I₂-Catalyzed Oxidative Cross-Coupling Reaction of Methyl Ketones and 2-(2-Aminophenyl) Benzimidazole: Facile Access to Benzimidazo[1,2-c]quinazoline

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Supporting Information

ABSTRACT: A general and efficient iodine-catalyzed metal-free oxidative cross-coupling reaction of methyl ketones with 2-(1H-benzo[d]imidazol-2-yl)aniline has been established. This is a new synthetic strategy for the synthesis of benzimidazo[1,2-c]quinazoline derivatives involving C(sp³)–H oxidation, condensation, and cyclization processes.

INTRODUCTION

The direct oxidative C–H bond functionalization has emerged as an effective tool for the construction of carbon–carbon and carbon–heteroatom bonds. Transition metals play vital role in oxidative C–H coupling reactions. Metal-free organic syntheses for the construction of C–C and C–X bonds are also popular. Molecular iodine is a popular catalyst in various organic transformations owing to its easy availability and inexpensive, nontoxic, eco-friendly, and nonmetallic nature. Additionally, molecular iodine has superfluous advantages as it has the lowest dissociation energy, no radioactivity, and a moderate redox potential. In 2010, Li et al. reported I₂-mediated oxidative cyclization of enamines via iodide intermediates.

Nitrogen-containing heterocycles are ubiquitous scaffolds in numerous natural products, biomolecules, and organic materials. Benzimidazo[1,2-c]quinazoline is a trinitrogen heterocycle that hosts both the fused structure of benzimidazole and quinazoline via a shared bond. The combination of benzimidazole and quinazoline framework, benzimidazoquinazoline derivatives, are valuable substrates with different biological activities as shown in Figure 1 and benzoimidazo[1,2-c]quinazoline derivatives exhibit wide spectrum of therapeutic activities such as antimicrobial, antitumor, anticancer, antiviral, anti-inflammatory, and anticonvulsants. Due to the remarkable importance of these molecules, we planned to propose a new method for construction of benzimidazo[1,2-c]quinazoline derivatives. A number of synthetic methodologies for construction of the compounds containing this core structure were reported. Hulme et al. reported a cesium carbonate-promoted three-component reaction, CuI-catalyzed Ullmann N-arylation. Fu et al. reported a copper-catalyzed cascade synthesis of benzimidazoquinazoline derivatives under mild conditions (Scheme 1a). Fu et al. developed a general method for the synthesis of benzoimidazo[1,2-c]quinazolines via copper-catalyzed reactions of substituted 2-(2-halophenyl)-1H-benzo[d]imidazoles with α-amino acids (Scheme 1b).

Later, Koutentis and co-workers reported Cu- and Pd-catalyzed oxidative and nonoxidative C–N coupling reactions to give the corresponding products in high yields (Scheme 1c). Recently, Sarada et al. established a nickel-catalyzed aerobic oxidative isocyanide insertion reaction for the synthesis of a novel benzimidazoquinazolines via sequential double annulation cascade protocol (Schemes 1d and 2). All of the above reports suffer from drawbacks such as the use of prefunctionalized starting materials, harsh reaction conditions, longer reaction time, and metal catalyst. Therefore, the development of new approaches to the synthesis of benzimidazoquinazolines using simpler and more readily available starting materials under milder conditions is still highly desirable.

In continuation of our ongoing research to develop new routes for the construction of various heterocyclic systems, we investigated the reaction of 4-methylacetophenone 1b with 2-(1H-benzo[d]imidazol-2-yl) aniline 2 as model substrates for the present study. The reaction has been carried out under various reaction conditions, as depicted in Table 1. On treatment of 1b with 2 and an equivalent of iodine as the catalyst in N,N-dimethylacetamide (DMA) at 110 °C for 6 h, the desired product 3b was not formed (Table 1, entry 1). Further optimization was done by the use of other common organic solvents including N,N-dimethylformamide (DMF), toluene, N-methylpyrrolidone (NMP), acetonitrile, and DMSO (Table 1, entries 2–6), and DMSO has been proved to be the best solvent. Next, we tried the reaction in the absence of the catalyst in dimethyl sulfoxide (DMSO), but there was no product obtained even after long reaction time. Hence, additional optimization experiments were performed in the presence of various iodides such KI, NIS, TBAI, KI, NIS, TBAI,
and NH4I in DMSO at 110 °C for 6 h. However, the desired product was not obtained (Table 1, entries 8–11). Further increase in the amount of iodine did not lead to significant differences in the yield (Table 1, entry 12). Further, we optimized the reaction in the presence of different stoichiometric amounts of iodine in DMSO (Table 1, entries 13–17), the corresponding product was obtained in 78, 80, 83, and 75% yield, respectively. The combination of iodine (20 mol %) and DMSO was found to be efficient for this transformation (Table 1, entry 16). So, all of the reactions were carried out under this reaction conditions.

