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Report

DMAP, C-N Bond, Fused Heterocyclic, Pyrimido[1,2-*a*]benzimidazoles, Imidazo[1,2-*a*]pyrimidines,

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DMAP-Catalyzed C-N Bond Formation for the Diverse Synthesis of Imidazo[1,2-*a*]pyrimidine and Pyrimido[1,2-*a*]benzimidazole Derivatives

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Summary of main observation and conclusion A DMAP-catalyzed condensation reactions for the successful direct construction of pyrimido[1,2-*a*]benzimidazole or imidazo[1,2-*a*]pyrimidine has been developed. The method utilizes readily available α-bromocinnamaldehydes with 2-aminobenzimidazole or 2-aminoimidazole as starting materials in the presence of 2-DMAP/TBHP. In the process, two C-N bonds were successfully constructed to synthesize target compounds. The current method features wide substrate scope, product diversification, and metal-free conditions.

Background and Originality Content

Nitrogen-containing fused heterocyclic compounds are important organic compounds. They are core structural fragments in various of natural products, pharmaceutical molecules, and functional materials.[1] Among them, the pyrimido[1,2-*a*]benzimidazole and imidazo[1,2-*a*]pyrimidine skeleton are related to the pharmacological activity of related drugs. For example, anticancer activity drugs, anxiolytic drugs, anti-inflammatory activity drugs, the HCV inhibitor and the PET tracer in imaging of Tau Pathologies.[2-7] More generally, pyrimido[1,2-*a*]benzimidazole derivatives also behave as antimicrobial agent drugs.[8] Moreover, the imidazo[1,2-*a*]pyrimidine motif has shown biological activities (Figure 1).

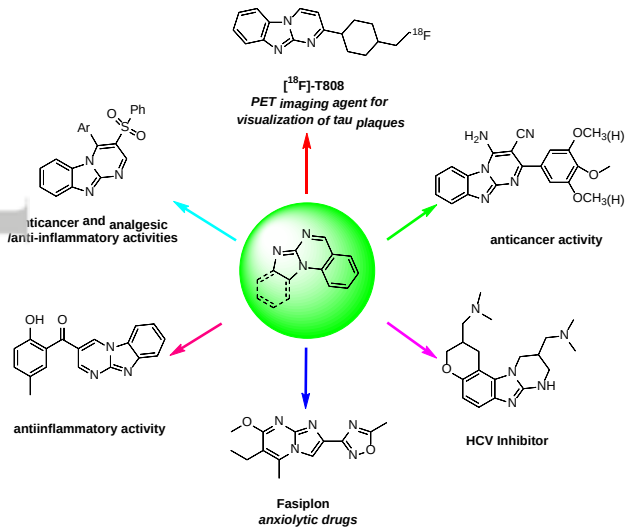
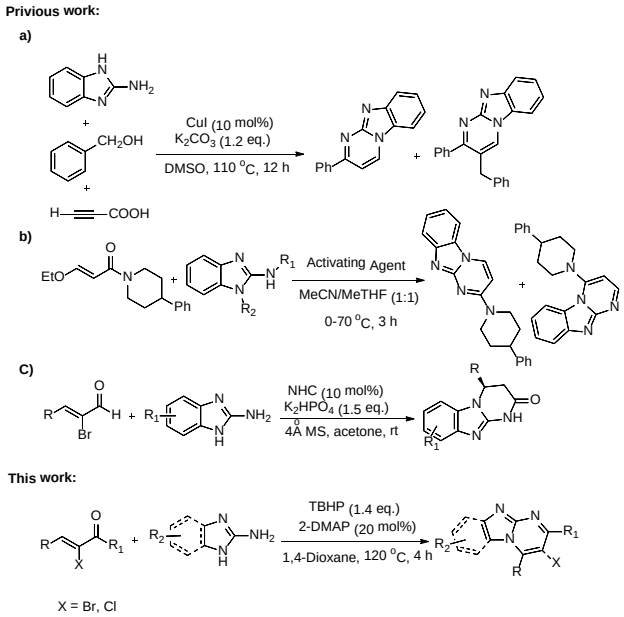


Figure 1. Typical Pyrimido[1,2-*a*]benzimidazole and Imidazo[1,2−*a*]pyrimidine scaffolds.

