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A one-pot, two-step microwave-assisted synthesis of highly functionalized benzoxazoles using solid-supported reagents (SSRs)

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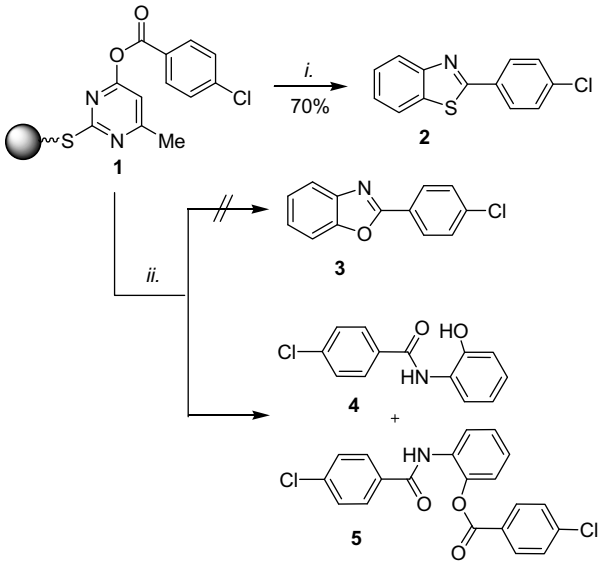
ABSTRACT

A one-pot, two-step protocol for the microwave-assisted solid-phase synthesis of substituted benzoxazoles has been developed starting from different polymer-bound esters we previously designed as solid-supported reagents (SSRs) for the acylation of amines, alcohols and phenols. The combination of a parallel synthesizer and a microwave reactor allowed to quickly prepare a collection of substituted benzoxaxoles in high purity and satisfactory yields. This protocol is amenable for automation and could be used for the preparation of combinatorial libraries in drug discovery programs.

Substituted benzoxazoles have drawn significant attention due to their biological activity and diverse medicinal uses such as gram-positive antibacterial agents,[1] antibiotics,[2] antiparasitic,[3] anti-inflammatory,[4] elastase inhibitors,[5] anti-stress ulcer,[6] and anticancer agents.[7] There are two commonly used approaches for the construction of the benzoxazole ring system: the first approach involves the coupling of the 2-aminophenols with carboxylic acid derivatives under strongly acidic conditions at high reaction temperatures[8] while the second approach uses the reaction of 2-aminophenols with an aldehyde via the oxidative cyclization of imine intermediates.[9] Due to the high biological significance of the benzoxazole scaffold, combinatorial chemistry techniques have been applied to the synthesis of benzofused derivatives to be screened in drug discovery programs. Although several reports for the solid-phase synthesis (SPS) of benzothiazoles, and benzimidazoles have been published,[10] a real need still exists for efficient solid-phase procedures to be applied for the generation of highly functionalized benzoxazole libraries. Hwang and Gong reported the SPS of 2-aminobenzoxazole library using a safety-catch linker[11] while Hioki et al. recently published the synthesis of benzothiazoles, benzoxazoles and benzimidazoles using a traceless-linker.[12] However, both these approaches suffer from long reaction times and were applied to introduce a high level of functionalization at the C2 position only.

Herein we report our results on the development of a one-pot, two-step microwave-assisted protocol for the synthesis of benzoxazoles functionalized at C2, C4, and C5 positions, starting from a series of solid-supported reagents (SSRs). We have previously reported the development of pyrimidine-based SSRs and their application to the microwave-assisted synthesis (MAS) of amides, esters, and thioesters.[13] Unexpectedly, when 2-amino-thiophenol was submitted to the same protocol, the cyclodehydrated



Scheme 1. Reagents and conditions: (i) 2-aminothiophenol, 160 °C, MW (open-vessel mode), neat, 10 min; (ii) 2-aminophenol, 160 °C, MW (open-vessel mode), neat, 10 min.

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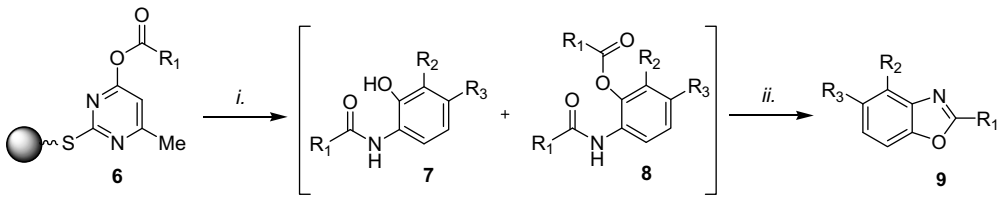

Scheme 2. Reagents and conditions: (i) substituted 2-aminophenols (see R_2 and R_3 in Table 1), MW, 300 W, sealed tube, neat, 10 min; (ii) polymer-bound *p*-toluenesulfonic acid, toluene, MW, 180 °C, sealed tube, 10 min.

benzothiazole was obtained as the only product. Optimization of the previous protocol allowed to obtain the desired benzothiazole **2** in 70% yield and more than 95% purity after simple removal of the resin by filtration (Scheme 1).

Despite this, approach to the synthesis of benzothiazole derivatives was noteworthy, similar results had already been obtained by Janda using different polymer-bound esters in the presence of a Lewis acid.[14] However, the Janda's procedure suffered from two major drawbacks: the need for a chromatographic purification in order to obtain the pure products and its failure in the synthesis of benzoxazole derivatives.

