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An efficient method to access 2-substituted benzimidazoles under solvent-free conditions

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Abstract

An expeditious method to access 2-substituted benzimidazoles was developed. Both aromatic (phenols, anilines, and thiophenols) and alkyl nucleophiles (amines and thiols) react with 2-methylsulfonyl benzimidazole under solvent-free conditions to generate a variety of 2-substituted benzimidazoles.

Substituted benzimidazoles are a widely used structural motif in drug discovery. In particular, 2-substituted benzimidazoles have been core structures of many biochemically important compounds.[1] The synthesis of 2-substituted benzimidazoles has been the subject of many reports.[2] For 2-aryl substituted benzimidazoles, 2-chlorobenzimidazoles are the most often used precursors. Arylthiols react with 2-chlorobenzimidazoles under basic conditions; however, the benzimidazole nitrogen must be protected.[3] Anilines also react with 2-chlorobenzimidazoles at high temperatures, albeit in low yield.[4] The construction of 2-phenoxy substituted benzimidazoles has represented an even bigger challenge whereby high temperatures (>180 °C) or a phenoxide anion must be utilized. The later approach also suffers from low yields as well as the need to protect the benzimidazole nitrogen.[5] Over the past several years, other approaches without using 2-chlorobenzimidazole as a precursor have been reported. For example, it was reported that an SnAr reaction of an arylfluoride with a benzimidazole-2-thione gave the desired 2-arylthio substituted benzimidazole; however, this approach usually requires the activation of arylfluoride by electron-withdrawing groups such as a nitro moiety thereby limiting access to electron rich derivatives.[6] Also, the synthesis of 2-phenoxy substituted benzimidazoles can be achieved by reacting 1,2-phenyldiamine with dichlorodiphenoxymethane, but the availability of other dichlorodiaryloxymethane derivatives has limited the value of this approach.[7]

The synthesis of 2-alkylheteroatom substituted benzimidazoles is even less general. For alkylthio-substituted compounds, the most frequently used method is the Mitsunobu reaction between benzimidazole-2-thiones and alcohols.[8] Various 2-alkylamino substituted benzimidazoles can be made from the corresponding thiourea in the presence of thiophilic metals such as mercury oxide;[9] however, the toxicity of this reagent is a concern for wider application of this method. This issue has recently been addressed by the use of less hazardous metals such as copper(I) chloride.[10] Using 2-chloro benzimidazole as a precursor to access alkylamino and alkoxy products has been reported, but the presence of a strong base such as NaH or *t*-BuOK is required and the protection of the benzimidazole nitrogen is necessary for the success of these reactions.[8,9]

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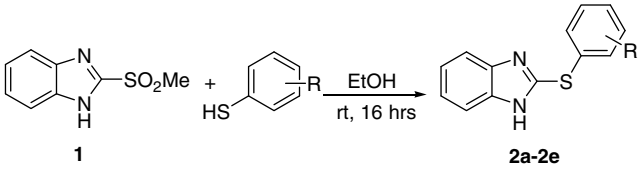
Recently, efforts have been made to apply a palladium catalyst to 2-chlorobenzimidazole to synthesize 2-alkylamino and -alkoxy benzimidazoles.[11]

Besides 2-chlorobenzimidazoles, 2-methylsulfonylbenzimidazoles have also served as intermediates to synthesize 2-substituted benzimidazoles. Methylsulfonylbenzimidazole was shown to react with alcohols formed in situ from epoxides in an intramolecular fashion with the methylsulfone acting as a leaving group.[12] Also, there are examples showing that the nucleophilic displacement of 2-methylsulfone moiety in compound **1** proceeded smoothly with thiophenol.[6] Alkylamines react with 2-methylsulfonylbenzimidazoles when the benzimidazole nitrogen was protected[13] or when harsh conditions were applied (>150 °C, high pressure).[14] Thus, the development of a more efficient and unified method for assembling 2-substituted benzimidazoles with more diverse functional groups could become a valuable addition to the synthetic arsenal toward the syntheses of these pharmaceutically important scaffolds.