As a result, Many people have put a great number of effort in preparing pyrimido[1,2-*a*]benzimidazole and imidazo[1,2-*a*]pyrimidine compounds, and a series of eminent approaches have been developed.[9] In 2019, Chai searched a highly efficient one-pot method for the synthesis of fused pyrimido[1,2-*a*]benzimidazoles from 2-aminobenzoimidazole, benzaldehyde and propiolic acid. (Scheme 1a).[10] Next, the

Scheme 1. Synthetic Approaches to Pyrimido[1,2-*a*]benzimidazole Scaffolds from Benzimidazole Precursors



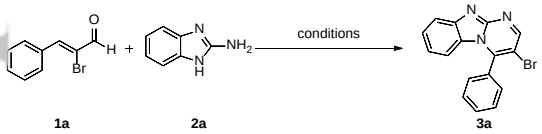
Gosselin group also reported that activation of the acrylamide with $POCl_3$ combined with the use of different *N*-phosphorylation of aminoimidazole products providing a string of pyrimido[1,2-*a*]benzimidazole derivatives (Scheme 1b).[11] In 2020, Wang proposed NHC-catalyzed [3+3] cyclization reaction, the raw materials of which were 2-aminobenzimidazole and α-bromoenals (Scheme 1c).[12] Although these protocols have some great advantages, they still have some limitations. For

example, severe conditions, narrow substrate range, toxic metal salt catalysts, which may restrict their wide applications in natural product synthesis. Therefore, the development of a simple, direct, and mild reaction system for the generation of pyrimido[1,2-*a*]benzimidazole and imidazo[1,2-*a*]pyrimidine skeleton is still highly desirable. DMAP is a commonly used organic base, but it also can be used as a catalyst or promoter for organic reactions. [13-14] Therefore, we propose a new method, the new method utilizes readily available *α*-bromocinnamaldehyde, 2-aminobenzimidazole and 2-aminoimidazole as starting materials in the presence of 2-DMAP/TBHP. The method features wide substrate scope, product diversification, and metal-free conditions.

Results and Discussion

The reaction of *α*-bromocinnamaldehyde (**1a**) and 2-aminobenzimidazole (**2a**) at 120 °C in the presence of 4-DMAP and TBHP in 1,4-dioxane gave the target product **3a** in 46% yield (Table 1, entry 1). Subsequently, other bases such as Et_3N, Cs_2CO_3, *t*-BuONa, and 2-DMAP were examined (Table 1, entries 1-5), and 2-DMAP showed the best result to obtain the product **3a** in 83% yield (Table 1, entry 5). Besides, various oxidants and solvents were screened (Table 1, entries 6-12). Further exploration of TBHP and 1,4-dioxane were shown to be an ideal oxidant and medium (Table 1, entry 5, 83% yield). Increasing the temperature to 130 °C did not afford a good yield (Table 1, entry 13). The yield declined when the temperature was decreased to 110 °C (Table 1, entry 14). Further optimization of using 2-DMAP as the base showed that the reaction efficiency was obviously affected by the amount of base catalyst. The yields of **3a** were obtained in 58% and 57% when the catalyst loading was reduced to 10 mol% or increased to 30 mol% (Table 1, entries 15 and 16). The amounts of TBHP did not affect the reaction efficiency, however the yield of the reaction decreased when the amount of catalyst was reduced (Table 1,entries 17-18). In addition, blank experiments showed that the oxidant played an indispensable role in the cyclization process (Table 1, entry 19). Therefore, the reaction conditions of entry 5 proved to be optimal.

Table 1 Screen of Reaction Conditions [a]

