Article

One-Pot Regioselective Synthesis of Benzo[4,5]imidazo[1,2-a]quinazoline Derivatives via Facile Transition Metal-Free Tandem Process

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One-pot Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinazoline Derivatives *via* Facile Transition Metal-free Tandem Process

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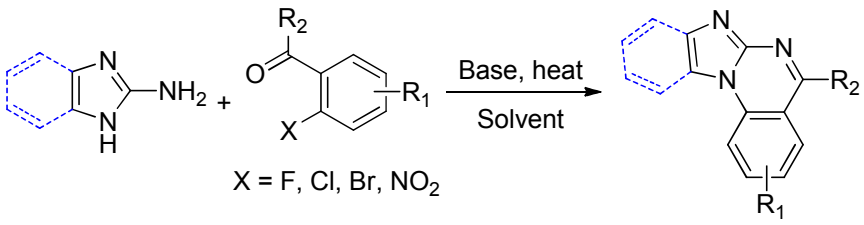
KEYWORDS

One-pot synthesis, transition metal-free, benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives，fluorescence property.

ABSTRACT

A one-pot transition metal-free method for synthesizing benzo[4,5]imidazo[1,2-*a*]quinazoline and imidazo[1,2-*a*]quinazoline derivatives has been developed. The approach is widely

applicable to 2-fluoro-, 2-chloro-, 2-bromo- and 2-nitro-substituted aryl aldehyde and ketone substrates. The fluorescence properties of target compounds were studied.



INTRODUCTION

Heterocyclic compounds containing nitrogen-atoms have been broadly applied in pharmaceuticals, and designing novel heterocyclic motifs has become an increasingly urgent mission for chemists.[1] Recently, attention has been paid to benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives due to their biological activities (Fig. 1). For instance, compound **A** exhibits anti-inflammatory activity against TNF-α and IL-6,[2] compound **B** has anticancer activity,[3] compound **C (T808)** can work as a specific PET tracer for imaging of Tau Pathologies,[4] and compound **D** shows anticancer and analgesic/anti-inflammatory activities.[5] Moreover, benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives also behave as antimicrobial agents.[6] In addition, imidazo[1,2-*a*]quinazoline also has some effective biological activities. Compound **E** is the inhibitor of apoptosis,[7] and it acts as potent farnesyl protein transferase inhibitor (Fig. 2).[8]

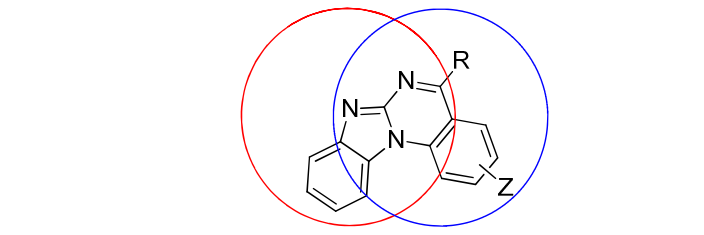


Figure 1. The structure of benzo[4,5]imidazo[1,2-*a*]quinazoline

We expect that benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives, the combined skeleton of benzo[4,5]imidazo[1,2-*a*]pyrimidine and imidazo[1,2-*a*]quinazoline (Fig. 1), might exert certain biological activities. Therefore, it is meaningful to explore a variety of benzo[4,5]imidazo[1,2-*a*]quinazoline scaffolds.

