Preparation of 1,2-substituted benzimidazoles via a copper-catalyzed three component coupling reaction†

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1,2-Substituted benzimidazoles were prepared by simply stirring a mixture of copper catalysts, N-substituted o-phenylenediamines, sulfonyl azides and terminal alkynes. Particularly, the intermediate N-sulfonylketenimine occurred with two nucleophilic addition and the sulfonyl group was eliminated via cyclization. In a way, sulfonyl azides and copper catalysts activated the terminal alkynes to synthesize benzimidazoles.

Introduction

Owing to their diverse biological activity and clinical applications, benzimidazole derivatives are the potential candidates for a diverse set of biological activities including antiviral, antifungal, antibacterial, antiamoebic, anti-HIV, anti-ulcer, anti-inflammatory and anti-hypertensive. One subset of such compounds are 1,2-substituted benzimidazole derivatives, such as 5-nitro-benzimidazoles (I) that exhibit antitumor activity against melanoma and breast cancer, telmisartan (II) that acts as AT1 receptor antagonists and tentative angiotensin receptor blocker for COVID-19, and bendamustine (III) that acts as an antileukemia agent (Fig. 1). The observed activity depends upon the functional group attached to the moiety. In order to obtain novel effective chemotherapeutic agents, more synthetic methods and routes are required.

Classical types of reactions have focused on the preparation of benzimidazole structural frameworks, such as metal catalyzed reaction, metal-free catalysed/reagent-based reaction, green synthesis and photocatalyzed reaction. The main synthesis reaction of benzimidazole drug candidates is the condensation of o-phenylenediamine with aldehydes, acyl chloride, carboxylic acids and esters. However, most of these protocols suffer from strong acidic conditions (HCl, H2SO4, or polyphosphoric acid), readily oxidized or unstable substrate, or presence of numerous oxidative catalytic reagents. Therefore, a catalytic approach without using oxidant and stable substrate would overcome the above-mentioned disadvantages.

Previous studies reported that the multicomponent reactions (MCRs) of CuI-catalyzed terminal alkyne, sulfonyl azide, and nucleophiles were applied to synthesize numerous oxygen-containing and nitrogen-containing heterocyclic compounds. The ketenimine intermediate generated by copper-catalyzed terminal alkyne and sulfonyl azide could be take reaction simultaneous employing of pronucleophiles (Nu–H) and electrophiles (E) by designing the substrates. The o-hydroxy or o-amino electrophiles-containing benzene was the best strategy for the substrates, such as salicylaldehyde/o-hydroxy-acetophenones, 2-acetyl aniline, phenolic schiff’s bases, α-(ortho-hydroxyphenyl)-β,β-unsaturated ketones/o-hydroxy-phenylpropiolates, o-hydroxybenzonitrile (Scheme 1a) etc. However, two pronucleophiles (Nu–H) simultaneous nucleophilic addition with the ketenimine intermediate is rare.

The compounds of above MCRs contain the sulfonyl group, which is stable and difficult to eliminate. Only a few examples could eliminate the sulfonyl group, including the hydrolysis of N-sulfonyl imidates with catalytic amounts of DBU, or N-sulfonyl acetimid amide treated with 2% H2SO4 under reflux conditions. However, previous studies reported that N-sulfonyl imidates can be hydrolyzed through in situ generated H2O (Scheme 1b). Considering these facts, our study

![Fig. 1: Some 1,2-substituted benzimidazole drug candidates.](image-url)
developed a novel strategy to eliminate the sulfonyl group through the power of cyclization reaction (Scheme 1c).

Results and discussion

We began our investigation by examining the synthesis of (2-benzyl-1H-benzo[d]imidazol-1-yl)(phenyl)methanone 3a via N-(2-aminophenyl)benzamide 1a, tosylazide and ethynylbenzene 2a. The reaction was carried out in the presence of CuI and Et₃N in CHCl₃ at 80 °C for 3.5 h, and 3a was isolated in 73% yield (Table 1, entry 1). Based on this finding, the reaction conditions were screened. Several other solvents were screened first, and a lower or comparable yield was obtained when toluene, THF, DMF, DCE were used as solvents, while the MeCN gave 3a the highest yield of 95% and the side product TsNH₂ (Table 1, entries 2–6). Thus, the optimal solvent was determined to be MeCN. Encouraged by this promising result, numerous catalysts were screened. Among the copper catalysts used, most Cu-catalysts exhibited high catalytic reactivity in this reaction whether CuI-catalysts or CuII-catalysts (Table 1, entries 7–11). Other catalysts such as AgTFA failed to produce the desired product (Table 1, entry 12). The effects of different bases were evaluated. Screening results revealed that the use of Et₃N achieved superior results than DMAP, DIPEA, tBuONa and other bases (Table 1, entries 13–16). When the reaction temperature was changed to 90 °C, the reaction yield decreased and produced side-products (Table 1, entries 17). It is worth noting that the other sulfonyl azides such as MsN₃ or PhSO₂N₃ were also suitable for this reaction (Table 1, entries 18).

