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Resin Capsules: Permeable Containers for Parallel/Combinatorial Solid-Phase Organic Synthesis

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A resin capsule is a permeable container for resin beads designed for multiple/combinatorial solid-phase organic synthesis. Resin capsules consist of a high density polyethylene ring sealed with peek mesh on both sides. The cylindrical shape of resin capsules enabled space-saving packing into plastic columnlike reaction vessels commonly used for solid-phase organic synthesis. Resin capsules have been evaluated for their use in combinatorial synthesis, and a set of model compounds with excellent purity was prepared.

Introduction

Resin beads are the most frequently used formulation of insoluble support for solid-phase organic synthesis (SPOS). In a traditional manner, one reaction vessel contains resin beads with one polymer-supported intermediate for reaction with one reagent/building block. The potential of combining a number of different solid-phase bound substrates for a reaction with a single reagent was recognized for the first time by Ronald Frank[1] using cellulose-based paper discs as solid-phase support for the synthesis of oligonucleotides. Each disk contained a different substrate (oligonucleotide), and only four reaction vessels were required for the synthesis of any number of oligonucleotides. "Whenever growing chains on different entities have to be elongated with the same building block these entities are gathered in the same reaction vessel."[1] Later, Frank applied the pooling strategy of paper discs to peptide synthesis.[2]

In order to take advantage of the pooling strategy with resin beads, Richard A. Houghten invented polypropylene meshed packets, which are similar in appearance to tea bags.[3] For the synthesis of peptides, before the addition of the next amino acid to the resin-bound growing peptide chain, the tea bags were distributed into different reaction vessels, each vessel containing resin-bound intermediates receiving the same amino acid. In order to perform steps common to all peptides (cleavage of the amino protecting group), all tea bags have been pooled into one reaction vessel. The compartmentalization of resin beads into permeable containers has been later used by IRORI in their canisterlike containers (MiniKan and MicroKan for 100 and 30 mg of resin, respectively) that allowed robot handling.[4,5] An alternative formulation of solid support for multiple synthesis included SynPhase Lanterns, [6] monolithic rods,[7] and resin plugs.[8]

Yet another solution was reported by Beattie and Frost who invented porous wafers[9] that housed insoluble support for multiple solid-phase synthesis of oligonucleotides and peptides.[10,11] The porous wafer was made from a Teflon ring covered on both sides by a porous Teflon membrane to form a cylindrical shaped permeable container. The use of wafers was reduced to practice in a column-based oligonucleotide synthesizer.[12] In this contribution we wish to report an alternative solution to Teflon wafers, resin capsules. Resin capsules are permeable containers designed for multiple/combinatorial solid-phase organic synthesis. The use of resin capsules is documented on multistep manual synthesis of bis-heterocyclic compounds.

Results and Discussion

Permeable resin capsules serve as a means of compartmentalization of resin beads to facilitate the pooling of different resin-bound intermediates in one reaction vessel for parallel/combinatorial solid-phase synthesis. Resin capsules are plastic containers made of a high density polyethylene (HDPE) ring sealed with peek mesh on both sides (Figure 1). Peek mesh (opening size 35 μm) prevents resin beads from escaping the capsule while facilitating free flow of reagent solutions in and out of a capsule. The mesh opening allowed the use of standard size resin beads (80−120 μm). The HDPE ring contains an opening for loading and removing resin beads. The capsules were manufactured in two sizes to fit into 20- and 50-mL syringes used as plastic reaction vessels. Two sizes of resin capsules were made with inner volumes of 1.1 and 2.0 mL that housed up to 190 and 330 mg resin, respectively (the calculation was based on a volume of 6 mL/g of dichloromethane (DCM) swollen PS-DVB resin). However, capsules of any reasonable size can be constructed.

