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A one-pot three-component reaction to access 1-alkyl-2-aryl-5-nitrobenzimidazoles under solvent-free conditions

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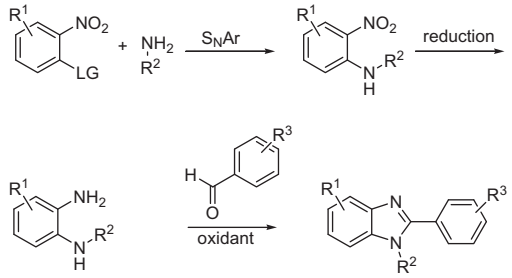
ABSTRACT

A novel and expeditious method to access 1-alkyl-2-aryl-5-nitrobenzimidazoles has been developed. Enlisting solvent-free conditions, 2-fluoro-5-nitroaniline, a primary amine, and substituted aldehyde were melted together in one-pot to generate a variety of 1-alkyl-2-aryl-5-nitrobenzimidazoles.

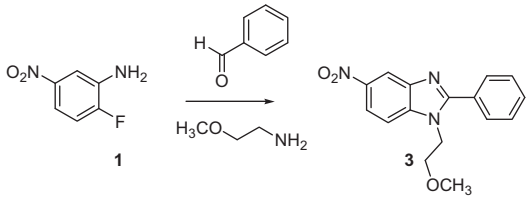
Benzimidazoles are a widely used motif in drug discovery. In particular, 1-alkyl-2-aryl-substituted benzimidazoles appear in numerous patents and publications for a variety of targets. Some recent examples are inhibitors of HIV replication,[1a] hedgehog pathway,[1b] and histone deacetylases.[1c] One method to access 1-alkyl-2-aryl-substituted benzimidazoles is via a multistep process (Scheme 1).[1c,2] First, a substituted nitrobenzene undergoes a S_NAr (nucleophilic aromatic substitution) reaction with a primary amine to afford the substituted nitroaniline. Reduction of the nitro group followed by benzimidazole formation with the requisite aldehyde provides the 1-alkyl-2-aryl-benzimidazole.

In connection with a drug discovery program we required a method to quickly access a variety of 5-substituted-1-alkyl-2-aryl benzimidazoles in a parallel approach. Most of our requisite analogs could be accessed through a 1-alkyl-2-aryl-5-nitrobenzimidazole. We chose to start our investigation with 2-fluoro-5-nitroaniline from which we could potentially derive our requisite compounds. We initially explored a multistep process as described in Scheme 1, but soon realized that the primary amine addition to 2-fluoro-5-nitroaniline (**1**) in the S_NAr reaction was not general with some leading to very little conversion and others taking several days to complete. In the literature there are not very many examples of S_NAr with compound **1**. Examples that are in the literature generally take at least 48 h to complete and the product is obtained in low yield.[1c,3] The poor reactivity of **1** is most likely due to the electron-donating amino group. One option we did consider was starting with 1,5-dinitro-2-fluorobenzene and performing a selective nitro reduction to the requisite diamino compound after the S_NAr with the amine (Scheme 1, where R^1 = 5-nitro and LG = F). As expected the S_NAr reactions proceeded smoothly with a variety of amines, but access to our final benzimidazoles was tedious since this method required a selective reduction of the 1-nitro group to the amine followed by



Scheme 1.

Table 1
Various conditions attempted for the one-pot 1,2-disubstituted benzimidazole formation



Entry	Solvent	Temperature	Time (h)	Result
1	EtOH	Reflux	16	No reaction
2	DMF	Reflux	16	No reaction
3	DMSO	160 °C	16	No reaction
4	NMP	200 °C	16	Partial conversion, 2%
5	NMP	100–200 °C (microwave)	2	Partial conversion, 5%
6	None	100 °C	8	Partial conversion, 22%
7	None	140 °C	8	Complete, 65%

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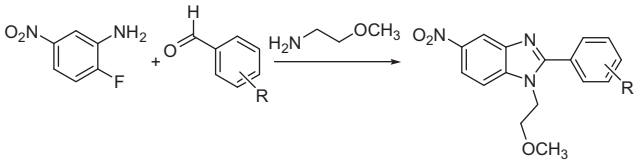
the benzimidazole formation. Although this method was productive, we felt that it was not practical for a parallel synthesis method.