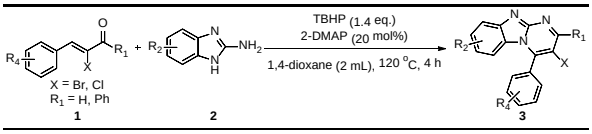


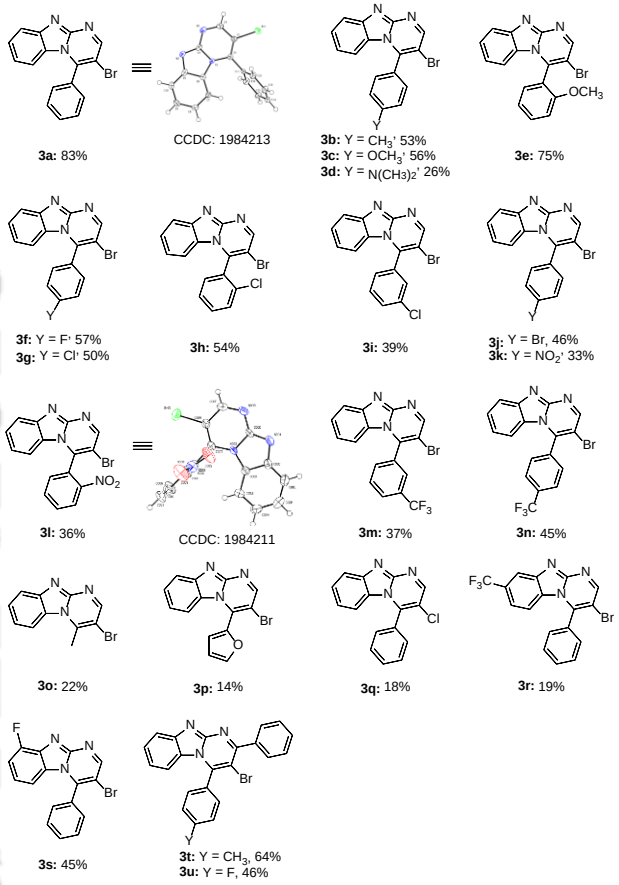
Entry	Base	Oxidant	Solvent	T (°C)	Yield[b] (%)
1	4-DMAP	TBHP	1,4-dioxane	120	46
2	Et_3N	TBHP	1,4-dioxane	120	52
3	Cs_2CO_3	TBHP	1,4-dioxane	120	10
4	*t*-BuONa	TBHP	1,4-dioxane	120	36
5	**2-DMAP**	**TBHP**	**1,4-dioxane**	**120**	**83**
6	2-DMAP	TBHP	EtOAc	120	32
7	2-DMAP	TBHP	THF	120	48
8	2-DMAP	TBHP	DCE	120	44
9	2-DMAP	TBHP	toluene	120	35
10	2-DMAP	H_2O_2	1,4-dioxane	120	26
11	2-DMAP	$K_2S_2O_8$	1,4-dioxane	120	37
12	2-DMAP	*m*-CPBA	1,4-dioxane	120	18
13	2-DMAP	TBHP	1,4-dioxane	130	58
14	2-DMAP	TBHP	1,4-dioxane	110	56
15[c]	2-DMAP	TBHP	1,4-dioxane	120	58
16[d]	2-DMAP	TBHP	1,4-dioxane	120	57
17[e]	2-DMAP	TBHP	1,4-dioxane	120	40
18[f]	2-DMAP	TBHP	1,4-dioxane	120	57
19	2-DMAP	-	1,4-dioxane	120	10

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (20 mol%), oxidant (1.4 eq.), solvent (2.0 mL), under air, 4 h. [b] Isolated yields. [c] 2-DMAP (10 mol %), [d] 2-DMAP (30 mol %). [e] TBHP (1.0 eq.), [f] TBHP (2.0 eq.).

Under the first-rank conditions, the scope of this *α*-bromocinnamaldehyde and 2-aminobenzimidazole was explored (Scheme 2). The structure of products **3a** and **3l** were further proved by X-ray crystallography. Generally, a string of electron-rich (Me, MeO, $N(CH_3)_2$) and electron-absorbing (F, Cl, Br, CF_3, NO_2) substituted *α*-bromocinnamaldehydes **1** were good substrates and produced target products (**3a**-**3n**) with moderate to good yields (26-83%). The aliphatic derivatives (**1o**) and heteroaryl derivatives (**1p**) also reacted smoothly with 2-aminobenzimidazole (**2a**) to give the corresponding products in moderate yields. Notably, α-chlorocinnamaldehyde (**1q**) also reacted smoothly with 2-aminobenzimidazole (**2a**) to afford the target product in 18% yield. The scope of 2-aminobenzimidazole was further studied. The electron-withdrawing groups (F, CF_3) substituted 2-aminobenzimidazoles **2** can also obtain the target products in moderate yields (**3r**-**3s**). Surprisingly, the phenyl substituted *α*-bromocinnamaldehydes **1** can also smoothly reacted with 2-aminobenzimidazole **2a** and produced the target products in moderate yields (**3t**-**3u**).

