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Graphical Abstract

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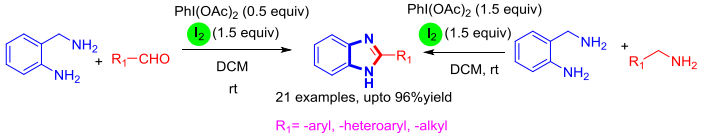

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Practical application of $PhI(OAc)_2/I_2$ combination to synthesize benzimidazoles from 2-aminobenzylamine through ring distortion strategy

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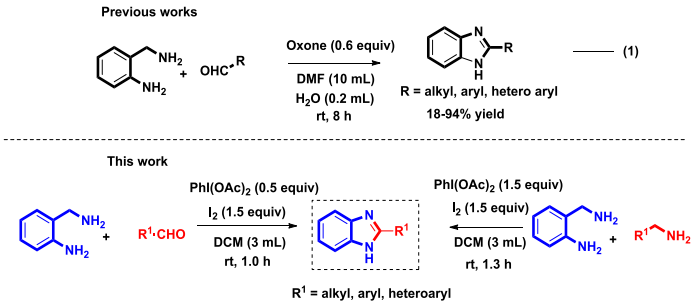
ABSTRACT

In this present work the combination of iodobenzenediacetate (PIDA)/iodine has been established as a promising reagent to promote the construction of 2-substituted benzimidazoles from 2-aminobenzylamine and a variety of easily available aldehydes/arylamines through a ring distortion strategy. The present protocol offers mild, metal free, robust conditions to synthesize 2-substituted benzimidazoles in good to excellent yields. In addition, the oxidation prone functional groups show tolerance during the reaction and after completion of the reaction pure products can be easily obtained applying hassle free filtration of the reaction mixture through silica gel bed.

1. Introduction

Nitrogen-containing heterocycles are well abundant in numerous natural products and synthesized compounds are extremely valuable due to their widespread biological activities and countless other significant utilities.[1] Among them, benzimidazoles have well recognized for their broad spectrum of bioactivity along with their several additional applications.[2] Furthermore, they have been found to be the key structural motif in several potent naturally occurring compounds.[3] Extensive studies for bioactivity have revealed benzimidazole cores are promising as antimicrobial compounds, anthelmintic and antipsychotic drugs, and also antiulcer, anticancer agents.[4] In addition several benzimidazole derivatives are used as phosphorescent emitters and ligands.[5] The emergent significance of benzimidazoles is also emphasized from the huge sale of the drugs containing this heterocyclic core.[6]

Consequently, many synthetic advances have been well established in order to access this particular heterocycle. Majority of the reported procedures to synthesize benzimidazoles largely rely on the reaction of o-phenylenediamine with carboxylic acids, acid chlorides and carbaldehydes in presence of acid and oxidizing agents at elevated temperature.[7] Although, during the past few decades several alternative methods have been developed involving transition metal catalyzed intra molecular C-N bond formation essentially.[8] However majority of these reported procedures suffers from harsh reaction conditions, prolonged reaction time and expensive metal catalysts. Thus developments of mild yet efficient protocols are still challenging to synthesize these valuable heterocyclic entities.



Scheme 1. Synthesis of benzimidazoles

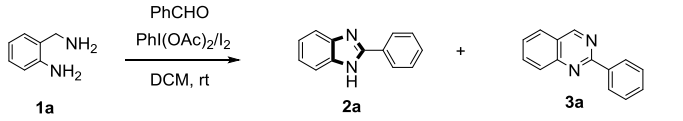
Recently, Sen et al, have demonstrated the synthesis of benzimidazole derivatives from aldehyde and 2-aminobenzylamine in presence of Oxone (scheme 1, entry 1).[9] Despite of the large substrate scope, this method suffers from the requirement of large amount of solvent (DMF), metal ion containing toxic oxidant, relatively long reaction time and low yield of the products which essentially demand an alternative superior protocol to synthesize benzimidazoles from carbaldehyde and 2-aminobenzylamine derivatives circumventing the shortcomings. Hypervalent iodine reagents, especially iodobenzenediacetate (PIDA) has successfully employed in several transformations.[10] Moreover, use of PIDA is beneficial since it is comparatively less toxic, cheap and easily available. Combination of PIDA and molecular iodine has been established earlier as an efficient radical generator.[11] However, despite its efficacy, only a handful of reactions are available in literature which apply this reagent combination.[12] Following our recent effort in hypervalent iodine promoted construction of