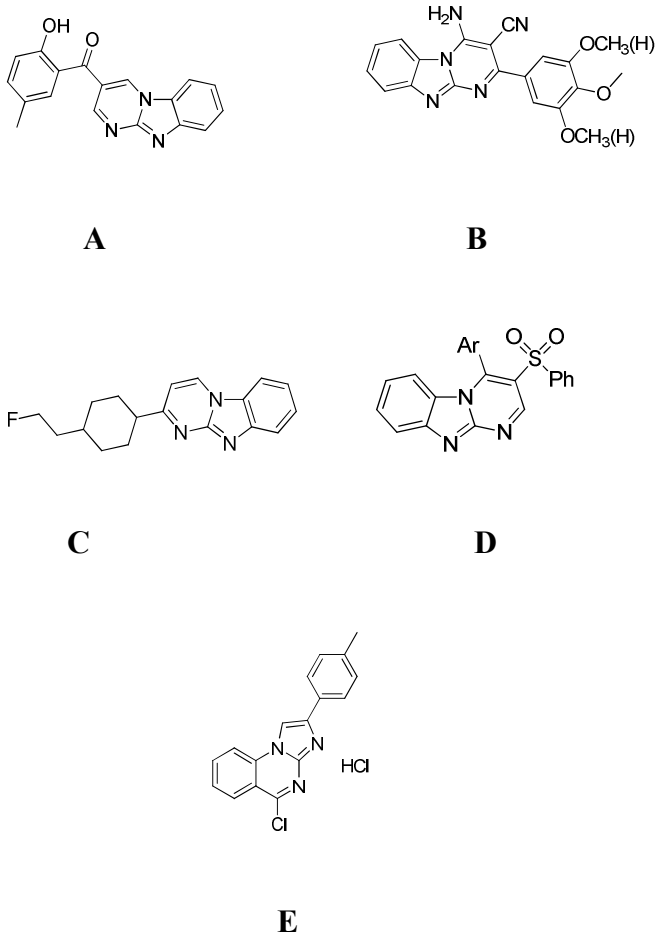


Figure 2. Some biologically important compounds.

The traditional way to obtain benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives generally requires a multi-step synthesis and harsh conditions. Marini and co-workers utilized 1*H*-benzo[*d*]imidazol-2-amine and 2-bromobenzoic acid as reactants. Ultimately, target compounds

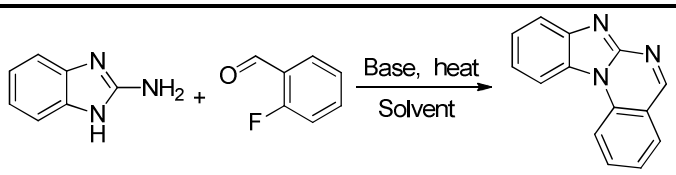
were obtained through a three-step process *via* Ullman reaction.[9] Pozharskii used 1,8-bis(dimethylamino)-2-naphthaldehyde and 2-aminobenzimidazole as the starting material to gain the desirable compounds, but yields were less than satisfactory.[10]

Notably, the previous literature methods to obtain these heterocyclic compounds were rare, and were not adequate in meeting the demands to research structure-activity relationships. Coincidentally, we engaged in constructing these heterocyclic scaffolds[11] and created a novel and efficient one-pot approach to assemble benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives through an addition-elimination/S_NAr process. 1*H*-Benzo[*d*]imidazol-2-amine and 2-fluoro-, 2-chloro-, 2-bromo- and 2-nitro-substituted aryl aldehydes and ketones were used as substrates in this process.

RESULTS AND DISCUSSION

Initially, we optimized the reaction conditions with 1*H*-benzo[*d*]imidazol-2-amine **1** and 2-fluorobenzaldehyde **2a**. As shown in Table 1, K_2CO_3 in DMF provided the best condition for this transformation (entry 6). Reaction temperature played a key role in the reaction, with the yield being excellent at 135 °C. Moreover, Cs_2CO_3 was equally efficient as K_2CO_3 (entry 1) and a stronger base like NaOH did not favor the reaction (entry 5). In entry 7, the effect of 4Å molecular sieves was inconspicuous in this reaction system. Solvents were screened as well: NMP and DMSO generated moderate yields, but the reaction in 1,4-dioxane failed to form the product (entries 10-12).

