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Solid-phase combinatorial synthesis of 1,4-benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives

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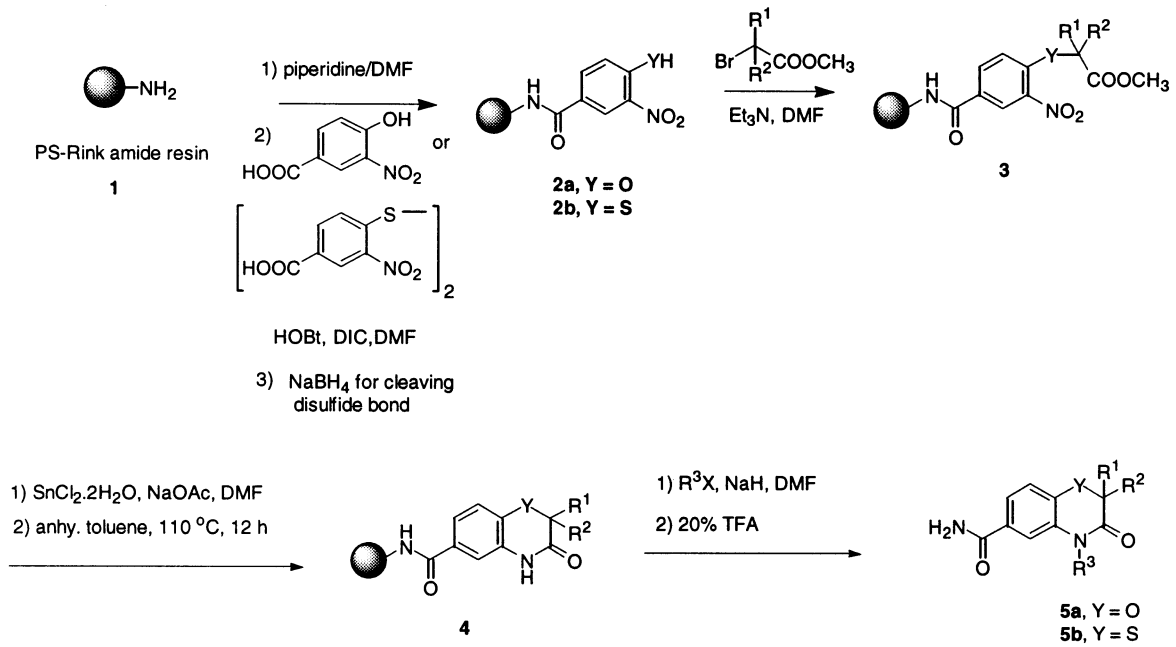
Abstract—The first solid-phase synthesis of 1,4-benzothiazin-3(4*H*)-ones and 1,4-benzoxazin-3(4*H*)-ones is reported. Alkylation of the immobilized 4-hydroxy-3-nitrobenzamide **2a** and 3-nitro-4-sulfanylbenzamide **2b**, followed by reduction and cyclization gave **4**. Further alkylation and acylation was performed on the amide nitrogen in the presence of sodium hydride followed by TFA cleavage to give the desired 1,4-benzothiazin-3(4*H*)-ones and 1,4-benzoxazin-3(4*H*)-ones.

The effort to prepare large numbers of diverse, novel and biologically active small molecules for drug discovery and development has caused an unprecedented growth in both combinatorial chemistry[1] and solid-phase organic synthesis.[2] Various classes of compounds, e.g. benzodiazepines,[3,4] β-lactams,[5] β-turns,[6] and quinazoline derivatives[7,8] have been synthesized in this manner. 1,4-Benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives are an interesting group of compounds both pharmacologically and agriculturally. The 1,4-benzoxazin-3(4*H*)-one moiety can be found in molecules which exhibit plant resistance fac-



Scheme 1. Solid-phase synthesis of 1,4-benzoxazine and 1,4-benzothiazine.

Keywords: solid-phase synthesis; 1,4-benzothiazin-3(4H)-one; 1,4-benzoxazin-3(4H)-one.

