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Facile synthesis of benzoxazoles from 1,1-dibromoethenes

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ABSTRACT

Direct coupling of 1,1-dibromoethenes with 2-aminophenols had been achieved to form the corresponding benzoxazoles under mildly basic reaction conditions. A variety of substituted 2-aminophenols provided the desired products in moderate to good yields. Even though 1,1-dibromoethenes have to be derived from arylcarboxaldehydes or glyoxalate for the reactions, this method still provides a new route to the preparation of benzoxazoles, complementing to existing synthetic strategies.

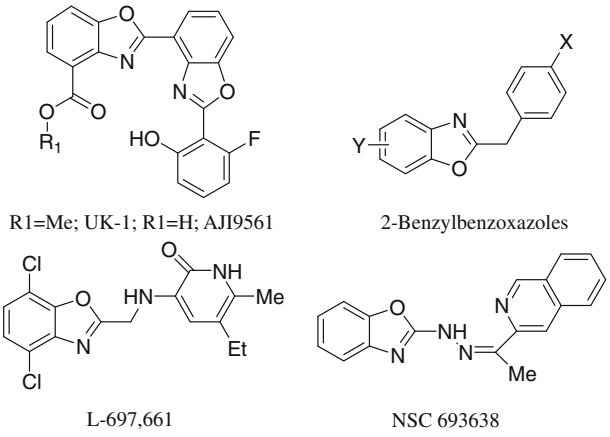
Benzoxazoles are an important class of heterocyclic compounds due to their wide spectrum of biological and photochromatic activities. Previous reports revealed that benzoxazoles possess diverse chemotherapeutic activities including anticancer agent[1] NSC-693638, L-697,661, antiviral,[2] and antibacterials[3] UK-1, AJI9561. Recent studies showed substituted 2-benzylbenzoxazoles have antibacterial, antifungal,[4] antimicrobial,[5] and anti-measles virus activities[6] (Scheme 1). Benzoxazoles also find applications in material sciences as photochromatic agents[7] and laser dyes.[8]

To date, a variety of methods were reported for the preparation of benzoxazoles. The most notable ones include the condensation of *o*-aminophenols with benzoic acids[9,10] or acid derivatives in strong acidic condition such as in polyphosphoric acid (PPA) (Scheme 2);[11] and with aldehydes under strong oxidative conditions using oxidants such as DDQ,[12] $PhI(OAc)_2$,[13] $ThClO_4$,[14] and PCC.[15] Other reported methods are copper-catalyzed intramolecular *ortho* arylation of *o*-haloanilides and intermolecular annulations of *o*-arylhalides with acylamides.[16]

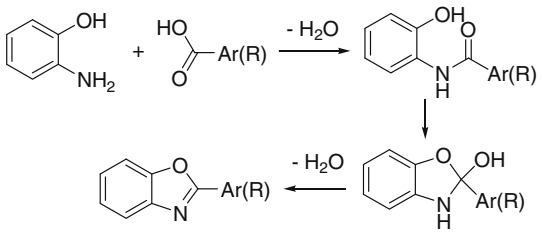
These methods[17] have the limitations when acid sensitive moieties are present, or when molecules are sensitive to strong oxidative conditions. Therefore, there is a need to develop an effective alternative method to produce benzoxazoles under milder conditions, especially without the presence of acid.

As part of a program to extend the recently developed method for an efficient synthesis of benzimidazole from 1,1-dibromoethenes,[18] we further investigated the direct coupling of 1,1-dibromoethenes with 2-aminophenols. Like the *o*-diaminobenzenes, the electrophilic 2-aminophenols were expected to couple with 1,1-dibromoethenes leading to the formation of benzoxazoles.

In line with our expectation, under the mildly basic conditions,[18a,b] 1,1-dibromoalkene (**1a**) and 2-aminophenol (**2a**) gave the desired benzoxazole (**3a**) in a moderate yield (Scheme 3). Under the same conditions, we expanded substrates to a variety of 1,1-dibromoalkenes and 2-aminophenols to investigate the scope of the reaction. The results are described herein.



Scheme 1. Various bioactive molecules containing benzoxazoles.



Scheme 2. The classical method for the preparation of benzoxazoles.