In connection with a drug discovery program, we recently required an efficient entry into the substitution of a benzimidazole at the 2-position with a diverse set of nucleophiles. We chose 2-methylsulfonylbenzimidazole (**1**) as the key intermediate to explore. Compound **1** can be readily synthesized under mild conditions via methylation of benzimidazole-2-thione followed by oxidation with 3-chloroperoxybenzoic acid.[15] By applying the same synthetic route, other substituted 2-methylsulfonyl benzimidazoles (e.g., 5-methoxy-2-(methylsulfonyl) benzimidazole) could also be accessed in good yield and on multigram scale.

With the desired intermediate **1** in hand, we initially set out to test the reactivity between **1** and thiophenols using ethanol as the solvent. Thiophenols substituted with both electron-withdrawing and electron-donating groups reacted smoothly with **1** (Scheme 1). It should also be noted that under these reaction conditions there is selectivity between a thiophenol and phenol (i.e., **2e**).

With the result of **2e** in hand, it was not surprising to observe that when similar conditions were applied to **1** and phenol **3**, no conversion to the desired product was observed with only starting material being recovered (Table 1). Raising the temperature of the reaction to

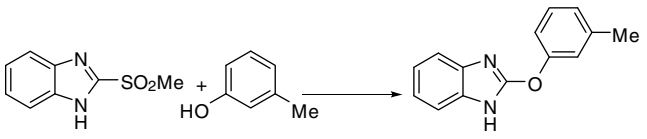


1 **2a-2e**

	R	Yield (%)
2a	H	62
2b	4-OMe	80
2c	3-F	78
2d	4-NHAc	75
2e	3-OH	68

Scheme 1.

Table 1
Substitution of 2-methylsulfonylbenzimidazole **1** with *m*-cresol (**3**) under various conditions



1 **3** **4**

Entry	Solvent	Base	Temperature[a]	Result
1	EtOH	None	rt to 180 °C	No reaction
2	DMF	None	rt to 180 °C	No reaction
3	DMF	NaH[b]	rt to 180 °C	No reaction
4	EtOH	Et_3N[b]	rt to 180 °C	Partial conversion
5	None	None	120 °C	Completion, 28%[c]
6	None	Et_3N[b]	120 °C	Completion, 49%[c]

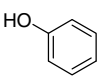
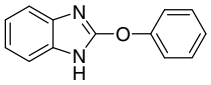
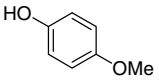
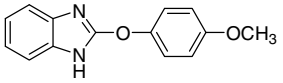
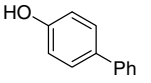
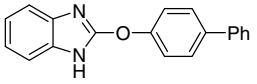
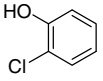
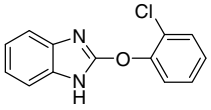
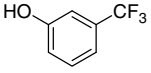
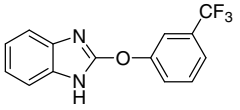
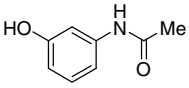
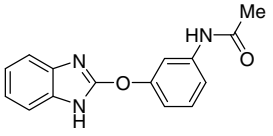
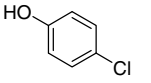
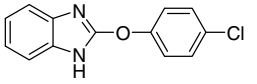
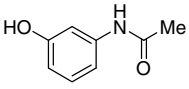
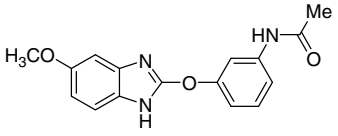
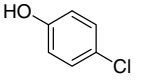
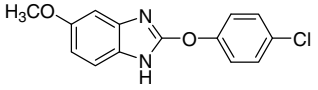
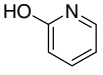
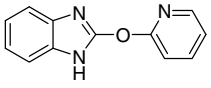
[a] Oil bath was used for heating at temperature lower than 160 °C; microwave was used for heating at 180 °C.
[b] Five equivalents of base was used.
[c] Isolated yields.

