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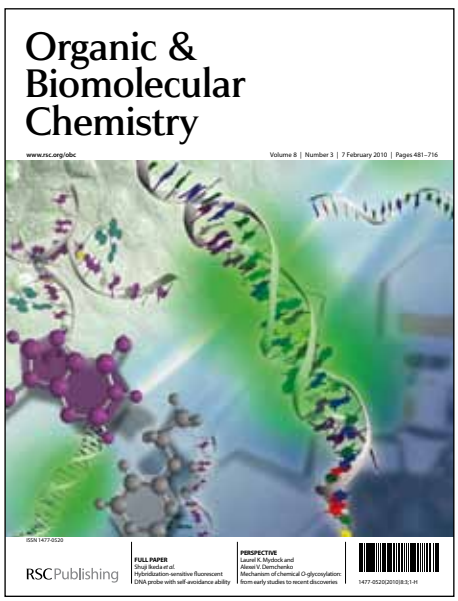

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ARTICLE TYPE

Synthesis of benzimidazoles by potassium *tert*-butoxide-promoted intermolecular cyclization reaction of 2-iodoanilines with nitriles

Shi-Kai Xiang,* Wen Tan, Dong-Xue Zhang, Xian-Li Tian, Chun Feng, Bi-Qin Wang,* Ke-Qing Zhao, Ping Hu and Hua Yang

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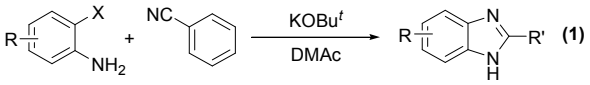
Synthesis of benzimidazoles by intermolecular cyclization reaction of 2-iodoanilines with nitriles has been developed. These reactions proceeded without the aid of any transition metals, ligands, and just using KOBu^t as the base. A variety of substituted benzimidazole derivatives can be synthesized by the approach.

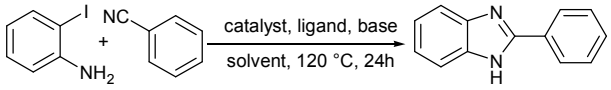
The benzimidazole scaffold is a crucial structural motif for the development of bioactive compounds in the pharmaceutical industry. Benzimidazole derivatives are widely found in commercial drugs and experimental drug candidates.[1] Therefore, it is not surprising that the efficient construction of benzimidazole core becomes one of the most exciting topics for organic and medicinal chemists.[2-5] Traditionally, benzimidazoles were prepared from the reaction of 1,2-diaminoarenes with carboxylic acids under harsh dehydrating conditions or aldehydes under oxidative conditions.[2] However, this procedure sometimes required multi-step reactions to prepare substituted 1,2-diaminoarenes, resulting in compromised yields. In the past few years, transition-metal-catalyzed syntheses of benzimidazoles through intramolecular amination have also been developed. Most of these methods required the presence of a metal catalyst in combination with a suitable ligand.[3]

Recently, transition metal-free processes for the formation of C-C, C-N, C-O, and C-S bonds aroused great interest of organic chemists.[4] In 2010, KOH/DMSO mediated cross-coupling reactions between aryl halides with various sulfur-, oxygen- and nitrogen-based nucleophiles under transition metal-free conditions were reported firstly by Yuan and Bolm.[4a] Next, related further study was made by Ramón,[4b] Wang[4c] and so on. Moreover, other base promoted intermolecular coupling reactions were developed by Bolm,[4d] Diness and Fairlie,[4e] Valdés,[4f] Olofsson,[4g] Majumdar[4h] and so on. In particular, base promoted intramolecular coupling showed great potential for synthesis of heterocyclic compounds. Chromone derivatives,[5a] benzimidazol-2-ones,[5b] *N*-substituted phenoxazines,[5c] oxindoles,[5d] and indazoles[5e] were synthesized by Fu and Bolm groups respectively using these effective approaches. In addition, KOH/DMSO mediated synthesis of benzoimidazole derivatives by intermolecular cyclization reaction of 2-iodoanilines with amides was reported in Ramón's work.[4b] However, only three examples were provided in their work, and a long reaction time (5 days) was required to improve the yields. Herein, we developed a potassium *tert*-butoxide-promoted intermolecular cyclization reaction of 2-iodoanilines with nitriles, and a variety of substituted benzimidazoles derivatives can be synthesized by the approach (eqn. 1).



