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Synthesis of benzimidazoles from 1,1-dibromoethenes

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ABSTRACT

A mild and efficient method for the preparation of substituted benzimidazoles from 1,1-dibromoethenes and *o*-diaminobenzenes is described. The reaction employs DABCO as the base and NMP as the solvent. A variety of substitutions on both 2-aryl-1,1-dibromoethenes and *o*-diaminobenzenes are tolerated. This new procedure is carried out under mildly basic conditions, which may provide a complementary route to the existing preparations of benzimidazoles.

Benzimidazoles are a common motif in medicinal chemistry, and have found their way to compounds in clinical testing and drugs in clinical use. For example, telmisartan[1] (an AT1 antagonist marketed for hypertension) and bilastine[2] (a selective H1 antagonist in phase 3 for allergic rhinitis) feature substituted benzimidazoles.[3] Numerous methods exist for the preparation of benzimidazoles.[4] The most common one involves the cyclization of *o*-diaminoarenes with carboxylic acids or their derivatives under acidic conditions.[5] Benzimidazoles can also be prepared from the coupling of aldehydes with *o*-diaminobenzenes under oxidative conditions[6] or with 2-nitroanilines under reductive conditions.[7] More recently, transition metal-catalyzed amination followed by condensation has also been reported for the preparation of various benzimidazoles[8] (see Fig. 1).

Previously in our laboratory, 1,1-dibromoethenes were found to be versatile substrates for the palladium-catalyzed syntheses of isocoumarins, trisubstituted alkenes unsymmetrical alkynes, and 1,3-dialkynes.[9,10] During the course of that investigation, 1,1-dibromoethenes were also found to serve as synthons for carboxyl groups. For examples, amides[11] and amidines[12] could be prepared in excellent yields from the reaction between 2-aryl-1,1-dibromoethenes and alkyl amines (Scheme 1). However, attempts to use aniline instead of alkylamines yielded no desired amide, but only recovered starting dibromoalkene **1a**.[11a] The lack of reactivity was attributed to the weak nucleophilicity of aniline.[13]

Since *o*-diaminobenzenes are stronger nucleophiles than aniline, it was envisioned that they may react with 2-aryl-1,1-dibromoethenes to give benzimidazoles in a similar fashion to the formation of amidines. Furthermore, the mild reaction conditions of this procedure could provide an attractive alternative to the preparation of this class of important heterocyclic compounds.

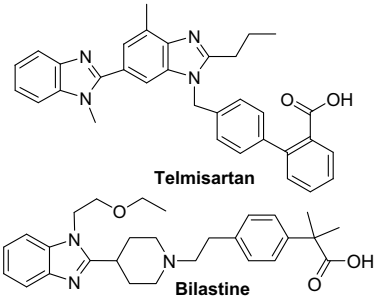
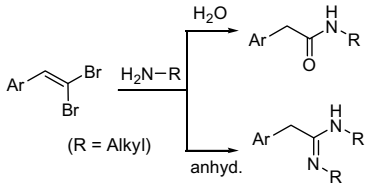


Figure 1. Selected drugs containing a benzimidazole substructure.



Scheme 1. Reaction of dibromoalkenes with alkylamines.

During the initial screening of reaction conditions, it was found that prolonged heating of 1,1-dibromoalkene **1a**, *o*-diaminobenzene **2a**, and diisopropylethylamine (DIEA) in NMP gave the desired benzimidazole **3a** in moderate yield (Table 1, entry 1). Unlike the formation of amides and amidines (Scheme 1),[11,12] this reaction requires an additional base besides **2a,** as the employment of 3 equiv of **2a** (entry 2) in the absence of another stronger base yielded no desired product. During the investigation of the bases for this reaction, it was found that strong bases such as DBU and cesium carbonate in NMP led to rapid disappearance of starting

