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Solid-Phase Synthesis of Benzoxazoles *via* Mitsunobu Reaction

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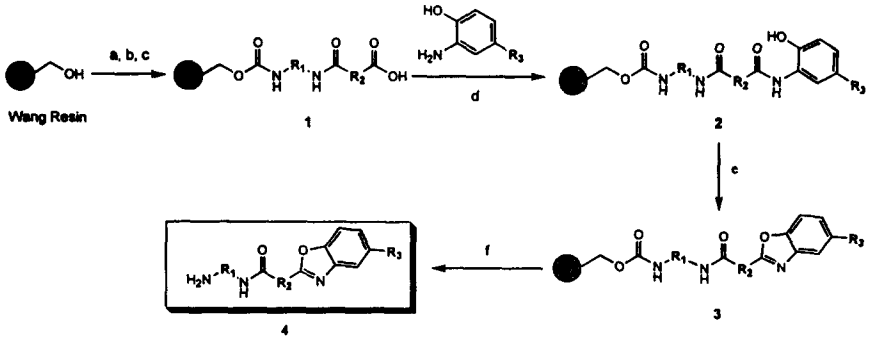
Abstract: 2-Amidophenol attached to a solid support can be converted to the corresponding benzoxazole by treatment with triphenylphosphine and diethyl azodicarboxylate in THF at room temperature in high yield and purity.

The synthesis and screening of small molecule combinatorial libraries has become an important new technology for drug discovery.[1] A convenient format for the generation of these libraries is the synthesis of organic compounds on a solid phase. Solid phase synthesis is especially useful for many synthetic transformations, since excess reagents can be used to drive the reactions to completion and the excess reagents and soluble byproducts are easily removed.[2]

There are no reports describing the solid-phase synthesis of benzoxazoles, although targets containing the benzoxazole moiety, either isolated from natural products or accessed by total synthesis, have remarkable biological activities.[3] For example, gram-positive antibacterials,[4] polycyclic antibiotics,[5] antiparasitics,[6] antiinflammatories,[7] elastase inhibitors,[8] and H_2-antagonists,[9] all contain the benzoxazole fragment. These examples highlight the level of interest in new synthetic approaches to benzoxazole derivatives and prompted us to explore this pharmacophoric scaffold in a combinatorial format *via* solid-phase synthesis.

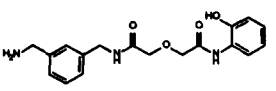
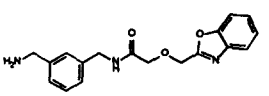
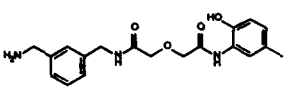
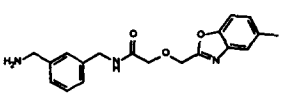
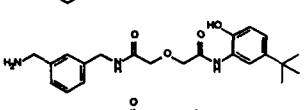
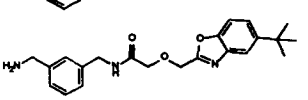
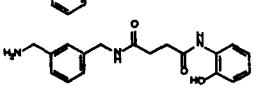
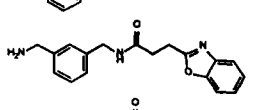
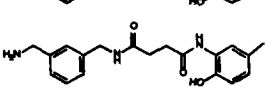
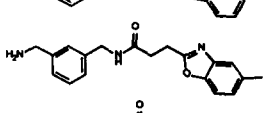
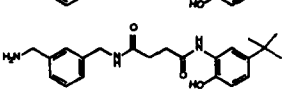
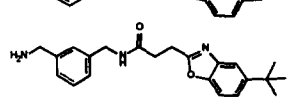
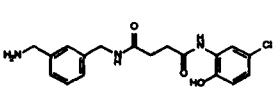
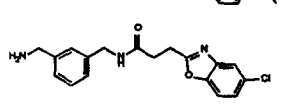
A representative synthesis of benzoxazole derivative **4** in solid phase is outlined in **Scheme 1**.[10] Treatment of Wang resin with 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran furnished the corresponding imidazolide resin,[11] which was allowed to react with diamines to generate the aminofunctionalized resin with an acid-labile carbamate linker. Acylation of the resulting resin with dicaboxylic anhydrides in pyridine/CH_2Cl_2 at rt gave carboxylfunctionalized **resin 1**. The reaction progress could be readily monitored by the Kaiser test,[12] wherein the beads should be colorless for the complete reaction. Utilizing well-developed PyBOP coupling chemistry,[13] either 2-aminophenol or aromatic ring substituted 2-aminophenol were coupled onto **resin 1** to provide **resin 2**. After cleavage of the carbamate linker with a mixture of TFA/CH_2Cl_2, the 2-amidophenol was released from **resin 2** in high yield (see Table 1). Importantly, there was no amino ester formation, since 2-amidophenol was the only product observed under the PyBOP coupling condition. This was confirmed by HPLC analysis, in which only a single peak appeared, and analysis of the infrared bands at 1645, 1545, and 1285 cm^{-1}, as well as NMR characterization supported the assigned structure. No ester bands were observed in the 1735 cm^{-1} region.

