ORGANIC LETTERS

2004
Vol. 6, No. 19
3237−3240

Demonstration of the Feasibility of a Direct Solid-Phase Split-Pool Biginelli Synthesis of 3,4-Dihydropyrimidinones

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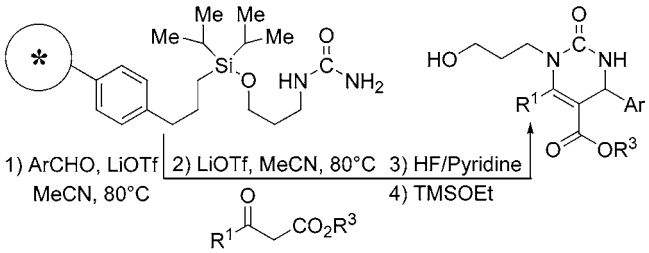
Received June 6, 2004

ABSTRACT



A direct, Lewis acid-catalyzed Biginelli synthesis of 3,4-dihydropyrimidinones has been performed on high-capacity polystyrene macrobeads with a polymer *O*-silyl-attached *N*-(3-hydroxypropyl)urea. Resin–urea was first reacted separately with either 4-bromo- or 4-chlorobenzaldehyde and LiOTf in MeCN at 80 °C. After washing, the beads were pooled and reacted with ethyl acetoacetate and LiOTf in MeCN at 80 °C. Formation of only *one* kind of Biginelli product per bead demonstrated the feasibility of a solid-phase non-Atwal two-step split-and-pool synthesis of 3,4-dihydropyrimidinones.

Small molecules have been used in recent years to explore many aspects of biological pathways in a *systematic* way, a process termed *chemical* genetics,[1] in a manner analogous to classical (mutational) genetic, and more recently genomic, approaches. Diversity-oriented[2] split-(and-)pool[3] synthesis has been shown to be an effective method for synthesizing structurally complex and diverse collections of small molecules[4] for use in forward (phenotypic) or reverse (proteomic) chemical genetics.

Recently, we have begun an exploration of the possibility of using the three-component Biginelli reaction[5] as the initial stage in a solid-phase split-pool diversity-oriented synthesis on high-capacity (500−600 μm) polystyrene macrobeads whose surface has been functionalized with a carbon- and silicon-based linker.[6,7a] The traditional Biginelli reaction involves the simultaneous acid-catalyzed interaction of an

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10.1021/ol048946r CCC: $27.50
Published on Web 08/24/2004

aldehyde (**1**, usually aryl), urea or an N-monosubstituted urea (**2**), and a β-ketoester (**3**) to produce a 3,4-dihydropyrimidinone product (**4**) (Figure 1). Such compounds have been found to possess a variety of biological activities.[5b−f]

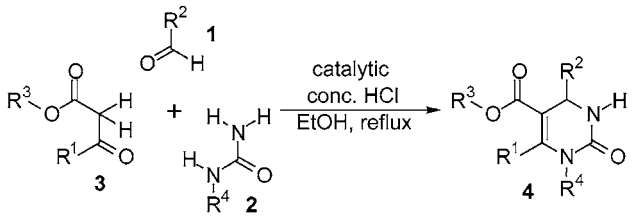

Figure 1. Biginelli 3,4-dihydropyrimidinone synthesis.

Wipf and Cunningham[8a] reported the first example of a classical Biginelli reaction performed on solid phase by treating a Wang resin-attached urea simultaneously with an aldehyde and a β-ketoester to give a series of parallel solid-phase syntheses of 3,4-dihydropyrimidin-2(1*H*)-ones. Kappe and co-workers[8b,c] have also published solid-phase examples of the acid-catalyzed Biginelli reaction in which resin-attached β-ketoesters were reacted with combinations of aldehydes and ureas in single-step parallel syntheses.