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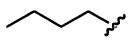
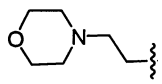
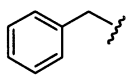
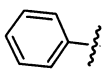
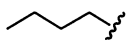
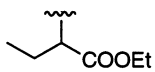
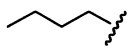
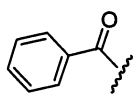
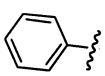
tors against microbial diseases and insects,[9] analgesic,[10] antimicrobial[11] and potassium channel modulating[12] properties, whilst 1,4-benzothiazin-3(4*H*)-ones, like semotiadil, are antihypertensive drugs,[13] calcium antagonists[14] and highly potent inhibitors of LDL-oxidation.[15] Spurred by the diverse biological activities and desirable pharmacokinetics of these compounds, a variety of synthetic procedures affording compounds with the 1,4-benzoxazine and 1,4-benzothiazine skeleton have been developed.[16,17] Herein, we describe the first solid-phase synthesis of 1,4-benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one libraries that incorporate a variety of chemical functionalities.

In the solution phase, the alkylation of methyl bromoalkenoates with 2-aminophenol and 2-aminothiophenol gave 1,4-benzoxazine and 1,4-benzothiazine derivatives, respectively.[17] However, the solid-phase alkylation of methyl bromoalkenoates with immobilized 2-aminophenol and 2-aminothiophenol gave dialkylated products due to the excess of bromo ester used. To circumvent this problem we proceeded to prepare 4-hydroxy-3-nitrobenzamide (**2a**) and 3-nitro-4-sulfanylbenzamide (**2b**). Deprotection of the Rink amide resin **1** followed by standard DIC and HOBt coupling with 4-hydroxy-3-nitrobenzoic acid gave **2a** whilst coupling of the resin with bis-(2-nitro-4-carboxyphenyl) disulfide followed by sodium borohydride cleavage of the disulfide bond yielded **2b** (Scheme 1). Alkylation of **2a** and **2b** with methyl bromoalkenoates in the presence of triethylamine base yielded **3**. The nitro group was reduced to the amine by tin(II) chloride dihydrate solution in the presence of a small amount of sodium acetate. The latter reagent was required to act as a buffer to prevent early cleavage of **3** from the resin. The reduction process was completed

Table 1. The yield and HPLC purity of compounds **5a** and **5b**

Entry	Y	R^1	R^2	R^3	% Yield[a]	HPLC Purity[b]
1	S	CH_3	CH_3		62	98
2	S	CH_3	CH_3		53	72
3	O	CH_3	CH_3		26[c]	88[c]
4	O		H		49	41
5	O	CH_2CH_3	H		32[c]	97[c]
6	O	CH_2CH_3	H	CH_3	36[c]	100[c]
7	S	CH_2CH_3	H		60	98
8	S	CH_3	CH_3		73	89
9	S	CH_3	H		86	87
10	O		H		81	62

[a]Yields calculated based on theoretical loading of the resins.
[b]HPLC purity at 254 nm with a Hypersil ODS C18 reverse-phase column (2.1 x 200mm).
[c]Purified by silica column chromatography. Purity determined by HPLC.

in 4 h and the reduced intermediate was cyclized to **4** in refluxing toluene. Alkylation and acylation of the amide nitrogen of **4** by alkyl halides and acyl chlorides in the presence of sodium hydride and anhydrous DMF, followed by acid cleavage from the resin, yielded **5**.

The cleaved 1,4-benzoxazin-3(4*H*)-ones (**5a**) and 1,4-benzothiazin-3(4*H*)-ones (**5b**) were characterized by ^{1}H NMR and MS. Ten representative examples were randomly selected and their yields and purities are summarized in Table 1. Alkylation on the sulfur or oxygen atom proceeded smoothly to give **3** in quantitative yields. In our hands, the reduced intermediates did not cyclize spontaneously to **4** as reported earlier.[18] Various bases like triethylamine, potassium hydroxide in ethanol and sodium methoxide in methanol, were used to facilitate the cyclization. The latter strong bases rendered degradation of the resin when the reaction time was more than 6 h. The reduced intermediates were eventually subjected to reflux in neat toluene to give **4**. The subsequent alkylation of **4** was problematic because of the low reactivity of the amide nitrogen. Hence a strong base such as sodium hydride was used. Aliphatic halides reacted smoothly at room temperature (entries 1, 2, 4 to 7). Alkyation with benzylic bromide (entry 3) was, however, less successful probably because of the steric hindrance from the bulkier phenyl group. Comparatively, acylation with the more reactive acyl chlorides (entries 8 to 10) afforded a better overall yield than those from alkyl halides. The low HPLC purity in entry 4 was due to incomplete alkylation of **4**.

In summary, this paper demonstrates the first solid-phase route to 1,4-benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives. Application to the synthesis of large benzoxazinone and benzothiazinone libraries is presently under investigation.

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