180 °C also resulted in no product formation (Table 1, entry 1). Replacing EtOH with DMF also had no effect on conversion (Table 1, entry 2). Generating the phenoxide with NaH (Table 1, entry 3) also resulted in no reaction. This is consistent with previous observations that 2-chlorobenzimidazole will not react with phenoxides and alkoxides unless the benzimidazole nitrogen is protected.[8,9] Adding Et_3N to the solvent appeared to have some beneficial effect with extremely low conversion to product being observed at higher temperatures (Table 1, entry 4). The use of microwave heating resulted in no obvious benefit over traditional heating.

On the other hand, it was gratifying to find that simply mixing the two reactants together neat at 120 °C resulted in the formation of the desired product **4** (Table 1, entry 5) with an isolated yield of 28%. Finally, when 5 equiv of Et_3N were added to the same reaction conditions reported in entry 5 the yield increased to 49% (Table 1, entry 6).[16]

Encouraged by this result, we set out to explore the scope of this reaction condition with other nucleophiles which include substituted phenols, anilines, alkylamines, and alkylthiols.[17] The results are summarized in Tables 2 and 3. We first explored the reaction of several substituted phenols with benzimidazole **1** and its 5-methoxy analog (Table 2). We were pleased to observe that both electron-withdrawing and electron-donating groups in the *ortho*, *meta*, and *para* positions of the phenol worked equally well (30–66% yield) under the solvent-free conditions. Most reactions required warming to 120 °C, but some needed 140 °C for complete conversion. Interestingly, 2-hydroxy pyridine worked well under these conditions providing the product in 62% yield. After the discovery of these reaction conditions with **1** we enlisted 2-chloro benzimidazole as the electrophilic partner with two different phenols (Table 2, entries 6 and 7; data in parentheses) and subjected them to the reaction conditions reported here. We observed similar yields to that obtained with **1**, albeit higher

Table 2
Substitution of 2-methylsulfonylbenzimidazoles with phenols as nucleophiles[a]

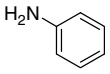
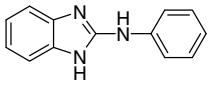
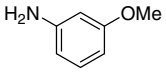
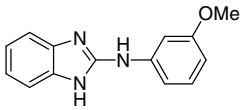
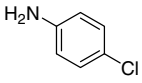
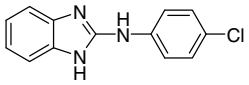
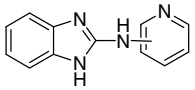
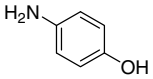
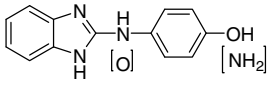
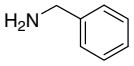
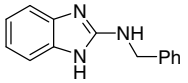
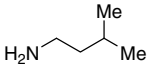
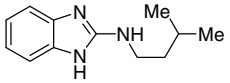
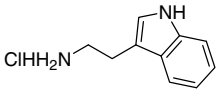
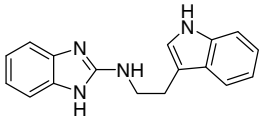
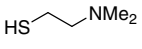
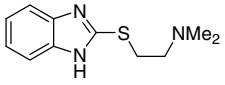
Entry	Nucleophile	Product	Temperature (°C)	Time (h)	Yield (%)
1			120	12	64
2			120	12	64
3			120	12	45
4			120	12	66
5			120	12	30
6			120 (165)[b]	15 (15)[b]	63 (59)[b]
7			120 (165)[b]	15 (15)[b]	59 (58)[b]
8			120	15	59
9			120	15	47
10			140	15	62

