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Parallel synthesis of benzoxazoles via microwave-assisted dielectric heating

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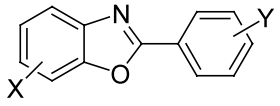
Abstract—A facile route to benzoxazoles has been developed using microwave-assisted dielectric heating. The ease of synthesis and workup allowed the parallel synthesis of a 48-membered library of benzoxazoles quickly and efficiently.

The parallel synthesis of small focused libraries has become an important strategy for the follow-up of screening hits. The benzoxazole scaffold **1** is found in many biologically active compounds, such as elastase inhibitors[1] and H_2-antagonists.[2] There are several reports[3] for the synthesis of benzoxazoles including one which uses solid-phase support.[4] Although the latter method does allow the parallel synthesis of libraries, product diversity is limited since one monomer must contain a functional group which can be tethered to the solid support. A solution-phase parallel synthetic approach would be more flexible with respect to usable reagents and would yield more diverse products. Therefore, we desired a solution-phase route to libraries of the scaffold **1**.



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The reported standard thermal cyclization routes to **1** are not amenable for a parallel approach due to long reaction times and difficult product isolation.[3] The use of microwave-assisted dielectric heating to accelerate reactions has been reported for a number of reactions[5] including benzoxazole formation from aldehydes and 2-aminophenols.[6] Unfortunately, this particular reaction was promoted with mineral supports such as MnO_2 or SiO_2 which prevents facile isolation of the products. An additional method for the microwave-assisted synthesis of benzoxazoles using *S*-methylisothioamides has been reported.[7] Disadvantages of this method are that the *S*-methyl isothioamides must be synthesized prior to use and that toxic methanethiol is produced during the reaction. Microwave-assisted reactions in a common solvent using readily available reagents would be a desirable approach to enhance synthetic throughput for benzoxazoles **1**.

Previous thermal cyclizations[3b] were reported to go through the preformed diacylated aminophenol (Scheme 1a). Since acylations are also promoted by microwave energy,[5] we thought a one-pot (acylation/cyclization) strategy (Scheme 1b) would be amenable for a solution-phase library approach. The effect of base, solvent, concentration, time and temperature on the reaction was systematically explored using the model reaction between **2a** and 3,4,5-trimethoxybenzoyl chloride **3h** to give the desired product **1h**. Product formation from these reactions was followed by gas chromatography.

Additives such as base to facilitate the acylation and Lewis acids to aid dehydration are thought to be necessary to promote high conversion to **1**.[3b,c] Several additives including triethylamine and pyridinium tosylate,[3c] toluenesulfonic acid,[3b] and triflic acid were explored. The control reaction in Scheme 1b (without additives)

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resulted in a 30% yield of **1h**, while basic or acidic additives resulted in yields varying from 8 to 60%. Ultimately, these additives were found to be unnecessary as other parameters resulted in a much higher yield of product. Presumably, as HCl is produced as a by-product during the acylation, it catalyzes the subsequent cyclization reaction.

Conventionally, benzoxazoles have been synthesized in non-polar high boiling solvents such as toluene and xylene.[3b] In the model reaction, other solvents such as dichloroethane, dichlorobenzene and 1,4-dioxane were equally efficient. In addition, aminophenols are markedly more soluble in dioxane. Polar solvents with high boiling points e.g. sulfolane, did not give satisfactory results.

Higher reactant concentrations improved the product yield considerably. A 30% yield was obtained when the aminophenol concentration was 0.9 mM, compared to 76% at 2.7 mM.

The exploration of temperature and reaction time with dioxane and xylene determined that temperatures of at least 200°C resulted in a high yield of the desired product in 10–15 min. Longer reaction times (20–30 min) resulted in partial decomposition of the product.

Optimization of the various parameters resulted in two preferred methods. Both of these methods in the model reaction shown in Scheme 1b resulted in yields of 92 and 81%, respectively.

Method 1: 2.5 mL dioxane, 1.8 mM of 2-aminophenol, 2.0 mM of acid chloride for 15 min at 210°C.

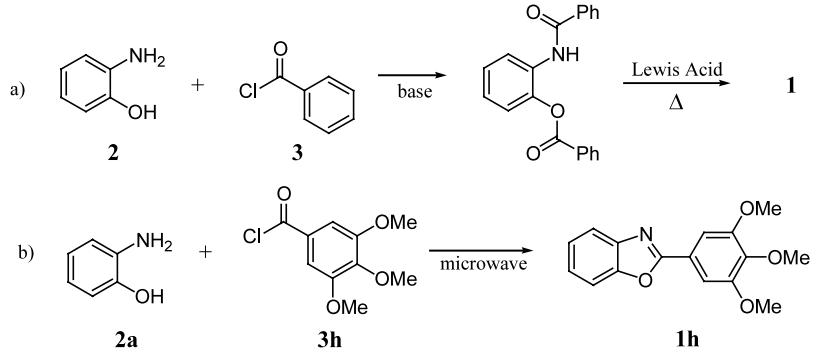
Method 2: 2.5 mL xylene, 2.7 mM of 2-aminophenol, 3.0 mM of acid chloride for 10 min at 250°C.