However, a solid-phase split-(and-)pool process mandates that the resin-bound reactant be subjected to *separate* reaction steps to introduce each of the other components of the reaction sequence (and the variation therein). Biginelli products have been prepared *in solution* in a *stepwise* fashion via separate generation of α,β-unsaturated ketoesters (by reacting β-ketoesters **3** with aldehydes **1**), and then treatment of these Knoevenagel condensation products with O(or S)-alkylated ureas under *basic* conditions to give 1,4-dihydropyrimidine derivatives of the traditional Biginelli 3,4-dihydropyrimidinone products (the "Atwal modification" of the Biginelli reaction).[9] Kappe[10a] has reported a solid-phase version of this method in which a resin-attached (via sulfur) isothiourea was reacted with Knoevenagel compounds (prepared separately by solution-phase reactions) to give pyrimidine derivatives, which were converted to typical Biginelli 3,4-dihydropyrimidinones only during cleavage from the resin.

The "Atwal modification" of the Biginelli condensation is conceptually adaptable to a solid-phase split-pool synthesis. Marzinzik and Felder[10b] have described a two-step solid-phase Atwal-like process beginning with a resin-bound aromatic aldehyde, condensing it first with a ketone to generate an α,β-unsaturated ketone, and then, in the one example given, reacting this in a separate second step with *N*-methylurea under basic conditions. This process, while conceptually allowing for a solid-phase split-pool synthesis, produced an atypical 3,4-dihydropyrimidinone product in which the *N*-methyl group derived from the urea was found at the N-3 rather than the usual N-1 position and which did not have a carboalkoxy or other carbonyl group typically found at the 5-position in the classical acid-catalyzed Biginelli condensation.

Hamper et al.[10c] have also described a solid-phase two-step Atwal-like process, beginning with a resin-esterified trifluoroethyl malonate diester that was reacted with a series of aldehydes in the first step of the synthesis. Subsequent treatment of the resulting α,β-unsaturated resin-malonates in a second step with amidines or *S*-alkylisothioureas under basic conditions produced a series of *5,6*-dihydropyrimidin-*4*(*3H*)-ones. In these products the aldehyde-derived ring substituent was found at the 6-carbon instead of typically at the 4-carbon, and the pyrimidinone carbonyl, derived from the distal malonate ester carbonyl with the loss of a trifluoroethoxy group instead of from the urea derivative, was found at the 4-carbon rather than the 2-carbon typical of classical Biginelli compounds. While this Atwal-like reaction would also be amenable to a solid-phase split-pool process, it too does not produce the products typical of the classical acid-catalyzed Biginelli reaction.

For the generation of large libraries of Biginelli structures without massive (parallel) synthetic effort, a split-and-pool solid-phase synthetic strategy would be desirable. This process would require that the classical acid-catalyzed three-component Biginelli reaction be carried out in *two* discrete steps on a solid-phase resin, first combining one resin-bound reactant (e.g., resin-linked urea) separately with a number of examples of a second reactant (e.g., aldehydes), followed by pooling of the resins and splitting of the collection into separate vessels for reaction with a variety of examples of the third component (e.g., β-ketoesters) in a discrete second step. To our knowledge, a non-Atwal solid-phase two-step Biginelli reaction has not previously been demonstrated. We herein report that such a protocol can be implemented on high-capacity polystyrene macrobeads with a resin-bound urea in a stepwise fashion that would be compatible with split-and-pool techniques.

To begin, the macrobeads were functionalized with an *O*-silyl-attached 3-aminopropanol group (Scheme 1), by activating the silyl-linker in **5**[6] with triflic acid (TfOH, trifluoromethanesulfonic acid) and then treating the resulting silyl triflate with 3-FMOC-aminopropanol (**6**). Removal of the FMOC protecting group[11a] from **7** analytically with 20% piperidine in DMF[11b−d] showed a loading of 0.88 mmol per