[a] Typical reaction conditions: methylsulfonylbenzimidazole (1 equiv), substituted phenol (5 equiv), triethylamine (5 equiv). Mixture heated at reported temperature and time.
[b] 2-Chlorobenzimidazole used as electrophilic partner.

temperatures (165 °C vs 120 °C) were needed for 2-chloro benzimidazole to be fully consumed. It has previously been demonstrated that in order for phenols to react with either 2-chloro or 2-methylsulfonyl benzimidazole that the benzimidazole must be protected to observe conversion to product. Under these solvent-free reaction conditions reported here we report for the first time that it is not necessary to protect the benzimidazole nitrogen. It is especially noteworthy that although only moderate yields are obtained, protection (and subsequent deprotection) of the benzimidazole is not required, thus allowing for an efficient method to access a library of 2-phenoxy substituted benzimidazoles. In addition, the reaction profiles by LCMS are very clean and the products can immediately be purified with ease without the need for workup.

We then turned our attention to other nucleophiles. Anilines with electron-donating or electron-withdrawing substituents also worked well under this solvent-free condition (Table 3, entries 2 and 3). However, both 2-amino and 3-amino pyridine resulted in no reaction with only starting material recovered (Table 3, entry 4). When 4-amino phenol was subjected to the same reaction conditions, complete consumption of compound **1** was observed, but the afforded final product was a mixture of both O- and N-substitution products with the selectivity slightly favoring the biaryl ether (ratio 1.4 to 1 based on NMR). Alkyl amines or their hydrochloride salt (Table 3, entry 8)

Table 3
Substitution of 2-methylsulfonylbenzimidazole **1** with anilines, amines, and an alkylthiol[a]

Entry	Nucleophile	Product	Temperature (°C)	Time (h)	Yield (%)
1			120	2	69
2			120	15	58
3			160	15	76
4			165	24	—
5			120	15	81[b]
6			120	15	91
7			140	15	95
8			140	15	76
9			120	2	72

[a] Typical reaction conditions: **1** (1 equiv), nucleophile (5 equiv), triethylamine (5 equiv, for anilines and alkylthiol only). Mixture was heated at reported temperature and time.
[b] The yield refers to combined yield for products of both O-substitution and N-substitution. The ratio is 1.4:1 based on ^{1}H NMR.

worked similarly well providing the product in good to excellent yield. An example with an alkyl thiol (Table 3, entry 9) showed even better reactivity than alkyl amines with the completion of the reaction in 2 h and in good yield.

In summary, we have developed an efficient and unified approach to quickly assemble a wide variety of 2-substituted benzimidazoles via a 2-methylsulfonyl benzimidazole (or 2-halobenzimidazole) as the common intermediate by using a robust solvent-free method. Phenols, anilines, alkylamines, and alkylthiols react equally well under these conditions. In particular, this method provides a novel and expeditious route to 2-aryloxy substituted benzimidazoles with no need for protection of the benzimidazole nitrogen. The green reaction conditions are not only cost-efficient but also eliminate solvent waste.

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References and notes

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16. *Representative experimental procedure*: Benzimidazole **1** (19.6 mg, 0.1 mmol), nucleophile **3** (54.0 mg, 0.5 mmol), and triethylamine (50.5 mg, 0.5 mmol) were placed in a vial with a stir bar. The vial was capped and put into a preheated oil bath (120 °C) with stirring. The reaction was monitored by LCMS. Upon completion of the reaction (after 15 h), the residue was purified by preparative reverse phase liquid chromatography to give the desired product **4** (10.9 mg, yield: 49%). NMR information for compound **4**: ^{1}H (DMSO-d_6, 400 MHz) δ 7.31–7.27 (m, 3H), 7.13–7.09 (m, 2H), 7.05–7.03 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157, 154, 140, 130, 126, 122, 121, 118, 22.
17. It should be noted that alkyl alcohols did not react with **1** under these conditions and only starting material was observed.