Control experiments were run with the model reaction between **2a** and **3h**. Conventional dioxane reflux at ambient pressure required 24 h to give an 85% product yield. Further heating resulted in decomposition and lower product purity. This reaction was also run in a sealed tube with refluxing dioxane. In this case, a 15 min reaction time resulted in only a 2% product yield. Clearly, the combination of high heat and pressure produced in the microwave-assisted reaction is the preferred methodology for the rapid synthesis of a focused library.

To demonstrate the advantages of the currently developed procedure for the parallel synthesis of benzoxazoles, a 48-compound library was synthesized (Table 1). Method 1 was chosen due the simple work-up and isolation of the products. An aqueous quench and filtration of the precipitate afforded the product. All entries of the library were synthesized by this method. For comparison, several examples were generated using Method 2. All benzoxazoles were obtained in good to excellent yields (46–98% pure). Method 1 resulted in a 6–25% increase in yield over Method 2. However, in a few cases, Method 2 resulted in a better yield compared to that obtained via Method 1. For example, **1b** was obtained in a 71% yield using Method 2 compared to 66% using Method 1. This may be due to the increased temperature used in Method 2 with this hindered acid chloride **3b**. Moreover, with Method 1 this *ortho*-substituted acid chloride **3b** gave lower yields (49–92%) compared to the *para*-substituted analog **3d** (75–98%) suggesting that steric constraints may limit the scope of this reaction. Electron-withdrawing substituents on the acid chlorides **3d**, **3e** facilitated benzoxazole formation with yields ranging from 75 to 98%.

The six aminophenols **2** gave high yields with the simple acid chloride **3a** with the exception of **2d** (52%). This reagent tended to work less well in all the examples using Method 1. However, significant improvement in the yield with this reagent was observed using Method 2 as shown for product **1y** (54% versus 73%). Reagent solubility may play a role in this observation as this method uses xylene and **2d** is a naphthalene derivative.

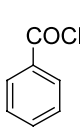
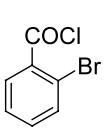
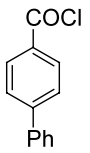
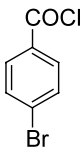
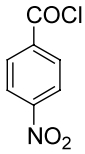
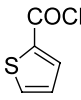
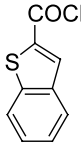
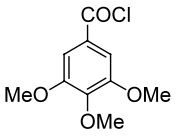
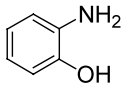
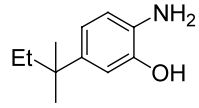
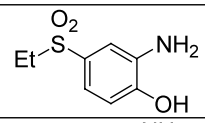
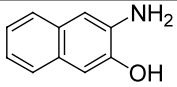
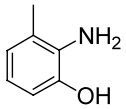
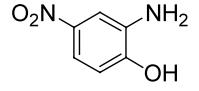
In conclusion, two efficient methods for the solution-phase synthesis of benzoxazoles have been developed. The fact that readily available reagents are used along with the short reaction time, no additives, and simple work-up and isolation of the product make the current approach a feasible and attractive protocol for generation of benzoxazole libraries as demonstrated in Table 1.



Scheme 1. (a) Conventional synthesis of benzoxazoles through diacylated intermediate.[3b] (b) Microwave-assisted synthesis of benzoxazoles in a one-pot acylation/cyclization step. Example shown is model reaction for optimization of reaction conditions.

Table 1. A 48-membered library of benzoxazoles synthesized via method 1[a]

A 48-membered library of benzoxazoles synthesized via method 1.[a]

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
Acid chloride **3** / **2** Amino phenol								
2a 	90 (84) **1a**	66 (71) **1b**	88 (81) **1c**	94 (77) **1d**	96 **1e**	74 **1f**	82 **1g**	92 (81) **1h**
2b 	83 (95) **1i**	56 **1j**	85 **1k**	97 **1l**	98 **1m**	64 **1n**	51 **1o**	87 (71) **1p**
2c 	86 (78) **1q**	52 **1r**	89 **1s**	75 **1t**	90 **1u**	66 **1v**	52 **1w**	91 (81) **1x**
2d 	52 (73) **1y**	54 **1z**	82 **1aa**	75 **1ab**	89 **1ac**	57 **1ad**	78 **1ae**	63 **1af**
2e 	94 (83) **1ag**	92 **1ah**	85 **1ai**	98 **1aj**	95 **1ak**	93 **1al**	96 **1am**	94 **1an**
2f 	90 (81) **1ao**	49 **1ap**	74 **1aq**	94 **1ar**	83 **1as**	72 **1at**	46 **1au**	89 (62) **1av**

[a] Yields obtained by method 2 are reported in parenthesis.