We then turned our attention back to our initial investigation with 2-fluoro-5-nitroaniline (**1**) because this would ultimately provide the most straightforward route. We attempted to explore a one-pot procedure to access the requisite benzimidazoles that would be highly amenable to a parallel approach. We explored various conditions by combining 2-fluoro-5-nitroaniline (**1**), 2-methoxyethyl amine and benzaldehyde in one-pot using air as the oxidant.[4] Some of the conditions are highlighted in Table 1. The solvent, temperature, and time were all investigated, but most conditions gave the unreacted starting material (Table 1, entries 1–3) or very little product (Table 1, entries 4 and 5: 2% and 5% isolated yield, respectively). Only the starting material and product were observed in the reaction mixture for entries 4–6. In one of our last attempts to probe this reaction we combined the above reagents neat and heated them to 100 °C for 8 h and partial conversion was observed with an isolated yield of 22%. When the temperature was raised to 140 °C for 8 h we gratifyingly observed excellent conversion and an isolated yield of 65%.[5]

Table 2
Exploration of substituted benzaldehydes



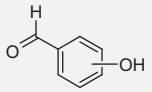
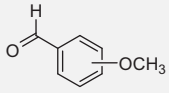
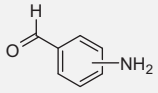
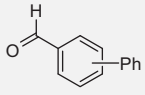
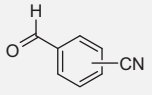
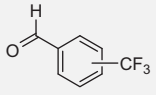
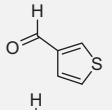
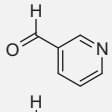
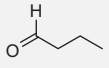
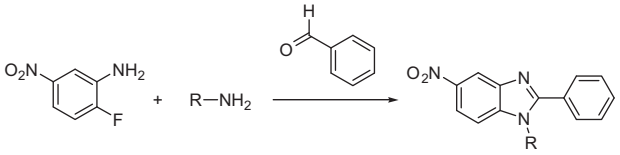
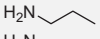
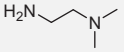
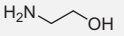
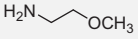
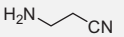
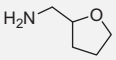
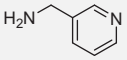
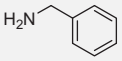
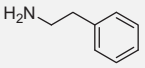
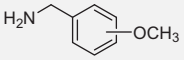
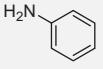
Aldehyde	Entry	Yield (%)
	1 *ortho*	36
	2 *meta*	71
	3 *para*	40
	4 *ortho*	71
	5 *meta*	63
	6 *para*	79
	7 *ortho*	67
	8 *para*	77
	9 *ortho*	72
	10 *meta*	82
	11 *para*	76
	12 *ortho*	80
	13 *meta*	89
	14 *para*	92
	15 *ortho*	60
	16 *meta*	59
	17 *para*	70
	18	72
	19	85
	20	0
	21	0

Table 3
Exploration of various primary amines



Aldehyde	Entry	Yield (%)
	1	54
	2	77
	3	57
	4	60
	5	65
	6	49
	7	65
	8	33
	9	52
	10	74
	11 *ortho* 12 *para*	24 57
	13	0

Encouraged by this result, we set out to explore the generality of this one-pot three-component reaction. The results are summarized in Tables 2 and 3.

