



Original article

A green and convenient approach toward benzimidazole derivatives and their antimicrobial activity



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ABSTRACT

N-Alkylated benzimidazole derivatives have been synthesized via the aza-Michael addition reactions of 1*H*-benzimidazoles to α,β -unsaturated compounds in water and palladium acetate obviously promoted these transformations. The reported method, overcoming the inactivation of palladium under the equivalent nitrogenous conditions, has the advantages of convenient manipulation, atom-economy, as well as environmental friendliness. The bioactive results showed that butyl 3-(5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)propanoate (**3c**) exhibited excellent inhibitory activity against *Bacillus subtilis* (MIC = 16 $\mu\text{g}/\text{mL}$) and *Bacillus proteus* (MIC = 8 $\mu\text{g}/\text{mL}$). Therefore, this process would facilitate the construction of various potential bioactive compounds based on the benzimidazole scaffold under mild conditions.

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1. Introduction

Benzimidazoles, which are an important class of nitrogen-containing heterocycles, display broad potential applications as medicinal agents [1], supramolecular blocks [2] as well as functional materials [3] and so on. 3-(1*H*-Benzimidazol-1-yl)propanehydrazide derivatives, for example, inhibit bacterial cell division (Fig. 1) and have been exhaustively investigated [4]. Additionally, medicines containing the benzimidazole skeleton such as Astemizole, have been successfully employed in clinic [1a] (Fig. 1). Recently, research on the construction and functionalization of the benzimidazole scaffold has attracted enormous interest and produced a large number of exciting findings [5]. However, the exploration of green and convenient synthetic strategies for preparing novel benzimidazole derivatives under mild conditions is still of current interest.

The aza-Michael addition reaction as a versatile and atom-economical method can construct multiple new C–N bonds via the 1,4-conjugate addition of various nitrogen nucleophiles to various Michael acceptors [6]. Compared with aliphatic and aromatic amines along with indoles, imidazoles as *N*-nucleophiles were

inert or less reactive to Michael acceptors [7]. There were just a limited number of examples involving the aza-Michael addition of imidazoles to a series of activated alkenes catalyzed by *N*-methyl imidazole or $\text{Y}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ or promoted under ultrasound (US) irradiation [8,9d,9h]. Nevertheless, the aza-Michael addition reaction of the 1*H*-benzimidazole, as a benzene-fused imidazole, is very difficult and has been rarely reported [9], especially in the water medium. Water as a medium can fully meet several requirements of Green Chemistry and has attracted much interest [10]. Besides, transition metal reagents in the water medium have shown great potential in catalyzing or promoting diverse organic transformations; for instance, the 1,4-addition of terminal alkynes to acrylates was catalyzed by palladium in water [11]. We intended to explore the synthesis of novel *N*-alkylated benzimidazole derivatives via the aza-Michael addition of 1*H*-benzimidazoles to α,β -unsaturated compounds in water and the evaluation of their antimicrobial activity.

2. Experimental

We initially investigated the aza-Michael addition of 1*H*-benzimidazole (**1a**) to butyl acrylate (**2a**) as a model reaction to synthesize butyl 3-(1*H*-benzo[d]imidazol-1-yl)propanoate (**3a**). It was an exciting finding that the reaction of **1a** and **2a** without any additives in neat water at 85 °C for 24 h formed the addition product **3a** in an isolated yield of 67% (Table 1, entry 1). However,

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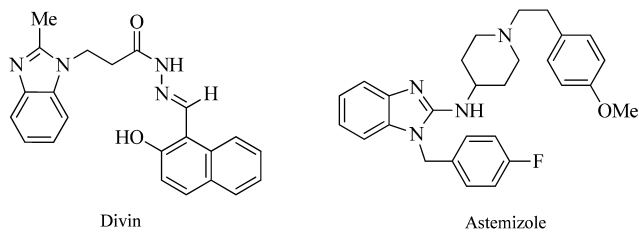


Fig. 1. Compounds with the benzimidazole skeleton.

Table 1
Optimization of the reaction conditions^a.

Entry	Catalyst	Solvent	Temp. (°C)	Isolated yield (%)
1	–	H ₂ O	85	67
2	Pd(OAc) ₂	H ₂ O	85	87
3	–	Toluene	85	16
4	PdCl ₂	H ₂ O	85	76
5	Cu(OAc) ₂ ·H ₂ O	H ₂ O	85	55
6	Ag ₂ O	H ₂ O	85	67
7	FeCl ₃	H ₂ O	85	46
8	Pd(OAc) ₂	Toluene	85	58
9	Pd(OAc) ₂	DCE	85	43
10	Pd(OAc) ₂	Dioxane	85	59
11	Pd(OAc) ₂	HOAc	85	33
12	Pd(OAc) ₂	ⁿ PrOH	85	76
13	Pd(OAc) ₂	H ₂ O	26	37
14	Pd(OAc) ₂	H ₂ O	50	61
15	Pd(OAc) ₂	H ₂ O	90	85
16 ^b	Pd(OAc) ₂	H ₂ O	85	74
17 ^c	Pd(OAc) ₂	H ₂ O	85	77
18 ^d	Pd(OAc) ₂	H ₂ O	85	87

^a Reaction conditions: Benzimidazole **1a** (0.5 mmol), butyl acrylate **2a** (1.0 mmol), and the catalyst (0.025 mmol) in solvent (2 mL) heated in a sealed tube at required temperature under air atmosphere for 24 h.

