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Report

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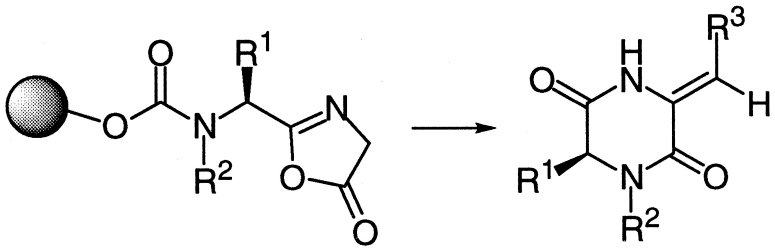

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Reports

Solid-Phase Synthesis of Unsaturated 3-Substituted Piperazine-2,5-diones

Wen-Ren Li* and Jian Hsiu Yang

Department of Chemistry, National Central University, Chung-Li, Taiwan 32054, ROC

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Introduction

The goal of rapid discovery and optimization of pharmaceutical lead compounds has stimulated investigations of the combinatorial synthesis of libraries of highly diverse low molecular weight molecules.[1−10] The key feature of combinatorial chemistry is a synthesis designed to produce a range of analogues under similar reaction conditions using solution-[11] or solid-phase synthetic techniques.[12] The majority of libraries described to date have used a solid support matrix for multiple-step syntheses. Using this technique, the chemist can prepare large numbers of diverse druglike compounds for their use in various screening protocols in a time- and resource-effective manner.

The piperazine-2,5-diones represent a rich source of biologically interesting compounds,[13−16] and this heterocyclic system is found in many unique natural products.[13,17−21] Several methods for the synthesis of piperazine-2,5-diones on solid support have already been described,[3,22−30] and most of them are based on the cleavage-induced cyclization of linear dipeptides.[3,22−25] To the best of our knowledge, the only solid-phase synthesis of unsaturated 3-substituted piperazine-2,5-diones was reported by our group.[31] As in our previous publication, we were interested in synthesizing unsaturated diketopiperazines as potential protein tyrosine kinase inhibitors from linear α-keto amides on solid support. When treated with ammonium acetate, these precursors cyclize to form the desired nitrogen-containing heterocycles and concomitantly cleave from the solid support. The published route would allow us to prepare unsaturated diketopiperazines such as **1** in only five steps. However, the α-keto acids, the key building blocks, are potentially unstable in some cases. This behavior would be detrimental to the synthesis of large diverse libraries in a reliable way. Furthermore, the scope of libraries available through this chemistry would also be limited by the availability of α-keto acids. To design a more general route, it was necessary to eliminate the use of such limited and reactive compounds. As a continuation of our interest in the development of methods for the solid-phase organic synthesis of protein tyrosine kinase inhibitors, we describe here a new route for the preparation of unsaturated piperazine-2,5-diones. All building blocks in the synthetic sequence are versatile, commercially available, and sufficiently stable to be stored over long periods of time.

* To whom correspondence should be addressed. Fax: +886-3-427-7972. E-mail: ch01@ncu.edu.tw.

Results and Discussion

The general reaction sequence for the solid-phase synthesis of the unsaturated diketopiperazine skeleton is outlined in Scheme 1. The Wang resin was first activated with *p*-nitrophenyl chloroformate in the presence of diisopropylethylamine.[32,33] The activated resin **2** was then treated with lithium amino acid salts (route 1) or lithium *N*-alkylamino acid salts (route 2) to provide resin intermediates **3** or **4**, respectively. The second step in route 1 involved alkylation of the anion generated from carbamate **3** with an alkyl halide to give resin **4**. A similar alkylation has been extensively studied in solution phase by Benoiton and his colleagues,[34] who examined solvent effects. For each resin-bound intermediate, the structures were verified by cleaving a small sample of resin with 50% TFA/CH_2Cl_2. Analysis by NMR and mass spectroscopy data confirmed that only monoalkylation of the carbamate occurred. Initially, the amino acid bound resin **4** was coupled with glycine methyl ester to afford the corresponding dipeptide methyl ester. However, basic hydrolysis of polystyrene resin-bound ester using LiOH or NaOH in different solvents (such as H_2O/EtOH/THF) at various temperatures was found to give low yields and poorly reproducible results, probably due to poor swelling of the resin. We then endeavored to select the most suitable temporary protecting group for glycine and to find suitable reaction conditions for the subsequent peptide coupling to afford acid **5**. After examining various protecting groups and a range of activated ester coupling techniques, we found that lithium glycinate[35] and activated *N*-hydroxysuccinimide ester were the reagents of choice for this transformation because their use eliminated protection and deprotection steps in the peptide synthesis. Again, cleavage of a small sample of resin **5** under acidic conditions followed by spectroscopic analysis confirmed complete coupling of the acid-bound resin **4** with lithium glycinate.

