotta, T.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. Aerobic photooxidative synthesis of benzimidazoles from aromatic aldehydes and diamines using catalytic amounts of magnesium iodide. *Tetrahedron Lett*, **2014**, *55*, 6543-6546.

[16] Joanne, L. P.; Rebecca, E. D.; Jean-Damien, C. A facile, one-pot procedure for the formation of benzimidazoles from esters using DABAL-Me3, an air stable source of AlMe3. *Tetrahedron Lett*, **2014**, *55*, 4853-4855.

[17] Bahrami, K.; Khodaei, M. M.; Kavianinia, I. A Simple and Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles. *Synthesis*, **2007**, *4*, 547-550.

[18] Bahrami, K.; Khodaei, M. M.; Naali, F. Mild and Highly Efficient Method for the Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzothiazoles. *J.Org. Chem*, **2008**, *73*, 6835-6837.

[19] Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C–N Bond Formation. *J. Org. Chem.*, **2011**, *76*, 9577-9583.

[20] Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. Copper-Catalyzed Intramolecular C−N Bond Formation: A Straightforward Synthesis of Benzimidazole Derivatives in Water. *J. Org. Chem.*, **2011**, *76*, 716-719.

[21] Khan, A. T.; Parvin, T.; Choudhury, L. H. A Simple and Convenient One-Pot Synthesis of Benzimidazole Derivatives Using Cobalt(II) Chloride Hexahydrate as Catalyst. *syn comm*, **2009**, *39*, 2339-2346.

[22] Massimo, C.; Francesco, E.; Francesca, M.; Ornelio, R.; Sara, T. Article Title. *Synlett*, **2004**, *10*, 1832-1834.

[23] Trivedi, R.; De, S. K.; Gibbs, R. A. A convenient one-pot synthesis of 2-substituted benzimidazoles. *J. Mol. Catal. A: Chem*. **2006**, *245*, 8-11.

[24] Shingalapur, R. V.; Hosamani, K. M. An Efficient and Eco-Friendly Tungstate Promoted Zirconia (WO_x/ZrO_2) Solid Acid Catalyst for the Synthesis of 2-Aryl Benzimidazoles. *Catal. Lett*. **2010**, *137*, 63-68.

[25] Heaney, H.; Newbold, A. J. The oxidation of aromatic aldehydes by magnesium monoperoxyphthalate and urea–hydrogen peroxide. *Tetrahedron Lett*, **2001**, *42*, 6607-6609.

[26] Jeon, B. J.; Kim, K. T.; Kim, S. H. Selective oxidation of sulfides to sulfoxides with cyanuric chloride and urea–hydrogen peroxide adduct. *Tetrahedron Lett*, **2014**, *55*, 3905-3908.

[27] Soldaini, G.; Cardona, F.; Goti, A. Catalytic Oxidation of Imines Based on Methyltrioxorhenium/Urea Hydrogen Peroxide: A Mild and Easy Chemo- and Regioselective Entry to Nitrones. *Org. Lett*, **2007**, *9*, 473-476.

[28] Rong, D.; Phillips, V. A.; Rubio, R. S.; Castro, M. A.; Wheelhouse, R. T. A safe, convenient and efficient method for the preparation of heterocyclic N-oxides using urea_hydrogen peroxide. *Tetrahedron Lett*, **2008**, *49*, 6933-6935.

[29] Varma, R. S.; Naicker, K. P. The Urea−Hydrogen Peroxide Complex: Solid-State Oxidative Protocols for Hydroxylated Aldehydes and Ketones (Dakin Reaction), Nitriles, Sulfides, and Nitrogen Heterocycles. *Org. Lett*, **1999**, *1*, 189-192.

[30] Caron, S.; Do, N. M.; Sieser, J. E. A practical, efficient, and rapid method for the oxidation of electron deficient pyridines using trifluoroacetic anhydride and hydrogen peroxide–urea complex. *Tetrahedron Lett*, **2000**, *41*, 2299-2302.

Table 1: Synthesis of 4-arylidene-2-phenyl-5(4)-oxazolones (3a) under different optimization conditions

Entry	**Oxidant (mol %)**	**Temp (^{0}C)**	**Time (min)**	**Yield (%)[a]**
1	----	70	72	25[b]
2	TFPA (20)	70	60	29
3	CHP (20)	70	56	54
4	TBHP (20)	70	51	58
5	H_2O_2 (20)	70	48	60
6	UHP (20)	70	40	87
7	UHP (20)	70	40	48[c]
8	UHP (25)	70	40	87
9	UHP (30)	70	40	87
10	UHP (20)	90	30	80
11	UHP (20)	100	30	78

a-Isolated yield after column chromatography.

b-Reaction was performed in absence of UHP.

