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# Iodine-catalyzed $C_{sp3}$-H functionalization of methylhetarenes: One-pot synthesis and cytotoxic evaluation of heteroarenyl-benzimidazoles and benzothiazole

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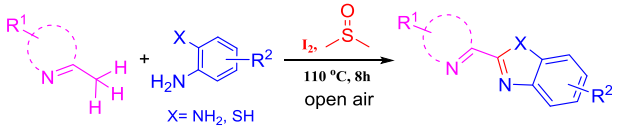
ABSTRACT

An efficient one-pot synthetic procedure has been developed for the preparation of heteroarenyl-benzimidazoles *via* oxidative $C_{sp3}$-H functionalization with *o*-phenylenediamine using $I_2$-DMSO in open air from easily available starting materials. Based on a logical plan a spectrum of multi fundamental reactions like iodination, Kornblum oxidation and amination were brought into one-pot. By using this simple method a library of heteroarenyl-benzimidazoles derivatives (**3a**–**t** and **5a**–**g**) and heteroarenyl-benzothiazole (**3u**) have been synthesized in good to excellent yield and screened for their cytotoxicity against a group of four human cancer cell lines. Among them **3h**, **3q** and **5b** showed significant cytotoxic activities with an $IC_{50}$ of 1.69, 1.62 and 2.81 μM respectively against lung cancer (A549) cell line.






Benzo-fused azoles containing heterocyclic compounds are biologically active and medicinally significant compounds.[1] Among them, benzimidazole and benzothiazole structural motifs are found in a wide range of natural products[2,3] as well as in materials.[4] They also exhibit important biological activities such as anticancer[5], anti-HIV[6] and antibacterial,[7] (Fig. 1). In spite of their biological importance, not many practical synthetic approaches have been reported in the literature.[8] Due to the importance of these fused heterocyclic skeletons and inadequate synthetic approaches, enlargement of competent methodologies for the synthesis of these fused heterocycles is highly required. Direct functionalization of $C_{sp3}$-H bonds has promoted the formation of C—N and C-heteroatom bonds and is one of the most striking and dominant strategies in organic synthesis. Alternatively, one-pot domino reactions have developed into powerful tools for the preparation of fused heterocycles from comparatively simple building blocks through atom and step monetary conversion by forming multiple bonds in single process, which facilitate the formation of large library of scaffolds for the high-throughput screening which is useful during the drug discovery process.[9,10]

On the other hand, the improvement of metal free $C_{sp3}$-H amination, especially iodine-mediated $C_{sp3}$-H amination has recently acquired extensive attention towards the construction of various nitrogen containing heterocyclic compounds including benzimidazoles and benzothiazoles. In 2004, Chen described a protocol for the preparation of 2-(1H-benzo[*d*]imidazol-2-yl)quinoline from quinoline-2-carboxylic acid and *o*-phenylenediamine with polyphosphoric acid (Scheme 1a).[11] In 2015 Xiweiand co-workers reported the synthesis of 2-(1H-benzo[*d*]imidazol-2-yl)quinoline from 2-methylquinoline and *o*-phenylenediamine with octasulfur

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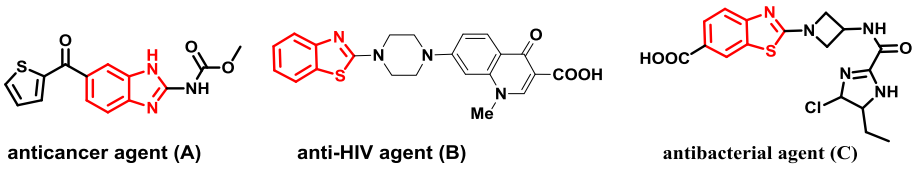
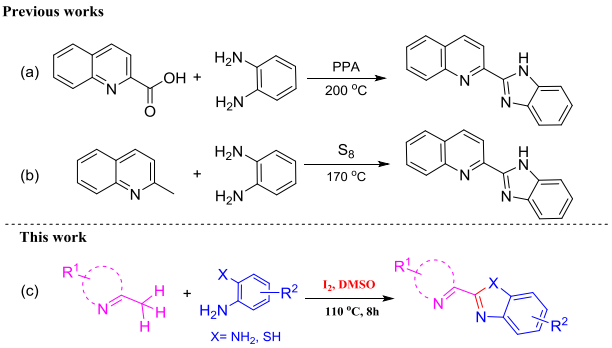