Before we carried out a trial synthesis, resin capsules were tested for compatibility of their components and the seal with commonly used solvents. We observed no mechanical changes, nor any resin beads leakage after more than a week exposure to solvents including DCM, tetrahydrofuran (THF), dioxane, *N,N*-dimethylformamide (DMF), MeOH, and *N*-methylpyrrolidinone (NMP). However, the peek mesh did

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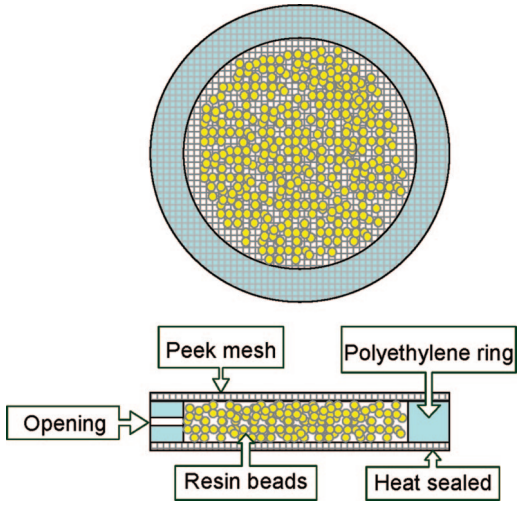


Figure 1. Schematic drawing of a resin capsule.

not tolerate trifluoroacetic acid (TFA), 50% TFA in DCM caused random perforation of the peek mesh. The diffusion of solutes into capsules was tested using a solution bromophenol blue in DCM, an acid−base indicator used to detect free basic groups on the resin.[13] A resin capsule containing 4-methylbenzhydrylamine resin was agitated with a solution of bromophenol blue. Fast discoloration of yellow solution and dark blue coloration of resin beads documented the excellent permeability of peek mesh.

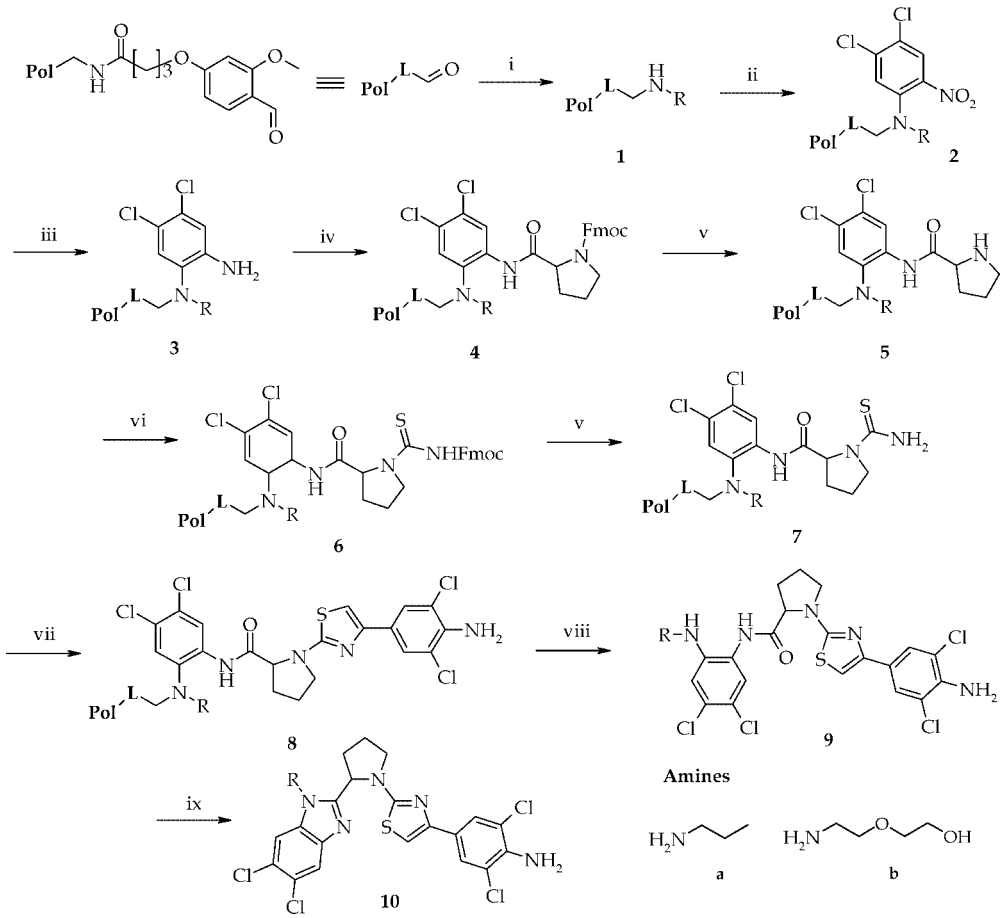
Space (volume) saving packing of cylindrical reaction vessels with resin capsules allowed solvent consumption to be reduced for washing of resin beads.[14,15] Washing of resin beads in capsules was carried out in cylindrical plastic reaction vessels (fritted syringes) on Domino Block synthesizer.[16] A reaction vessel was connected to the evacuated waste container, and a solvent was poured on a stack of capsules in the reaction vessel.