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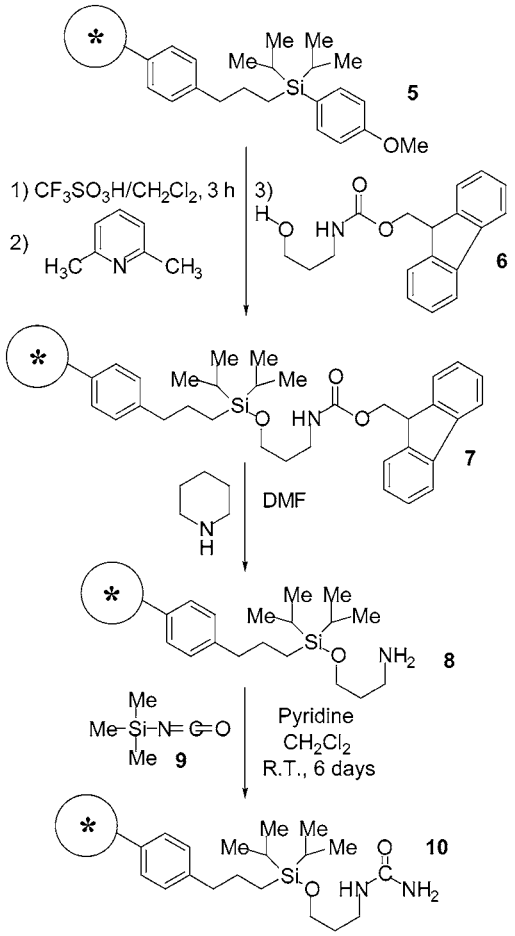
Scheme 1. Synthesis of Resin-Attached Urea **10**

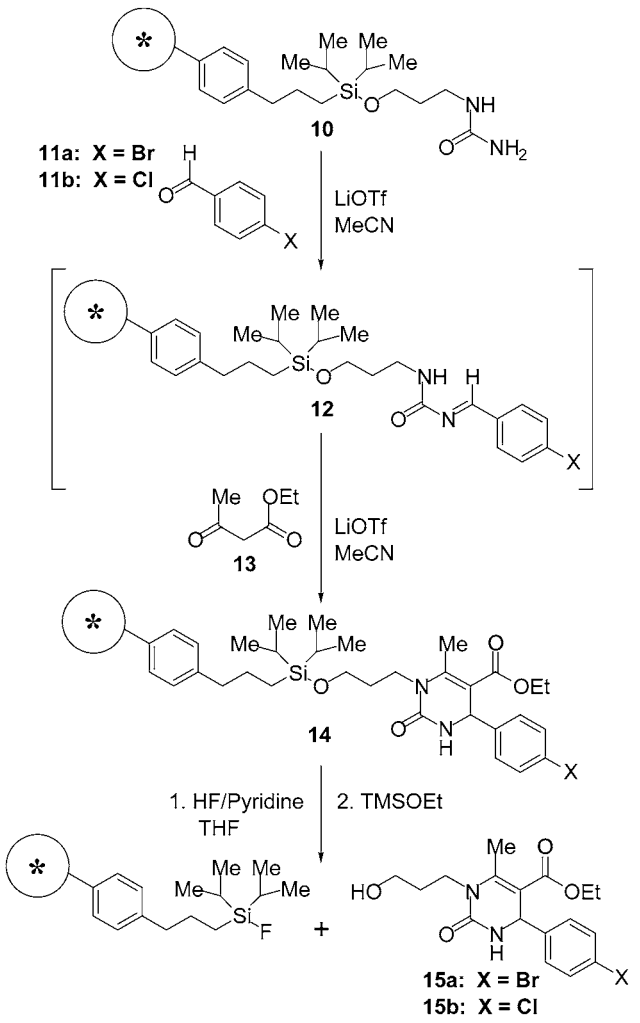


gram of resin (79.5%; 132.5 nmol/bead), and bulk deprotection under similar conditions gave the 3-silyloxypropylamine-functionalized resin **8**. This amino-resin was converted into urea−resin **10** by treatment with TMSNCO (trimethylsilylisocyanate, **9**) and pyridine in CH_2Cl_2.[12]