carbon-heteroatom bond to synthesize biologically relevant heterocycles,[13] herein we wish to report a metal free, robust synthesis of benzimidazoles employing carbaldehydes/arylamines and 2-aminobenzylamine upon application of PIDA/iodine combination using DCM as solvent at room temperature (Scheme 1).

2. Results and Discussion

To study the possibility of our hypothesis for the synthesis of benzimidazoles, 2-aminobenzylamine **1a** and benzaldehyde were chosen as the model substrate. Initially, **1a** (1.0 mmol) and benzaldehyde (1.0 mmol) were taken in a 25 mL rb fitted with a calcium chloride guard tube and then treated with 1.0 mmol PIDA and 1.0 mmol of iodine in 3 mL DCM at rt. After 1.2 h complete conversion of the starting materials was observed and **2a** was obtained in 80% yield (Table 1, entry 1). Having such an

Table 1. Optimization of reaction condition to synthesize benzimidazoles[a]



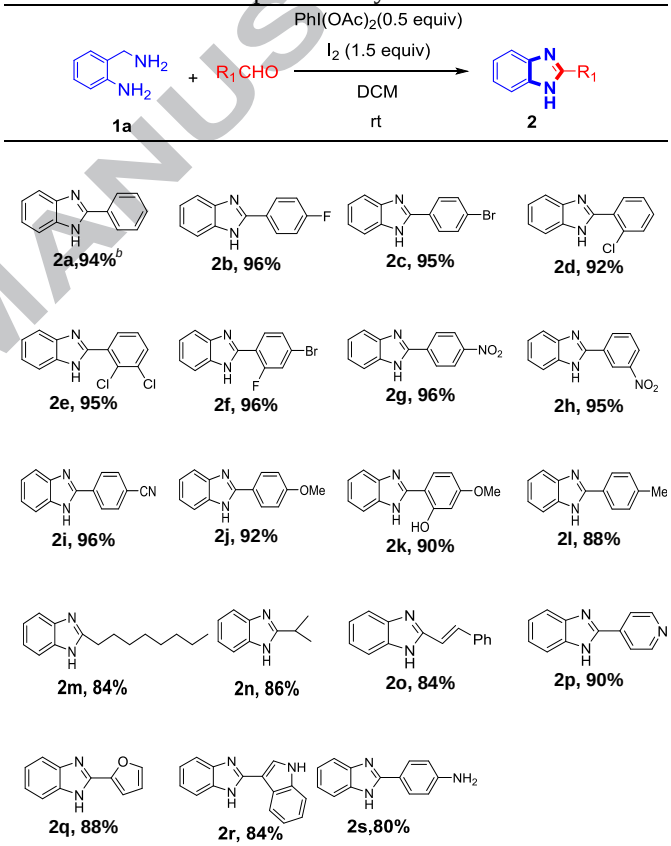
entry	$PhI(OAc)_2$ (mmol)	I_2 (mmol)	solvent	time (h)	yield[b] (%) 2a	3a
1	1.0	1.0	DCM	1.2	80	nd
2	1.5	0.5	DCM	1.1	30	50
3	0.8	1.2	DCM	1.2	86	nd
4	**0.5**	**1.5**	**DCM**	**1.0**	**94**	**nd**
5	0.4	1.6	DCM	1.3	75	nd
6	0.5	1.0	DCM	2.0	60	nd
7	0.5	1.5	DCE	2.0	84	nd
8	0.5	1.5	MeCN	2.0	70	nd
9	0.5	1.5	THF	4.0	60	nd
10	0.5	1.5	Toluene	3.0	72	nd
11	0.5	1.5	EtOAc	4.0	52	nd