To evaluate resin capsules in SPOS, several model compounds were synthesized. We applied our traceless solid-phase heterocyclic synthesis[17–19] to prepare bis-heterocyclic compounds, where both heterocyclic rings were formed during the synthesis in a combinatorial manner. Details for the synthetic design and combinatorial library synthesis will be described in a dedicated communication. In the first trial synthesis, we prepared two model 2-[1-(4-phenyl-thiazol-2-yl)-pyrrolidin-2-yl]-1*H*-benzoimidazoles **10**, which we had synthesized previously on loose resin (Scheme 1). The objective of this trial synthesis was to evaluate resin capsules in the synthesis and compare results (yield and purity) with compounds made on loose resin. The synthesis was carried out on acid-cleavable BAL linker which was reductively aminated with *n*-propylamine and 2-(2-aminoethoxy)ethanol to obtain resin-bound amines (**1**). At this stage, two capsules were charged with corresponding polymer supported secondary amines (**1**) and placed into one reaction vessel (50-mL polypropylene fritted syringe). After the overnight arylation with 1,2-dichloro-4-fluoro-5-nitrobenzene, the nitro groups of 2-nitroanilines (**2**) were reduced with tin(II) chloride dihydrate to the anilines (**3**). The subsequent acylation of the electron-poor anilines (**3**) with Fmoc-protected amino acids required more forceful conditions, using carboxylic acid anhydrides in dry THF at elevated temperature. For the acylation reaction, both capsules were transferred to a vial and heated with an in situ prepared solution of Fmoc-Pro anhydride. After 4 h, the reaction was completed and the capsules were transferred back to the fritted syringe for washings and additional steps. It is necessary to point out that the manipulation with the resin capsules at this stage of the synthesis (i.e., transfers between a syringe and a vial) was much more comfortable and faster in comparison to the loose resin synthesis used earlier for the same reaction. The Fmoc-protection from acylated anilines (**4**) was cleaved with piperidine in DMF and resulting amines (**5**) were treated with a solution of freshly prepared Fmoc-NCS in dry THF to yield Fmoc-protected isothioureas (**6**). Then, the Fmoc-protection was cleaved and the corresponding thioureas (**7**) were exposed to solution of 2-bromo-3′,5′-dichloro-4′-amino-acetophenone in DCM overnight. The S-alkylation and spontaneous thiazole ring closure afforded polymer supported intermediates (**8**). Since the peek mesh of the capsules was not stable toward the cleavage cocktail (50% TFA in DCM), the resin was transferred from the capsules to polypropylene fritted syringes for the cleavage step. The circular shape of the capsules allowed very quick and quantitative discharge of their content (dry resin) directly into syringes. The cleaved intermediates (**9**) were then cyclized to the corresponding target bis-heterocycles (**10**). Two cyclization methods were compared. Heating in acetic acid provided the cyclic product in 2−5 h, depending on the substitution of the nitrogen of the benzimidazole precursor. In the case of hydroxyderivative (**10b**), the formation of stable side acetyl-product was detected (25% after the complete cyclization, HPLC traces). Quantitative saponification of the ester required overnight heating in 5% methanolic sodium hydroxide. When TFA was used instead of acetic acid, the cyclization was slower and had to be kept overnight. Using this method, the cyclized product (**10b**) was O-trifluoroacetylated quantitatively. The lability of the trifluoroacetyl group allowed its smooth saponification by the treatment with 1% methanolic sodium hydroxide at room temperature for several minutes. Crude product **10b** of respectable purity 75% (considering the number of reaction steps), comparable with product prepared on loose resin, was obtained.