**Fig. 1.** Biologically active benzimidazole and benzothiazole derivatives.



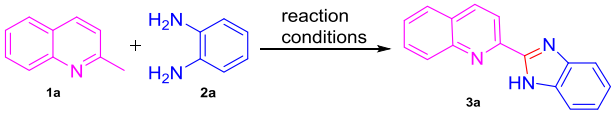

**Scheme 1.** Synthesis of 2- heteroarenyl-benzimidazoles and benzothiazole.

(Scheme 1b),[12] Gleaning from these reports, we envisioned a one-pot process for the synthesis of 2-heteroarylbenzimidazole/benzothiazole derivatives by the oxidative condensation of 2-methylhetarenes with *o*-phenylenediamine/2-aminothiophenol under mild conditions (Scheme 1c). And the results were reported herein.

Initially, we optimized the reaction conditions by performing the reactions using 2-methylquinoline (**1a**) and *o*-phenylenediamine (**2a**) as the model substrate (Table 1). In the first experiment, 2-methylquinoline (**1a**, 1equiv) was solubilized in DMF and NIS (20 mol%) was added. The mixture was stirred for 1 h at 110 °C under atmospheric pressure which resulted in the *in situ* formation of quinoline-2-carbaldehyde; after this time the *o*-phenylenediamine **2a** (1 equiv) was added. After stirring for 8 h under these conditions, the expected product **3a** was obtained in 39% yield (Table 1, entry 1). Changing the solvent system from DMF to DMSO resulted in enhancement of the yield of the product (Table 1, entry 2). Moreover, solvents such as DCE, toluene and $CH_3CN$ diminished the yield of the product (Table 1, entries 3, 4 and 5). Among the catalysts employed such as CuI, KI, TBAI and $I_2$ it was found that $I_2$ was the best catalyst of choice for this transformation at 10 mol% catalyst load (Table 1, entries 6, 7, 8 and 9). Thus, in an attempt to increase the reaction yield, we verified the influence of stoichiometry of the catalyst and noticed that the reaction yield increased to 86% with the increase in amount of catalyst from 10 mol% to 20 mol% (Table 1, entry 10). However, a further increase in the amount of the catalyst has no effect on the reaction yield; instead a decrease in the yield of the product is observed at 30 mol% catalyst load (Table 1, entry 11). With these results, we then examined the effect of temperature on the yields of the product, where decrease in the yield of the product is observed when the reaction temperature is increased to 130 °C (Table 1, entry12). Among the solvents screened, we observed that DMSO was the best solvent for this transformation (Table 1, entries 13 and 14).