Initially, the reaction of 2-iodoaniline **1a** with benzonitrile **2a** was carried out using CuI as the catalyst and DMEDA (*N*,*N*′- dimethyl-1,2-ethanediamine) as the ligand (Table 1). Different bases were screened to indicate that KOBu^t was the best base affording the desired product **3a** in 60% yield (entries 1-4, Table 1). Encouraged by recent transition metal-free processes, we tried to conduct the reaction in the absence of catalysts and ligands. As a result, **3a** was obtained in 56% yield (entry 5, Table 1). The screening of solvents showed that the reaction in DMAc (*N*,*N*-dimethylacetamide)

Table 1. The cyclization reaction of 2-iodoaniline **1a** with benzonitrile **2a** under different conditions.[a]



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

entry	CuI / DMEDA (mmol%)	base (3.0 equiv.)	solvent	yield (%)
1	10 / 15	K_2CO_3	DMF	ND
2	10 / 15	Cs_2CO_3	DMF	ND
3	10 / 15	NaH	DMF	27
4	10 / 15	KOBu^t	DMF	60
5	none	KOBu^t	DMF	56
6	**none**	**KOBu^t**	**DMAc**	**93**
7	none	KOBu^t	DMSO	54
8	none	KOBu^t	DMAc	83
9	none	KOH	DMAc	31

[a] Reaction Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst, ligand, base, solvent, 120 °C, 24 h, under Ar. The yields were isolated yields.

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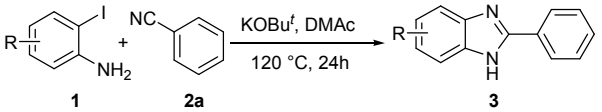
performed the best efficiency and gave the best yield of 93% (entries 5-7, Table 1). Although other bases such as $NaOBu^t$ and KOH can also promote this reaction to generate the desired product, their efficiency was lower than $KOBu^t$ (entries 6, 8-9, Table 1).

Table 2. The cyclization reactions of substituted 2-iodoanilines **1** with benzonitrile **2a**.[a]



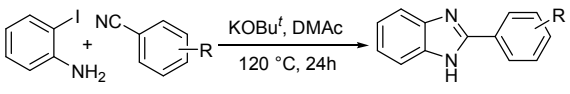
1 **2a** **3**

entry	1	3	yield (%)
1	**1a**	**3a**	93
2	**1b**	**3b**	80
3	**1c**	**3b**	91
4[b]	**1d**	**3c**	82
5	**1e**	**3c**	62
6[c]	**1f**	**3d**	84
7	**1g**	**3d**	68
8[c]	**1h**	**3e**	75
9[b]	**1i**	**3f**	41
10	**1j**	**3a**	47

[a] Reaction Conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $KOBu^t$ (0.9 mmol), DMAc (1.0 mL), 120 °C, 24 h, under Ar. The yields were isolated yields. [b] The reaction was carried out at 80 °C. [c] The reaction was carried out at 100 °C.

The scope of the cyclization reaction of 2-iodoanilines with nitriles was expanded to a variety of substituted 2-iodoanilines **1**. 2-Iodoanilines **1** with both electron-donating groups and electron-withdrawing groups smoothly underwent the transformation generating the desired products **3** in moderate to excellent yields (41-93%, Table 2). 2-Iodoanilines with a methyl substituent at the 4- or 5-positions (**1b**, **1c**) gave the corresponding products with good yields of 80%, 91% respectively (entries 2-3, Table 2). Substituted 2-iodoanilines with Cl, Br, I or F at the 4- or 5-positions (**1d-1i**) smoothly led to the corresponding benzimidazoles derivatives with the halogen substitute intact which could be further transformed into other functionalities (entries 4-9, Table 2). It is notable that the functional group I at the 4-position was tolerant although the functional group I at the 2-position was involved in the reaction (entry 8, Table 2). The substrate **1i** with functional group F at the 4-position gave the corresponding product in lower yield of 41% (entry 9, Table 2). In addition, 2-bromoaniline **1j** could also be converted into the corresponding product in spite of lower efficiency than 2-iodoaniline **1a** (entry 10, Table 2).

