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Solid phase synthesis of styrylquinazolinones

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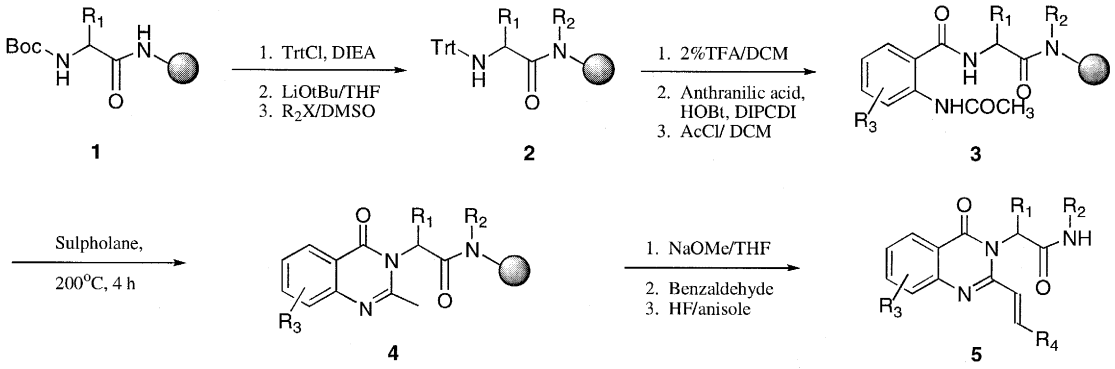
Abstract

The solid phase synthesis of styrylquinazolinones is described. Starting from resin-bound amino acids, and employing alkylation, acylation, and condensation reactions, the desired styrylquinazolinones have been synthesized in good yield and high purity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: combinatorial chemistry; solid phase synthesis; styrylquinazolinones.

In recent years, substantial developments have been made in the field of combinatorial chemistry, and solid phase synthesis has been a key component in this area.[1] The discovery of new, biologically active compounds has been driven by the application of combinatorial methods to the synthesis of heterocycles and small molecules.[2] In our laboratory, one focus has been on the use of amino acids and small peptides as starting materials in the development of heterocyclic combinatorial libraries.[3]



Scheme 1. Synthesis of styrylquinazolinones

Due to their wide range of biological activity, a variety of synthetic methods have been developed for quinazolinones.[4] A wide variety of quinazolinone analogs have been shown to possess antibacterial,[5]

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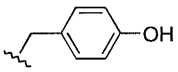
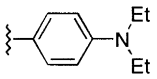
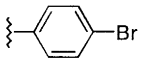
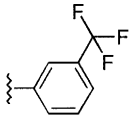
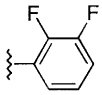
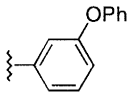
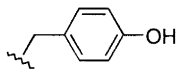
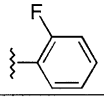
Table 1
Selected styrylquinazolinones

Compound #	R_1	R_2	R_3	R_4	Purity
5a		H	H	Ph	88%
5b	H	Me	H		70%
5c	H	H	H		85%
5d	Me	H	H		83%
5e	H	Me	8-Br	Ph	71%
5f	Me	H	H		72%
5g	Me	H	H		62%
5h	H	H	7-Me		90%
5i	Me	H	H		93%
5j	Me	H	8-NO_2	Ph	76%
5k	Me	H	H		78%
5l	Me	H	H		88%
5m		Et	H		68%

CNS depressant,[6] and pesticidal[4c] activities, among others. Similarly, styrylquinazolinones have been shown to have analgesic[7] and anticonvulsant[8] activity. This broad range of activity allows this class of compounds to be an interesting template for combinatorial library synthesis. In our development of methods to synthesize combinatorial libraries of quinazolinones and styrylquinazolinones,[9] we have designed a novel scheme for synthesizing styrylquinazolinones in the solid phase.[10]

We report here the design, optimization, and solid phase synthesis of styrylquinazolinones derived

from resin-bound amino acids (Scheme 1). Boc-protected amino acids were initially coupled to *p*-methylbenzhydrylamine (MBHA) resin contained within polypropylene mesh packets [11] to yield a resin-bound amino acid **1**. In order to add additional potential diversity to the compounds being synthesized, selective *N*-alkylation[12] of the amide bond was carried out to form intermediate **2**. This was accomplished, following cleavage of the Boc-protecting group and tritylation, by treatment with lithium *t*-butoxide, and addition of an alkyl halide. We have found that the potential alternative approach of reductive alkylation, followed by subsequent coupling of the resultant alkylated MBHA resin, generally does not proceed to completion. Removal of the trityl protecting group, coupling of appropriate anthranilic acid, and acetylation at room temperature yielded compound **3**.[13]