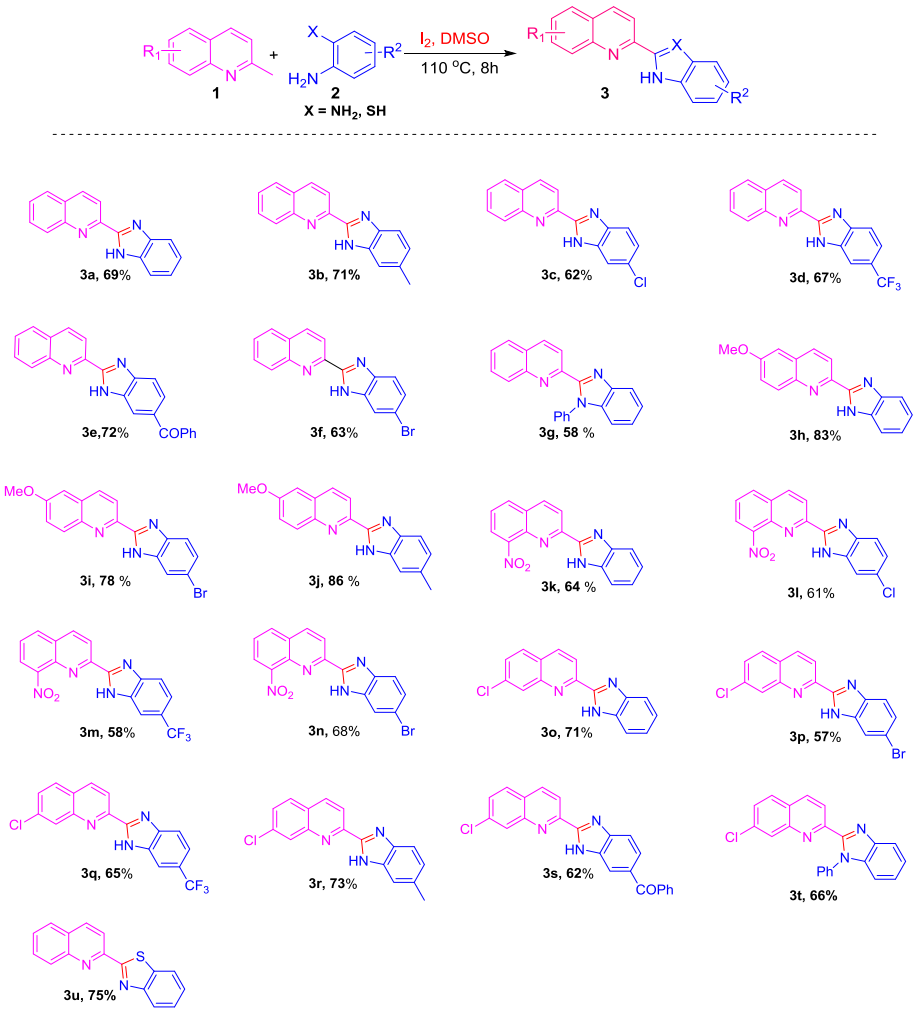
With the optimized reaction conditions in hand, the substrate scope of this method was examined. A variety of 2-heteroaromatic benzimidazole/benzothiazoles were synthesized in moderate to good yield (Scheme 2). When 2-methylquinoline was used as the

**Table 1**
Optimization of reaction conditions for synthesis of **3a**.[a]




| Entry | Catalyst (equiv) | Solvent | Temp (°C)/Time(h) | Yield%[c] |
|---|---|---|---|---|
| 1 | NIS(20%) | DMF | 110/8 | 39 |
| 2 | NIS(20%) | DMSO | 110/8 | 45 |
| 3 | NIS(20%) | Toluene | 110/8 | Trace |
| 4 | NIS(20%) | DCE | 110/8 | Trace |
| 5 | NIS(20%) | $CH_3CN$ | 110/8 | Trace |
| 6 | CuI(20%) | DMSO | 110/8 | 28 |
| 7 | KI(20%) | DMSO | 110/8 | 35 |
| 8 | TBAI(20%) | DMSO | 110/8 | 43 |
| 9 | $I_2$(10%) | DMSO | 110/8 | 57 |
| **10** | **$I_2$(20%)** | **DMSO** | **110/8** | **86** |
| 11 | $I_2$(30%) | DMSO | 110/8 | 78 |
| 12 | $I_2$(20%) | DMSO | 130/8 | 76 |
| 13 | $I_2$(20%) | $CH_3CN$ | 110/8 | Trace |
| 14 | $I_2$(20%) | Toluene | 110/8 | Trace |
| 15[b] | $I_2$(10%) | DMSO | 110/8 | 55 |
| 16[b] | $I_2$(20%) | DMSO | 110/8 | 81 |

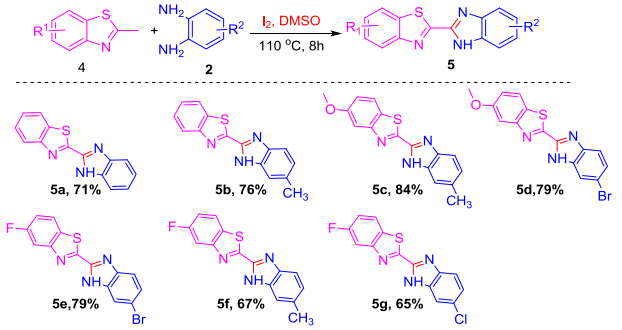
[a] All reactions were performed with **1a** (1equiv), **2a** (1 equiv), DMSO (2 ml) and catalyst according to Table 1 for **3a**.
[b] Under argon atmosphere.
[c] Isolated yield.