Table 3. The cyclization reactions of 2-iodoaniline **1a** with different nitriles **2**.[a]



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

entry	2	3	yield (%)
1	**2a**	**3a**	93
2	**2b**	**3g**	35
3	**2c**	**3h**	84
4	**2d**	**3i**	92
5[b]	**2e**	**3j**	91
6	**2f**	**3k**	60
7	**2g**	**3l**	57
8[b]	**2h**	**3m**	61
9[c]	**2i**	**3n**	62
10[c]	**2j**	**3o**	76

[a] Reaction Conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $KOBu^t$ (0.9 mmol), DMAc (1.0 mL), 120 °C, 24 h, under Ar. The yields were isolated yields. [b] The reaction was carried out at 80 °C. [c] The reaction was carried out at 100 °C.

To investigate the scope of the nitriles in this transformation, 2-iodoaniline **1a** was selected as the partner to react with different aromatic nitriles. The results in Table 3 show that a variety of aromatic nitriles can undergo this transformation to generate the desired products **3** in moderate

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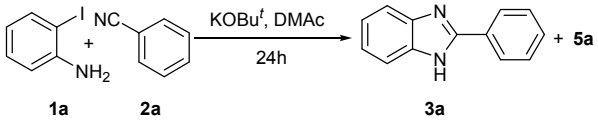
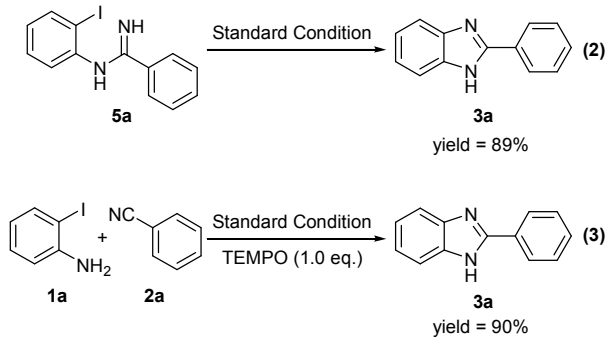
to excellent yields (35-93%). Benzonitriles with both electron-donating groups and electron-withdrawing groups smoothly underwent the transformation generating the corresponding benzimidazoles derivatives (entries 2-8, Table 3). Benzonitrile with a methyl substituent at the ortho-position gave the corresponding products in a lower yield than at the meta- or para-position, which indicated that the reaction wound be powerfully affected by steric effects (entries 2-4, Table 3). 4-Methoxybenzonitrile **2e** underwent this transformation to generate the desired product **3j** in an excellent yield of 93% (entry 5, Table 3). Substituted benzonitrile with Cl, I or F smoothly led to the corresponding benzimidazoles with the halogen substitutes compatible under these reaction conditions (entries 6-8, Table 3). The heterocyclic aromatic nitriles **2i**, **2j** also sucsessfully underwent the reaction to get the desired products **3n**, **3o** in yields of 61%, 76% respectively (entry 9-10, Table 3).

Table 4. The cyclization reaction of 2-iodoaniline **1a** with benzonitrile **2a** at different temperatures.[a]



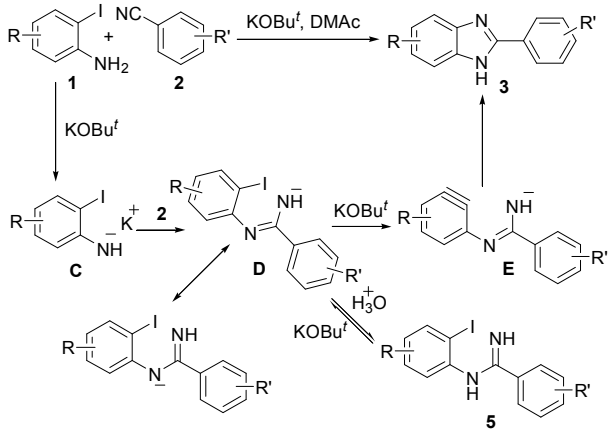
entry	T (°C)	yield of **3a** (%)	yield of **5a** (%)
1	20	0	90
2	60	27	65
3	120	93	0

[a] Reaction Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), KOBu^t (0.9 mmol), DMAc (1.0 mL), 24 h, under Ar. The yields were isolated yields.