During the synthesis, we have not observed any mechanical damage of the capsules. Since the polypropylene syringe used as the reaction vessel was equipped with a porous disk, we could easily monitor any eventual leak of the resin from capsules. No resin leak was detected as well as no contamination of the capsules content by each other was detected. The reaction conditions were identical to those we have already used for the synthesis of the same compounds using loose resin. The purity (checked after each step) of compounds prepared by these two methodologies was indistinguishable.

The first synthesis was carried out in 50-mL plastic syringes that served as a reaction vessel. Since the diameter of capsules used in this synthesis was 25 mm (capsules were made from 1 in. HDPE rod) and the inner diameter of 50-mL syringe is 29 mm, we could not use the continuous flow method for washing resin beads. The solvent flowed around rather than through capsules. Tight-fitting capsules were not

Scheme 1. Synthesis of 2-[1-(4-Phenyl-thiazol-2-yl)-pyrrolidin-2-yl]-1*H*-benzoimidazoles[a]



[a] Reagents: (i) amine, 10% AcOH/DMF, overnight, $NaBH(OAc)_3$, 5 h; (ii) 1,2-dichloro-4-fluoro-5-nitrobenzene, DIEA, DMSO, rt, overnight; (iii) $SnCl_2 \cdot 2H_2O$, DIEA, DMF, rt, 2 h; (iv) Fmoc-Pro, DIC, dry THF, 50 °C, 4 h; (v) 50% piperidine, DMF, rt, 60 min; (vi) Fmoc-NCS, DCM, rt, 2 h; (vii) 2-bromo-3′,5′-dichloro-4′-amino-acetophenone, DCM, rt, on; (viii) 50% TFA, DCM, rt, 30 min; (ix) (**10a**) AcOH, 60 °C, 2 h.; (**10b**) method A, TFA, 60 °C, on, then 1% NaOH in MeOH, rt, 15 min; method B, AcOH, 60 °C, 5 h, then 5% NaOH in MeOH, 60°C, on.

used because of problematic removal of capsules from the syringe. To take full advantage of the continuous flow washing, we constructed a simple cylindrical reaction vessel that could be opened from both ends and allowed the use of capsules that tightly fitted into the cylindrical reaction vessel.

The reaction vessel was made from Teflon tubing enclosed on both sides using Teflon cylinders equipped with Luer connectors. To secure tight, leak proof enclosure of the Teflon tube and Teflon cylinders, plastic sleeves were shifted over both the bottom and top cylinders (Figures 2 and 3). To open the reaction vessel, the sleeves were shifted toward the middle of the tube and both Teflon cylinders were removed.

The design of capsules enabled very effective washing of resin beads using the flow technique.[2,20–23] Whereas in the traditional batchwise washing operation freshly added solvent dilutes the solution contained in swollen beads (1 g of PS-DVB resin swollen in DCM retains ~5 mL of solvent), the flow technique displaces the bead-contained solution by fresh solvent in a chromatography columnlike manner.

The Teflon reaction vessel was used in the second trial synthesis for preparation of 10 6-(4-thiazol-2-yl-piperazin-1-yl)-1*H*-benzoimidazoles **18** according to the Scheme 2. Five amines (Figure 4) were used to reductively aminate polymer-supported BAL linker to yield polymer supported

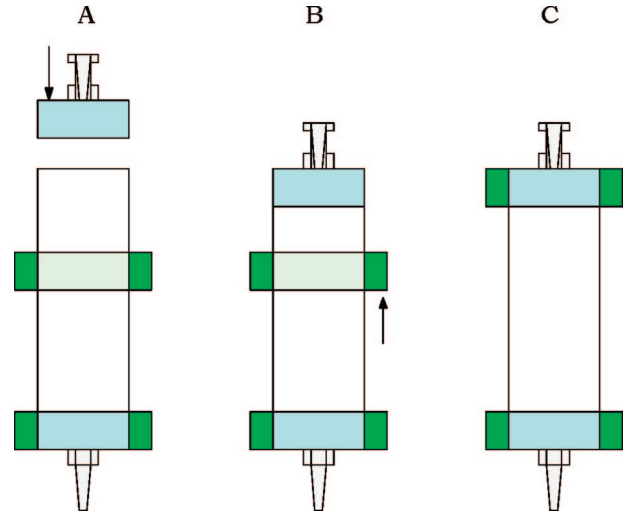


Figure 2. Teflon reaction vessel for SPOS with capsules. Panel A shows insertion of the upper cylinder; panel B shows the movement of the sleeve to the upright position to lock the upper cylinder; and panel C shows the enclosed reaction vessel.

