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Solid Phase Synthesis of Quinazolinones

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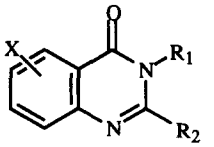
Abstract. Substituted 4(3H)-quinazolinones were synthesized under acidic conditions from polymer supported anthranilamide precursors and aldehyde inputs. Dehydrogenation using potassium permanganate followed by trifluoroacetic acid cleavage afforded the desired compounds in acceptable yields and purities. Additional diversity at the 3 position was realized by employing amino acid derivatized polymer support.

The high speed synthesis of organic compounds by solid phase or solution phase methods is rapidly becoming established as an enabling technology in modern medicinal chemistry.[1] While the solid phase approach offers a number of inherent advantages over solution phase methods, especially in the context of robotic format, its practical implementation frequently poses a number of challenges. The compatibility of a solid support and linker with a particular set of reaction conditions may restrict the scope of chemistry employed, and the retention of polar groups by the target molecules following cleavage can influence the chemical and biological diversity within the resulting library.



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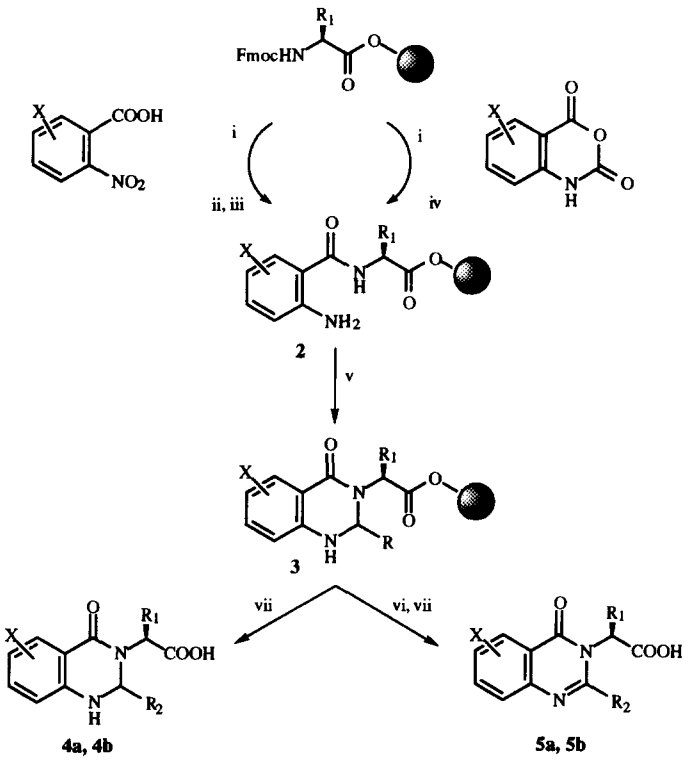
The quinazoline skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including anticonvulsant,[2] antibacterial,[3] and antidiabetic agents.[4] The 2-substituted quinazolinones **1** in particular have been utilized as peptidomimetic scaffolds with specificity for cholecystokinin,[5] angiotensin[6] and certain cell adhesion receptors.[7] While several previous reports[8] have described solid phase syntheses of the related quinazoline-2,4-diones, our goal was the development of a general route permitting the introduction of a wide range of substituents into the 2-position of this ring system. In this communication we report a versatile solid phase approach to the 2-substituted quinazolinones using anthranilic acid and aldehyde inputs with the option of a traceless release from the support.[9]

The following procedure, outlined in Scheme 1, was utilized for the synthesis of compounds summarized in Table 1. Commercially available Fmoc amino acid derivatized Wang resins[10] were deprotected by two successive treatments with 20% piperidine in DMF, and then converted, either through a two step

sequence using o-nitrobenzoic acids, or directly, by utilizing isatoic anhydrides to the anthranilamide intermediate **2**. Incorporation of o-nitrobenzoic acids involved DCC/HOBt mediated coupling in DMF followed by treatment with $SnCl_2$ in DMF.[11] Alternatively, the deprotected resin was exposed to three equivalents of isatoic anhydride in DMF and heated at 55° C overnight. The progress of the isatoic anhydride reaction and the o-nitrobenzoic acid coupling reaction was conveniently monitored by the ninhydrin test. The option of introducing anthranilic acids via commercially available o-nitrobenzoic acids or isatoic anhydrides effectively expanded the range of aromatic substituents beyond that which could be realized through either



Scheme **1.** Legend : i) 20% piperidine/DMF, ii) DCC/HOBt/DMF, iii) $SnCl_2$/DMF, 5hr., iv) DMF, 55°C, O/N, v) RCHO/5% AcOH /DMA, 100°C, 24hr., vi) $KMnO_4$/acetone O/N, vii) 50% TFA/DCM, 1 hr.