Thermal cyclization with acid catalysts is commonly employed to synthesize benzoxazoles.[3] For example, 2-amidophenols have been treated with PPA or PPE,[4b, 6b] propionic acid,[14] $POCl_3$,[15] and $SOCl_2$[16] at



Scheme 1 (a) CDI, THF, rt. (b) Diamine, THF, rt. (c) Dicarboxylic anhydride, DMAP, pyridine/CH_2Cl_2 (1:1), rt. (d) PyBOP, NMM, DMF, rt. (e) Ph_3P, DEAD, THF, rt. (f) TFA/CH_2Cl_2, rt.

Table 1. 2-Amidophenols **2** and Benzoxazoles **4**

	2-Amidophenols[a]	Yield% (Purity%)[b,c]		Benzoxazoles	Yield% (Purity%)[b,c]
2a		92 (86)	4a		90 (85)
2b		95 (87)	4b		95 (90)
2c		97 (95)	4c		97 (94)
2d		88 (85)	4d		86 (82)
2e		96 (92)	4e		95 (88)
2f		99 (92)	4f		99 (90)
2g		83 (61)	4g		79 (57)

a) Compounds were cleaved from resin **2** with TFA/CH_2Cl_2. b) Yields are based on mass balance of lyophilized product relative to the resin substitution level. c) Purity was determined by HPLC analysis.

high temperature to give benzoxazoles. It is noted that those conditions are not suitable for solid phase synthesis, since the polymer support and the linker normally do not survive under such harsh reaction conditions. When we exposed solid phase linked 2-amidophenols to either $POCl_3$ or $SOCl_2$ with 1 equivalent of pyridine in toluene at 80° C, more then 50% of the 2-amidophenol was cleaved from solid support in 30 min.

Our attention turned to use of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD), since the cyclo dehydrative reaction would now proceed under mild, neutral conditions.[17]

The intramolecular dehydrative cyclization of the 2-amidophenol attached to a solid support (**resin 2**) employing excess of TPP and DEAD in THF proceeded smoothly at room temperature to provide **resin 3**. The resin was then treated with TFA/CH_2Cl_2, dried and lyophilized to yield the desired benzoxazole **4**. Overall conversion and purity of compounds **4** obtained upon cleavage of the heterocycles from the resin are listed in Table 1. In general, the reaction of **resins 2** under Mitsunobu conditions gave benzoxazoles in high yield (>90%) and in high purity (>80%). With electron-withdrawing groups on the aromatic ring (entry **4g**) the yield and the purity of the resulting benzoxazoles were adversely effected.[18] All the compounds in Table 1 were fully characterized by HPLC, mass spectroscopy (low or high resolution), ^1H NMR, and ^{13}C NMR.

In summary, we have, for the first time, demonstrated a very convenient methodology for the solid-phase synthesis of benzoxazoles *via* Mitsunobu reaction conditions. This procedure has been applied to synthesis of a combinatorial library with satisfactory results.