^b H₂O (1 mL).

^c H₂O (4 mL).

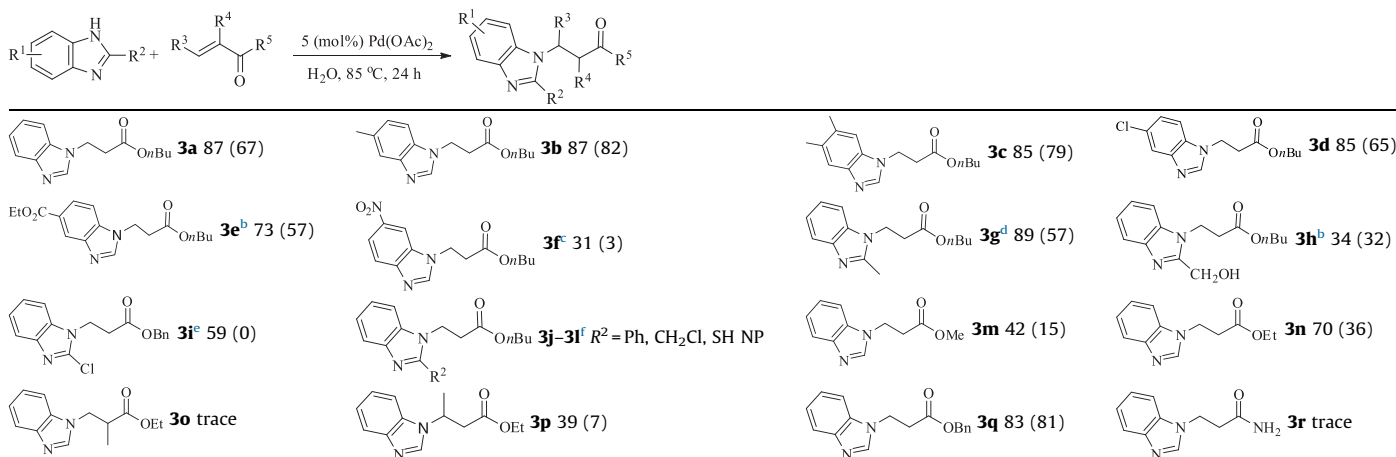
^d Fresh distilled butyl acrylate.

this transformation was incomplete by TLC analysis. In order to improve this transformation, Pd(OAc)₂ as a catalyst was tested. To our delight, the nearly complete conversion of **1a** into **3a** was realized in the presence of 5 mol% of Pd(OAc)₂ in a 87% isolated yield (Table 1, entry 2). Moreover, the result of anhydrous toluene as a solvent instead of water without any additives verified the promoting action of water to this aza-Michael addition (Table 1, entry 3). Also, the result of 5 mol% of PdCl₂ illustrated that the chlorine anion of PdCl₂ had a negative effect on this reaction (Table 1, entry 4). Other transition metal salts, such as Cu(OAc)₂·H₂O, Ag₂O and FeCl₃, showed inferior efficiency for this transformation (Table 1, entries 5–7). Compared with water, other solvents were not suitable for this transformation (Table 1, entries 8–12). The above experimental results confirmed that the synergistic effect of palladium acetate and water played a critical role in this addition reaction. Besides, the tests of lowering or increasing reaction temperature, in comparison with the reaction temperature of 85 °C, showed that the lower reaction temperature clearly reduced the addition reaction rate, but the higher temperature could not significantly promote the reaction (Table 1, entries 13–15). The molar concentration of the starting materials also had a certain influence on this transformation by changing the amount of water (Table 1, entries 16–17). Furthermore, the yield of freshly distilled butyl acrylate was the same as that of commercial available butyl acrylate (Table 1, entry 18), which demonstrated inhibitors in commercial acrylates having no effect on this addition reaction. Finally, the optimal conditions of the aza-Michael addition reaction had been established.

3. Results and discussion

A variety of substituted 1*H*-benzimidazoles reacting with **2a** were explored in neat water under the conditions with palladium acetate and without palladium, respectively (Table 2). 1*H*-Benzimidazoles bearing electron-donating groups on the phenyl gave the desired products in excellent yields under both palladium acetate and palladium-free conditions (Table 2, **3b**, **3c**). Because of the tautomerism, 5-methylbenzimidazole having a tautomer of 6-methylbenzimidazole produced a tautomeric mixture of 1,5- and 1,6-disubstituentbenzimidazoles (Table 2, **3b**). In particular,

Table 2
Preparation of compounds **3**^a.



^a Reaction conditions: **1** (0.5 mmol), butyl acrylate **2a** (1.0 mmol), Pd(OAc)₂ (0.025 mmol), water (2 mL), 85 °C, 24 h. The isolated yield was from the average of at least two experiments. The yield in parentheses obtained from the palladium-free conditions.

^b Reaction time is 48 h.

^c 10 mol% Pd(OAc)₂ (0.05 mmol) and 48 h.

^d Reaction conditions: 5 mol% Pd(OAc)₂ (0.025 mmol), 50 mol% LiCl, 90 °C and 24 h.

^e Benzyl acrylate (1.0 mmol) and 48 h.

^f NP: no product.

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