secondary amines **1**. This reaction was carried out on loose resin. Capsules were charged with resin-bound amines **1**, two capsules per one polymer-supported amine. The Teflon reaction vessel was loaded with 10 capsules. First, the resins were swollen in DCM and then reacted with 1,2-dichloro-

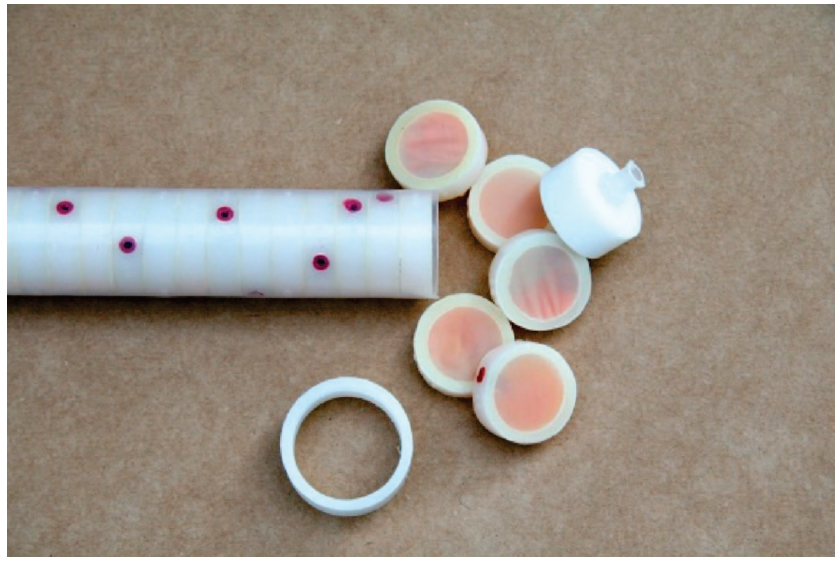
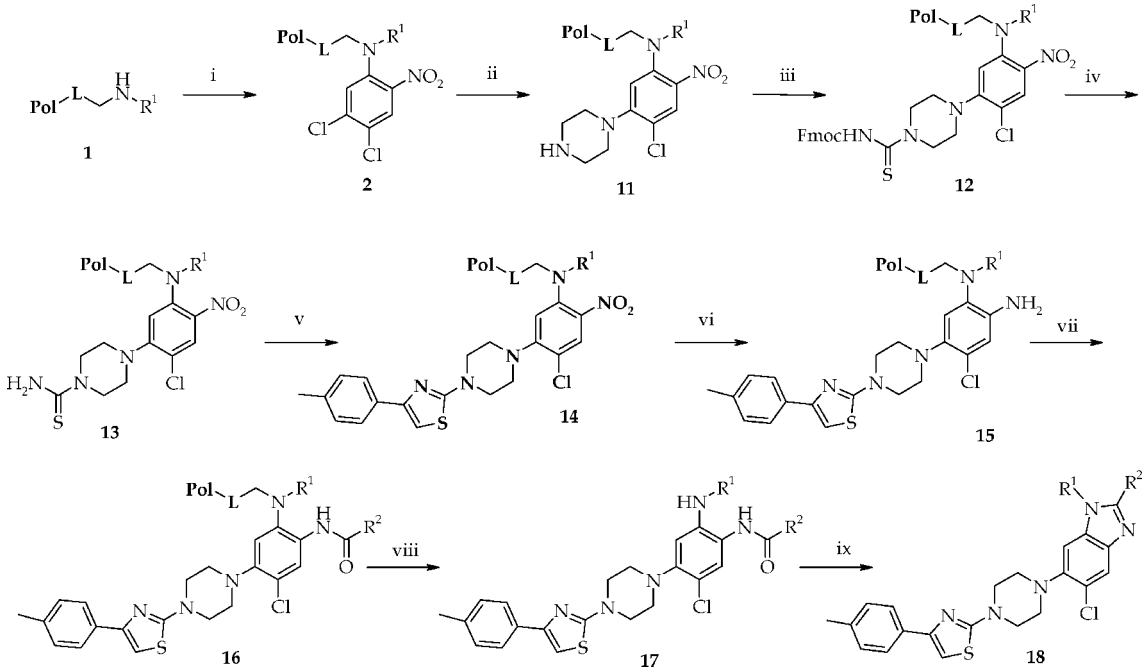


Figure 3. Teflon reaction vessel with capsules.