Since the strong protonic acid catalyst of the classical Biginelli reaction would not be compatible with the *O*-silyl linker on the polystyrene macrobeads, it was first necessary to identify an appropriate catalyst for use with the beads. Polyphosphate ester (PPE), which was quite effective as a catalyst for solution-phase Biginelli reactions,[13] was found to produce no on-bead Biginelli product when used as a catalyst in the reaction of urea−resin **10** with 4-bromobenzaldehyde (**11a**) and ethyl acetoacetate (**13**) in a wide variety of solvents (THF, $ClCH_2CH_2Cl$, 100% EtOH, CF_3CH_2OH, MeCN, PhMe, Dioxane, EtOAc, NMP, DMF). Acetic acid/morpholine[12e] in THF or $ClCH_2CH_2Cl$ was also found to be ineffective.

Eventually, the mild Lewis acids $LiClO_4$,[14] LiOTf,[14] and $Yb(OTf)_3$[15] were tested in MeCN and THF solvents (0.1 M Lewis acid, 0.5 M **11a** and **13**, 75 °C, 40 h) (Scheme 2).

Scheme 2. Solid-Phase Split-and-Pool Synthesis of 3,4-Dihydropyrimidinones



The $Yb(OTf)_3$ catalyst produced no on-bead Biginelli product **14** at all in either solvent, as judged by subsequent HF/pyridine cleavage and LC/MS analysis for the free hydroxypropyl Biginelli adduct **15a**. Both $LiClO_4$ and LiOTf catalysts gave on-bead product in either solvent, but the best results appeared to be with LiOTf/MeCN, which gave the greatest amount of desired product **15a** with the least amount of impurities upon cleavage from the solid support. LiOTf/MeCN was therefore chosen as the catalyst/solvent for subsequent studies.

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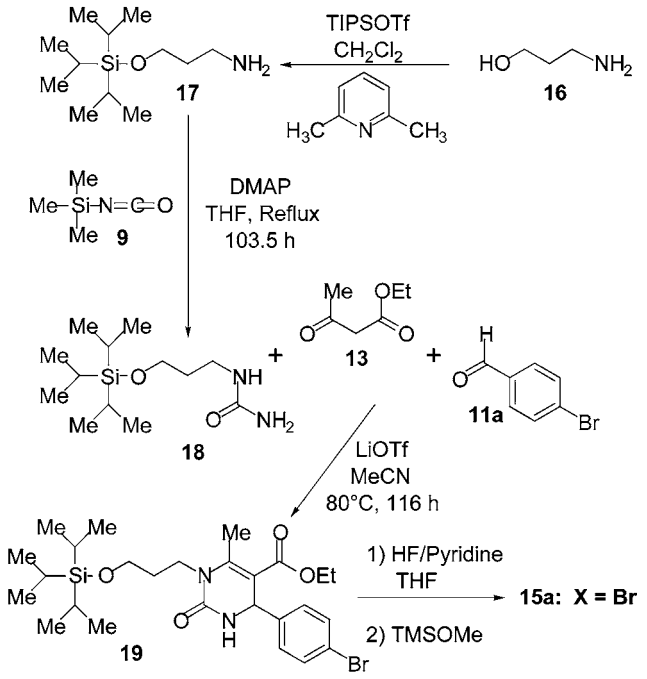
The identity of the on-bead Biginelli product was confirmed by alternate solution-phase synthesis (Scheme 3).

Scheme 3. Alternate Solution-Phase Synthesis of **15a**



3-Aminopropanol (**16**) was selectively protected on the hydroxyl-oxygen by treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and 2,6-lutidine in CH_2Cl_2. The resulting 3-TIPSO-propylamine **17** was then converted to urea **18** with TMSNCO and pyridine/CH_2Cl_2 at rt or DMAP/THF[12d] at reflux. Biginelli reaction of **18** with **11a** and **13** catalyzed by LiOTf in MeCN gave crude **19** containing a small amount of desilylated product **15a**. Silyl cleavage with HF/pyridine in THF, followed by quenching with methoxytrimethylsilane (TMSOMe), gave 1-(3-hydroxypropyl)-3,4-dihydropyrimidinone **15a** identical with the on-bead product by LC/MS.