Table 1. Optimization of reaction conditions[a]



1 **2a** **3a**

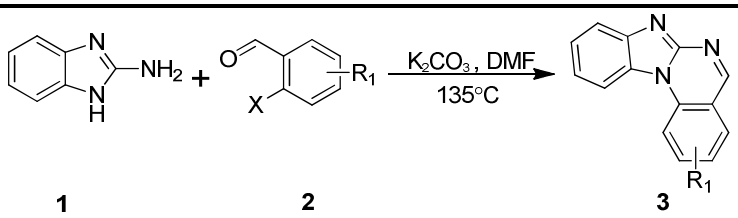
Entry	Solvent	Base	T/°C	Time/h	Yield/%[b]
1	DMF	Cs_2CO_3	120	2	75
2	DMF	NaOH	120	2	79
3	DMF	K_2CO_3	120	2	76
4	DMF	Cs_2CO_3	135	2	93
5	DMF	NaOH	135	2	58
6	**DMF**	**K_2CO_3**	**135**	**2**	**97**
7	DMF	K_2CO_3	135	2	93[c]
8	DMF	K_2CO_3	135	1	55
9	DMF	Cs_2CO_3	135	1	76
10	NMP	Cs_2CO_3	135	2	86
11	Dioxane	K_2CO_3	110	2	Trace
12	DMSO	Cs_2CO_3	135	2	68

[a]Reaction conditions: 2-aminobenzimidazole **1a** (1.0 equiv) ,2-fluorobenzaldehyde **2a** (1.2 equiv) and base (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction with 4Å molecular series.

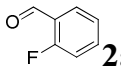
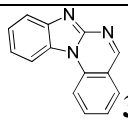
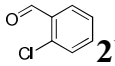
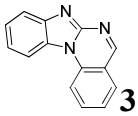
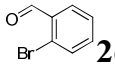
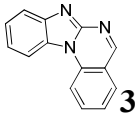
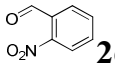
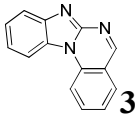
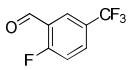
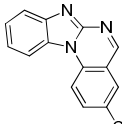
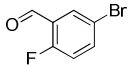
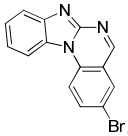
To verify the generality of this reaction, a variety of electron deficient 2-halo- and 2-nitro-substituted aryl aldehydes were tested and found to work efficiently (Table 2, entries 1-4). Particularly, 2-bromobenzaldehyde derivatives coupled efficiently in the absence of a transition metal (entry 3).[12] Interestingly, an excellent yield resulted from the reaction of 1*H*-benzo[*d*]imidazol-amine **1** and 2-nitrobenzaldehyde **2d** (entry 4). The nitro group has rarely been

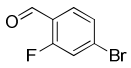
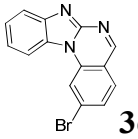
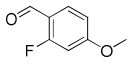
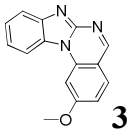
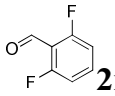
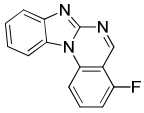
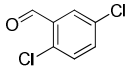
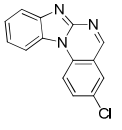
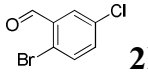
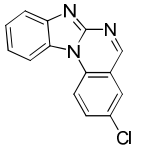
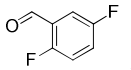
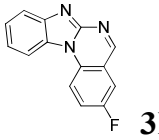
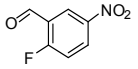
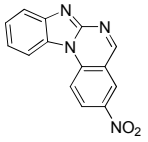
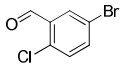
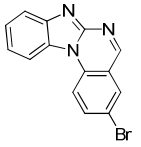
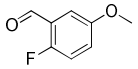
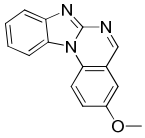
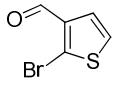
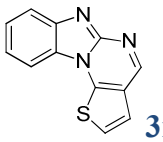
utilized as a leaving group.[13] The yield from compounds with an electron-donating group was better than those with an electron-withdrawing group (for example, entries 7 and 8). Except for 2-fluoro-5-nitrobenzaldehyde **2m** (entry 13), all the compounds afforded excellent yields.

