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# C—N bond formation and cyclization: A straightforward and metal-free synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles

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ABSTRACT

A straightforward and metal-free synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles from the corresponding *o*-fluoro aryl formamidines and primary amines using microwave irradiation is described. The displacement of -F by the primary amine and cyclization to form the corresponding benzimidazoles took place in one pot.



The benzimidazole ring is one of the most important nitrogen-containing heterocycles, which are widely explored and utilized by the pharmaceutical industry for drug discovery (FDA approved drugs containing the benzimidazole motif were found to be the fifth most commonly used five-membered aromatic nitrogen heterocycle) [1]. Many efforts have been devoted to the development of methods for the preparation of *N*-1-alkyl-2-unsubstituted benzimidazoles. Among these methods, three representative approaches have been highlighted for the synthesis of such benzimidazole derivatives (Scheme 1). The condensation of 1,2-diaminoarene **1** (Route 1) with formic acid to form benzimidazole **2**, followed by the direct *N*-alkylation of one nitrogen of the benzimidazole ring generates two regioisomers **3** and **4**. However, the regioselective alkylation of one nitrogen over the other is difficult in most cases, giving rise to mixtures of the two regioisomers [2–11]. The alkylation of 2-nitroaniline **5** (Route 2), nitro group reduction to the amino group, and then cyclization of **7** with formic acid selectively gives the desired compound **3** [12–15]. *o*-Fluoro nitrobenzene compound **8** can also be used to form intermediate **6** *via* $S_NAr$ substitution by a primary amine (Route 3) [16–20].

After reviewing current methodologies for the synthesis of *N*-1-alkyl-2-unsubitituted benzimidazoles, we believed that it might be possible to form the benzimidazole ring *via* the intramolecular $S_N$-Ar reaction of a formamidine onto a pendant aryl fluoride in one-pot (Scheme 2).

Herein, we report a novel and straightforward method for the preparation of *N*-1-alkyl-2-unsubstituted benzimidazoles from *o*-fluoro aryl formamidines and the corresponding primary amines using microwave irradiation.

Firstly, we prepared four substrates (**10a–d**, Scheme 3) in high yields (68–95%) *via* the reaction of compounds **9a–d** with DMF in the presence of benzene sulfonyl chloride at room temperature for 1 h.

Secondly, formamidine **10a** and benzylamine were chosen as model substrates for reaction optimization. Initial experiments utilizing **10a** and **11a** (1:1) in THF or 1,4-dioxane in the presence of DIPEA (or without DIPEA) resulted in the formation of by-product **13** to a significant extent (**12a**:**13** = 1:2 by LC-MS analysis), presumably due to nucleophilic attack of the dimethylamine which was formed during desired product formation (Scheme 4).

To overcome this issue, we increased both the reaction temperature and the reaction time. Unfortunately, these attempts failed to prevent the formation of compound **13**. Gratifyingly, increasing the equivalents of **11a** resulted in the decreased formation of by-product **13** (Table 1). The base (DIPEA) was not necessary to change the product:by-product ratio due to the excess of **11a**. Compound **11a** (5 eq.) in the presence of DIPEA (0.4 mmol) or without DIPEA gave same ratios of **12a** and **13** (Entry 5).

With the reaction conditions now optimized, we then explored the scope by employing a diverse set of amines in conjunction with either **10a–b** (Table 2). The general procedure of preparation of title compound and typical examples were showed [21–24]. The results showed that both aliphatic amines and benzylamines give good to moderate yields. Also, free hydroxyl groups and tertiary