With the optimized reaction conditions obtained, the substrate diversity with the N-substituted o-phenylenediamines 1 were tested first. As shown in Table 2, the electron effects of the substituents R¹ had slight influences. For example, substrates bearing 4-Me-C₆H₄CO–, 4-OMe-C₆H₄CO–, 4-F-C₆H₄CO–, and 2-thienyl-C₆H₄CO– groups were examined, and 90–86% yield of 3b–3e were obtained. The substrates R¹ bearing the (CH₃)₂CHCO– and p-tosyl (Ts-) groups also can obtain 3f in moderate yield of 54% and 3g in good yield of 86%. Next, the scope and limitation of substrates R² were examined by employing 3,4-dimethyl and 3,4-dichloro groups, which provided the corresponding benzimidazole derivatives, 3h and 3i, in moderate yield of 65% and 60%. It is noteworthy to mention that when R¹ was changed for methyl instead of electron-withdrawing group acyl, the reaction also could...
smoothly obtain corresponding methyl-substituted products 3j–3m. However, interestingly, unsubstituted o-phenylenediamines 1k could not obtain the desired product and gave complex compounds.

Finally, the scope and limitation of terminal alkynes 2 were examined. As shown in Table 3, the steric effects were clearly observed for two groups of products, namely 3n–3o and 3p–3r, in which both the substituents led to high yields and got influenced slightly. The electronic effects of substituents had an obvious impact on the efficiency of this transformation. The analogues R3 bearing an electron-withdrawing group (e.g., 4-Cl-C6H4– and 4-Br-C6H4–) and strong electron-donating group (e.g., -OMe) substituents produced a good yield of 3s, 3t and 3u. The aliphatic alkynes were also suitable for this reaction obtaining 3v, 3w, 3x in moderate yields of 77%, 58% and 68%, respectively. However, the other functional groups of terminal yrones such as the ethyl propiolate, propiolamide, propiolic acid made the reactions less effective, which obtained complex compounds or no corresponding desired products because the terminal yrones undergo self-condensation under the alkaline conditions.

According to the above-mentioned experiments, there was no sulfonyl group in the target product and detected only the side product TsNH2. In addition, it could not obtain the desired product when test the unsubstituted o-phenylenediamines 1k (Table 2). To confirm the effects of tosylazide and elucidate the mechanism of eliminating the sulfonyl group, few control experiments were performed under the standard conditions. As shown in Scheme 2, the reaction of 1a and 2a, without tosylazide under the standard conditions was performed, and the corresponding products 3a failed to generate. Other test was carried out using the reactant of N,N′-(1,2-phenylene) dibenzamide 1l, which could not detect the target product 3a.

On the basis of these above experimental results, a possible reaction pathway for the synthesis of [2-benzyl-1H-benzo[d] imidazol-1-yl][phenyl]methanone 3a was proposed (Scheme 3). According to the previous proposal, ketenimine A was generated first by the reaction of TsN3 and 2a. Then, similar to the published work by Wang,29 ketenimine A was attacked by the nucleophile to generate intermediate B. Subsequently, intermediate B underwent an intramolecular cascade addition to form intermediate C. At last, the desired product 3a and side product TsNH2 were obtained by the cyclization of intermediate C. Irrespective of change in the conditions, intermediates B and C could not be detected. Therefore, the procedure from B to 3a was fast and almost simultaneous. The sulfonyl group was eliminated via cyclization and activated the terminal alkynes to decompose into TsNH2 and N2.

Conclusions

We developed a novel and an effective three-component coupling approach to synthesize 1,2-substituted benzimidazoles in the presence of N-substituted o-phenylenediamines, terminal alkynes, copper catalyst and TsN3. TsN3 activated the terminal alkynes to generate ketenimine, took two nucleophilic addition in the process, and eliminated through cyclization. Nonetheless, we expect that this methodology could be applied to build more 1,2-substituted benzimidazole block facility.

