The experimental number of compounds which are to be made in the particular library. Because the final product of this library is a discrete array, biological screening of individual compounds of known structure can provide an SAR profile of the complete library. The development of READ/Write strategies which further improve the efficiency of this approach are currently underway and will be reported in due course.

**Experimental Procedure**

The tea bags were apportioned and scanned as described in text and Fig. 1. a) Each of the four FMOC-amino acids (4.59 mmol), DIC (4.59 mmol), and HOBt (3.44 mmol) were dissolved in THF (10 ml) individually and stirred for 20 min, filtered, and the filtrate added to 1.275 g of Wang resin (Advanced Chemtech, 0.9 mmol/g) in tea bags containing the transponders (16/flash). After 18 h of gentle stirring, the resin was washed with DMF, MeOH, and CH₂Cl₂. The tea bags were immersed in 20% piperidine/DMF for 30 min and then rinsed with MeOH and CH₂Cl₂, then scanned and sorted to four new reaction vessels. b) To each reaction vessel was added 15 ml of MeOH/CH₂Cl₂ (1:1), one of four aldehydes (15 mmol), p-hydroxyphenylacetic acid (15 mmol), and benzyl isocyanate (15 mmol). The resin was gently stirred for 12 h, then rinsed repeatedly with MeOH and CH₂Cl₂ and sorted to four new reaction vessels. c) To each of the reaction vessels was added the acid (14 mmol) followed by DCC (15 mmol) in 15 ml of pyridine. After 18 h, the resin was rinsed with DMF (50%), then MeOH and CH₂Cl₂. d) The tea bags were scanned and sorted into individual wells of a polypropylene microtiter plate (96 well, 2 ml well). A soln. (1 ml) of 20% TFA/CH₂Cl₂ was added to each well and let stand for 20 min. The tea bags were removed and rinsed with CH₂Cl₂ and the solvents stripped i.v.

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**The Solid-Phase Synthesis of Complex Small Molecules**

Jonathan A. Ellman*

The design, synthesis, and evaluation of small-molecule libraries currently being performed in our laboratory is overviewed. We consider a number of factors in the selection of a compound class for library synthesis. One strategy that we have employed is to select 'privileged' structures, where the display of different functionality upon the structure has previously provided a number of potent and specific drugs or candidates towards different therapeutic targets. The first class of 'privileged' structures that we focused on were the 1,4-benzodiazepines, one of the most prescribed classes of orally active drugs that target a wide range of different receptors and enzymes. Other examples include libraries based upon tropane, prostaglandin, and tricyclic frameworks. An alternative strategy that we have employed is to design compound classes bound on important biological recognition motifs. One example where we have applied this strategy is the synthesis of libraries of mimetics of β-turns, which play a key role in molecular recognition events in biological systems. A second example is the...
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The Solid-Phase Part of Supported Small-Molecule Synthesis

Mark J. Kurth*

Abstract. The synthesis of small molecules on solid phase must not only address the vagaries of C-C-bond formation and functional-group manipulation, but must also take into account solid-support issues such as 'point of attachment', 'resin compatibility', 'reagent accessibility', and 'product liberation'. Hence, the resin plays a vital role in the solid-phase venture and the polymer advantages can be summarized as reactions can be driven to completion by addition of excess solution-phase reagents, reaction products are 'isolated' by filtration and washing, and multiple-step synthesis terminating with a 'selective' liberation step can deliver essentially pure product. These issues, as well as a number of strategies for the preparation and functionalization of resin supports, are discussed.

Introduction

Adapting solution-phase organic reactions to solid-phase techniques is one of the important challenges embraced by the burgeoning field of small-molecule combinatorial chemistry. In a solid-phase arena, strategic synthetic planning must not only address the vagaries of C-C-bond formation and functional-group manipulation, but must also take into account solid-support issues such as 'point of attachment', 'resin compatibility', 'reagent accessibility', and 'product liberation'.

The Polymer Advantage

The pioneering small-molecule solid-phase work of Leznoff [1] and the more recent efforts of many academic and industrial chemists [2] have established three principal synthetic advantages of solid-phase techniques (i.e., the polymer advantage): i) many solid-phase reactions can be driven to completion by addition of excess solution-phase reagents (removed by filtration and washing), ii) solid-phase reaction products are 'isolated' by filtration and washing, and iii) multiple-step synthesis terminating with a 'selective' liberation step can deliver essentially pure product. Collectively, these advantages suggest that the solid-support can play a much broader role in solid-phase chemistry than merely that of an inert matrix. When appropriately designed, its implications can be far reaching and can elevate solid-phase techniques to exceptional synthetic advantage. Consider the sequent-auxiliary concept [3] outlined in Scheme 1 where a polymer-bound chiral auxiliary (AUX) is called upon to mediate a diastereoselective Cz-alkylation reaction in Step 1 and a diastereoselective iodolactonization reaction in Step 2. Thus, in addition to embracing the polymer advantage, there is significantly improved synthetic economy and atom efficiency in that the chiral auxiliary is called upon to mediate two diastereoselective transformations, and the chiral auxiliary can be recovered by simple filtration.

To effect this strategy, C1-symmetric pyrrolidine-based auxiliary 1 was attached to Merrifield resin (R = polystyrene) and the remaining OH group blocked by benzoylation to give the pseudo-C2-symmetric auxiliary 2. AUX-Mediated Cz-alkylation (93.5:6.5 diastereoselectivity) followed by AUX-mediated iodolactonization (>99:1 diastereoselectivity) delivered targeted lactone 4 (R = CH2) essentially

*Correspondence: Prof. M.J. Kurth
Department of Chemistry
University of California, Davis
Davis, California 95616, USA

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