Scheme 2 Substrate Scope [a]

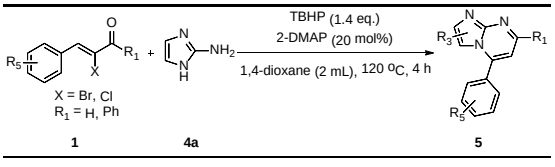


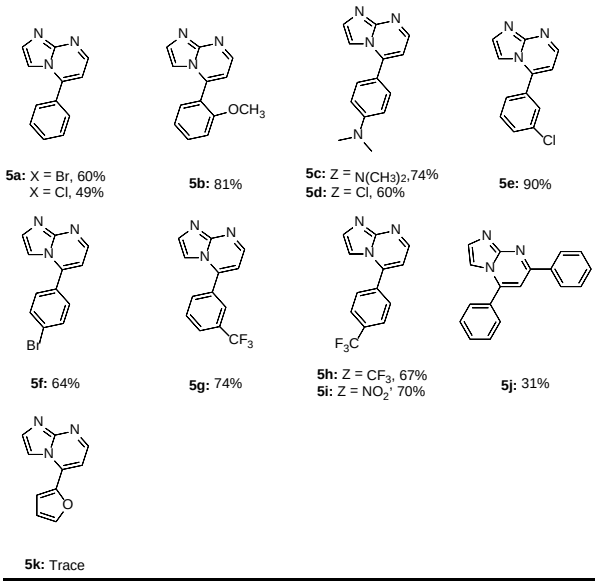


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), 2-DMAP (20 mol%), TBHP (1.4 eq.), 1,4-dioxane (2 mL), under air, 4 h.

Interestingly, the reaction of *α*-bromocinnamaldehydes (**1**) with 2-aminoimidazole (**4a**) was conducted to form a set of imidazo[1,2-*a*]pyrimidine derivatives (**5**) (Scheme 3). Under optimal conditions, a series of *α*-bromocinnamaldehydes with electron-withdrawing (Cl, Br, CF_3, NO_2) or electron-rich (MeO, $N(CH_3)_2$) groups attached to the phenyl ring were all fitting for this transformation, and the corresponding imidazo[1,2-*a*]pyrimidine compounds were generated in good yields (**5a**—**5i**). Satisfactory result was obtained for the phenyl substituted products **5j**. It is also regrettable that when the phenyl ring of reactant **1a** was replaced by a heteroaromatic ring, only a trace amount of product is detected.

Scheme 3 Substrate Scope [a]

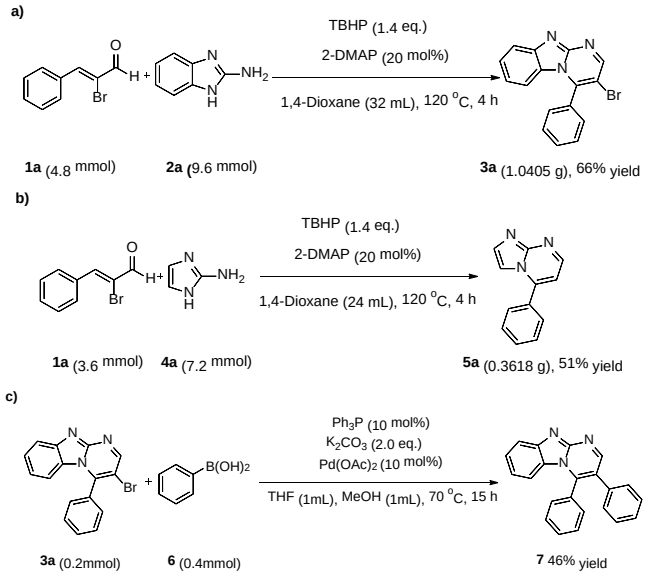




[a] Reaction conditions: **1** (0.3 mmol), **4a** (0.6 mmol), 2-DMAP (20 mol%), TBHP (1.4 eq.), 1,4-dioxane (2.0 mL), under air, 4 h.

In order to test the practicability of this method, we conducted gram scale reaction. Our catalytic reaction could also be performed on gram scale with the desired product **3a** in good yield (Scheme 4a). We also conducted a gram scale reaction of 5a in Scheme 4b. No significant reduction in yield was observed under gram-scale conditions. Due to the compatibility of bromine in the reaction, this leaves a modification site, so we then connected 3-bromo-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine **3a** and phenylboronic acid together through the Suzuki-Miyaura reaction, producing a new compound which has potential new bioactivity (Scheme 4c).