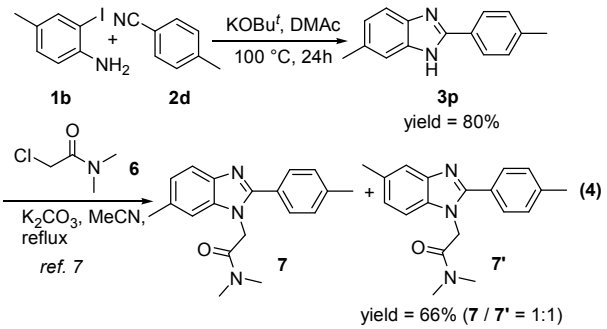
Some control experiments were carried out to understand the mechanism of the cyclization reaction (Table 4, eqns. 2 and 3). The reaction of 2-iodoaniline **1a** with benzonitrile **2a** were carried out at different temperatures according to the standard condition (Table 4). It is notable that only **5a** was obtained in yield of 90% without **3a** detected at 20 °C, on the contrary, only **3a** was acquired in yield of 93% without **5a** observed at 120 °C. Both **3a** and **5a** were produced in yields of 27%, 65% respectively when the reaction was carried out at 60 °C. The result in Table 4 implied compound **5a** may be the intermediate of this reaction. When compound **5a** was tested as substrate under the standard condition, compound **3a** was produced in good yield of 89% (eqn. 2). All the experiments supported the compound **5a** was the intermediate of this transformation. In addition, TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl) didn't inhibit the reaction indicating it is possible that the cyclization reaction didn't involve the radical process[6] (eqn. 3).

On the basis of the above experimental results, a probable catalytic mechanism for this transformation is illustrated in Scheme 1. Initially, the 2-iodoanilines **1** encountered strong base KOBu^t to generate the amine anions **C**. Nitriles **2** underwent the nucleophilic attack by amine anions **C** to get the intermediate anions **D** with two tautomers. The final products **3** can be produced through the intramolecular nucleophilic attack of benzyne intermediate anions **E**, which were produced from intermediate anions **D** under the condition of strong base. In addition, the intermediate anions **D** and the intermediates **5** can transform mutually into each other through the protonation and deprotonation reactions



Scheme 1. Proposed mechanism for this transformation.

We have also been able to apply this cyclization reaction toward the synthesis of the agonist **7** against the g-aminobutyric acid A receptor (GABAA).[7] As outlined in eqn. 4, the cyclization reaction of 4-methyl-2-iodoaniline **1b** with 4-methylbenzonitrile **2d** provides the benzimidazole **3q** in yield of 80%. The resulting benzimidazole **3q** was then *N*-alkylated in the presence of K_2CO_3 with chloroacetamide **6** to generate the compounds **7** and **7'** in yield of 66% with the ratio of 1:1 (The ratio was determined by ^{1}H NMR on the crude products).



In summary, we developed a transition metal-free intermolecular cyclization reaction of 2-iodoanilines with nitriles. This transformation realized one-step synthesis of benzimidazole derivatives using directly *2*-iodoanilines as the reactant without the aid of any transition metals, ligands, and

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just using KOBu^t as the base. A variety of substituted benzimidazole derivatives can be synthesized by the approach. Moreover, this approach was also applied to the synthesis of the agonist **7** against the g-aminobutyric acid A receptor (GABAA). Some other reactions of nitriles and the related applications are ongoing in our laboratory.

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Notes and references

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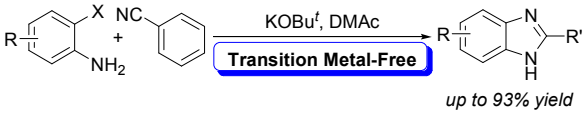

Synthesis of benzimidazoles by potassium *tert*-butoxide-promoted intermolecular cyclization reaction of 2-iodoanilines with nitriles

Synthesis of benzimidazoles by intermolecular cyclization reaction of 2-iodoanilines with nitriles has been developed. These reactions proceeded without the aid of any transition metals, ligands, and just using $KOBu^t$ as the base. A variety of substituted benzimidazole derivatives can be synthesized by the approach.