Nitrogen Heterocycles

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Synthesis of 1,2-Disubstituted Benzimidazoles by a Cu-Catalyzed Cascade Aryl Amination/Condensation Process**

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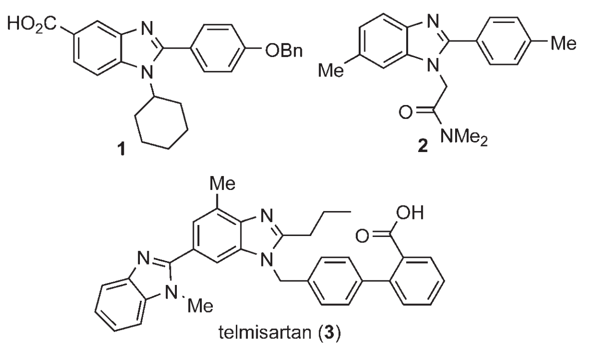
1,2-Disubstituted benzimidazoles are an important class of heterocyclic compounds that exhibit a wide range of biological properties.[1] Previous syntheses of 1,2-disubstituted benzimidazole structures not only led to drug leads such as the hepatitis C virus (HCV) NS5B polymerase inhibitor **1**[2] and the agonist **2** against the γ-aminobutyric acid A receptor ($GABA_A$),[3] but also resulted in commercial pharmaceutical products such as the antihypertensive telmisartan (**3**, Scheme 1).[4]

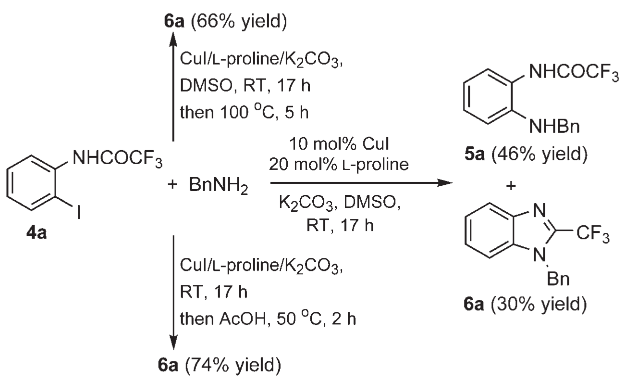


Scheme 1. Structures of pharmacologically important 1,2-disubstituted benzimidazoles. Bn = benzyl.

Although 1,2-disubstituted benzimidazoles play an important role in pharmaceutical science, the available synthetic strategies that lead to these compounds are limited compared with those that lead to the structurally related indoles. The classical methods for the assembly of these molecules include acylation/cyclization processes from *ortho*-aminoanilines,[2] reduction/cyclization processes from *ortho*-nitroanilines,[5] and alkylation of 2-substituted benzimidazoles.[3,6] The drawback of these procedures is the limited diversity of the available starting materials. In an attempt to circumvent this restriction, a metal-catalyzed intramolecular amination approach was recently reported.[7] However, the products are limited to the 2-aminobenzimidazoles. Herein, we report a new cascade process for the formation of 1,2-disubstituted benzimidazoles from 2-haloanilides and primary amines.

In recent years, we have witnessed great progress in the development of mild Cu-catalyzed Ullmann-type reactions using N,N-, N,O-, and O,O-bidentate ligands.[8,9] Several useful domino processes have been developed based on these investigations.[10] During studies on the CuI-catalyzed assembly of diaryl ethers using amino acids as ligands we discovered that there is an *ortho*-substituent effect directed by NHCOR groups in Ullmann-type C−O bond formations.[11] Further explorations revealed that the same effect exists in the coupling of aryl halides with activated methylene compounds.[12] We were interested in whether this effect could promote aryl amination to afford *ortho*-aminoanilides at low reaction temperatures, which in turn would provide 1,2-disubstituted benzimidazoles through an intramolecular condensation. It is noteworthy that low reaction temperatures are essential for obtaining *ortho*-aminoanilides because *ortho*-haloanilides can undergo the Cu-catalyzed cyclization at 80 °C to afford benzoxazoles.[13]

With this idea in mind, we carried out the reaction of 2-iodotrifluoroacetanilide (**4a**) with benzylamine catalyzed by CuI/L-proline (Scheme 2). We were pleased to find that after 12 h at room temperature, **4a** was consumed to give a mixture of aniline **5a** (46 % yield) and benzimidazole **6a** (30 % yield). Since iodobenzene does not couple with benzylamine under the same conditions,[9f,h] the formation of **5a** and **6a** clearly demonstrate that the *ortho*-$NHCOCF_3$ group promotes the amination. We then tried to transform **5a** into **6a** in a one-pot reaction, and found that **6a** was formed exclusively when the



Scheme 2. Coupling of **4a** with benzylamine catalyzed by CuI/L-proline. DMSO = dimethyl sulfoxide.

