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Jonathan A. Ellman*

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synthesis of libraries of compounds that are based on an isostere that mimics the tetrahedral intermediate for peptide hydrolysis as catalyzed by the therapeutically important aspartic-acid class of proteases.

For each library synthesis project the synthesis approach is designed to achieve three goals: *1*) Several different building-block sets should be incorporated to provide rapid access to a large number of diverse compounds. *2*) The chemistry should be compatible with the display of as much functionality as possible including reactive functionality that is commonly found in drugs such as alcohols, phenols, indoles, carboxylic acids, amides, nitriles, nitro groups, and halides. *3*) The building blocks used in the synthesis of the library should be commercially available or at least readily accessible to facilitate rapid library synthesis. A considerable number of synthesis methods are explored in order to achieve these goals. Two main areas of focus are C–C-bond forming processes and linkage strategies for attaching compounds to the solid support. Some of the solid-phase chemistry that is developed is based upon analogous chemistry in solution; however, much of chemistry that is developed does not have a current solution-phase counterpart.

According to the above strategies and goals we have generated libraries of thousands to tens of thousands of compounds. Library synthesis is performed in a microtiter plate format either using the *Chiron Mimotope* pin method initially developed by *Geysen* for peptide epitope mapping or by analogous bead-based approaches. Evaluation of these compound libraries has lead to the identification of numerous ligands to different receptor targets to serve as tools to probe receptor function. Selected examples include the identification of benzodiazepine-based inhibitors of $pp60^{src}$ tyrosine kinase, which is implicated in cancer, in collaboration with *Victor Levine* at the *M.D. Anderson* Cancer Institute, benzodiazepine-based ligands to DNA-binding autoantibodies implicated in the autoimmune disease systemic *lupus erythematosus* which are currently being evaluated in mouse models of the disease in collaboration with *Gary Glick* at the University of Michigan, and hydroxyethylamine isostere-based nonpeptide inhibitors of cathepsin D with low nanomolar Ki values.

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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 accesibility', 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 Cα-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 transformation, and the chiral auxiliary can be recovered by simple filtration.

To effect this strategy, C_2-symmetric pyrrolidine-based auxiliary **1** was attached to *Merrifield* resin (® = polystyrene) and the remaining OH group blocked by benzylation to give the pseudo-C_2-symmetric auxiliary **2**. AUX-Mediated Cα-alkylation (93.5:6.5 diastereoselectivity) followed by AUX-mediated iodolactonization (>99:1 diastereoselectivity) delivered targeted lactone **4** (R = CH_3) essentially

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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 Cα-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 transformation, and the chiral auxiliary can be recovered by simple filtration.

To effect this strategy, C_2-symmetric pyrrolidine-based auxiliary **1** was attached to *Merrifield* resin (® = polystyrene) and the remaining OH group blocked by benzylation to give the pseudo-C_2-symmetric auxiliary **2**. AUX-Mediated Cα-alkylation (93.5:6.5 diastereoselectivity) followed by AUX-mediated iodolactonization (>99:1 diastereoselectivity) delivered targeted lactone **4** (R = CH_3) essentially

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