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10. **General Procedure for Preparation of Compounds 4.** Dry Wang resin was added to a solution of 0.4 N 1,1'-carbonyldiimidazole in anhydrous THF and shaken at rt for 6 hours. The resin was washed thoroughly with THF to remove excess CDI and treated with 0.4 N *m*-xylylenediamine in THF at rt for 15 hours. To the aminofunctionalized resin was added 0.4 N succinic anhydride or diglycolic anhydride in pyridine/CH_2Cl_2 (v:v = 1:1) and a catalytic amount of DMAP, then shaken at rt for 4 hours. The resulting carboxylfunctionalized **resin 1** was washed with DMF, CH_2Cl_2, and MeOH, and dried under high vacuum. Kaiser test of the beads was negative indicating complete reaction. To **resin 1** (100 mg, 0.075 mmol) was added PyBOP (195 mg , 0.375 mmol) and substituted or unsubstituted 2-aminophenol (0.375 mmol) in 1mL of DMF, followed by N-methylmorpholine (NMM) (41 μL, 0.375 mmol). The mixture was shaken at rt for 17 hours. The resulting **resin 2** was washed extensively with DMF, CH_2Cl_2, and MeOH, and dried under high vacuum. To the mixture of **resin 2** and TPP (98 mg, 0.375 mmol) in 1 mL of anhydrous THF was added dropwise DEAD (59 μL, 0.375 mmol) at rt. The mixture was shaken at rt for 17 hours, followed by washing with THF, CH_2Cl_2, and MeOH. The resulting **resin 3** was dried under vacuum, and treated with a solution of 50% TFA in CH_2Cl_2 at rt for 30 min to release the polymer-bound heterocycle **4**. Removal of the volatiles under a stream of nitrogen followed by lyophilizing with 50% CH_3CN in water afforded the highly pure compound as a powder. **4a:** ^{1}H NMR (DMSO-d_6) δ 4.01 (dt, J = 5.1 Hz, J' = 6.0 Hz, 2H), 4.16 (s, 2H), 4.32 (d, J = 6.3 Hz, 2H), 4.90 (s, 2H), 7.27-7.44 (m, 7H), 7.73 (d, J = 8.1 Hz, 1H), 8.25 (bs, 2H), 8.53 (t, J = 6.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 41.6, 42.3, 66.9, 70.3, 115.3, 119.0, 121.6, 124.8, 125.5, 127.2, 127.3, 127.6, 128.7, 134.0, 139.9, 147.6, 162.4, 168.8. High-resolution mass spectrum calcd for $(C_{18}H_{19}N_3O_3 + H)^+$ *m/z* 326.1509, found 326.1517. **4b:** ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 4.01 (dt, J = 4.5 Hz, J' = 6.0 Hz, 2H), 4.14 (s, 2H), 4.32 (d, J = 6.0 Hz, 2H), 4.87 (s, 2H), 7.22-7.36(m, 6H), 7.55 (s, 1H), 8.25 (bs, 3H), 8.52 (t, J = 6.3 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 20.9, 41.6, 42.3, 65.1, 69.9, 114.4, 119.7, 121.9, 125.0, 125.2, 127.3, 127.6, 127.7, 128.7, 134.0, 139.9, 145.3, 162.5, 168.5. High-resolution mass spectrum calcd for $(C_{19}H_{21}N_3O_3 + H)^+$ *m/z* 340.1661, found 340.1674. **4c:** ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9H), 4.01 (dt, J = 4.5 Hz, J' = 6.0 Hz, 2H), 4.15 (s, 2H), 4.33 (d, J = 6.0 Hz, 2H), 4.88 (s, 2H), 7.26-7.37 (m, 4H), 7.49 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.74 (s, 1H), 8.26 (bs, 2H), 8.52 (t, J = 6.3 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 31.4, 33.8, 41.6, 42.3, 65.4, 70.3, 115.2, 119.0, 121.5, 124.8, 127.2, 127.3, 127.7, 128.7, 134.0, 139.9, 141.3, 145.5, 162.5, 168.4. High-resolution mass spectrum calcd for $(C_{22}H_{27}N_3O_3 + H)^+$ *m/z* 382.2130, found 382.2122.

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18. The impurity resulted from the incomplete PyBOP coupling reaction due to the electron-withdrawing groups on the aromatic ring. For less nucleophilic substrates, the yield and purity could be improved by using PyBroP, a more reactive coupling reagent. See, Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259.

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