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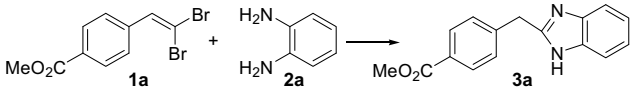
Table 1
Optimization of benzimidazole formation[a]



	Solvent	Base (equiv)	T (°C), t (h)	Yield (%)
1	NMP	DIEA (3)	100, 48	64
2	NMP	None	100, 14	0[b]
3	NMP	Cs_2CO_3 (2)	100, 14	Dec[c]
4	NMP	DBU (3)	100, 14	Dec.
5	NMP	Pyridine (3)	120, 20	Dec.
6	NMP	DABCO (2.2)	100, 7	73
7	NMP	DABCO (2.2)	80, 40	82
8	NMP	DABCO (2.2)	120, 4	61
9	DMF	DABCO (2.2)	100, 7	55
10	DMSO	DABCO (2.2)	100, 7	51
11	1,4-diox.	DABCO (2.2)	120, 24	0[d]

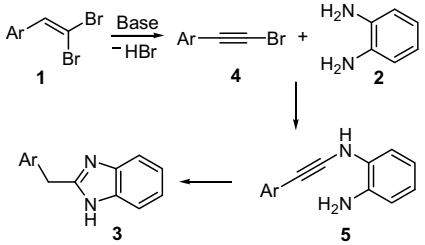
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), base and anhydrous solvent (5 mL).
[b] 3 equiv of **2a** are used, recovery of **1a**.
[c] Decomposition (dec.) of **1a** without formation of **3a** (HPLC monitoring).
[d] Reaction was run in a sealed tube (1,4-diox = 1,4-dioxane).

material **1a**, albeit with no desired product formed. On the other hand, employment of pyridine as a mild base resulted in decomposition with no desired product detected after prolong heating.[14] However, when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used, good yield of benzimidazoles was obtained after seven hours at 100 °C (Table 1, entry 6).

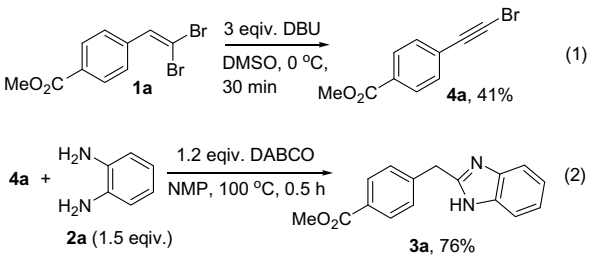
When the reaction temperature was lowered from 120 to 100 to 80 °C (Table 1, entries 6–8), the yield was improved albeit with longer reaction time. A strong polar aprotic solvent is required for the reaction. No product was observed in a moderately polar 1,4-dioxane solvent (entry 11) even after prolong heating (starting material remains). Based on the survey, reaction conditions exemplified by entry 6 were used to carry on the exploration of the scope and limitation of this reaction.

A plausible mechanism is proposed in Scheme 2. It is believed that alkynyl bromides **4** is generated upon treatment of dibromide **1** with a suitable base.[15] Alkynylamine **5** is then formed through amine displacement of bromide, which is followed by an intramolecular cyclization to give the desired product **3.** The proposition of 2-arylethynyl bromide **4** as the active intermediate stems from experimental observations. Upon treatment of 1,1-dibromoethene **1a** with DBU in DMSO at 0 °C (Scheme 3, Eq. 1), alkynyl bromide is isolated at 41% yield from dibromide **1**.[16] It is then reacted with *o*-diaminobenzene **2a** under prior optimized reaction conditions to afford benzimidazole **3a** in 30 min and 76% yield. It is worth noting that much shorter reaction time is required to convert **4a** to the desired product as compared to dibromide **1a**.

The optimized reaction conditions (Table 1, entry 6) were applied to the syntheses of a wide variety of benzimidazoles as shown in Table 2. Both alkyl (**2d**, **2k**) and aryl (**2f**) substituents



Scheme 2. A plausible mechanism.