With the optimized reaction conditions in hand, we then investigated the substrate scope of the aryl methyl ketones, as
Scheme 2. Synthesis of Benzoimidazo Quinazolinones

![Scheme 2](image)

Table 1. Optimization of Reaction Conditions

| entry | catalyst (equiv) | solvent | temp | yield (%) |
|-------|-----------------|---------|------|-----------|
| 1     | I₂ (1.0)        | DMA⁺    | 110 °C | NR        |
| 2     | I₂ (1.0)        | DMSO    | 110 °C | NR        |
| 3     | I₂ (1.0)        | toluene | 110 °C | NR        |
| 4     | I₂ (1.0)        | NMP⁻    | reflux | NR        |
| 5     | I₂ (1.0)        | CH₂CN   | reflux | NR        |
| 6     | I₂ (1.0)        | DMSO⁴   | 110 °C | 78        |
| 7     | –               | DMSO⁴   | 110 °C | NR        |
| 8     | KI (1.0)        | DMSO    | 110 °C | NR        |
| 9     | NIS (1.0)       | DMSO⁴   | 110 °C | NR        |
| 10    | TBAI (1.0)      | DMSO⁴   | 110 °C | NR        |
| 11    | NH₄I (1.0)      | DMSO⁴   | 110 °C | NR        |
| 12    | I₂ (1.2)        | DMSO⁴   | 110 °C | 73        |
| 13    | I₂ (0.8)        | DMSO⁴   | 110 °C | 78        |
| 14    | I₂ (0.6)        | DMSO⁴   | 110 °C | 80        |
| 15    | I₂ (0.4)        | DMSO⁴   | 110 °C | 80        |
| 16    | I₂ (0.2)        | DMSO⁴   | 110 °C | 83        |
| 17    | I₂ (0.1)        | DMSO⁴   | 110 °C | 75        |

"Reaction conditions: 1b (1.0 equiv) additive and solvent (2 mL) are heated in a sealed tube at 110 °C for 6 h and then 2 (1.0 equiv) is added. Yield of the isolated product. DMA = N,N-dimethylformamide, DMA = N,N-dimethylacetamide, NMP = N-methylpyrrolidone, DMSO = dimethyl sulfoxide.

shown in Scheme 3. Aryl methyl ketones bearing electron-donating and electron-withdrawing substituents were successfully converted into the corresponding products in moderate to good yields (73–83%; 3a–3h). Moreover, sterically hindered acetyl naphthalene has only little influence on the reaction efficiency (73–83%; 3i and 3k). Notably, heterocyclic methyl ketones also participated in the reaction affording the corresponding products 3n–3p in 59–62% yields, respectively.

To have a better understanding of the reaction mechanism, a series of control experiments were performed (Scheme 4). The reaction of acetophenone 1a with 2 in presence of I₂ affords 3a in good yields (Scheme 4a). Next, the reaction was carried out α-iodoketone 1ab with DMSO and phenylglyoxal was obtained in 81% yield (Scheme 4b). Subsequently, the reaction of α-iodoketone 1ab with 2-(1H-benzo[d]imidazol-2-yl) aniline 2 was found to be effective and the product 3a was obtained in 69% yield (Scheme 4c). When the acetophenone was replaced with phenylglyoxal 1ac, the desired product was obtained in 75% yield (Scheme 4d). These results confirmed that α-iodoketone 1ab is a possible precursor of α-ketoaldehyde 1ac. Moreover, the results also indicated that phenacyl iodide 1ab and phenylglyoxal 1ac are the key intermediates in the transformation. Finally, the radical trapping experiments were tested (Scheme 4e). 2,2,6,6-Tetramethylpiperidinooxy (TEMPO) was used as a radical scavenger. In the presence of TEMPO, desired product was observed in good yield (71%) and this result shows that radical intermediates were not involved in this reaction.

Structural elucidation of benzoimidazoquinazoline was accomplished by using one-dimensional and two-dimensional, as described for 3b. In the 1H NMR spectrum (see the SI) of 3b, the methyl protons appear as a sharp singlet at 2.43 ppm, which gives C–H COSY correlation with the carbon at 22.5 ppm and β-hydroxy β-methylbutyrate (HMB) correlation with the carbons at 130.2 and 145.7 ppm (Figure 2). The two-proton signal appears as a doublet at 8.09 ppm (J = 7.8 Hz), which gives C–H COSY correlation with the carbon at 130.2 ppm and HMB correlation with the carbons at 145.7 and 191.9 ppm.