Experimental

All reactions were performed on a SmithSynthesizer™ from Personal Chemistry, Uppsala, Sweden. This instrument typically initiates microwave irradiation at 300 W to raise the temperature to the desired endpoint and then monitors the temperature and reduces the microwave power to 50–100 W to maintain this temperature. Since the reactions are run in a closed vessel, typical pressures observed during reaction were approximately 6 atm. Acyl chlorides and 2-aminophenols were purchased from Aldrich and were of the highest purity available. 1,4-Dioxane and toluene were distilled from sodium prior to use. ^{1}H NMR spectra[8] were recorded on a Varian 200 MHz spectrometer. Low-resolution mass spectral analyses were performed on an HP-6890 mass spectrometer. TLC analysis was performed using silica gel 60 F_{254} plates purchased from Merck.

Typical reaction conditions: A mixture of 1.8 mmol of 2-aminophenol, 2.0 mmol of acyl chloride in 2.5 mL of 1,4-dioxane (or xylene) was treated with microwave in a sealed reaction vessel for 15 min at 210°C (or 250°C). After cooling, the reaction mixture was slowly transferred to a stirred solution of 1N NaOH (50 mL). The precipitated product was filtered, washed with water and dried in vacuo.

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8. All compounds in Table 1 were fully characterized by ^{1}H NMR, mass spec and TLC. Representative examples NMR data for compounds in Table 1: **2-(4-Bromophenyl)benzoxazole (1d)** ^{1}H NMR ($CDCl_3$) δ 8.17–8.09 (m, 2H), 7.81–7.30 (m, 1H), 7.72–7.63 (m, 2H), 7.62–7.54 (m, 1H), 7.43–7.32 (m, 2H). **2-(3,4,5-Trimethoxyphenyl) benzoxazole (1h)** ^{1}H NMR ($CDCl_3$) δ 7.82–7.72 (m, 1H), 7.64–7.53 (m, 1H), 7.50 (s, 2H), 7.41–7.30 (m, 2H), 3.99 (s,

6H), 3.94 (s, 3H). **6-(1,1-Dimethylpropyl)-2-(4-nitrophenyl) benzoxazole** (**1m**) ^{1}H NMR ($CDCl_3$) δ 8.46–8.34 (m, 4H), 7.79 (dd, $J=1.8$, 0.7 Hz, 1H), 7.56 (dd, $J=8.8$, 0.7 Hz, 1H), 7.43 (dd, $J=8.8$, 1.8 Hz, 1H), 1.72 (q, $J=7.4$ Hz, 2H), 2.37, (s, 6H), 0.69 (t, $J=7.4$ Hz, 3H). **2-Thiophen-2-ylnaphtho[2,3-*d*]oxazole** (**1ad**) ^{1}H NMR ($CDCl_3$) δ 8.15(s, 1H), 8.04–7.90 (m, 4H), 7.63 (dd, $J=5.1$, 1.1 Hz, 1H), 7.54–7.43 (m, 2H), 7.23 (dd, $J=5.1$, 3.6 Hz, 1H). **2-Biphenyl-4-yl-4-methylbenzoxazole** (**1ai**) ^{1}H NMR ($CDCl_3$) δ 7.71–7.64 (m, 2H0, 7.54–7.38 (m, 4H), 7.25 (dd, $J=8.0$, 7.4 Hz, 1H), 7.19–7.12 (m, 1H), 2.70 (s, 3H). **2-(2-Bromophenyl)-5-nitrobenzoxazole** (**1ap**) ^{1}H NMR ($CDCl_3$) δ 8.55 (dd, $J=2.2$, 0.7 Hz, 1H), 8.37 (dd, $J=8.8$, 2.2 Hz, 1H), 8.16 (dd, $J=7.6$ 2.0 Hz, 1H), 7.95 (d, $J=8.8$ Hz, 1H), 7.83 (dd, $J=7.6$, 1.6 Hz, 1H), 7.53 (ddd, $J=7.6$, 7.6, 1.6 Hz, 1H), 7.44 (ddd, $J=7.6$, 7.6, 2.0 Hz, 1H).