route alone. The polymer bound intermediate **2** was portioned into smaller (0.1 mmole) batches and used in discrete cyclocondensation reactions. A number of cyclization protocols based on published solution phase precedents were evaluated for compatibility with automated solid phase format. Time-course studies carried out utilizing HPLC analysis and gel phase ^{13}C NMR[12] indicated that optimal results could be obtained by employing an 8 to 10 fold excess of the aldehyde input in dimethylacetamide (DMA) in the presence of 5% acetic acid at 100°C. These conditions were subsequently validated for a broader range of aldehyde and

anthranilamide inputs. A 24 hour reaction time was neccessary to accomodate less reactive aromatic aldehydes within a general synthetic protocol. The resulting polymer bound dihydroquinazolinones **3** were either released by suspension in 50% (v/v) trifluoroacetic acid/ dichloromethane for one hour to give compounds **4a** and **4b,** or converted with nearly quantitative efficiency to the corresponding polymer bound 4-(3H)-quinazolinones by exposure to 10 equivalents of $KMnO_4$ in acetone overnight, followed by TFA cleavage to give compounds **5a** and **5b**. A traceless application of this chemistry was achieved under identical conditions through the substitution of Rink resin[13] in place of amino acid derivatized Wang resin in Scheme 1 to produce N-3 unsubstituted compounds **6a-6e**. Characterization was provided by ^{1}H-NMR and electrospray mass spectrometry.[14] Table 1 summarizes purity[15a] and yield[15b] data from a representative set of compounds.

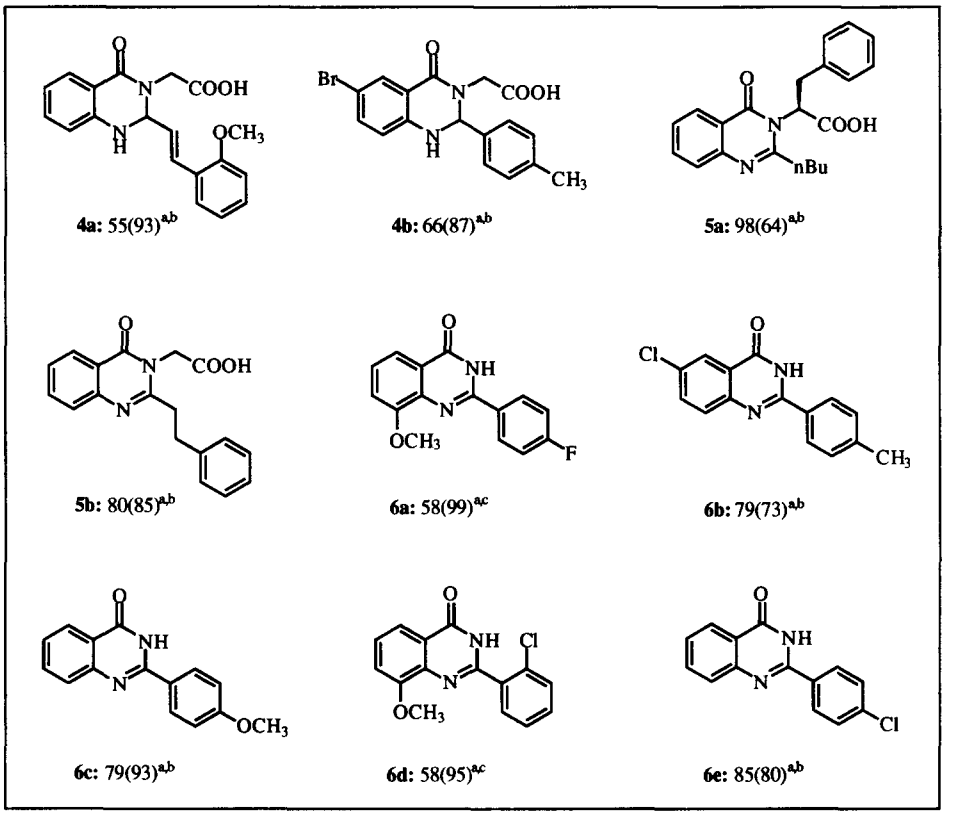


Table 1. Representative products and results. [a] Crude yield ; number in brackets refers to HPLC assessed purity. [b] Product synthesized via isatoic anhydride route. [c] Product synthesized via o-nitrobenzoic acid route.

In summary we have developed a straightforward, easily automated solid phase procedure allowing for the synthesis of N-3 substituted and unsubstituted quinazolinones and corresponding dihydroquinazolinones. A single, general protocol was validated for a wide range anthranilamide and aldehyde combinations.

Acknowledgment

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15. a) Analysis was carried out by HPLC (Vydac C_{18} column, 4.6 x 250mm, 0-50% acetonitrile/water containing 0.1% TFA with integration of peak areas at 220nm). b) yields were calculated from the weight of crude material and the initial loading level of starting resin.

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