Scheme 4 Gram-Scale Reaction and Derivatization Reaction

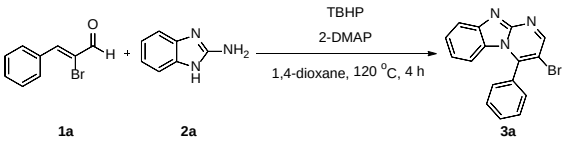


We conducted control experiments to gain a deeper

understanding of the reaction mechanism (Scheme 5). Under the action of radical inhibitors, the efficiency of the model reaction was not completely except with TEMPO, indicating that an ionic process maybe involved in this reaction (Scheme 5a). The radical scavengers TEMPO and BHT were engaged in this reaction, but the reactions were not significantly inhibited when 2.0 equiv of TEMPO or BHT was used. When 2.0 equiv of 1,4-benzoquinone was added to the reaction mixture, **3a** was detected in 23% yield (Scheme 5b). The outcome further suggested that this reaction was not a radical process. In order to test the electronic effect of **1** on the reaction, we conducted a competition experiment and found that the electron-donating group was beneficial to the reaction (Scheme 5c).[15]

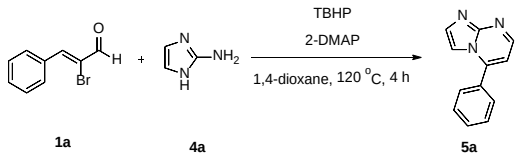
Scheme 5 Mechanistic Studies

a) Radical trapping experiments



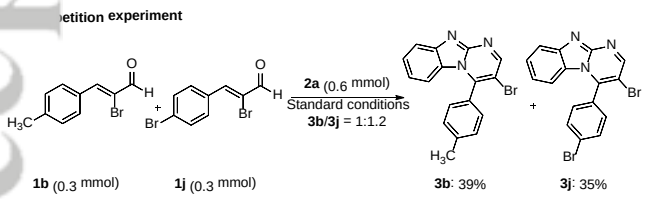
Entry	Radical scavengers (eq.)	Yield of **3a** (%)
1	TEMPO (2.0)	Trace
2	BHT (2.0)	58%
3	1,1-diphenylethylene (2.0)	64%

b) Radical trapping experiments

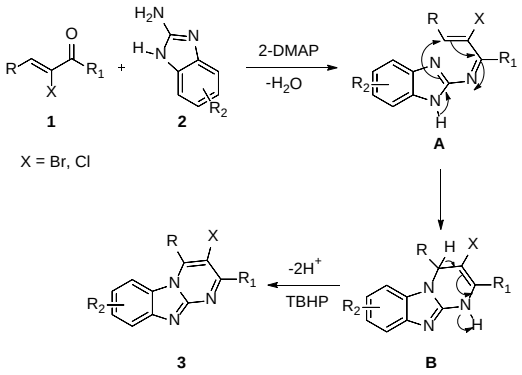


Entry	Radical scavengers (eq.)	Yield of **5a** (%)
1	TEMPO (2.0)	56%
2	BHT (2.0)	58%
3	1,4-benzoquinone (2.0)	23%

c) Competition experiment



Scheme 6 A proposed mechanism



According to the results of control experiments and literature report, a plausible reaction mechanism was proposed in Scheme 6.[16,17] First of all, the imine intermediate **A** is formed by the condensation of **1** and **2** in the presence of 2-DMAP which is converted into intermediate **B** through a rapid intramolecular cyclization reaction. Finally, the corresponding product pyrimido[1,2-*a*]benzimidazole **3** is conveniently obtained by aromatization to emit a molecule of H_2O in the presence of TBHP (Scheme 6).

Conclusions

In conclusion, we described a mild and environmentally friendly reaction system for the synthesis of pyrimido[1,2-*a*]benzimidazole or imidazo[1,2-*a*]pyrimidine derivatives through the DMAP-catalyzed condensation of *α*-bromocinnamaldehyde compounds with 2-aminobenzimidazole or 2-aminoimidazole compounds. The process constructed two new C-N bonds. It was an useful supplement to enrich and develop the synthetic methods of pyrimido[1,2-*a*]benzimidazole and imidazo[1,2-*a*]pyrimidine compounds.

Experimental

Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz NMR spectrometer using $CDCl_3$ as solvent and TMS as an internal standard.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

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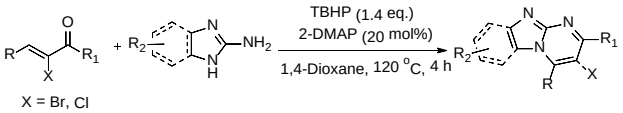
DMAP-Catalyzed C–N Bond Formation for the Diverse Synthesis of Imidazo[1,2-*a*]pyrimidine and Pyrimido[1,2-*a*]benzimidazole Derivatives



A DMAP-catalyzed condensation reactions for the successful direct construction of pyrimido[1,2-*a*]benzimidazole or imidazo[1,2-*a*]pyrimidine has been developed. The current method features wide substrate scope, product diversification, and metal-free conditions.

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