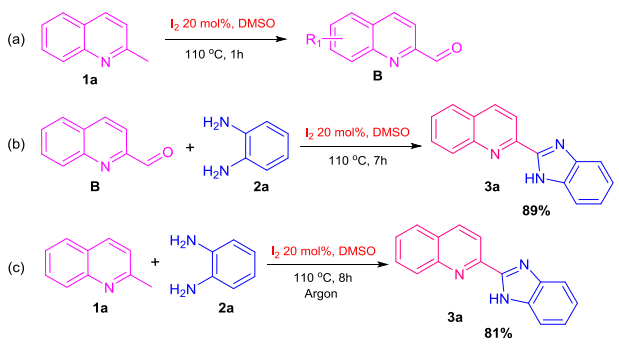

**Scheme 2.** Scope of 2-methylquinoline and *o*-phenylenediamine. All reactions were performed with **1a** (1 equiv), **2a** (1 equiv), and $I_2$ (20 mol%) in DMSO (2 ml) at 110 °C for 6 h. Isolated yield.

starting materials, the corresponding products were also obtained in good yields (Scheme 2, **3a–g**). 2-methylquinolines substituted with both electron-donating and electron-withdrawing groups smoothly reacted under the optimized reaction conditions to give the target molecules. Generally, electron-donating groups on the quinoline ring gave higher yields than those with electron-withdrawing groups (Scheme 2, **3h–k**). However, performing the reaction with 3- and 7-methylquinolines did not resulted in fruitful results leaving the reactants unreacted. This concludes that only 2-methylquinolines are suitable for this transformation.

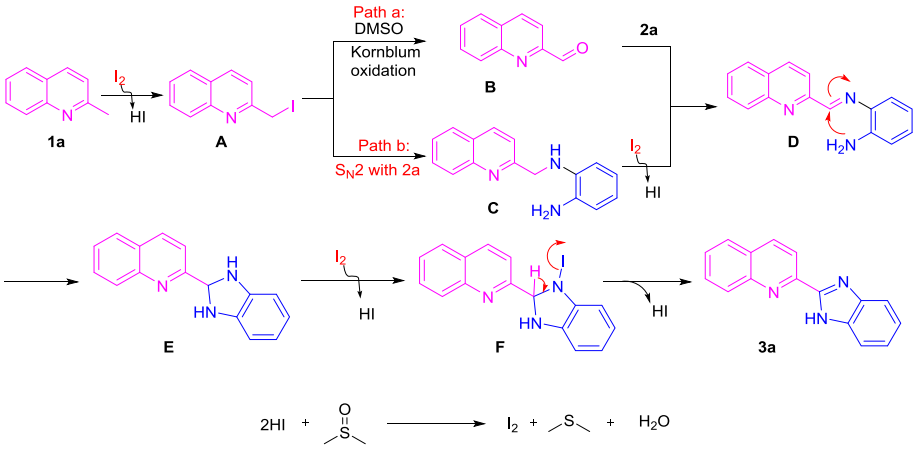
We then turned our attention to explore the substrate scope of various benzene-1, 2-diamines. Various substituted benzene-1,2-diamines having substituents like Me, Cl, Br, $CF_3$ and COPh reacted well and afforded the corresponding products in 62–86% yields (Scheme 2). To further explore the scope of this protocol, we investigated the compatibility of the reaction with 2-aminothiophenol and 2-aminophenol. It is fortunate to observe that 2-aminothiophenol delivered corresponding product (**3u**) in good yields under




**Scheme 3.** Scope of 2-methylbenzo[*d*]thiazole and *o*-phenylenediamine. All reactions were performed with **4a** (1 equiv), **2a** (1 equiv), and $I_2$ (20 mol%) in DMSO (2 ml) at 110 °C for 8 h. Isolated yield.