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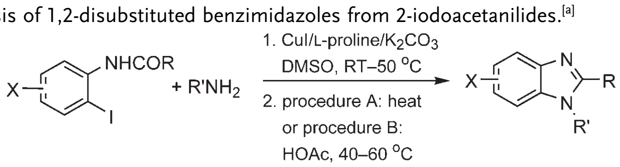
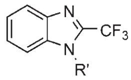
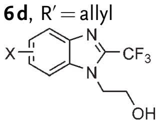
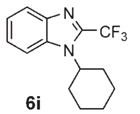
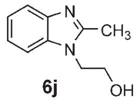
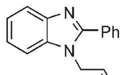
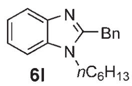
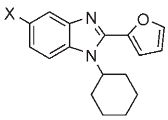
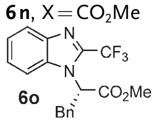
coupling-reaction mixture was heated at 100 °C for five hours (procedure A), or when acetic acid was added and the reaction mixture heated at 50 °C for two hours (procedure B).

In response to this encouraging result, we used a range of 2-iodoacetanilides and primary amines to investigate the scope and limits of this reaction. As shown in Table 1, less-sterically hindered amines couple with both electron-rich and electron-deficient 2-iodotrifluoroacetanilides at room temperature, thus providing benzimidazoles **6b**–**6h** in good yield (Table 1, entries 1–7). These results differ to those observed when using benzylamine, which indicates that subtle changes in the size of the amines will alter the reaction process. Cyclohexylamine was found to be similar to benzylamine and further heating in HOAc was required for the completion of the condensation/cyclization reaction (procedure B, entry 8).

The coupling reaction of 2-iodoacetanilide with 2-hydroxyethylamine had to be carried out at 40 °C to ensure complete conversion, and condensation product **6j** was formed after the reaction mixture had been heated at 120 °C for 12 h or after treatment of the reaction mixture with HOAc at 40 °C for 4 h (Table 1, entries 9 and 10). It is noteworthy that during the coupling reaction, no **6j** was observed, which indicates that for both coupling and condensation steps, substrates bearing a trifluoroacetyl group instead of an acetyl group are generally more reactive. However, the relatively low reaction temperature[9f,h] required for the coupling with 2-iodoacetanilide indicates that an *ortho*-substituent effect from the $HNCOCH_3$ group remained influential during the course of the reaction. Similar results were obtained when other iodides that contain aliphatic and aromatic amido groups were used (Table 1, entries 11–17), which indicates that the *ortho*-substituent effect is not limited to the $HNCOCF_3$ group and that variation at the 2-position of the benzimidazoles is possible by using this method. For the condensation/cyclization reaction, treatment of the coupling-reaction mixture with HOAc generally gave better results than direct heating (Table 1, entries 9–16). Furthermore, entry 18 illustrates that a benzimidazole **6o** with an amino ester group can also be obtained. Similar compounds have shown potential for the treatment of hypertension,[14] diabetes,[15] hyperglycemia-related disorders,[16] as well as bone diseases.[17]

Table 1: Synthesis of 1,2-disubstituted benzimidazoles from 2-iodoacetanilides.[a]



Entry	Step 1 T [°C]/t [h]	Step 2 procedure/T [°C]/t [h]	Product	Yield [%][b]
				
1	25/24	–	**6b**, R' = CH_2CH_2OH	92
2	25/24	–	**6c**, R' = n-C_6H_{13}	90
3	25/10	–	**6d**, R' = allyl	94
				
4	25/17	–	**6e**, X = 4,6-dimethyl	94
5	25/15	–	**6f**, X = 6-OMe	89
6	25/24	–	**6g**, X = 6-CO_2Me	72
7	25/24	–	**6h**, X = 6-$COCH_3$	90
8	25/24	B/50/5	 **6i**	94
9		A/120/12	 **6j**	64
10	40/2	B/40/4		75
11		A/120/12	 **6k**	79
12	40/4	B/40/8		81
13		A/120/20	 **6l**	70
14	40/6	B/40/10		97
15		A/140/30		73
16	40/10	B/60/12	**6m**, X = H	88
17	40/8	B/60/10	**6n**, X = CO_2Me	83
18	40/36	B/70/12	 **6o**	61