Suspension of resin-bound acid **5** in hot dichloromethane and addition of 3 equiv of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDC) led to the formation of oxazolone **6**.[36] This resulting resin-bound oxazolone **6** was then treated with a suitable aldehyde at 80 °C for about 2 h to give *Z*-azalactone **7**. After extensive experimentation, the best yield was obtained in toluene, using triethylamine as a base. Under these experimental conditions, no regioisomer was detected. For this library, we chose to use three

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Scheme 1

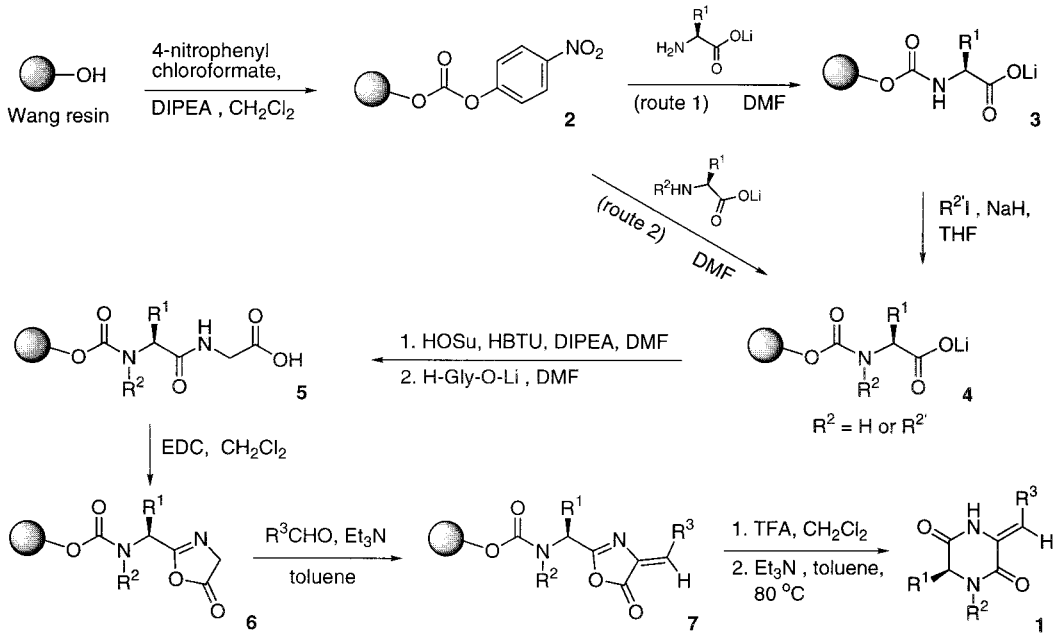
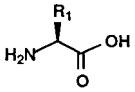


Table 1. Unsaturated Piperazine-2,5-diones Generated on Solid Support

entry	1		R_2	R_3	yield[a] (8 steps), %
1	**1a**	L-Phe	CH_3	$(CH_2)_6CH_3$	12
2	**1b**	L-Pro		$C_6H_4-CH_3$	24
3	**1c**	L-Phe	CH_3	C_4H_3O (2−furanyl)	53
4	**1d**	L-Ala	CH_3	$C_6H_4-CH_3$	23
5	**1e**	L-Leu	CH_3	C_6H_4-Br	11
6	**1f**	L-Gly	$C_6H_5CH_2$	$C_6H_4-OCH_3$	12
7	**1g**	L-Pro		C_6H_5	20
8	**1h**	L-Ala	H	C_4H_3O (2−furanyl)	18

[a] Reported yields are isolated yields after flash chromatography on silica gel. The overall yields are based on the initial loading of the Wang resin.

different types of aldehydes, neutral, electron-rich, and aliphatic, to demonstrate the broad utility of the condensation reaction. Finally, the optimal method of assembling the target piperazine-2,5-diones employed a TFA-mediated resin cleavage followed by a short heating (80 °C) of the evaporated filtrate in toluene to induce cyclization. Without the thermolysis in toluene, no diketopiperazine formation was observed in any of our work. Representative products were prepared on solid support by the protocol described above, and these results are summarized in Table 1. Each compound was fully characterized by ^1H and ^{13}C NMR and mass spectrometric techniques. The overall yield of unsaturated piperazine-2,5-dione **1d** was about 23% (see Table 1) from the Wang resin, which translates to an 83% yield per transformation in this eight-step solid-phase procedure.

The unsaturated piperazine-2,5-dione **1a** was evaluated by the sulforhodamine B colorimetric assay[37,38] in a panel of human large lung cancer cell line (H460) and showed slight inhibitory activity (IC_{50} = 90 μM). This result was comparable to those for guercetin (IC_{50} = 25 μM) and genistein (IC_{50} = 30 μM) tested under the same conditions. All details regarding the biological activities of the unsaturated piperazine-2,5-diones tested by various assays, including protein tyrosine kinase assay, will be published elsewhere. We anticipate that further synthesis of highly functionalized *Z*-3-alkylidene (or arylidene)-piperazine-2,5-diones using this new synthetic methodology will allow a better understanding of the structure−activity relationships of these compounds and the development of more potent inhibitors based on the diketopiperazine structure.

In summary, we have developed an efficient, highly regioselective methodology for the preparation of biologically active unsaturated 3-substituted piperazine-2,5-diones on solid support. This method will allow the variation of the three substituents using commercially available and stable starting materials. Hence, our protocol can be applied to the combinatorial library synthesis of a diverse collection of structurally novel unsaturated diketopiperazines with potential therapeutic properties. The production of a larger library of these heterocycles and their biological evaluation are currently under investigation. The iteration of library synthesis with structural analysis of the lead compounds should provide an effective strategy for the development of more potent and selective protein tyrosine kinase inhibitors. We are continuing to apply this approach to the synthesis of other diketopiperazine libraries.

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Supporting Information Available. Representative experimental procedures and ^1H and ^{13}C NMR spectra of compounds **1a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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