**Scheme 4.** Control experiments.




**Scheme 5.** Plausible mechanism.

the optimized reaction conditions. However, 2-aminophenol was ineffective for this transformation resulting in formation of no desired products.

Later, the scope of the study was also extended to substituted 2-methylbenzothiazoles and the results were summarized in Scheme 3. It is observed that various substituted 2-methylbenzothiazole were found compatible with *o*-phenylenediamine for this transformation and furnished corresponding products in good to excellent yields. Gratifyingly, 2-methylbenzothiazoles substituted with both electron-rich as well as electron-deficient groups on the phenyl ring were reacted smoothly and afforded the corresponding products (**5a**–**g**) in good to excellent yields (Scheme 3, 65–84%).

To elucidate the mechanistic pathway, few control experiments were conducted as shown in Scheme 4. Accordingly, treatment of 2-methylquinoline (**1**) with $I_2$ in presence of DMSO (optimized conditions) delivered quinoline-2-carbaldehyde (**B**) in quantitative yield which was isolated and characterised by spectroscopic studies, which upon exposure to *o*-phenylenediamine (**2a**) under standard conditions afforded the corresponding desired benzimidazole product (**3a**) in good yield (Scheme 4b). In accordance with the results, a possible mechanism for this reaction is illustrated in Scheme 5. It is assumed that 2-methylquinoline (**1a)** may initially undergo iodination to afford 2-iodomethylquinoline intermediate (**A**) which further transforms into quinoline-2-carbaldehyde (B) via Kornblum oxidation.[13] the formed aldehyde then condenses with *o*-phenylenediamine (**2a**) to give imine intermediate D. The formed imine Intermediate after intramolecular nucleophilic addition by the free $NH_2$ of the phenyl ring results in cyclic intermediate **E**. Finally, $I_2$ mediated oxidation followed by aromatization provides the desired product **3**.[14]

Based on the results obtained from the Table 1, it is noticed that the protocol also works even in the absence of DMSO which is required for Kornblum oxidation (entry 1, Table 1). From these results an alternate mechanism is depicted in Scheme 5 (path b), where in 2-iodomethylquinoline intermediate (**A**) is formed after iodination could directly undergo nucleophilic amination with *o*-phenylenediamine (**2**) to generate the intermediate **C**, which in the presence of $I_2$ yields the imine D via oxidation. Finally, intramolecular cyclization, oxidation followed by aromatisation of D affords the benzimidazole product (**3a**).

It was considered of interest to evaluate these 2-(1H-benzo[*d*]imidazol-2-yl)quinoline and 2-(1H-benzo[*d*]imidazol-2-yl)benzo[*d*]thiazole analogues (**3a**–**t** and **5a**–**g**) as potential cytotoxic agents. And the results of MTT assay[15] are summarized in Table 2. The results obtained by this cytotoxicity assay indicated that some