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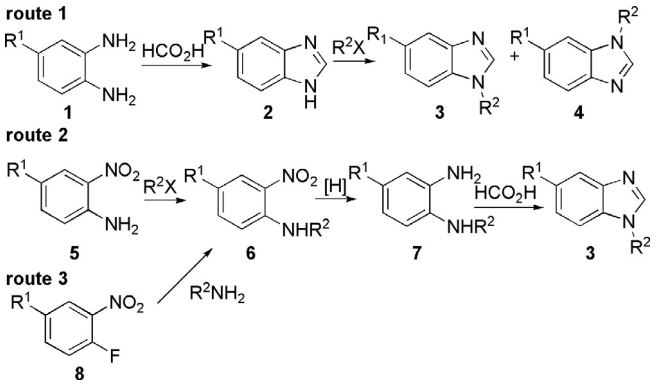
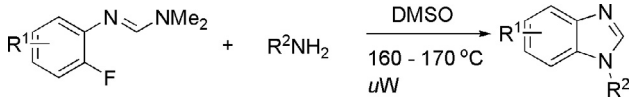
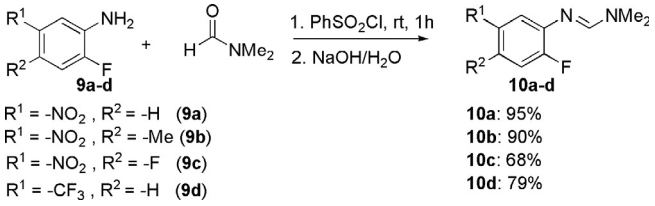


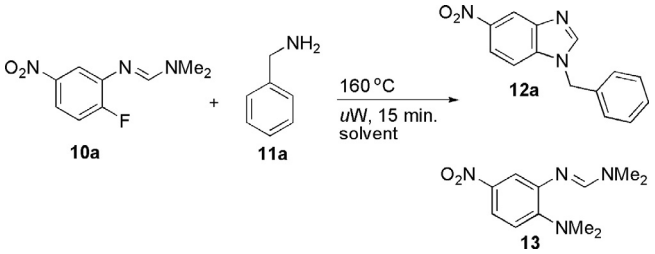

**Scheme 1.** Selected routes for the synthesis of 2-unsubstituted benzimidazoles **3**.




**Scheme 2.** The formation of benzimidazole.




**Scheme 3.** Synthesis of formamidines **10a–d.**




**Scheme 4.** Formation of compounds **12a** and **13**.

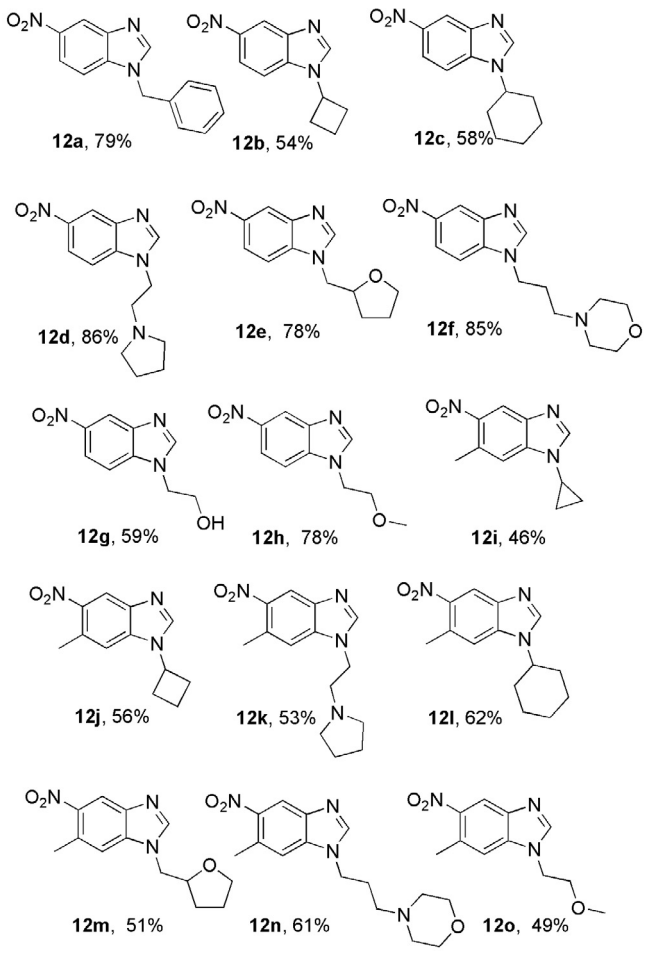
**Table 1**
Optimization of the reaction conditions: effect of increasing the equivalents of **11a**.[a]

