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Iodine-mediated direct synthesis of multifunctional 2-aminobenzimidazoles from *N*-substituted *o*-diaminoarenes and isothiocyanates

Zhen Wang [a], Qiongli Zhao [b, c], Jiao Hou [a], Wenquan Yu [a, *], Junbiao Chang [a, b, **]

[a] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province, 450001, China
[b] Collaborative Innovation Center of New Drug Research and Safety Evaluation, Henan Province, Zhengzhou University, Zhengzhou, Henan Province, 450001, China
[c] School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, Henan Province, 450001, China

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ABSTRACT

Multifunctional 2-aminobenzimidazoles were directly synthesized through sequential addition of *N*-substituted *o*-diaminoarenes to isothiocyanates, formation of carbodiimides via I_2-mediated oxidative desulfurization, and intramolecular cycloaddition. This efficient and eco-friendly synthetic process provides a facile access to diverse 2-aminobenzimidazole derivatives from readily accessible substrates under mild reaction conditions in a scalable fashion.

1. Introduction

Benzimidazole has been recognized as a privileged structure in medicinal chemistry and drug discovery.[1] Among its various derivatives, the 2-aminobenzimidazole unit is distributed widely in compounds with diverse pharmaceutical properties, including kinase inhibitory,[2] anticancer,[3] antibacterial,[4] anti-angiogenic,[5] and anti-inflammatory activities.[6] Consequently, a variety of synthetic pathways have been reported for 2-aminobenzimidazole synthesis.[7] In particular, the annulation reactions of *o*-diaminoarenes and isothiocyanates have drawn considerable attentions owing to the readily accessibility and structural diversity of both substrates. Such transformations have been previously accomplished using reagents, such as methyl iodide,[8] HgO,[9] PS-carbodiimide,[10] $PhI(OAc)_2$,[11] EDPBT,[12] BOP reagent,[13] $La[N(SiMe_3)_2]_3$,[14] and Ph_3P/I_2 under ultrasonic conditions.[15] However, the existing synthetic methods utilize *N*-unsubstituted *o*-diaminoarenes as substrates. To the best of our knowledge, few attempts have been made for direct access to 2-aminobenzimidazole derivatives from *N*-substituted substrates.

Molecular iodine, an inexpensive and low-toxic reagent, plays an important role in oxidative C–X (X = C, N, O, or S) bond formation to synthesize heterocyclic compounds.[16] In particular, this mild and versatile oxidant has been successfully employed in the construction of amino-containing heterocyclic skeletons, such as indoles,[17] benzoxazoles,[18] imidazo[1,2-*a*]pyridines,[19] 1,3,4-oxadiazoles/thiadiazoles,[20] and 1,2,4-thiadiazoles.[21] Inspired by these advances, herein we describe an I_2-mediated sequential approach for facile synthesis of multifunctional 2-aminobenzimidazoles from *N*-substituted *o*-diaminoarenes and isothiocyanates under transition-metal free conditions.

2. Results and discussion

We initiated this study by investigating the annulation reaction of *N*-tosyl-1,2-phenylenediamine (**2a**) and phenyl isothiocyanate (**3a**). Base-promoted addition of substrate **2a** to isothiocyanate **3a**

* Corresponding author. College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province, 450001, China.
** Corresponding author. College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province, 450001, China.
E-mail addresses: wenquan_yu@zzu.edu.cn (W. Yu), changjunbiao@zzu.edu.cn (J. Chang).

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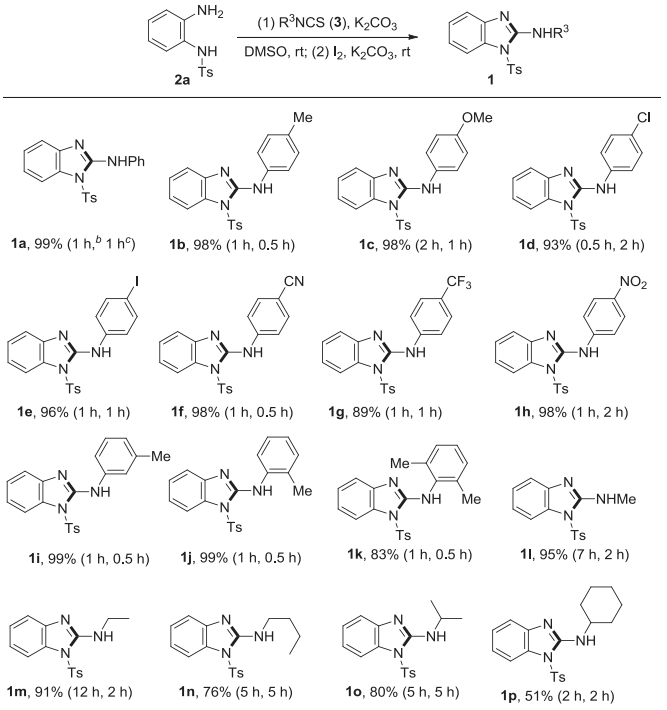
gave a thiourea intermediate **4a**. Further treatment of this thiourea with iodine in the presence of base resulted in the expected 2-aminobenzimidazole product **1a** (Table 1). Solvent screening (entries 1–8) indicated that the first step addition proceeds faster in DMF and DMSO. The subsequent I_2-mediated oxidative cyclization can finish within 1 h in most solvents, of which DMSO is the most effective media for the formation of **1a** (entry 6). Under these optimal reaction conditions, this synthetic process was conveniently conducted in gram scale. Further replacement of K_2CO_3 with a weaker inorganic base (entry 9) or organic bases (entries 10–13) affected both the reaction rate and the yield of the product. For the first-step addition, at least 1 equiv of K_2CO_3 is required; on the other hand extra base will slightly decrease the yield of **1a**.[22] Thus, under the optimal reaction conditions, the first-step reaction was performed in the presence of 1 equiv of K_2CO_3 and the second portion of base (1.2 equiv) was added in the second step (entry 6).

