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Solution-Phase Parallel Synthesis of Benzoxazines Using a Polymer-Supported Carbodiimide

Brad O. Buckman,* Michael M. Morrissey and Raju Mohan

Pharmaceuticals Discovery, Berlex Biosciences
15049 San Pablo Avenue, Richmond, CA 94804

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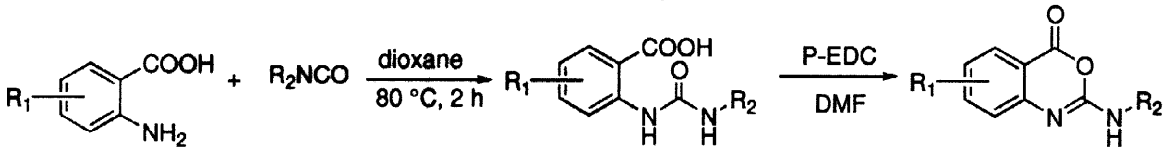
Abstract: A diverse library of 2-aminobenzoxazines **3** has been synthesized using a two step approach. Addition of anthranilic acids to isocyanates affords ureas **2** that can be cyclized by polymer-supported EDC to give 2-aminobenzoxazines **3**.

In the recent years, the desire to generate large numbers of diverse and novel small molecules for drug discovery has caused the rapid growth of both combinatorial chemistry and solid-phase organic synthesis of heterocyclic compounds.[1] A number of structural families known to possess high biological activity have been synthesized in this manner (e.g., benzodiazapines, β-lactams and β-turn mimetics). Alternatively, solution-phase parallel synthesis, in which reagents are polymerically bound or reaction products are purified by solid-phase techniques, has attracted attention, as well.[2] We have earlier reported the solid-phase synthesis of 1,3-dialkyl quinazoline-2,4-diones from anthranilic acid derivatives.[3] A related family of compounds, 2-substituted benzoxazines, has recently been shown as inhibitors of serine proteases, such as HLE,[4a] HSV-1 protease,[4b] and human cytomegalovirus protease.[4c] These and other reported syntheses employ traditional techniques of using an equimolar or greater excess of reagents or aqueous extraction. In this communication, we wish to report an easily automated parallel solution-phase synthesis of substituted 2-amino benzoxazines using a polymer-supported carbodiimide.

Our strategy towards developing a synthesis of benoxazines consists of two steps: urea formation and dehydration/cyclization (Scheme 1). The aromatic ring and the 2-amino position of the benzoxazine **3** are used as sites of attachment for R_1 and R_2, respectively. These substituents are derived from two readily available classes of reagents: anthranilic acids **1** and isocyanates.



1 **2** **3**

Scheme 1

We were intrigued by the possibility of using polymer bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (P-EDC)[5] as a reagent for cyclization/dehydration that could be easily filtered from the reaction. Formation of 2-aminobenzoxazine **3** is achieved in a two-step process (Scheme 1).[6] Reaction of anthranilic acid **1** with an aryl or alkyl isocyanate in dioxane/toluene at 80 °C generates urea **2**. Cyclization of the urea is achieved by addition of P-EDC to the reaction mixture. Both the urea **2** and excess unreacted anthranilic acid **1**, which was added to force conversion of the isocyanate to the urea intermediate, are bound to the P-EDC. Cyclization of the urea intermediate releases benzoxazine **3**, while the unreacted anthranilic acid remains bound to the P-EDC and is removed from the reaction mixture by filtration. Both aryl and alkyl isocyanates and a range of substituted anthranilic acids react successfully. Table 1 shows a representative selection of compounds synthesized. In order to facilitate robotic automated parallel synthesis, dioxane was chosen to provide a general solvent for dissolution of the diverse array of anthranilic acids, which have relatively low solubility in non-protic organic solvents. In many cases, urea intermediate **2** precipitates

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from the dioxane/toluene reaction solution. Addition of P-EDC as a slurry in DMF solubilizes any precipitated urea intermediate.

Table 1. 2-Aminobenzoxazines **3**

Cmpd	R_1	R_2	Hplc purity (%)[a]	Yield (%)[c]
3a	4-methyl	Butyl	97	88
3b	4-methyl	Allyl	92	79
3c	4-methyl	2,6-diisopropylphenyl	87	93
3d	4-methyl	2-bromophenyl	88	90
3e	4-fluoro	Benzyl	96	89
3f	H	4-methoxyphenyl	95[b]	82
3g	H	4-chlorophenyl	90[b]	92
3h	2-chloro	Isopropyl	97	75
3i	2,4-dimethyl	4-isopropylphenyl	89	73
3j	2-methyl	2-ethylphenyl	89	86
3k	2-methoxy	2-chlorophenyl	85	75
3l	2-trifluoromethyl	2-methylphenyl	83	94
3m	4-iodo	Ethyl	80	81

[a]Purity determined by hplc analysis of crude products. Products show satisfactory ^{1}H NMR or MS data. Side-products consist of symmetrical urea derived from the isocyanate. [b]Compared to authentic sample prepared by independent synthesis. [c]Determined from weight of crude sample.

In conclusion, we have developed an easily automated solution-phase parallel synthesis of 2-aminobenzoxazines using anthranilic acids, isocyanates and P-EDC. This approach offers the potential of providing diverse libraries of benzoxazine derivatives for assay in biological systems.

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6. Experimental Procedure: Using proprietary liquid handling equipment, anthranilic acid (110 uL, 0.2 M in dioxane, 0.022 mmol, 1.1 equiv.) and p-methoxyphenyl isocyanate (100 uL, 0.2 M toluene, 0.020 mmol, 1.0 equiv.) are added to 250 uL of dioxane and heated at 80 °C for 2 h. The reaction is cooled to rt and polymer supported EDC is added (33 mg, 3 meq/g, 0.5 mL slurry in DMF, 0.10 mmol, 5 equiv.) and the reaction is vortexed for 16 h. The product benzoxazine is filtered from the P-EDC and concentrated *in vacuo*. ^{1}H NMR (dmso-d_6) 3.75 (s, 3), 6.95 (d, 2, J = 4, 7.20-7.40 (m, 2), 7.65 (d, 1, J = 4), 7.75 (dd, 1, J = 4,4), 7.95 (d, 1, J = 4). MS (m/z) 268.