[a] In each case **1a** (1.0 mmol), benzaldehyde (1.0 mmol) and 3 mL of solvent were taken in a 25 mL rb fitted with a calcium chloride guard tube at rt. [b] Yield of the isolated product.

admirable result, we have then immediately started to optimize the reaction conditions in favour of the formation of **2a**. To observe the effect of the amount of oxidants on the yield of **2a** we have then carried out the reaction employing PIDA and iodine in different ratios (Table 1, entry 2-6).When a combination of 1.5 mmol PIDA and 0.5 mmol of iodine was used, **2a** was obtained in very low yield along with the formation of **3a** in a considerable amount (Table 1, entry 2). Interestingly, an increase in the amount of iodine with a decrease in amount of PIDA improved the yield of **2a** to 86% yield (Table 1, entry 3) and **2a** was obtained in 94% when a combination of 0.5 mmol PIDA and 1.5 mmol molecular iodine was employed (Table 1, entry 4). However, additional increase in the amount of iodine results in the formation of **2a** in low yield and an increase in reaction time (Table 1, entry 5). When 0.5 mmol PIDA and 1.0 mmol iodine were used 60% of **2a** was obtained after 2 h. After that, solvents such as DCE, MeCN, THF, toluene and ethyl acetate were also screened for this reaction. However, in each case **2a** was obtained in comparatively low yield after a much longer period of time (Table 1, entry 7-11).

Achieving the optimized reaction conditions for our protocol to synthesize benzimidazoles, we have then investigated the substrate scope for this particular reaction. A large variety of aromatic, heteroaromatic and aliphatic aldehydes were employed for this reaction. These aldehydes along with 2-aminobenzylamine were treated with PIDA (0.5 mmol) and iodine (1.5 mmol) in 3 mL of DCM at room temperature. To our delight, this protocol was found to be extremely facile to access a library of functionalized benzimidazoles (Table 2, entry 2a-2s). It is noteworthy to mention that the reaction is absolutely clean producing solely 2-substituted benzimidazoles and no other side products were detected. After completion of the reaction the pure product was isolated by filtration of the reaction mixture through a silica gel bed (mesh 100-200). A wide range of aromatic

Table 2. Substrate scope for the synthesis of benzimidazoles[a]

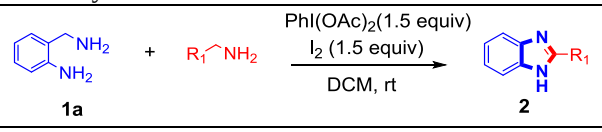


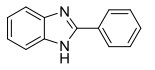
[a] reaction conditions: **1a** (1.0 mmol), aldehyde (1.0 mmol), DCM (3 mL), PIDA (0.5 mmol) and I_2 (1.5 mmol) were stirred for 1.0 h in a 25 mL rb fitted with a calcium chloride guard tube. [b] isolated yield of the product.

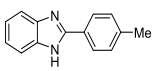
aldehydes, possessing electron withdrawing as well as electron donating functional groups, was chosen in this purpose. Agreeably the efficiency of the reaction remained unperturbed and product yield was found to be excellent in all the cases (Table 2, entry 2a-2l). On the other hand the protocol was found to be equally competent in case of aliphatic and heteroaromatic aldehydes (Table 2, entry 2m-2r). It is worth mentioning that PIDA and iodine promote the product formation chemoselectively intacting the oxidation prone electron rich aromatic rings as well as functional groups during the reaction (Table 2, entry 2k, 2o, 2r and 2s). All the synthesized benzimidazole derivatives have been well characterized by spectral analysis (^{1}H NMR, ^{13}C NMR, HRMS, IR) and finally the

structural motif of the benzimidazole scaffold was established through X-ray crystallographic analysis of single crystal of one representative compound **2l** (CCDC 1507083, see the Supporting Information). In view of the above impressive results, we have then tried to extend the scope of these protocols in realizing benzimidazoles and quinazolines from 2-aminobenzylamine and arylamine derivatives. To synthesize benzimidazole, some selected aryl amines (1.0 mmol) were stirred in 3mL DCM in