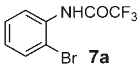
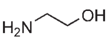
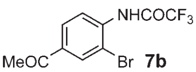
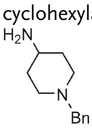
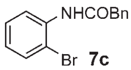
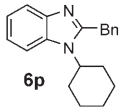
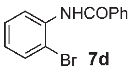
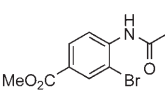
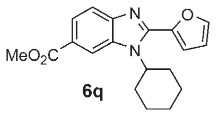
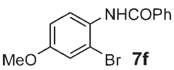
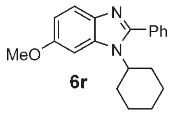
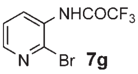
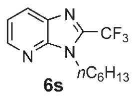
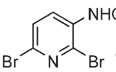
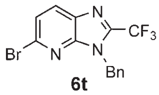
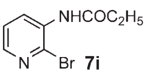
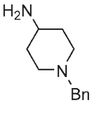
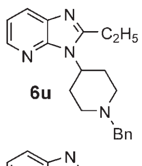
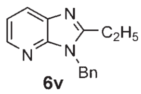
[a] Reaction conditions: step 1. Aryl iodide **4** (0.5 mmol), amine (0.75 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (1 mmol), DMSO (1 mL); step 2. Procedure A: the reaction mixture was heated at the indicated temperature; procedure B: 5 mL of AcOH was added, and then the reaction mixture was heated at the indicated temperature. [b] Yield of isolated product.

During the course of our research we investigated the coupling reaction of 2-bromoacetanilides with primary amines. To our delight, the reaction of 2-bromotrifluoroacetanilides **7a** and **7b** with several primary amines took place at room temperature to provide the benzimidazoles **6b**, **6c**, **6i**, and **6h** after treatment with HOAc (Table 2, entries 1–4). The smooth coupling reaction displayed by these bromides most likely results from the *ortho*-substituent effect, and represents the first example of a room-temperature amination of aryl bromides.[9i]

As with the aryl iodides, aryl bromides with different amide groups in the *ortho* position were compatible under the reaction conditions, and delivered the corresponding benzimidazoles in satisfactory yields (Table 2, entries 5–8). However, in comparison with the aryl iodides, slightly higher reaction temperatures were required to complete the coupling reaction. Aryl bromides with electron-withdrawing and electron-donating groups were compatible, although the use of the latter gave relatively low yields (entries 7 and 8).

When 3-amido-2-bromopyridines were employed, the process afforded polysubstituted imidazo[4,5-b]pyridines (entries 9–12), which are found in the core skeletons of a number of pharmaceutically important compounds.[18,19] In the case of the dibromopyridine **7h**, no coupling at the 6-position was observed, which indicates that good regioselectivity can be obtained (Table 2, entry 10), and the remaining bromide functionality in **6t** can undergo further coupling reactions. For the formation of imidazo[4,5-b]pyridines **6u** and **6v**, treatment with HOAc at 100 °C was found to give poor yields as a result of decomposition. However, satisfac-

Table 2: Synthesis of 1,2-disubstituted benzimidazoles from 2-bromoacetanilides.[a]

Entry	Bromide	Amine	Step 1 T [°C]/t [h]	Step 2 procedure/T [°C]/t [h]	Product	Yield [%][b]
1	 **7a**		25/24	B/50/1	**6b**	90
2		*n*-hexylamine	25/10	B/50/2	**6c**	80
3		cyclohexylamine	25/10	B/50/5	**6i**	90
4	 **7b**		25/24	B/50/1	**6h**	85
5	 **7c**	cyclohexylamine	45/10	B/50/6	 **6p**	70
6	 **7d**	allylamine	50/10	B/50/6	**6k**	80
7	 **7e**	cyclohexylamine	50/12	B/80/10	 **6q**	70
8	 **7f**	cyclohexylamine	50/10	B/90/10	 **6r**	62
9	 **7g**	cyclohexylamine	40/12	B/90/4	 **6s**	72
10	 **7h**	benzylamine	40/7	B/90/4	 **6t**	78
11	 **7i**		45/6	A/150/12	 **6u**	76
12		benzylamine	45/7	A/150/12	 **6v**	78

[a] Reaction conditions: step 1. Aryl bromide **7** (0.5 mmol), amine (0.75 mmol), CuI (0.1 mmol for entries 1–4, 0.05 mmol for entries 5–12), L-proline (0.2 mmol for entries 1–4, 0.1 mmol for entries 5–12), K_2CO_3 (1 mmol), DMSO (1 mL); step 2. Procedure A: the reaction mixture was heated at the indicated temperature; procedure B: 5 mL of AcOH was added, and then the reaction mixture was heated at the indicated temperature. [b] Yield of isolated product.

tory yields were obtained when the coupling-reaction mixture was heated at 150 °C (Table 2, entries 11 and 12).

In conclusion, we have demonstrated that NHCOR groups provide an *ortho*-substituent effect in the amination of 2-haloacetanilides catalyzed by CuI/L-proline. Based on this observation, a novel and highly practical method for elaborating benzimidazoles has been developed. Variation at the 1- and 2-positions of the benzimidazole is possible when different primary amines are employed and with variation in the amido groups of the 2-haloacetanilides. Moreover, in contrast to the existing methods, our strategy allows the introduction of substituents in different positions of the benzimidazole phenyl ring. Thus, the present cascade process allows the assembly of a wide range of polysubstituted benzimidazoles.

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