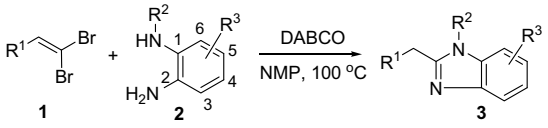


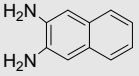
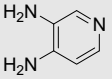
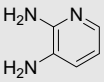
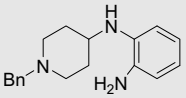
Scheme 3. Formation of benzimidazole from alkynyl bromide.

on the nitrogen are well tolerated, leading to corresponding 1,2-disubstituted benzimidazoles in good yields. Substitutions on the aromatic ring of *o*-diaminobenzenes have minimal impact on the formation of benzimidazole **3**, even with mildly electron-withdrawing groups (**2i**, **2l**). However, no product was isolated from the reaction of **2a** with *o*-diaminopyridines (**2g, 2h**), presumably due to its lower nucleophilicity than other diamines.

Substitutions on the aryl group in dibromoalkenes are also well tolerated, as electron-withdrawing (**1a**, **1e**), electron neutral (**1c**, **1f**), and electron rich (**1d**) substitutions on 2-aryl-1,1-dibromoeth-

Table 2
Preparation of benzimidazoles[a]



R1	*o*-Diaminobenzene (**2**)		Prod, yield (%)
	R2	R2 (**2x**)	
4-(MeO_2C)C_6H_4-(**1a**)	H	3-Me (**2b**)	**3b**, 49
	H	4-Br (**2c**)	**3c**, 54
	Me	H (**2d**)	**3d**, 68
		(**2e**)	**3e**, 84
	Ph	H (**2f**)	**3f**, 63
		(**2g**)	**3g**, 0
		(**2h**)	**3h**, 0
	H	3-Cl–5-CF_3 (**2i**)	**3i**, 60
EtO_2C-(**1b**)	H	4-Cl (**2j**)	**3j**, 70
		(**2k**)	**3k**, 73
Ph-(**1c**)	H	H (**2a**)	**3l**, 53
	Ph	H (**2f**)	**3m**, 55
4-(MeO)Ph-(**1d**)	H	H (**2a**)	**3n**, 86
	Ph	H (**2f**)	**3o**, 70
2-Py-(**1e**)	H	H (**2a**)	**3p**, 65
	H	4-CN (**2l**)	**3q**, 71
2-PhC_6H_4-(**1f**)	H	H (**2a**)	**3r**, 86
	Me	H (**2d**)	**3s**, 70

[a] Reaction conditions: **1** (2.0 mmol), *o*-diaminobenzene (3.0 mmol), and DABCO (4.4 mmol) in NMP (10 mL) were heated at 100 °C for 8–10 h.

enes all afforded good yields of benzimidazoles. Furthermore, the steric hindrance from *ortho*-substitution (**1f**) on 2-aryl-1,1-dibromoethenes has no impact to the reactivity or to the yield.

Under the reaction conditions described herein for the formation of benzimidazoles, 2-alkyl-1,1-dibromoethenes yielded no corresponding benzimidazoles when alkyl groups are electronically neutral or donating.[17] However, electron-withdrawing ethyl 3,3-dibromoacrylate **1b** reacts with *o*-diaminobenzenes readily to give the desired benzimidazoles **3j, 3k**. These products may serve as versatile intermediates for the preparation of a wide variety of 2-alyklbenzimidazoles.[18]

In summary, we have developed a new method for the preparation of substituted benzimidazoles in good to excellent yields. This method employs mildly basic conditions, which complement the existing methods for benzimidazole synthesis under acidic or oxidative/reductive conditions. Preparation of heterocycles from the reaction of 1,1-dibromoethene **1** with other nucleophiles (e.g., 2-aminophenol and 2-aminothiophenol) is under investigation.[19]

Acknowledgments

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