**Table 2**
$IC_{50}$values[a] (in μM) for heteroarenyl-benzimidazoles (**3a**–**t** and **5a**–**g**).

| Compound | MDA MB231[b] | A549[c] | DU-145[d] | HCT-116[e] |
|---|---|---|---|---|
| **3a** | 23.63 | 17.27 | 76.95 | 72.50 |
| **3b** | 52.78 | 50.09 | 102.6 | 97.20 |
| **3c** | 19.52 | 16.21 | 27.35 | 21.24 |
| **3d** | 26.61 | 32.06 | 62.31 | 98.20 |
| **3e** | 15.76 | 14.27 | 22.25 | 15.43 |
| **3f** | 57.00 | 53.11 | 102.2 | 70.86 |
| **3g** | 22.82 | 14.16 | 67.00 | 73.43 |
| **3h** | 2.042 | 1.698 | 12.70 | 14.59 |
| **3i** | 79.43 | 67.29 | 84.77 | 102.0 |
| **3j** | 55.25 | 53.00 | 83.67 | 97.40 |
| **3k** | 11.67 | 9.652 | 24.84 | 22.10 |
| **3l** | 62.28 | 32.93 | 126.5 | 123.5 |
| **3m** | 236.0 | 124.9 | 101.6 | 103.2 |
| **3n** | 12.80 | 11.45 | 13.57 | 31.00 |
| **3o** | 12.11 | 7.893 | 13.24 | 28.73 |
| **3p** | 15.48 | 10.73 | 20.50 | 45.20 |
| **3q** | 3.548 | 1.622 | 10.09 | 13.23 |
| **3r** | 20.68 | 15.88 | 28.05 | 22.00 |
| **3s** | 23.78 | 24.84 | 38.83 | 30.47 |
| **3t** | 17.12 | 15.54 | 30.80 | 41.80 |
| **5a** | 14.03 | 9.057 | 55.63 | 73.43 |
| **5b** | 17.85 | 2.818 | 21.05 | 28.39 |
| **5c** | 18.00 | 17.24 | 18.95 | 43.75 |
| **5d** | 13.74 | 55.75 | 96.20 | 63.98 |
| **5e** | 29.20 | 11.42 | 30.33 | 39.62 |
| **5f** | 20.58 | 11.58 | 38.33 | 43.73 |
| **5g** | 23.10 | 23.97 | 37.58 | 42.41 |
| Nocodazole | 1.862 | 1.513 | 1.698 | 1.262 |

[a] 50% Inhibitory concentration and the values are average of four individual experiments after 48 h of drug treatment.
[b] Breast cancer.
[c] Lung cancer.
[d] Prostate cancer.
[e] Colon cancer.

of these compounds like **3h**, **3q** and **5b** showed significant cytotoxic activity against lung cancer cell lines (A549) in comparison to other tested cell lines with $IC_{50}$ values of 1.69, 1.62 and 2.81 μM respectively. It is interesting to note that these results are comparable to the nocodazole employed as the standard. In order to investigate the structure activity relationship (SAR), we have varied the substitution pattern of the both benzene rings of heteroarenyl-benzimidazoles. The cytotoxicity data of most potential compounds i. e **3h** and **3q** deciphered that inductively electron donating substituents (e.g., OMe) at 6th position as well as withdrawing substituents at 7th position (e.g., Cl) on benzene ring of quinoline and electron-neutral/withdrawing (H/$CF_3$) substituents

at 6th position on benzene ring of benzimidazole are essential for cytotoxic potential. It was observed that electronegative substituent like bromo at 6th position on benzimidazole (**3f**, **3i** and **5d**) ring of heteroarenyl-benzimidazoles decreases the cytotoxicity. From a set of compounds (**3a** and **5a**), (**3b** and **5b**) and (**3j** and **5c**) with same substituents it was observed that 2-(1H-benzo[*d*]imidazol-2-yl)benzo[*d*]thiazole compounds are more potent than 2-(1H-benzo[*d*]imidazol-2-yl)quinoline compounds. The cytotoxic data of compounds **5a**–**g** indicated that electron donating substituents like hydrogen on benzothiazole and methyl on benzimidazole rings are essential for the cytotoxicity of 2-(1H-benzo[*d*]imidazol-2-yl)benzo[*d*]thiazoles.

In conclusion, we have described a simple and efficient molecular $I_2$ mediated strategy for the synthesis of variously substituted heteroarenyl-benzimidazoles by using methylhetarenes and substituted *o*-phenylenediamine in a one-pot open air reaction. It is noteworthy to state that this metal-free and simple strategy is useful for the construction of heteroarenyl-benzimidazoles (**3a**–**u** and **5a**–**g**) and heteroarenyl-benzothiazole (**3u**). Among the synthesized analogues, **3h**, **3q** and **5b** showed significant cytotoxicity with an $IC_{50}$ of 1.69, 1.62 and 2.81 μM respectively against A-549 cancer cell line.

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.07.051.

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