Experimental

General

All the melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All the spectra of 1H NMR (400 MHz) and 13C NMR (100 MHz) were recorded on a JEOL JNM-ECA 400 spectrometer in DMSO-d6 or
CDCl₃ (otherwise as indicated) with TMS was used as an internal reference and J values are given in Hz. HRMS were obtained on a Bruker microOTOF-Q II spectrometer. All the o-phenylenediamines (1a–1j, see ESI section 1f) were prepared by previously reported methods.²³

Preparation and characterizations of compounds 3a–3x

(2-Benzyl-1H-benzo[d][1H-imidazol-1-yl][phenyl]methanone (3a)). To a solution of N-(2-aminophenyl)benzamide (1a, 106 mg, 0.5 mmol) and CuCl (9.5 mg, 0.05 mmol) in MeCN (3 mL) was added ethynylbenzene (2a, 61 mg, 1.2 mmol), TsN₂ (118 mg, 1.2 mmol), Et₃N (61 mg, 1.2 mmol). After the mixture was stirred at room temperature for 10 min, and then at 80 °C for 3.5 h (monitored by TLC), the solvent was removed. The residue was purified via flash chromatography (silica gel, 9% EtOAc in petroleum ether) to give 148 mg (95%) of product 3a as a white solid, mp 88–89 °C (lit.²⁴ 308–310 °C).¹ H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.27–7.17 (m, 7H), 7.15–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 2.43 (s, 3H);¹³C NMR (100 MHz, CDCl₃) δ 168.5, 153.2, 145.2, 144.2, 136.4 (2C), 134.2, 130.1 (2C), 129.5 (2C), 128.8 (2C), 128.4 (2C), 126.7, 126.3, 126.2, 119.8, 113.1, 35.8, 21.8; HRMS (ESI-TOF) (m/z). Calcd for C₂₂H₁₈N₂O₂, [M + H]+ 343.1441; found 343.1442.

(2-Benzyl-1H-benzo[d][1H-imidazol-1-yl][p-toly]methanone (3b)). Calcd for C₂₃H₂₀N₂O, [M + H]+ 341.1649; found 341.1650.

(2-Benzyl-1H-benzo[d][1H-imidazol-1-yl][4-fluorophenyl]methanone (3c)). 147 mg (90%), white solid, mp 104–105 °C. IR (KBr) ν 3048, 2930, 1691, 1451 cm⁻¹;¹ H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.27–7.17 (m, 7H), 7.15–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 2.43 (s, 3H);¹³C NMR (100 MHz, CDCl₃) δ 167.8, 167.0, 141.7, 135.6, 142.6, 136.1, 136.0, 132.6 (2C), 125.6, 124.2, 123.2, 122.3, 121.8, 121.7, 120.4, 112.8, 36.9, 35.8, 18.6 (2C); HRMS (ESI-TOF) (m/z). Calcd for C₁₉H₁₄Cl₂N₂O, [M + H]+ 381.0556; found 381.0557.

(2-Benzyl-1H-benzo[d][1H-imidazol-1-yl][3-fluorophenyl]methanone (3d)). Calcd for C₁₈H₁₆F₂N₂O, [M + H]+ 331.1241; found 331.1242.
(ESI-TOF) (m/z). Caled for C_{15}H_{13}FN_{2}, [M + H]^{+} 241.1136; found 241.1137.

2-(4-Chlorobenzyl)-1-methyl-1H-benz[d]imidazol-1-yl (3i). 118 mg (92%), white solid, mp 115–116 °C (lit. 117–119 °C). 1H NMR (400 MHz, CDCl₃) δ 7.76–7.74 (m, 1H), 7.26–7.22 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 4.22 (s, 2H), 3.51 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 152.5, 142.2, 135.8, 134.4, 132.6, 129.6 (2C), 128.8 (2C), 122.3, 121.8, 119.3, 109.0, 33.4, 29.8.

2-(4-Bromobenzyl)-1-methyl-1H-benz[d]imidazol-1-yl (3m). 136 mg (91%), white solid, mp 119–121 °C (lit. 110–121 °C no report). 1H NMR (400 MHz, DMSO-d₆) δ 7.58–7.56 (m, 1H), 7.51–7.46 (m, 3H), 7.25–7.14 (m, 4H), 4.28 (s, 2H), 3.69 (s, 3H); 13C NMR (100 MHz, DMSO-d₆) δ 153.1, 142.1, 136.3, 135.8, 131.4 (2C), 131.0 (2C), 121.7, 121.4, 119.7, 118.5, 109.9, 32.3, 29.8.

2-(Methylbenzyl)-1H-benz[d]imidazol-1-yl(phenyl) methanone (3n). 142 mg (87%), white solid, mp 164–166 °C. IR (KBr) ν 3049, 2978, 2821, 1624, 1432 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 7.8 Hz, 1H), 7.64–7.56 (m, 3H), 7.45–7.41 (m, 2H), 7.27–7.22 (m, 1H), 7.10–6.99 (m, 5H), 6.64 (d, J = 8.2 Hz, 1H), 4.48 (s, 2H), 2.22 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 166.8, 154.9, 154.2, 134.6, 134.1, 133.9, 133.2, 133.1, 126.8 (2C), 129.1 (2C), 128.8 (2C), 128.6 (2C), 128.3, 127.5, 125.8, 123.8, 123.7, 119.8, 113.1, 35.9, 20.9. HRMS (ESI-TOF) (m/z). Caled for C_{22}H_{18}N_{2}O, [M + H]^+ 327.1492; found 327.1495.