| Entry | **11a** (eq.) | Conversion of **10a**[b] | Ratio (%) of **12a** and **13**[b] |
|---|---|---|---|
| 1 | 1 | 61 | 37:63 |
| 2 | 2 | 72 | 52:48 |
| 3 | 3 | 77 | 63:37 |
| 4 | 4 | 88 | 79:21 |
| 5 | 5 | 87 | 80:20[c] |
| 6 | 6 | 94 | 93:7 |
| 7 | 7 | 100 | 98:2 |
| 8 | 8 | 100 | 100:0 |

[a] Reagents and conditions: DMSO (0.5 mL), **10a** (0.2 mmol), 160–170 °C, 15 min. in a Biotage Initiator.
[b] Based on LC-MS analysis.
[c] With DIPEA (0.4 mmol) or without DIPEA.

amines were tolerated, having no effect on the yields. However, the reaction of anilines with **10a** only resulted in the formation of trace amounts of the corresponding products (detected by LC-MS analysis) due to the weak reactivity of anilines. During the reaction of **10c** and **11a**, a mixture was detected by LC-MS analysis which

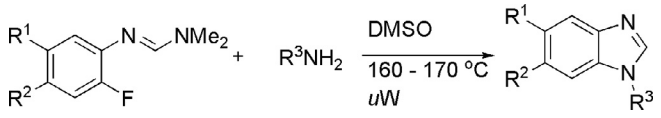
**Table 2**
Synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles *via* microwave irradiation.[a]




[b] Isolated yield.
[a] Reagents and conditions: formamidine **10** (0.4 mmol) primary amine **11** (2.8 mmol), dry DMSO (1 mL), 160–170 °C, 15 min. in a Biotage Initiator.

showed the desired product, single substitution of one and two fluorides by benzylamine, and **10c**. The reaction of **10c** with aniline and pyrimidin-2-amine, respectively, gave 15% and 7% conversion of **10c** to the desired products at 170 °C for 1 h (LC-MS analysis). The reactions of **10d** with benzylamine and 3-morpholinopropan-1-amine, respectively, gave 32% and 38% conversion to the corresponding products at 170 °C for 1 h while **10d** remained. Note that formamidines which contained a strong electron withdrawing group (—$NO_2$) and strongly nucleophilic amines are important to carry out those reactions (see Scheme 5.).

These findings support a mechanism in which fluorine is displaced by benzylamine, followed by rapid cyclization of the amine onto the pendant formamidine and liberation of dimethylamine (Scheme 6). The dimethylamine competes with benzylamine as the nucleophile, giving rise to by-product **13**. Predictably, this by-product formation can be minimized by using a large excess of benzyl amine giving only the desired product.




**Scheme 5.** Synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles.

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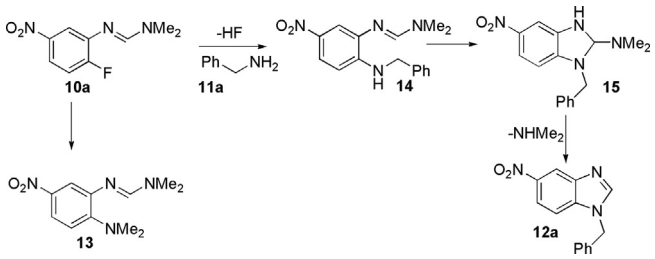


**Scheme 6.** Proposed mechanism for the formation of compounds **12a** and **13**.

In summary, we have developed a novel regiospecific synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles. This new methodology facilitates the preparation of 2-unsubstituted benzo[*d*]imidazol-1-amine derivatives in an effective manner. The reaction offers some advantages over previous methods: (1) a practical and short synthetic route. (2) the displacement of fluorine and cyclization in one-pot.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.03.028.