Then, a range of aryl isothiocyanates **3** were subjected to the above optimal reaction conditions to probe the scope and generality of this synthetic approach. All these substrates were smoothly converted into the corresponding 2-aminobenzimidazoles (**1a**–**k**) (Scheme 1) through the addition reaction with **2a** followed by I_2-mediated oxidative cyclization. The present methodology is compatible with phenyl isothiocyanates bearing both electron-donating and electron-withdrawing groups (EDGs and EWGs) at the *para*-, *meta*-, and *ortho*-positions. Replacement of aryl isothiocyanates with aliphatic ones afforded a series of *N*-alkyl products (**1l**–**p**), which require longer reaction times in both steps. *o*-Diaminoarene substrates with various *N*-protecting groups (**1q**–**x**) were all successfully transformed into the corresponding 2-aminobenzimidazoles under the above annulation conditions (Scheme 2). For the reaction with unsubstituted *o*-diaminobenzene (**1y**–**aa**), the presence of EWG in phenyl isothiocyanate substrate favored the formation of the desired product (**1aa**).

A tentative reaction mechanism is proposed for this 2-aminobenzimidazole synthesis (Scheme 3). With the formation of the product **1a** as an example, firstly, addition of *o*-phenylenediamine **2a** to isothiocyanates **3a** generates a thiourea intermediate **4a**. Then I_2-mediated oxidative desulfurization of thiourea **4a** under basic conditions results in a carbodiimide[23] **B**. Subsequently,



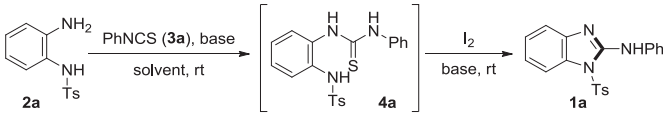
Scheme 1. Scope of Isothiocyanates[a].

intramolecular cycloaddition of compound **B** followed by the proton translocation afford the 2-aminobenzimidazole framework **1a**. Intermediate **4a** can be isolated in nearly quantitative yield after completeness of the first-step addition, and then successfully converted into product **1a** under the standard desulfurative cyclization conditions (Scheme 4).

3. Conclusion

In summary, we have developed a practical and transition-metal free protocol for 2-aminobenzimidazole synthesis. Under mild

Table 1
Reaction conditions optimization for the synthesis of 2-Aminobenzimidazole **1a**[a].



entry	solvent	base	time (h)	yield[b]
1	MeCN	K_2CO_3	24 h,[c] 1 h[d]	76%
2	1,4-dioxane	K_2CO_3	24 h, 1 h	80%
3	CH_2Cl_2	K_2CO_3	24 h, 1 h	62%
4	DCE	K_2CO_3	24 h, 1 h	66%
5	DMF	K_2CO_3	1 h, 1 h	91%
6	**DMSO**	**K_2CO_3**	**1 h, 1 h**	**99% (94%[e])**
7	MeOH	K_2CO_3	24 h, 1 h	86%
8	EtOH	K_2CO_3	24 h, 1 h	82%
9	DMSO	$NaHCO_3$	1 h, 3 h	77%
10	DMSO	NEt_3	5 h, 5 h	82%
11	DMSO	pyridine	5 h, 3 h	79%
12	DMSO	imidazole	5 h, 12 h	85%
13	DMSO	NMI	5 h, 12 h	87%

[a] Reaction conditions: (1) **2a** (0.5 mmol), **3a** (0.55 mmol), base (0.5 mmol), DMSO (5 mL), rt; (2) base (0.6 mmol), I_2 (0.5 mmol), rt.
[b] Isolated yields are given.
[c] Time for the first step.
[d] Time for the second step.
[e] Yield of gram-scale reaction in parentheses.