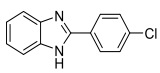
Table 3. Synthesis of benzimidazoles[a]



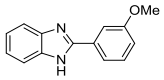

2a, 88%[b]



2l, 85%



2t, 92%

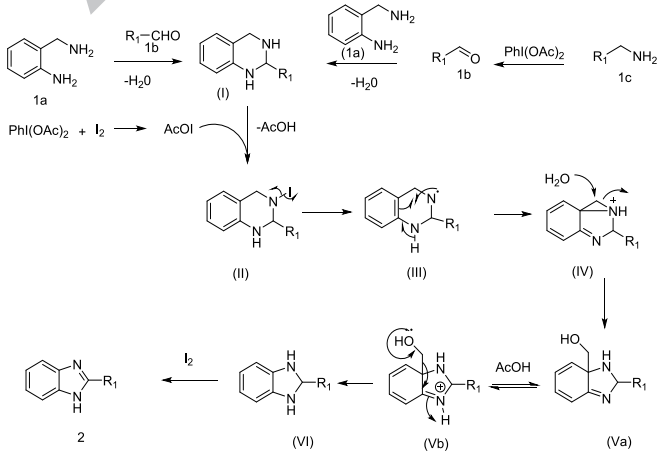


2u, 90%

[a] reaction conditions: **1a** (1.0 mmol), aryl amines (1.0 mmol), PIDA (1.5 mmol), iodine (1.5 mmol) and DCM (3 mL) at rt for 1.3 h. [b] yield of the isolated product.

presence of 1.0 mmol of PIDA for 15 min followed by the addition of **1a** (1.0 mmol), 0.5 mmol PIDA and 1.5 mmol of iodine at rt. Satisfyingly the corresponding benzimidazoles were obtained in excellent yield (Table 3, entry 2a, l, t and u). However, when n-octylamine was employed in place of aryl amine this protocol have failed to generate the desired benzimidazole derivative and the reactants have found to be remain unaffected after a prolong time (24h). This may be due to the less reactivity of alkyl amines towards the applied reagent combination than that of arylamines under the experimental condition as developed. In this case also, all the products were fully characterized through spectral analysis (^{1}H NMR, ^{13}C NMR, HRMS, IR).

A plausible mechanism for the formation of benzimidazole is depicted in scheme 2. Initially **1a** reacts with aldehyde 1b to form the intermediate I. Reaction between 1.0 equiv PIDA and 1.0equiv iodine generates 2.0 equiv of IOAc in situ.[14] This electrophilic IOAc then reacts with (I) to generate intermediate II which then immediately undergoes homolytic bond cleavage in order to produce the radical intermediate III. Intermediate III then undergoes a rearrangement in order to afford the strained aziridinium intermediate IV. Then subsequent opening of



Scheme 2. Plausible mechanism for the formation of benzimidazoles

aziridine ring by a water molecule leads to the formation of intermediate Va. Va then gets protonated to generate Vb which can undergo fragmentation in order to produce VI. Oxidation by molecular iodine then transforms VI to the desired benzimidazole 2. In case of arylamines (1c) initial oxidation of the amine takes place in presence of PIDA to generate the corresponding aldehyde. Then it follows essentially the same path to afford product 2.

3. Conclusions

In conclusion 2-substituted benzimidazoles have been efficiently synthesized from 2-aminobenzylamine and a variety of easily available aldehydes/arylamines (possessing electron donating as well as electron withdrawing groups) by employing iodobenzenediacetate/iodine combination. through a ring distortion strategy. The protocol offers mild, metal free, robust conditions to synthesize these heterocycles in good to excellent yields by assisting the C-N bond formation at room temperature.

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Highlights

- 2-substituted benzimidazoles from 2-aminobenzylamine and aldehydes.
- $PhI(OAc)_2/I_2$ reagent combination materializes ring distortion strategy.
- Benzylamines can also be used in lieu of aldehydes.
- Protocol offers well tolerance towards oxidation prone functional groups.
- Pure products can be obtained applying chromatography free technique.