Tetrahedron Letters 59 (2018) 2520–2525

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

I_2/TBHP promoted oxidative C–N bond formation at room temperature: Divergent access of 2-substituted benzimidazoles involving ring distortion

Moumita Saha, Asish R. Das *

Department of Chemistry, University of Calcutta, Kolkata 700009, India

ARTICLE INFO

Article history:
Received 11 April 2018
Revised 11 May 2018
Accepted 13 May 2018
Available online 25 May 2018

Keywords:
2-substituted benzimidazole
Iodine
TBHP
Ring distortion
C–C bond cleavage

ABSTRACT

A new 'one pot' tandem synthesis of 2-substituted benzimidazoles has been developed from 2-aminobenzyl alcohol/2-aminobenzamide and different coupling partners (nitriles, aldehydes and 1,3-diketones) via iodine and TBHP promoted oxidative ring contraction. The present strategy involves sequential C–N bond formation, cyclization, subsequent ring contraction and dehydrogenation to afford various medicinally important benzimidazole derivatives in moderate to good yields. This operationally simple synthetic approach proceeds at room temperature under base-free condition, broadly applicable to a wide array of nitriles and aldehydes bearing oxidation prone functional groups and noteworthy to mention that various acyclic 1,3-diketones undergo selective C–C bond cleavage leading to 2-alkyl benzimidazoles under mild condition.

Introduction

In recent years, reactions referring to the carbon-heteroatom bond formations have constituted the central theme of modern organic synthesis. Among those, direct oxidative C-N bond forming reactions have witnessed a sudden expansion to construct numerous pharmacology oriented heterocycles.[1,2] Again, amid several pharmaceutical constituents, *N*-heterocycles are the most abundant and integral scaffolds.[3] In particular, benzimidazoles are an important class of *N*-heterocycles due to their diverse pharmacological properties and therapeutic potentials like anti-cancer, anti-fungal, anti-bacterial, anti-leishimanial and antiviral.[4] Therefore, synthesis of benzimidazole nucleus with enhanced scope and biological activity is interesting to several synthetic and medicinal chemists. The conventional route for the synthesis of benzimidazole core mainly involves coupling of 1,2-phenylenediamines with aldehydes, carboxylic acids, nitriles, methylarenes and *ortho*-esters followed by oxidative cyclization.[5,6] Other new methods such as transition metal-catalyzed C–N coupling of N-(*ortho*-haloaryl)amidines or N-(*ortho*-haloaryl) amides, aromatic C–H activation, iodobenzene catalyzed C–H amination of *N*-substituted amidines, oxidative C(sp^3)–H amination of *N*-substituted 1,2-phenylenediamines and *N*-Aryl imines have also been reported.[7]

In spite of enough diversity, these methods are plagued with certain limitations such as harsh reaction condition, toxic metal oxidants, thermal energy and noxious halogenated reagents. Hence, synthesis of biologically important heterocycles using mild and inexpensive reaction condition is still highly challenging. During the last few decades molecular iodine has emerged as the key reagent in numerous oxidative transformations due to its easy handling, commercial availability, low toxicity and versatility.[8] Particularly, the combination of I_2 and TBHP has been proven as a promising reagent for the construction of biologically significant scaffolds through C–C, C–N, C–X (X = O, S) bond formation at room temperature.[9] Currently, ring distortion strategy is an interesting approach which enables generation of complex heterocyclic framework from easily available precursors under mild condition. However, only two examples on ring distortion strategy have been documented in literature.[10a,10b] Sen and co-workers first described oxone catalyzed ring contraction to synthesize benzimidazoles from 2-aminobenzylamine and aldehydes.[10a] Later, our group reported the synthesis of 2-substituted benzimidazoles from 2-aminobenzyl amine and aldehydes/aryl amines through molecular iodine and iodobenzene diacetate promoted ring contraction.[10b] Considering the synthetic advantages of ring distortion strategy, additional mechanistic investigation and expansion of its scope is desirable. Moreover, selective cleavage of unstrained C—C bond using 1,3-diketones as starting materials hold significant potentials for developing useful transformations in organic synthesis. However, most of

* Corresponding author: Tel.: +913323501014, +919433120265; fax: 913323519754.
E-mail addresses: ardchem@caluniv.ac.in, ardas66@rediffmail.com (A.R. Das).