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[21] **(*E*)-*N*′-(2-Fluoro-5-nitrophenyl)-*N*,*N*-dimethyl formimidamide** (**10a**): To a 250 mL flask equipped with a magnetic stirrer bar was added DMF (60 mL) and benzene sulfonyl chloride (27.2 g, 154 mmol). The solution was stirred for 20 min and the solution turned to a slight yellow color. 2-Fluoro-5-nitroaniline (12 g, 77 mmol) was added as a solid and the mixture stirred for 30 min at room temperature. The solid was filtered and washed with diethyl ether and dried under vacuum. The crude material was transferred into a flask and neutralized by adding NaOH (4 M) and ethyl acetate (150 mL). The solution was transferred into a funnel, separated, and the organic layers extracted with ethyl acetate (2 x 100 mL). After combining the organic layers, it was washed with brine and dried with $Na_2SO_4$ for 3 h. A yellow solid was obtained, 15.5 g, 95% yield. $^1$H NMR (500 MHz, DMSO-$d_6$) δppm 2.97 (s, 3 H), 3.07 (s, 3 H), 7.35 (t, *J* = 9.77 Hz, 1 H), 7.79 (dt, *J*=8.77, 3.40 Hz, 1 H), 7.90 (dd, *J* = 7.63, 2.75 Hz, 1 H), 7.98 (s, 1 H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ ppm 33.92, 116.15, 117.21, 141.24 (d, $^3J_{C\text{-}F}$ = 11.34 Hz)), 144.20, 155.73, 159.21 ($^1J_{CF}$ = 254.52 Hz); HRMS calcd. for $C_9H_{10}FN_3O_2$: 211.0757, found 211.0750.
[22] **General procedure for the preparation of *N*-alkyl-2-unsubstituted benzimidazoles:** To a solution of formamidine **10** (0.4 mmol) in dry DMSO (1 mL) was added amine **11** (2.8 mmol) in a microwave vial (0.5–2 mL) with a stirrer bar. The vial was capped, and the reaction mixture heated at 160–170 °C for 15–20 min in a Biotage Microwave. All desired products were purified by preparative chromatograph with 20 x 20 cm plates.
[23] **Benzyl-5-nitro-1*H*-benzo[*d*]imidazole** (**12a**, 79% yield). $^1$H NMR (500 MHz, MeOD) δ ppm 5.60 (s, 2H), 7.30–7.52 (m, 5H), 7.65 (d, *J* = 8.85 Hz, 1H), 8.22 (dd, *J* = 8.85, 1.83 Hz, 1H), 8.58 (s, 1H), 8.62 (d, *J* = 2.14 Hz, 1H); $^{13}$C NMR (126 MHz, MeOD) δ ppm 49.09, 111.41, 115.66, 118.74, 127.57, 128.49, 129.15, 135.88, 138.13, 142.75, 144.29, 148.03; HRMS calcd. for $C_{14}H_{11}N_3O_2$: 253.0851, found 253.0837.
[24] **Cyclobutyl-5-nitro-1*H*-benzo[*d*]imidazole** (**12b**, 54% yield): $^1$H NMR (500 MHz, MeOD)) δ ppm 1.94–2.15 (m, 2H), 2.51–2.73 (m, 4H), 4.98–5.10 (m, 1H), 7.72 (d, *J* = 8.85 Hz, 1H), 8.20 (d, *J* = 8.85 Hz, 1H), 8.54 (d, *J* = 8.85 Hz, 2H);$^{13}$C NMR (126 MHz, MeOD) δ ppm 15.12, 29.83, 50.46, 111.27, 115.61, 118.50, 137.66, 142.76, 144.22, 145.75; HRMS calcd. for $C_{11}H_{11}N_3O_2$: 217.0851, found 217.0838.