2-(3-Methylbenzyl)-1H-benz[d]imidazol-1-yl(phenyl) methanone (3o). 119 mg (89%), white solid, mp 111–113 °C. IR (KBr) ν 3055, 2836, 2684, 1655, 1429 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.8 Hz, 1H), 7.65–7.61 (m, 1H), 7.58–7.56 (m, 2H), 7.45–7.41 (m, 2H), 7.28–7.24 (m, 1H), 7.10–7.04 (m, 2H), 6.99–6.93 (m, 3H), 6.66 (d, J = 8.2 Hz, 1H), 4.48 (s, 2H); 2.21 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 168.6, 155.2, 142.2, 138.0, 136.1, 134.1, 133.9, 133.0, 129.9 (2C), 129.4, 128.8 (2C), 128.3, 127.5, 125.8, 123.8, 123.7, 119.8, 113.1, 35.9, 20.9. HRMS (ESI-TOF) (m/z). Caled for C_{22}H_{18}N_{2}O, [M + H]^+ 327.1492; found 327.1493.

2-(4-Fluorobenzyl)-1H-benz[d]imidazol-1-yl(phenyl) methanone (3p). 150 mg (91%), white solid, mp 78–79 °C. IR (KBr) ν 3047, 2870, 2616, 1635, 1508 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.2 Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.57 (m, 2H), 7.47–7.43 (m, 2H), 7.28–7.24 (m, 1H), 7.22–7.18 (m, 2H), 7.08–7.04 (m, 1H), 6.92–6.87 (m, 2H), 6.62 (d, J = 8.3 Hz, 1H), 4.50 (s, 2H); 13C NMR (100 MHz, CDCl₃) δ 168.5, 161.7 (d, J = 244.1 Hz, 1C), 155.0, 142.2, 134.05, 134.00, 132.9, 131.9 (d, J = 2.9 Hz, 1C), 130.4 (d, J = 7.6 Hz, 2C), 129.8 (2C), 128.9 (2C), 123.9, 123.8, 119.9, 115.3 (d, J = 37.7 Hz, 2C), 113.2, 35.1; HRMS (ESI-TOF) (m/z). Caled for C_{22}H_{18}FN_{2}O, [M + H]^+ 331.1244; found 331.1243.

2-(3-Fluorobenzyl)-1H-benz[d]imidazol-1-yl(phenyl) methanone (3q). 140 mg (85%), white solid, mp 71–73 °C. IR (KBr) ν 3060, 2873, 2635, 1653, 1454 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 7.8 Hz, 1H), 7.67–7.63 (m, 1H), 7.60–7.58 (m, 2H), 7.48–7.44 (m, 2H), 7.29–7.25 (m, 1H), 7.20–7.15 (m, 1H), 7.09–7.05 (m, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.96–6.93 (m, 1H), 6.87–6.82 (m, 1H), 6.63 (d, J = 8.3 Hz, 1H), 4.53 (s, 2H); 13C NMR (100 MHz, CDCl₃) δ 168.5, 162.7 (d, J = 245.0 Hz, 1C), 154.4, 144.2, 138.7 (d, J = 7.6 Hz, 1C), 134.1, 134.0, 132.9, 129.9, 129.8 (2C), 128.9 (2C), 124.5 (d, J = 2.9 Hz, 1C), 129.3, 129.2.
(2-(Cyclohexylmethyl)-1H-benzo[d]imidazol-1-yl)(phenyl) methanone (3w), 92 mg (58%), white solid, mp 77–78 °C. IR (KBr) ν 3056, 2925, 2625, 1711, 1449 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.76–7.67 (m, 4H), 7.54–7.50 (m, 2H), 7.26–7.22 (m, 1H), 7.08–7.04 (m, 1H), 6.73 (d, J = 8.2 Hz, 1H), 2.98 (d, J = 7.3 Hz, 2H), 1.92–1.86 (m, 5H), 1.73–1.60 (m, 5H), 1.26–0.99 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 155.8, 142.3, 134.0, 168.6, 156.6, 142.3, 134.0, 133.8, 133.2, 129.9 (2C), 128.9 (2C), 123.6, 123.3, 119.5, 113.0, 37.4, 36.9, 33.0 (2C), 26.1, 25.9 (2C); HRMS (ESI-TOF) [m/z]. Calecd for C₂₁H₂₄N₂O, [M + H]+ 321.1962; found 321.1964.

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