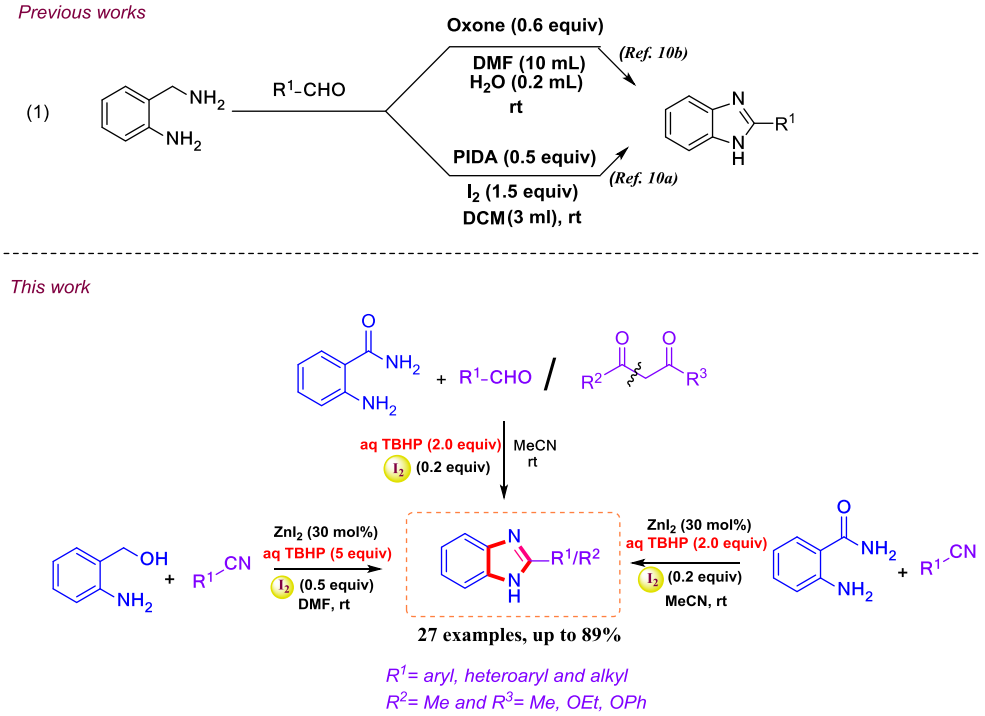
https://doi.org/10.1016/j.tetlet.2018.05.028
0040-4039/

the reported methods require transition-metal catalyst, strong acidic condition and high thermal energy to avail selective C–C bond cleavage.[11]

Besides, the literature survey reveals that nitrile compounds are viable nitrogen sources for the synthesis of several nitrogen containing compounds.[12] However, coupling of 2-aminobenzaldehyde and benzonitrile is less favourable due to the rapid homo condensation tendency of 2-aminobenzaldehyde.[13] Therefore, coupling of 2-animobenzyl alcohol with benzonitriles is not well-explored and requires enough investigation to employ these substrates in benzimidazole synthesis. The present transformation proceeds via initial coupling of 2-aminobenzyl alcohol or 2-aminobenzamide with benzonitriles, aldehydes or 1,3-diketones followed by intramolecular cyclization, successive ring contraction and oxidation. To our knowledge, this is the first attempt of benzimidazole synthesis from the reaction of 2-aminobenzyl alcohol or 2-aminobenzamide and various coupling agents (nitriles, aldehydes or 1,3-diketones) (Scheme 1) through a cascade ring distortion. The present method is environmentally transcendent, features a simple experimental procedure, accommodates a broad substrates variety, generates clean by-products and thus presents an efficient synthetic tool to achieve a good number of benzimidazoles satisfactorily.

Results and discussion

To establish the optimal conditions of above hypothesis, 2-aminobenzyl alcohol **1** and benzonitrile **2** were chosen as model substrates. Initially, the reaction between **1** and **2** were carried out in 5 mL DCM at r.t. using anhydrous ZnI_2 (30 mol%), iodine (0.2 equiv) and TBHP (3.0 equiv) as Lewis acid, additive and oxidant respectively (Table 1, entry 1) at room temperature. Gratifyingly, after 10 h almost complete conversion of the starting materials was noticed (TLC monitoring) and the desired product **3a** was isolated in 30% yield (Table 1, entry 1). The ESI mass spectral data of the crude mixture (see SI, RM-1) indicates the presence of unreacted 2-aminobenzyl alcohol and probably the coupling product **3aa** in traces. No quinazoline product **4a** was detected in ESI-MS data. The mass spectral analysis indicates that increase in the ratio of both oxidant and additive might improve the yield of **3a**. However, the elevation of reaction temperature was not effective. Moreover, the model reaction under microwave condition (100 W, 0.8 h) furnished **3a** in trace amount accompanied by the formation of an inseparable reaction mixture of several side products (Table 1, entry-21). The impact of different Lewis acids was also examined and ZnI_2 appeared to be the most effective for this transformation (Table 2, entry 2). With the increase in the amount of iodine (from 0.2 equiv to 0.5 equiv) and TBHP (from 3 equiv to 5 equiv), the yield of **3a** was significantly increased to 72% (Table 1, entry 1–9). Further increase in the amount of oxidant or additive led to slight decrease in product yield (Table 1, entries 13, 14) showing iodine (0.5 equiv) and TBHP (5.0 equiv) to be the most effective reagent combination. After fixing the optimal conditions, the combination of TBHP with other iodine salts such as KI, TBAI etc. were tested but they showed lower catalytic activities (Table 1, entry 15, 16). Screening of similar oxidants such as DTBP, H_2O_2, Oxone etc. revealed that TBHP is the best choice (Table 1, entries 17–19). Afterwards, different solvent systems were screened including polar and non-polar such as toluene, dichloroethane (DCE), acetonitrile (MeCN), DMF and DMSO (Table 1, entries 7–11). Other solvents were inferior to DMF with regard to the yield of **3a** (66% yield in AcCN, 52% yield in toluene) (Table 1, entries 8–11). When the model reaction was performed using degassed solvent (DMF) under nitrogen atmosphere, the product yield was significantly reduced (Table 1, entry-20). Additional experiments (control reactions, Scheme 2, 1–3) showed the necessity of both additive (I_2) and oxidant (TBHP) to achieve the targeted desired product. After identifying the selective reaction condition, we next explored the substrate scope of the cascade process (Table 3). The electronic properties of the substituents on the aryl ring of nitriles influenced the reaction yield to some extent. Generally, the nitriles



Scheme 1. Synthesis of benzimidazole involving ring distortion.