Table 2. Reaction of 1*H*-benzo[*d*]imidazol-2-amine with 2-substituted aryl aldehydes[a]



1 **2** **3**

Entry	Substrate	Product	Yield/%[b]
1	 **2a**	 **3a**	97
2	 **2b**	 **3a**	63[c]
3	 **2c**	 **3a**	70[c]
4	 **2d**	 **3a**	90
5	 **2e**	 **3b**	68
6	 **2f**	 **3c**	71

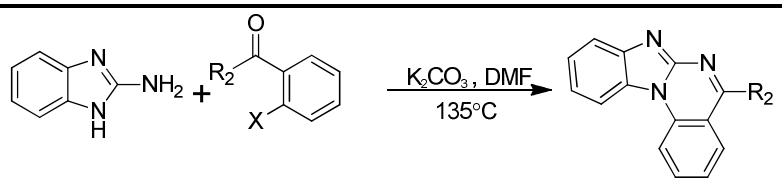
7	 **2g**	 **3d**	76
8	 **2h**	 **3e**	91
9	 **2i**	 **3f**	92
10	 **2j**	 **3g**	63[c]
11	 **2k**	 **3g**	59[c]
12	 **2l**	 **3h**	80
13	 **2m**	 **3i**	Trace
14	 **2n**	 **3c**	65[c]
15	 **2o**	 **3j**	96
16	 **3t**	 **3n**	Trace

[a]Reaction conditions: 2-aminobenzimidazole **1** (1.0 equiv) , **2** (1.2 equiv) and K_2CO_3 (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF,

145 °C, 2h.

To extend the reaction scope, aryl ketone derivatives were tested (Table 3). Although the reaction between aryl ketone derivatives and arylamines generally demand harsh conditions, [14] reactions worked well for both alkyl aryl ketones (entries 1–4) and diaryl ketones (entry 4). Steric hindrance had no effect on the yield (entry 4).

Table 3. Reaction of 1*H*-benzo[*d*]imidazol-2-amine with 2- substituted aryl ketones[a]



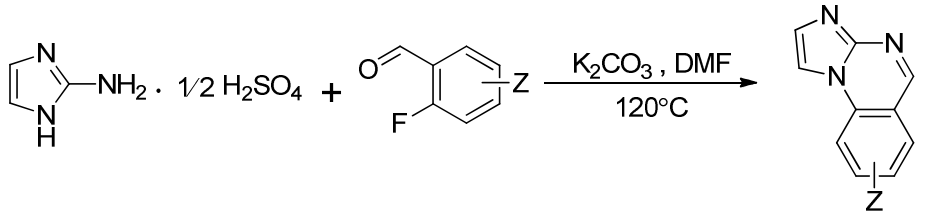
1 **2** **3**

Entry	Substrate	Product	Yield/%[b]
1	**2p**	**3k**	84
2	**2q**	**3k**	56[c]
3	**2r**	**3l**	78
4	**2s**	**3m**	78

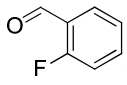
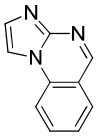
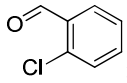
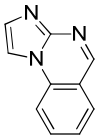
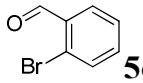
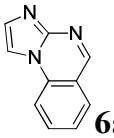
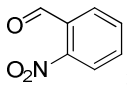
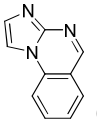
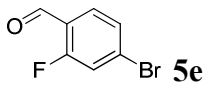
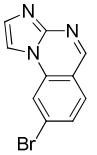
[a]Reaction conditions: 2-aminobenzimidazole **1** (1.0 equiv) , **2** (1.2 equiv) and K_2CO_3 (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF, 145 °C, 2h.

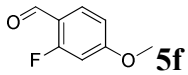
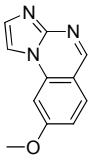
The reaction between 2-aminoimidazole sulfate and 2-substituted aryl aldehydes was also explored and target products were obtained with moderate yields (Table 4). As previously noted, 2-fluorobenzaldehyde with an electron-donating group achieved a better yield than that with an electron-withdrawing group (entries 5 and 6). Overall, 2-aminoimidazole sulfate **5** (Table 4) was not as efficient as 1*H*-benzo[*d*]imidazol-amine **1** (Table 2 and 3).