Scheme 2. Synthesis of 6-(4-Thiazol-2-yl-piperazin-1-yl)-1*H*-benzoimidazoles[a]



[a] Reagents: (i) 1,2-dichoro-4-fluoro-5-nitrobenzene, DIEA, DMSO, rt, overnight; (ii) piperazine, DMSO, 60 °C, overnight; (iii) Fmoc-NCS, THF, rt, 60 min; (iv) 50% piperidine, DMF, rt, 10 min; (v) 2-bromo-4′-methyl-acetophenone, 1,8-bis(dimethylamino)naphtalene, DCM, rt, 4h; (vi) $SnCl_2 \cdot 2H_2O$, DIEA, DMF, rt, overnight, (vii) (a) acetic anhydride, DCM, rt, on; (b) isonicotinyl chloride hydrochloride, DIEA, DCM, rt, 30 min; (viii) 50% TFA, DCM, rt, 30 min; (ix) AcOH, 60 °C, 2 h; then 5% of NaOH in MeOH, rt, overnight (for the **18A** and **18B** series).

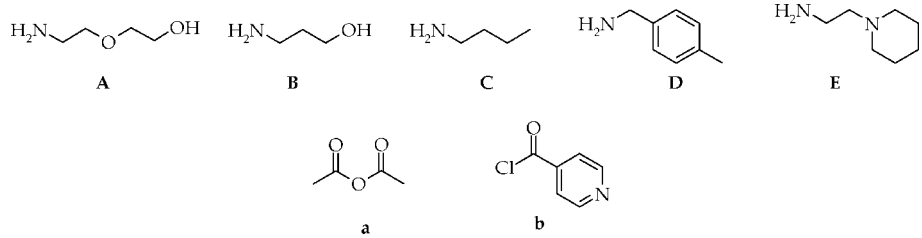


Figure 4. Amines and acylating agents used in the synthesis.

4-fluoro-5-nitrobenzene to yield resin **2**. The capsules were washed using the flow technique with DMF, DCM, and MeOH. Yellow reagent solution allowed simple visual monitoring of the washing procedure and 3 min flow of a solvent washed the excess of reagent. To ensure that there was no residual unwashed reagent left in the capsules, we filled the Teflon reaction vessel with DCM and shook the vessel for 5 min. The removal of the solvent using a vacuum did not show any coloration. The resins were dried in a vacuum and then 5 mg of each resin was cleaved to check