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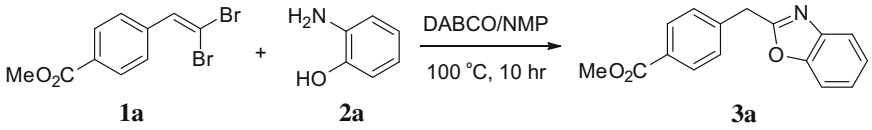
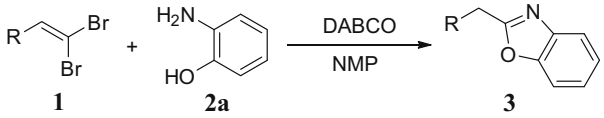


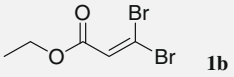
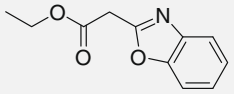
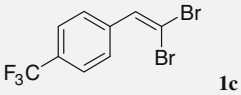
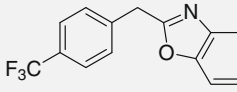
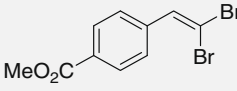
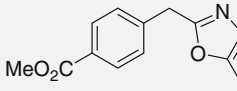
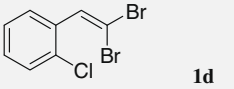
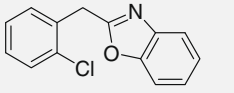
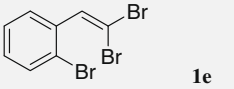
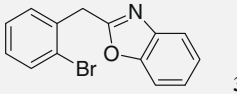
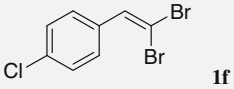
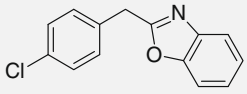
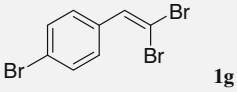
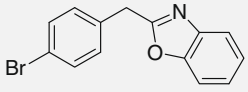
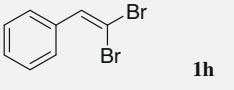
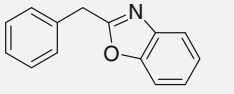
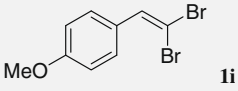
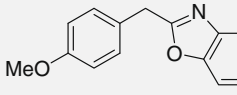
1a 2a 3a

Scheme 3. The new route for the preparation of benzoxazoles.

Table 1
Coupling of 1,1-dibromoalkenes with 2-aminophenol[19]



1 2a 3

Entry	1,1-Dibromoalkene **1**	2-Aminophenol **2**	Temp, time	Benzoxazole **3**	Yield[a] (%)
1	 **1b**	**2a**	100 °C 10 h	 **3b**	84
2	 **1c**	**2a**	100 °C 10 h	 **3c**	80
3	 **1a**	**2a**	100 °C 10 h		72
4	 **1d**	**2a**	100 °C 10 h	 **3d**	62
5	 **1e**	**2a**	100 °C 10 h	 **3e**	59
6	 **1f**	**2a**	100 °C 10 h	 **3f**	65
7	 **1g**	**2a**	100 °C 10 h	 **3g**	61
8	 **1h**	**2a**	100 °C 10 h	 **3h**	62
9	 **1i**	**2a**	100 °C 10 h	 **3i**	54

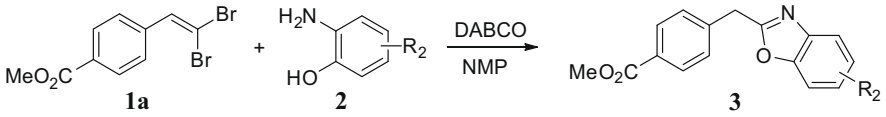
[a] Isolated yield.

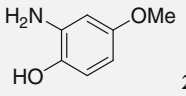
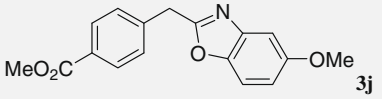
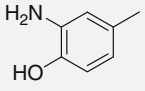
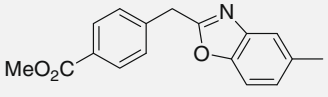
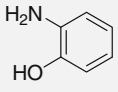
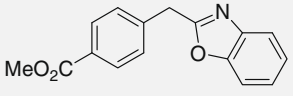
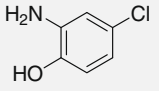
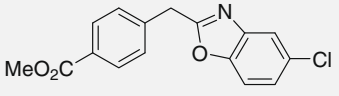
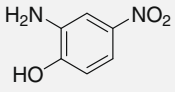
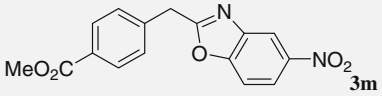
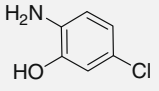
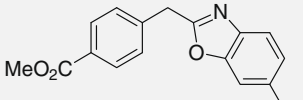
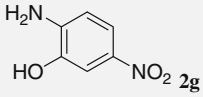
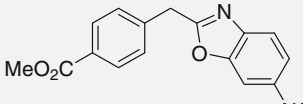
2-Aminophenol was coupled with substituted 1,1-dibromoalkenes successfully (Table 1). Interestingly, higher yields were obtained when 1,1-dibromoalkenes was substituted with electron-withdrawing groups, so the readily prepared electron-deficient methyl 4-(2,2-dibromovinyl)benzoate was chosen to couple with various 2-aminophenols.