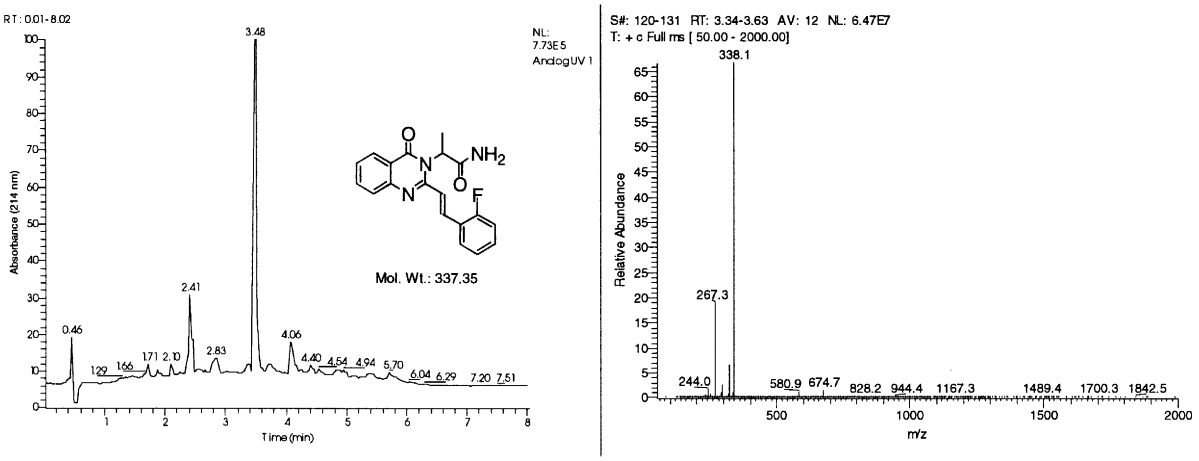


Fig. 1. LC-MS of crude styrylquinazolinone **5d**

In contrast to other solid phase strategies,[14] cyclization to obtain the resin-bound quinazolinone **4** was achieved by heating in sulfolane at 200°C for 4 h. This approach is straightforward and avoids side reactions that can occur with the use of dehydrating agents such as phosphorus oxychloride and phosporous pentoxide. Synthesis of the styrylquinazolinones was completed by treatment with NaOMe and reaction with the desired aromatic aldehyde. The products were cleaved from the resin with anhydrous HF in the presence of anisole.[15]

Products were obtained in good yield (75%–90%) and high purity (Table 1). The identity of the compounds was verified by LC-MS and purity was determined by RP-HPLC. Selected compounds were analyzed by ^{1}H NMR. The LC-MS spectra of the styrylquinazolinone **5d** ($[M+H]^+$=338; R^1=CH_3, derived from the side chain of alanine; R^2=H; R^3=H, derived from anthranilic acid; and R^4=3-fluoro, derived from 3-fluorobenzaldehyde) (Fig. 1), is representative of the purities obtained in each case.

The method described is a reliable approach for the solid phase synthesis of a wide variety of individual styrylquinazolinones. The generation of combinatorial libraries of styrylquinazolinones and their use for the identification of highly active compounds will be described elsewhere.

Acknowledgements

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10. A typical preparation of a styrylquinazolinone is as follows. (a) *Amino acid coupling:* Following neutralization of MBHA resin (50 mg, 1.00 meq/g) with 5% disopropylethylamine (DIEA) in dichloromethane (DCM), and washing with DCM, the Boc-protected amino acid (6 equiv.) was coupled for 2 h using diisopropylcarbodiimide (DIPCDI) (6 equiv.) in DCM. Following removal of the Boc group using 55% trifluoroacetic acid (TFA) in DCM, and neutralization with 5% DIEA in DCM, the resin packet was reacted overnight, in the presence of DIEA (25 equiv.), with trityl chloride (5 equiv., 0.1 M) in 10% dimethylformamide (DMF) in DCM. Following decantation of the reaction solution, and neutralization with 5% DIEA in DCM, the trityl chloride coupling was repeated a second time to ensure complete of the reaction. (b) *Alkylation:* If necessary, *N*-alkylation was performed by treatment of the resin with 1 M lithium *t*-butoxide (10 equiv.) in anhydrous THF for 30 min. Excess base was removed by decantation and the desired alkylating agent (1 M) in dimethylsulfoxide (2 ml) was added and allowed to react for 2 h. The alkylation step was repeated three times to ensure completion of the reaction. Following removal of the trityl group with 2% TFA in DCM, the anthranilic acid (10 equiv.) was coupled using 0.2 M HOBt (10 equiv.) and DIPCDI (10 equiv.) in DMF for 24 h. (c) *Acetylation:* The resin was acetylated by reacting with a solution of 10% acetyl chloride in DCM for 1 h at room temperature, followed by addition of 1 M potassium carbonate in water (6.6 ml). The resin was then allowed to react for a further 16 h. (d) *Quinazolinone condensation:* The quinazolinone was formed by temporarily removing the resin from its polypropylene mesh packet and heating in sulfolane (10 ml) for 4 h at 200°C. (e) *Styryl formation:* Following decantation of the reaction mixture and washing, styryl formation was carried out by adding 0.54 g NaOMe in anhydrous THF (5 ml). Following reaction for 2 h, the solution was removed by decantation and the desired aldehyde (1 M) in DMF was added and allowed to react for 16 h. Products were cleaved from the resin with anhydrous HF, in the presence of anisole (0.2 ml). The desired products were then extracted with 50% CH_3CN in water (3×5ml) and lyophilized overnight.
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