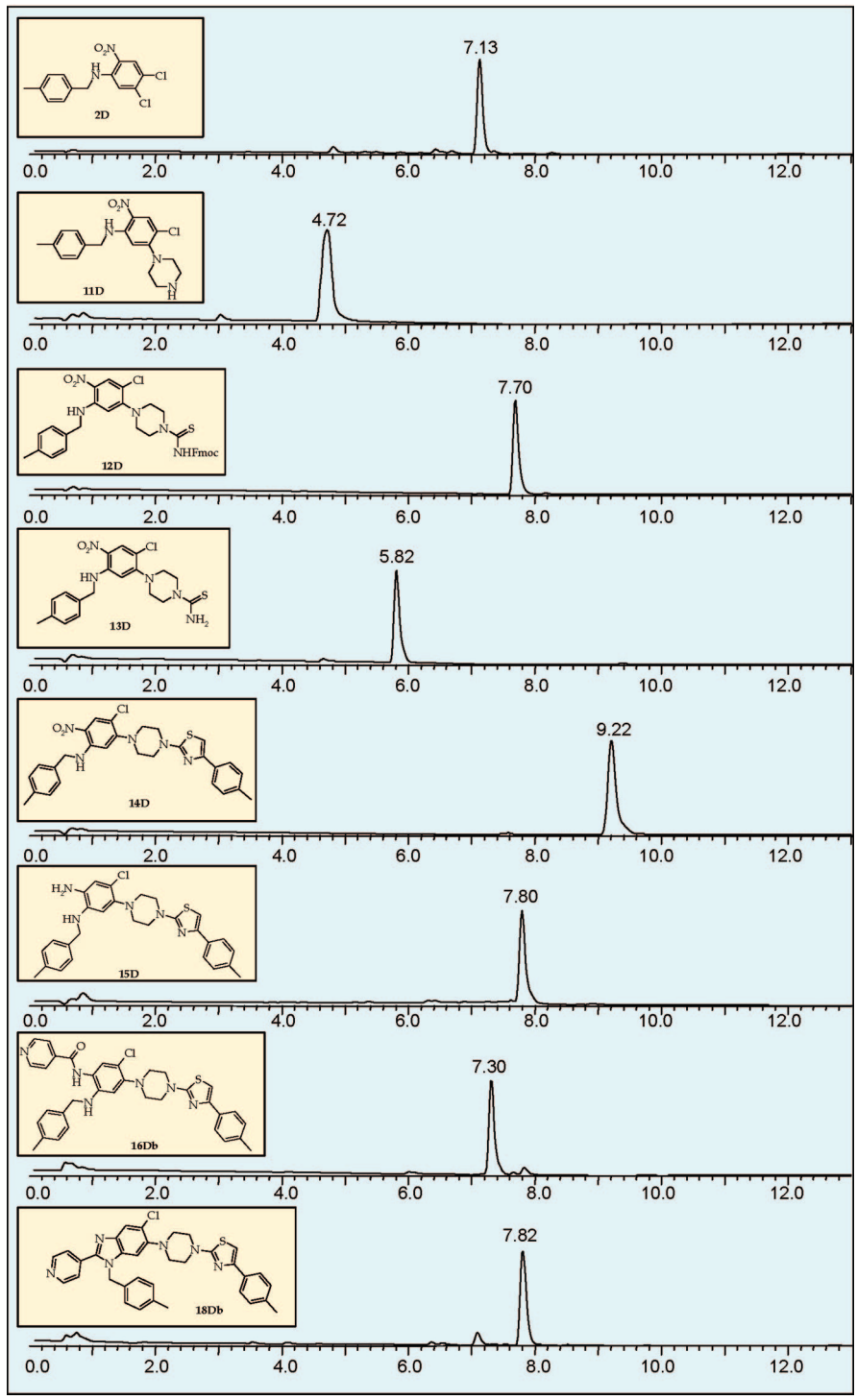


Figure 5. HPLC traces of intermediates leading to target compound **18Db**.

the purity and the efficiency of the method. In all cases we obtained product with purity >98% without any traces of unwashed 1,2-dichloro-4-fluoro-5-nitrobenzene (HPLC traces). Thus, for the rest of the synthesis we used the flow technique to wash the capsules. The next transformation, reaction with piperazine, was carried out in a heated hybridization oven and the vessels were tumbled overnight. After washing the resin, the resin-bound intermediates **11** were treated with solution of freshly prepared Fmoc-NCS in dry THF to yield Fmoc-protected thioureas (**12**). Subsequent Fmoc group cleavage by piperidine resulted in thioureas (**13**). Their alkylation with 2-bromo-4′-methyl-acetophenone in the presence of proton sponge (1,8-bis(dimethylamino)naphthalene) led to spontaneous thiazole ring formation (**14**). The nitro derivatives **14** were reduced with tin(II) chloride dihydrate in a presence of a tertiary base (DIEA) and yielded corresponding anilines (**15**). As model acylating reagent, acetanhydride (**a**) and isonicotinyl chloride hydrochloride (**b**) were used to obtain corresponding compounds (**16**). The intermediates (**16**) were cleaved from the resin and the final cyclization to the corresponding bisheterocycles (**17**) was completed by the heating in acetic acid. In the case of hydroxyl group containing derivatives (**17Aa**, **17Ab**, **17Ba**, and **17Bb**), we observed partial acetylation. The acetyl side-products were saponificatied with

methanolic sodium hydroxide at room temperature. The crude products were isolated in excellent purity (average purity 85%, HPLC traces) with only minor impurities. Figure 5 shows step-by-step analytical HPLC traces of synthesis of one model compound.