Different substituted 2-aminophenols were coupled with methyl 4-(2,2-dibromovinyl)benzoate to provide the desired products in moderate to good yields (Table 2, entries 1–7). However, regardless of the difference of electron-donating or electron-withdrawing nature in the 2-aminophenols, no clear trend was found to influence the yield among these derivates. The interesting observation could be rationalized that a similar 'isoelectric point' phenomenon in the 2-aminophenols containing basic NH_2-group and acidic OH-group at the same time, when electron-donating groups were substituted in 2-aminophenols, the nucleophilicity of NH_2 group was enhanced, meanwhile, the nucleophilic reactivity of OH group was weakened. Similarly, electron-withdrawing groups in 2-aminophenols would weaken the nucleophilicity of the 'NH_2' and enhance the nucleophilicity of the 'OH' group.

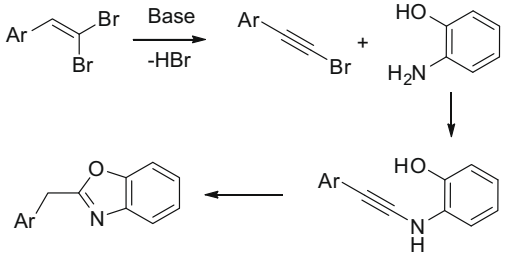
A plausible mechanism is proposed in Scheme 4. It is believed that alkynyl bromides were generated upon treatment of dibromide with a suitable base.[18] Alkynylamines are then formed and followed by an intramolecular cyclization to give the benzoxazole products.

Table 2
Coupling of different 2-aminophenols with methyl 4-(2,2-dibromovinyl)benzoate[19]



Entry	1,1-Dibromoalkene **1**	2-Aminophenol **2**	Temp, time	Benzoxazole **3**	Yield[a] (%)
1	**1a**	 **2b**	100 °C 10 h	 **3j**	61
2	**1a**	 **2c**	100 °C 10 h	 **3k**	58
3	**1a**	 **2a**	100 °C 10 h	 **3a**	72
4	**1a**	 **2d**	100 °C 10 h	 **3l**	57
5	**1a**	 **2e**	100 °C 10 h	 **3m**	66
6	**1a**	 **2f**	100 °C 10 h	 **3n**	76
7	**1a**	 **2g**	100 °C 10 h	 **3o**	56

[a] Isolated yield.



Scheme 4. A proposed mechanism for the formation of benzoxazoles.

In summary, the synthesis of benzoxazoles with direct coupling of 1,1-dibromoethenes with 2-aminophenols has been achieved under mildly basic conditions. This new method is restricted to 1,1-dibromoethenes derived from arylaldehydes and glyoxalate or similar aldehydes, therefore limiting its scope. However, the wide spread application of benzoxazoles could render this method a useful addition to the existing methods, especially with the milder conditions employed. A further investigation of the scope and limitation of this novel preparative method and detailed mechanism of these types of reactions is on-going and will be reported in due course.

Acknowledgment

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19. A typical reaction procedure: A mixture of methyl 4-(2,2-dibromovinyl)-benzoate (**1a**, 640 mg, 2.0 mmol), 5-chloro-2-aminophenol (**2f**, 430 mg, 3.0 mmol), and DABCO (494 mg, 4.4 mmol) in NMP (8 mL) was heated at 100 °C for 10 h. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL), washed with water (2 × 20 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was subjected to silica gel chromatography using ethyl acetate to petro ether as 1–6 to give **3n** (435 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.28 (dd, J = 6.4, 2.0 Hz, 1H), 4.32 (s, 2H), 3.91 (s, 3H). MS (ESI+) m/z: 302.0 (M+H).