Table 4. Reaction of 2-aminoimidazole sulfate with 2-substituted aryl aldehydes[a]



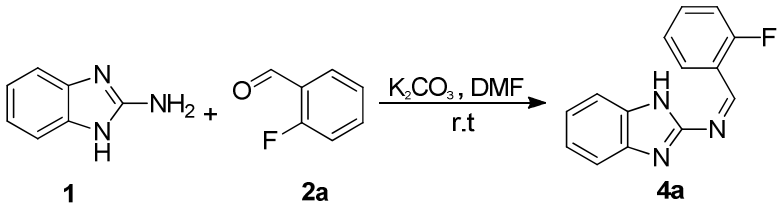
5 2 6

Entry	Substrate	Product	Yield/%[b]
1	 **5a**	 **6a**	70
2	 **5b**	 **6a**	45[c]
3	 **5c**	 **6a**	52[c]
4	 **5d**	 **6a**	69
5	 **5e**	 **6b**	60

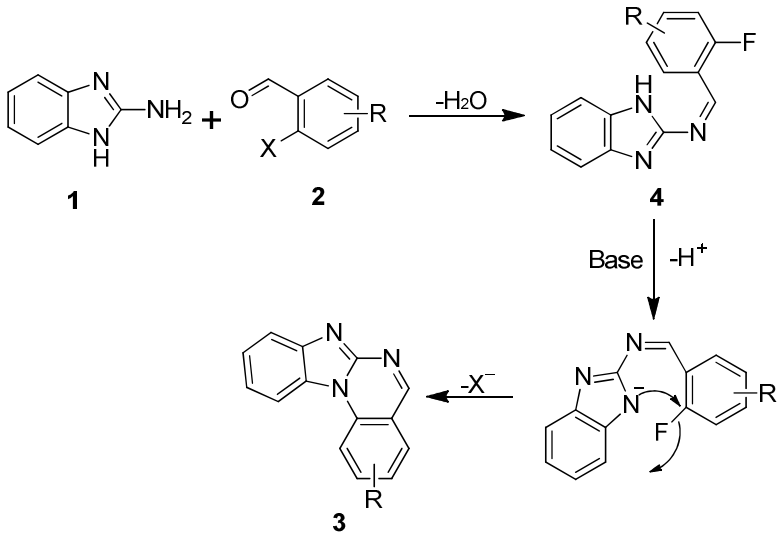
6	 **5f**	 **6c**		67

[a]Reaction conditions: 2-aminoimidazole sulfate **5** (1.0 equiv) , **2** (1.2 equiv) and K_2CO_3 (4.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF, 135 °C, 2h.

To exam the mechanism of these cascade reactions, 1*H*-benzo[*d*]imidazol-2-amine **1** and 2-fluorobenzaldehyde **2a** were reacted as substrates under optimized condition but at room temperature (Scheme 1). Not surprisingly, intermediate **4a** was detected by High Resolution Mass Spectrum (HRMS) after 30min. Indeed, Schiff base was produced in the first step of this cascade process. From this intermediate, a plausible mechanism is proposed (Scheme 2), wherein intramolecular nucleophilic aromatic substitution reaction (S_NAr) delivers **3**.