We first explored the scope of the reaction of substituted aryl aldehydes with 2-fluoro-5-nitroaniline and 2-methoxyethyl amine (Table 2). It should be noted that while a few substrates (in Tables 2 and 3) required less time and/or lower temperature for completion, we identified 8 h at 140 °C as the optimal conditions as a general parallel synthesis protocol for this reaction. The yield proved relatively independent of whether the substituent on the benzaldehyde was an electron-donating or electron-withdrawing group that might significantly alter the reactivity (Table 2, entries 1–17). In addition, the placement of this substituent on the benzaldehyde (*ortho*, *meta*, *para*) also appeared to not have a significant effect on the yield of the reaction. Heteroaryl aldehydes worked equally well (entries 18 and 19). However, alkyl aldehydes (Table 2, entries 20 and 21) do not appear to work under these conditions. Only the starting material was observed for entries 20 and 21 (Table 2).

Next we turned our attention to investigating various amines with 2-fluoro-5-nitroaniline and benzaldehyde (Table 3). Both alkyl and heteroalkyl amines (entries 1–7) proved successful under these conditions. Steric bulk close to the amine such as in entry 1 of Table 3 appeared to not have a significant impact on the yield as compared to the others in the table. While benzyl and heterobenzyl amine derivatives (entries 8–12) provided good conversion, aniline (entry 13) did not and only the unreacted starting material was observed.

We postulate that the reaction proceeds first through the S_NAr reaction followed by the cyclization with the aldehyde and

subsequent air oxidation to the benzimidazole.[6] Under inert reaction conditions the reaction does not proceed and only the intermediate S_NAr product is isolated. Also, when we run this reaction under the same conditions without any aldehyde we obtain an excellent conversion to the substitution product suggesting that this step occurs first. Currently, we have no explanation as to why the substitution proceeds readily with **1** without a solvent as compared to with a solvent (even in high concentration; up to 1 M).

In summary, we developed a highly efficient and novel method to access a wide variety of 1-alkyl-2-aryl-5-nitrobenzimidazoles by enlisting a solvent-free melt procedure using air as the oxidant. The reaction is quite versatile and robust with a variety of functional groups on the amine and the aryl moieties. This method allowed for an expeditious route to a large library of 1-alkyl-2-aryl-5-nitrobenzimidazoles without the need of the multistep method that has been used by others to assemble these types of molecules. Without the need for solvent or added oxidant, this reaction condition eliminates solvent waste and is both green and cost-efficient.

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4. Example of benzimidazole formation from a phenylenediamine and aldehyde using air as the oxidant: (a) Li, Y.; Zhao, N.; Wang, Y.-L.; Wang, J.-Y. *Henan Shifan Daxue Xuebao Bianjibu* **2008**, *36*, 92; (b) Abonia, R.; Castillo, J.; Cuervo, P.; Insuasty, B.; Quiroga, J.; Ortíz, A.; Nogueras, M.; Cobo, J. *Eur. J. Org. Chem.* **2010**, 317.
5. *Representative experimental procedure*: 2-Fluoro-5-nitroaniline **1** (100 mg, 0.64 mmol), 2-ethanolamine (78.3 mg, 1.28 mmol) and benzaldehyde (136 mg, 1.28 mmol) were all added to a 1 dram vial with a stir bar. The vial was capped and heated to 140 °C for 8 h. The residue was purified by flash chromatography (EtOAc/hexanes; a gradient of 0–100% EtOAc) to yield entry 4 in Table 3 (110 mg, 60%): ^{1}H ($CDCl_3$, 400 MHz) δ 8.41 (d, J = 2.0 Hz, 1H), 8.18 (dd, J = 9.0, 2.0 Hz, 1H), 7.81 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.53 (m, 1H), 7.45 (m, 2H), 4.40 (t, J = 5.1 Hz, 2H), 4.13 (t, J = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 143.6, 142.4, 141.2, 130.9, 130.4, 130.2, 129.4, 118.4, 115.7, 112.7, 59.9, 48.0.
6. The reaction is run under a sealed vial to prevent the loss of the volatile primary amine. Although a sealed vial is used, no care is used to exclude air from the reaction vessel.