Resin capsules represent an alternative solution to Teflon wafers.[9–11] Although the use of stackable wafers provided significant simplification of the synthetic process, the porous wafers have not become spread among practitioners of solid-phase organic synthesis. Potential reasons can be commercial unavailability of wafers, its components, dedicated synthesizer, or their sole application in the oligonucleotide and peptide synthesis.

We compared SPOS of model compounds **10** in both permeable containers. The purity of crude compounds synthesized in wafers and capsules was excellent and indistinguishable. Thus none of the permeable containers provided any advantage from the point of view of purity and yield. Comparing practical aspect of the synthesis, capsules offered benefits including simple manufacturing (i.e., lower price), smaller overall size, particularly relevant for small scale syntheses, and easy withdrawal of analytical samples during the synthesis. Teflon wafers are superior containers with respect to inertness, thus chemical transformations requiring harsh reagents such as liquid hydrogen fluoride benefit from using Teflon wafers. The wafers versus capsules comparison is described in detail in the Supporting Information.

In conclusion, we have designed, constructed, and evaluated, in SPOS resin capsules, an alternative form of a permeable container for resin beads. Two trial syntheses documented full compatibility of resin capsules with a variety of reaction conditions and provided target compounds without compromising either purity or the yield. Resin capsules, charged with standard size (80−120 μm) resin beads, were used in a simple manually operated synthesizer to integrate common steps in parallel solid-phase synthesis. Although developed for SPOS, the capsules can find their application in solution-phase synthesis to enclose resin-bound reagents, scavengers, catalyst, etc.

Experimental Section

Resin capsules consist of a polyethylene ring sealed with peek mesh on both sides. The rings were made from HDPE rods, and peek mesh (opening size 0.0014 in. or 35 μm) was purchased from McMaster-Carr (Elmhurst, IL, www.mcmaster.com). Mesh opening allowed the use of standard size resin beads (80−120 μm). Resin capsules were manufactured by heat sealing (∼200 °C) high density polyethylene (HDPE) rings (melting point ∼ 120 °C) to peek mesh (melting point ∼ 350 °C). A 1/8 in. hole was drilled into polyethylene ring of each resin capsule to allow charging and discharging of a capsule and collecting a test sample during synthesis. The opening was plugged by tapered polyethylene plug (MOCAP, St. Louis, MO, http://www.mocap.com/). Individual capsules were labeled by dots in the HDPE rings. Peek mesh was found compatible with solvents typically used in SPOS (DCM, THF, dioxane, MeOH, DMF, and NMP) with the exception of TFA. Resin-bound products were transferred to plastic reaction vessels prior to cleavage of target products from the resin.

Two different sizes were manufactured: larger capsules outer diameter 25.4 mm (1 in.), inner diameter 19.1 mm (3/4 in.), height 7.1 mm (9/32 in.), and inner volume 2.0 mL and smaller capsules outer diameter 19.1 mm (3/4 in.), inner diameter 14.3 mm (9/16 in.), height 7.1 mm (9/32 in.), and inner volume 1.1 mL. Empty capsules were charged with a resin slurry using plastic Pasteur pipet or with dry resin using a small funnel made from plastic Pasteur pipet.

Resin capsules in polypropylene syringes were washed on Domino Block Synthesizer.[16] A 50 mL syringe loaded with capsules was connected to an evacuated container, and after the content of the syringe was discharged, the syringe was reconnected to a solvent reservoir. Resin capsules in the polypropylene fritted syringe were shaken with the fresh solvent for at least 1 min before changing the solvent.

To wash beads in resin capsules using the flow technique, the Teflon reaction vessel was placed on the 6-port Domino Block and the solvent line was connected to the top of the Teflon vessel. The Domino Block was connected to the vacuum line. Because the solvent reservoirs were kept under atmospheric pressure, the difference in pressure caused the solvent to flow through Teflon vessel containing capsules. Using a colored solution, we experimentally determined that a 3-min wash was sufficient to remove the solute from beads.

Reagent solution was introduced into the Teflon reaction vessel from a plastic syringe connected to the reagent port of the Domino Block synthesizer. The Teflon vessel was connected to the evacuated reservoir and the evacuated reaction vessel was then connected to the reagent port. To ensure that all capsules were filled with the solution, the upper connector of the Teflon vessel was connected to a vacuum source for ca. 1 s and then the vacuum was released.

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Supporting Information Available. Details of experimental procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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