The structure of the product 3 was confirmed by an electrospray ionization mass spectrometry (ESI-MS). On the basis of the above results and literature reports, a plausible mechanism suggest that this reaction could have occurred through a self-sequenced iodination/Kornblum oxidation/C–H amination and intramolecular cyclization reactions.

**General Methods.** The melting points were measured in open capillary tubes and were uncorrected. The 1H and 13C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard either CDCl₃ or DMSO-d₆ as solvent. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz (Hz). Silica gel-G plates (Merck) were used for thin layer chromatography (TLC) analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. High-resolution mass spectra were recorded on a Waters Q-TOF micromass spectrometer using ESI mode.

**General Experimental Procedure for 3 Benzo[4,5]-imidazo[1,2-c]quinazolin-6-yl(phenyl)methanone (3a–3n).** A mixture of aryl methyl ketone 1 (100 mg, 0.83 mmol) and 2-(1H-benzo[d]imidazol-2-yl) aniline 2 (174 mg, 0.83 mmol) was taken in a 10 mL round-bottom flask in DMSO and 2 mL of I₂ (42 mg, 20 mol %) was added and reaction mixture was refluxed at 110 °C for 6 h. The reaction was monitored by TLC.
using n-hexane/ethyl acetate mixture (3:2) as eluent. After the completion of the reaction, the mixture was poured into ice water, worked up with sodium thiosulphate, and extracted with ethyl acetate. The organic layer was collected, dried on anhydrous sodium sulfate, and the solvent was evaporated on a rotary evaporator to get the crude product. The crude product was purified by silica gel column using 30:70 n-hexane/ethyl acetate.

**Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(phenyl)methanone (3a).** Yellow solid (215 mg, 80%); mp 222−224 °C; 1H NMR (300 MHz, DMSO-d₆) δ 8.18 (d, J = 7.9 Hz, 1H), 8.03 (d, J = 7.7 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.56−7.44 (m, 2H), 7.29−7.14 (m, 3H), 7.00 (s, 1H), 6.93 (t, J = 7.1 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.28 (s, 1H); 13C NMR (75 MHz, CDCl₃ with DMSO-d₆) δ 190.1, 147.4, 143.0, 140.0, 133.2, 132.1, 130.6, 128.1, 127.4, 124.1, 121.6, 118.7, 118.0, 115.0, 112.3, 108.2.

**Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(p-tolyl)methanone (3b).** Yellow solid (209 mg, 83%); mp 226−228 °C; 1H NMR (300 MHz, DMSO-d₆) δ 8.13 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.28−7.19 (m, 3H), 7.16−7.10 (m, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.88 (dd, J = 9.8, 5.1 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 3.4 Hz, 1H), 2.39 (s, 3H); 13C NMR (75 MHz, CDCl₃ with DMSO-d₆) δ 191.9, 149.0, 145.8, 144.7, 142.1, 134.0, 132.2, 131.2, 130.4, 130.2, 125.4, 123.1, 122.9, 119.7, 119.5, 116.2, 113.8, 110.5, 22.1; HRMS (m/z) (ESI): calcd for C₂₂H₁₅N₃O 337.1215; found 337.1219 [M + H]⁺.

**Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(4-methoxyphenyl)methanone (3c).** Yellow solid (191 mg, 81%); mp 194−196 °C; 1H NMR (300 MHz, DMSO-d₆) δ 8.11 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 6.78 (s, 1H); 13C NMR (75 MHz, CDCl₃ with DMSO-d₆) δ 191.9, 149.0, 145.8, 144.7, 142.1, 134.0, 132.2, 131.2, 130.4, 130.2, 125.4, 123.1, 122.9, 119.7, 119.5, 116.2, 113.8, 110.5, 22.1; HRMS (m/z) (ESI): calcd for C₂₂H₁₄N₃O 335.1087; found 335.1093 [M + H]⁺.

**Scheme 3. Substrate Scope of the Transformation**

\( ^a\) Reaction conditions: 1 (1.0 equiv), 2 (1.0 equiv), and I₂ (0.2 equiv) in DMSO (2 mL) at 110 °C. \(^b\) Isolated yield.
Scheme 4. Investigation Into the Reaction Mechanism

8.8 Hz (2H), 8.06 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 3.5 Hz, 1H), 7.29–7.12 (m, 5H), 7.00 (d, J = 8.8 Hz, 2H), 6.83 (dd, J = 15.2, 7.8 Hz, 2H), 3.87 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 189.3, 164.0, 148.2, 143.8, 141.1, 132.9, 131.4, 131.2, 125.6, 124.7, 122.4, 122.2, 119.1, 118.7, 115.4, 114.1, 112.9, 108.9, 55.5; HRMS (m/z) (ESI): calcd for C23H17N3O3 383.1270; found 383.1274 [M + H]+.

Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(4-chlorophenyl)methanone (3g). Yellow solid (144 mg, 72%); mp 200–202 °C; 1H NMR (300 MHz, CDCl3) δ 8.14 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.22 (dd, J = 17.1, 10.6, 4.2 Hz, 4H), 7.01 (d, J = 4.3 Hz, 1H), 6.90 (dd, J = 9.2, 5.8 Hz, 2H), 6.79 (d, J = 7.9 Hz, 1H); 13C NMR (75 MHz, CDCl3) δ 189.5, 148.2, 144.4, 140.8, 133.3, 132.5, 132.2, 131.8, 130.9, 129.6, 125.6, 123.1, 123.0, 120.5, 119.6, 116.3, 113.8, 109.0; HRMS (m/z) (ESI): calcd for C21H12ClN3O 357.0669; found 357.0676 [M + H]+.

Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(4-bromophenyl)methanone (3h). Yellow solid (140 mg, 68%); mp 192–194 °C; 1H NMR (300 MHz, CDCl3) δ 8.28 (d, J = 1.8 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.95 (dd, J = 8.4, 1.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 4.5 Hz, 1H), 7.29–7.17 (m, 4H), 6.92–6.77 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 194.3, 153.3, 149.2, 145.7, 143.4, 138.3, 138.1, 133.6, 130.3, 127.9, 127.8, 125.2, 124.3, 121.3, 118.8, 114.2; HRMS (m/z) (ESI): calcd for C21H12BrN3O 391.0279; found 391.0279 [M]+.

Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl(4-naphthalen-2-yl)methanone (3j). Yellow solid (138 mg, 63%); mp 186–188 °C; 1H NMR (300 MHz, CDCl3) δ 8.25 (d, J = 8.1 Hz, 1H), 8.19–8.00 (m, 3H), 7.90 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 1H), 7.66–7.47 (m, 3H), 7.38–7.27 (m, 1H), 7.22 (dd, J = 17.7, 10.8 Hz, 2H), 7.07–6.93 (m, 1H), 6.82–6.14 (m, 1H), 6.63 (d, J = 8.4 Hz, 1H); 13C NMR (75 MHz, CDCl3) δ 194.6, 143.3, 141.0, 132.9, 132.6, 131.5, 131.3, 130.8, 129.8, 128.0, 127.3, 126.0, 125.3, 124.7, 124.2, 124.0, 123.4, 122.3, 121.8, 121.6, 118.9, 118.5, 118.1, 115.6, 114.8, 112.5, 109.3; HRMS (m/z) (ESI): calcd for C21H12N3O 373.1215; found 373.1216 [M + H]+.

[1,1′-Biphenyl]-4-yl(benzo[4,5]imidazo[1,2-c]quinazolin-6-yl)methanone (3k). Yellow solid (136 mg, 65%); mp 230–232 °C; 1H NMR (300 MHz, CDCl3) δ 8.21 (d, J = 8.1 Hz, 2H), 8.09 (d, J = 7.0 Hz, 1H), 7.75 (dd, J = 7.4, 2.9 Hz, 3H), 7.65 (d, J = 6.8 Hz, 1H), 7.60–7.53 (m, 5H), 7.48–7.40 (m, 2H), 6.96–6.73 (m, 4H), 6.32–6.06 (m, 4H), 5.62–5.28 (m, 4H), 4.47–4.21 (m, 4H), 4.10–3.84 (m, 4H), 3.81–3.54 (m, 4H), 3.50–3.24 (m, 4H), 3.17–2.91 (m, 4H), 2.87–2.70 (m, 4H), 2.70–2.53 (m, 4H), 2.47–2.20 (m, 4H), 2.18–1.91 (m, 4H), 1.89–1.72 (m, 4H), 1.70–1.43 (m, 4H), 1.42–1.25 (m, 4H), 1.25–1.08 (m, 4H), 1.08–0.91 (m, 4H), 0.91–0.74 (m, 4H), 0.74–0.57 (m, 4H), 0.57–0.40 (m, 4H), 0.40–0.23 (m, 4H), 0.23–0.06 (m, 4H), 0.06–0.00 (m, 4H).
**Scheme 5. Plausible Mechanism for the Formation of Benzoimidazoquinazoline Derivatives**

**Figure 2.** $^1$H, $^{13}$C chemical shifts and HMB correlations of 3b.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00067.

Typical procedure and characterization data for benzoimidazo[1,2-c]quinazoline and NMR and HRMS spectra of all synthesized compounds (PDF)

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**Notes**

The authors declare no competing financial interest.
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