Demonstration of the feasibility of a solid-phase split-pool stepwise Biginelli 3,4-dihydropyrimidinone synthesis was carried out in the following manner. Four reaction vials, each containing six beads of resin **10**, were prepared. Into each of two vials was placed 100 μL of a MeCN solution 0.1 M in LiOTf and 0.5 M in *4-bromobenzaldehyde* (**11a**). Into each of the other two vials was placed 100 μL of a MeCN solution 0.1 M in LiOTf and 0.5 M in *4-chlorobenzaldehyde* (**11b**). These four vials were then heated under N_2 at 80 °C for 43 h, presumably to generate the acylimines **12** from the on-bead urea and the aldehydes. The reaction solutions were then removed from each of the vials; the beads in each vial were rinsed briefly with fresh MeCN (2 × 100 μL), and one set of 4-bromobenzaldehyde beads was pooled with one set of 4-chlorobenzaldehyde beads. The pooled set of 12 beads was treated with 200 μL of a MeCN solution 0.1 M in LiOTf and 0.5 M in ethyl acetoacetate (**13**), while the remaining two six-bead vials were treated with 100 μL each of the same solution. These three vials were then heated under N_2 at 80 °C for 69 h.

After cooling, the reaction solutions were removed and the beads in each vial were rinsed with MeCN (2 × 30 min) and THF (2 × 30 min) with vortex agitation. The resins were then transferred into separate small fritted chromatography columns and washed sequentially with tumbler agitation 2 × 30 min in each of the following solvents: THF; 3:1 THF/IPA (IPA = isopropyl alcohol); 3:1 THF/H_2O; 3:1 THF/IPA; THF; DMF; and finally THF again. Each of the 12 beads from the pooled Br/Cl vial was then placed in a separate 0.5 mL Eppendorf vial, while the 6 beads from the Br- or Cl-only reactions were placed in their own 1.5 mL vials. Each of these samples was cleaved with HF/pyridine/THF and quenched with TMSOEt, and the cleavage solutions were evaporated in vacuo and analyzed by LC/MS.

The 6 pure 4-bromobenzaldehyde beads formed 4-bromophenyl Biginelli product **15a**, while the 6 pure 4-chlorobenzaldehyde beads formed 4-chlorophenyl Biginelli product **15b**. *Significantly, of the 12 pooled beads, 6 of the individually analyzed beads showed only bromo product* **15a**, *while the other 6 showed only chloro product* **15b**, indicating that there was no cross-reaction between chloro- and bromo-beads in the pooled reaction.

This finding suggests that the presumed acylimine intermediate **12** derived from the resin-attached *N*-alkylurea and an aldehyde is sufficiently stable on the polystyrene macrobead support to allow the beads to be washed to remove excess aldehyde, pooled, and then split into collections of beads for subsequent reaction with a β-ketoester. The generation of the final 3,4-dihydropyrimidinone product can therefore be accomplished *without crossover of the aldehyde reactant from one bead to another*, thus preserving the integrity of the split-(and-)pool process. No other report of which we are aware has yet demonstrated the above-described process. We therefore conclude that it should be possible to conduct a direct solid-phase split-and-pool synthesis of a collection of Biginelli compounds on polystyrene macrobeads using a variety of aryl aldehydes in the first stage of acylimine formation, followed by a variety of β-ketoesters in the second stage. Efforts will continue to implement such a solid-phase split-and-pool synthesis of Biginelli compounds, as well as subsequent studies of the further elaboration of these products, as a beginning point in a diversity-oriented synthesis of collections of small molecules.

Acknowledgment. We thank Max Narovlyanski for synthesizing the silyl-linker resin **5** used in this study and Kerry Pierce and Jennifer Tee for assistance with the LC/MS. Harvard ICCB is financially supported by Merck & Co., Merck KGaA, the Keck Foundation, and the National Cancer Institutes.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048946R