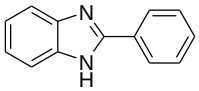
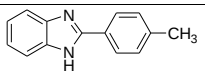
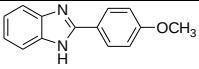
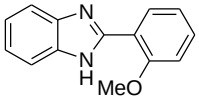
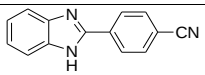
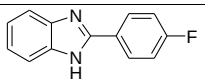
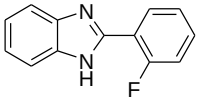
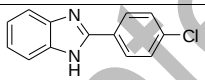
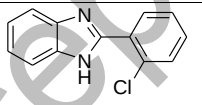
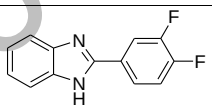
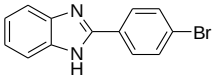
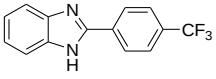
c-Reaction was performed in absence of I_2.

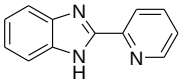
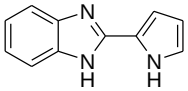
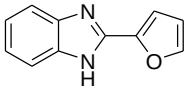
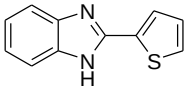
Table 2. Effect of various solvents in the synthesis of **3a**

Entry	**Solvent**	**Time (min)**	**Yield (%)[a]**
1	THF	90	10
2	$CHCl_3$	58	15
3	CH_2Cl_2	63	45
4	CH_3CN	50	72
5	DMSO	30	87
6	Toluene	88	54

[a]Isolated yield after column chromatography

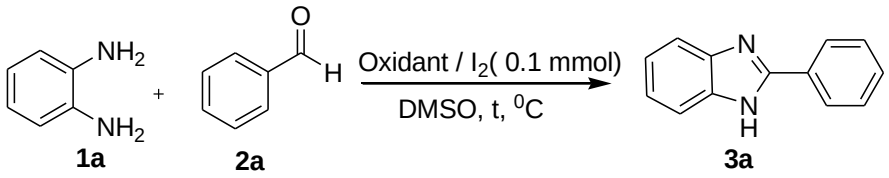
Table 3. Synthesis of 2-substituted benzimidazoles using UHP/I_2 in DMSO solvent.

Entry	R_1	R	Yield (%)[b]
3a		Ph	87
3b		4-MePh	91
3c		4-MeOPh	93
3d		2-MeOPh	85
3e		4-CNPh	89
3f		4-FPh	94
3g		2-FPh	85
3h		4-ClPh	91
3i		2-ClPh	86
3j		3,4-FPh	91
3k		4-BrPh	90
3l		4-CF_3Ph	93

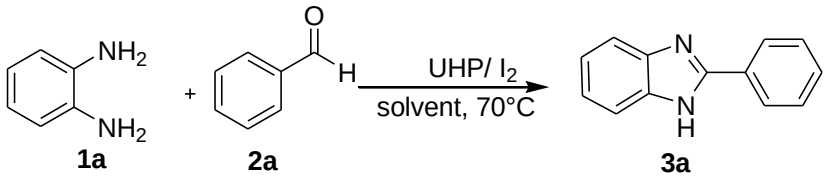
3m		2-py	81
3n		2-pyrryl	84
3o		2-furyl	81
3p		2-thionyl	79

[b]isolated yield of pure product after purification of crude reaction mixture using column chromatography.

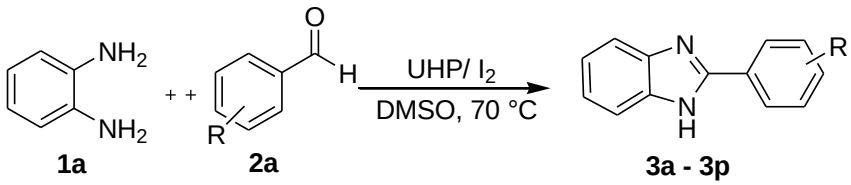
Scheme 1. Model reaction



Scheme 2. Optimization of solvent system

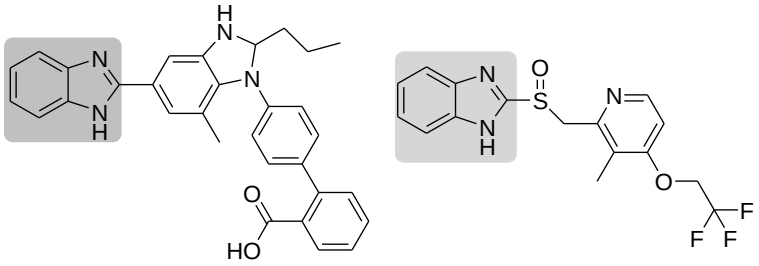


Scheme 3. Preparation of product **3a-3l**



1a **2a** **3a - 3p**

Figure 1. Medicinal drugs containing a benzimidazole motif.



Telmisartan **Lansoprazole**