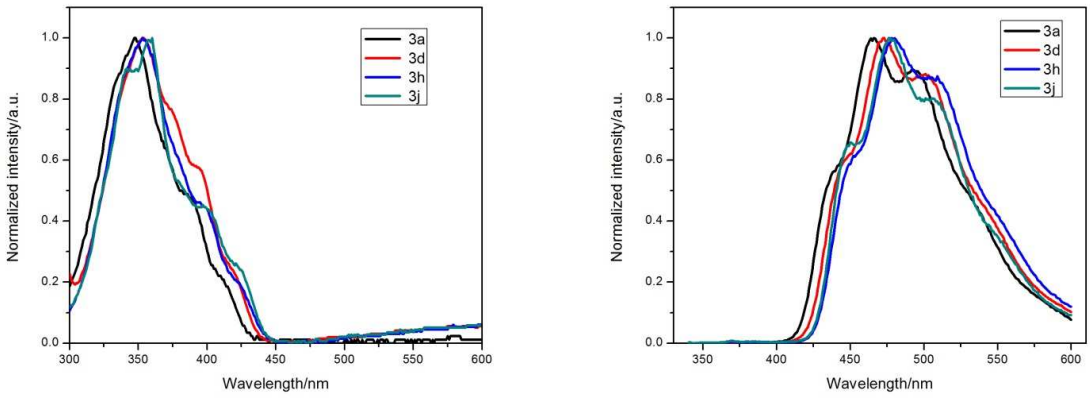


Scheme 1. Reaction of 1*H*-benzo[*d*]imidazol-2-amine and 2-fluorobenzaldehyde

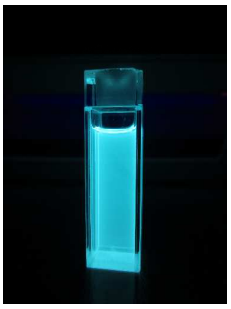


Scheme 2. Plausible mechanism

The UV/vis absorption and emission spectra of **3a**, **3d**, **3h** and **3j** in highly dilute solution were collected (Figure 3). The longest absorption of these products was at 350 nm and the longest emission was at 475 nm. Solution luminescence of **3a** upon irradiation at 365 nm was displayed. The fluorescence efficiency of **3d** is 0.95 in DCM, compared to the quinine sulfate dehydrate.



a b



c

Figure 3. (a) Absorption spectra of **3a**, **3d**, **3h** and **3j** in DCM. (b) Fluorescence spectra of **3a**, **3d**, **3h** and **3j** in DCM. (c) Solution luminescence of **3a** in DCM (upon irradiation at 365 nm).

CONCLUSION

We have developed an efficient method to synthesize a variety of benzo[4,5]imidazo[1,2-*a*]quinazoline and imidazo[1,2-*a*]quinazoline derivatives *via* a transition metal-free cascade process. A wide range of 2-fluoro-, 2-chloro-, 2-bromo- and 2-nitro-substituted aryl aldehyde and ketone substrates performed well in this process. In addition, we tested the fluorescence properties of these compounds. Further pharmaceuticals and materials studies are in process.

EXPERIMENTAL

General experimental procedure for **3a**

A mixture of 1*H*-benzo[*d*]imidazol-2-amine **1** (1.0 mmol), 2-fluorobenzaldehyde **2a**（1.2 mmol） and K_2CO_3 (3 mmol) in DMF (5 mL) was stirred at 135 °C under a nitrogen atmosphere. TLC was employed to monitor the end of the reaction. After the mixture was cooled, water was added. The solution was extracted with ethyl acetate (20 ml × 3). The combined organic phase

was dried with $MgSO_4$ and the solvent was removed in *vacuo* to obtain the residue. The residue was purified by column chromatography on silica gel to afford **3a**.

ASSOCIATED CONTENT

Acknowledgment

We are grateful to the National Science Foundation of China (No. 21172131) and State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (No. GTZK201405) for financial support of this research.

Supporting Information

Representative experimental procedures, copies of HRMS, ^{1}H NMR and ^{13}C NMR spectra of all compounds. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Funding

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The authors declare no competing financial interest.

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One-pot Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinazoline Derivatives *via* Facile Transition Metal-free Tandem Process

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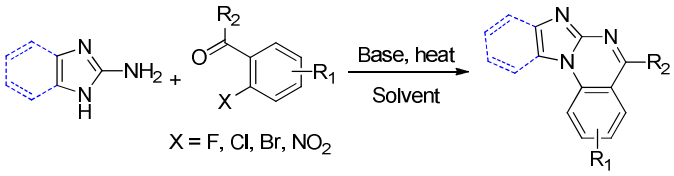

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