Accordingly, we decided to focus our attention on the development of a simple procedure for the synthesis of highly functionalized benzoxazoles. In a first attempt, we tried to apply the optimized protocol described above to the synthesis of the benzoxazole derivatives. The SSR **1** (1 equiv) was dissolved in 3 mL of CH_2Cl_2 and swollen for 10 min; 2-aminophenol (1 equiv) was then added and, after evaporation of the solvent, the reaction mixture was irradiated at 160 °C for 10 min. Unfortunately the desired benzoxazole **3** was never obtained while amide **4** together with a small amount of the diacylated derivative **5** was isolated as the only product after removal of the solid support by filtration (Scheme 1). The liquid-phase synthesis of benzoxazoles starting from analogues of compounds **4** and **5** in the presence of *p*-toluenesulfonic acid has been previously reported by DeLuca and Kerwin.[15] Accordingly, we decided to develop a one-pot, two-step procedure in which the product/s of the first step (**4** and **5**) could be converted, in a second step, into the desired benzoxazole by heating in the presence of *p*-toluenesulfonic acid (PTSA) polymer bound which could be removed by filtration at the end of the reaction. The optimized procedure is reported in Scheme 2:[16] in the first step, we reacted a series of SSRs (**6**)[17] with an excess of different aminophenols (2 equiv) to shift the equilibrium toward the formation of the uncyclized intermediates (**7** and **8**). The PTSA-polymer bound added in the second step allowed to scavenge the unreacted basic species and to catalyze the cyclodehydration reaction. Final removal of the combined solid supports by filtration allowed to isolate the pure products **9** (Table 1).

Running the reactions into the 10 mL microwave vials, it was possible to combine the characteristics of the Buchi Syncore parallel synthesizer with that of the CEM microwave reactor in order to speed up the generation of the combinatorial collection of benzoxazoles **9**: in the first step of the parallel synthesis,the reaction vessels containing the adequate reaction mixture swelled in dichloromethane, were placed into the syncore and evaporated in parallel. The resulting neat reaction mixtures were then irradiated into the microwave. In the second step, the Syncore was used for the parallel filtration and washing of the resins. Parallel evaporation of the filtrate afforded the pure benzoxazoles **9** (Scheme 2, Table 1). As summarized in Table 1, our procedure allowed to generate a collection of functionalized benzoxazoles (**9**) with an high level of functional group tolerance: both electron-withdrawing and electron-donating groups were well tolerated on the aminophenol moiety while the only completely unreactive acylating species was proved to be the acetyl-SSR. In the case of entries 6, 17–18, 21–22, and 25–28 the benzoxazoles were not formed since the uncyclized intermediates were never obtained.

Table 1
Summary for the synthesis of benzoxazoles **9**

Entry	Loading of the SSRs **6** (mmol/g)[a]	R_1	R_2	R_3	Yield (%)
1	0.353	4-Chlorp-Ph	H	H	61
2		4-Chlorp-Ph	NO2	H	56
3		4-Chlorp-Ph	H	Cl	47
4		4-Chlorp-Ph	H	Me	94
5	0.750	2-Fluoro-Ph	H	H	42
6		2-Fluoro-Ph	NO2	H	—
7		2-Fluoro-Ph	H	Cl	88
8		2-Fluoro-Ph	H	Me	71
9	0.404	2,4-Difluoro-Ph	H	H	47
10		2,4-Difluoro-Ph	NO2	H	42
11		2,4-Difluoro-Ph	H	Cl	38
12		2,4-Difluoro-Ph	H	Me	99
13	0.287	2-Thiophenyl	H	H	73
14		2-Thiophenyl	NO2	H	41
15		2-Thiophenyl	H	Cl	41
16		2-Thiophenyl	H	Me	67
17	0.275	4-Cyano-Ph	H	H	—
18		4-Cyano-Ph	NO2	H	—
19		4-Cyano-Ph	H	Cl	50
20		4-Cyano-Ph	H	Me	24
21	0.265	3-Cyano-Ph	H	H	—
22		3-Cyano-Ph	NO2	H	—
23		3-Cyano-Ph	H	Cl	57
24		3-Cyano-Ph	H	Me	31
25	0.338	Acetyl	H	H	—
26		Acetyl	NO2	H	—
27		Acetyl	H	Cl	—
28		Acetyl	H	Me	—

[a] The loading was calculated as described in Ref. 17.

In conclusion, an efficient one-pot, two-step protocol for the microwave-assisted solid-phase synthesis of substituted benzoxazoles has been developed starting from acylating solid-supported reagents (**6**). The combination of a parallel synthesizer and a microwave reactor allowed to quickly prepare a collection of highly functionalized benzoxaxoles **9**. This protocol is amenable for automation and could be used for the preparation of combinatorial libraries in drug discovery programs.

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16. *Microwave reactions* were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The reaction was performed in glass vessels (capacity 10 mL) sealed with septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. *General procedure for the synthesis of benzoxazoles* **9**: the SSRs **6** (1 equiv) were partitioned into four different microwave tubes, each placed within the Syncore and swelled in CH_2Cl_2 (3 mL) for 10 min. The required aminophenols were added, the resulting mixture stirred for additional 10 min, and finally evaporated in parallel (14 per time). The neat crude mixtures were irradiated into the microwave at 300 W for 10 min each. The resins were then swelled with toluene (3 mL), PTSA-polymer bound (8 equiv) was added and the resulting mixtures were irradiated into the microwave for 10 min at 180 °C. The combined solid supports were removed by parallel filtration then evaporation and trituration with hexane gave the desired benzoxazoles **9** in high purity.
17. The SSRs **6** were prepared following the previously published procedure[13] and their loading was calculated by cleavage of the corresponding benzylamides: considering the theoretical loading of the SSR equal to that of the Merrifield resin (1.25 mmol/g), reaction with 1.25 mmol of benzylamine gave an amount of benzylamide equal to the real loading (see Table 1).