Polymer-Supported Quenching Reagents for Parallel Purification

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Abstract: The preparation of polystyrene−divinylbenzene-supported derivatives of tris(2-aminoethyl)amine and methyl isocyanate are described. These polymeric reagents are used to quench excess reactants and remove known impurities from the crude reaction products obtained from the solution-phase, parallel syntheses of ureas, thioureas, sulfonamides, amides, and pyrazoles. In conjunction with the use of other polymeric reactants during the course of a reaction, the addition of polymer-supported quench reagent(s) at the conclusion of the reaction allows isolation of the desired product by a single filtration and evaporation of solvent. The mechanical simplicity and efficiency of this methodology make possible the rapid, parallel purification of crude reaction products obtained via solution-phase syntheses, regardless of whether the intended product is a single compound or a mixture of compounds, and hence offers an attractive alternative to solid-phase organic synthesis in the practice of combinatorial chemistry.

Introduction

The recent medicinal chemistry literature has shown a dramatic rise in the interest of utilizing combinatorial chemistry and automation to increase the rate at which novel drug candidates may be prepared.[1] By and large, this interest has grown out of the pioneering peptide library work of Geysen[2] and Houghten.[3] The efficiency of preparing combinatorial peptide libraries via solid-phase synthesis has increased the popularity of research upon solid-phase organic synthesis methods that are applicable to libraries of low molecular weight, nonoligomeric, druglike molecules.[4]

It is commonly argued that the major impediment to parallel, solution-phase synthesis of large numbers of individual organic molecules is the time and effort required for purification of the reaction products at each synthetic step. Furthermore, if one approaches combinatorial chemistry from the standpoint of intentionally synthesizing compound mixtures in solution, the alternatives for enhancing purity of that mixture are extremely limited. The problem associated with purification of a mixture is further exacerbated by the fact that it is desirable to produce library mixtures consisting of structurally diverse molecules which are present in equal molar quantities in order to increase the likelihood of finding a biologically active compound upon *in vitro* screening of the mixture and deconvolution. Particularly in the cases where a large number of diverse products are involved, i.e. 100 to 1000 compounds, methods that are well established for the purification of single compounds such as crystallization, extraction, and flash chromatography will not be applicable. Even if the crude reaction product is a relatively simple mixture, consisting only of an equimolar mixture of desired products and lesser quantities of starting materials, the ability to separate a structurally diverse array of undesired starting materials from a structurally diverse array of desired products based upon physical properties such as solubility or partition coefficient presents a difficult problem, especially if one wants to maintain the equimolar ratio of desired products.

Solid-supported synthesis offers a practical solution to purification for both parallel and batch modes of combinatorial synthesis. The ability to remove excess reagents from solid-supported products by filtration and rinsing of the support dramatically reduces the time allotted to purification in parallel synthesis and makes possible the separation of complex mixtures associated with batch mode synthesis. The price paid for this convenient purification is the time and effort necessary to develop a solid-phase synthetic route to the molecules of interest. On the other hand, solution-phase synthesis has numerous benefits over solid-phase synthesis: A great many more solution-phase reactions have been optimized and documented in the literature than are currently available to solid-phase synthesis. Reaction progress as well as identity and purity of products may be analyzed by well established chromatographic and spectroscopic means. A large variety of protecting group reagents are available at reasonable cost whereas only a limited variety of relatively expensive solid-phase synthesis resins, often strategically employed as solid-phase protecting reagents in anchoring of starting materials, are commercially available. Last, but not least, there is no need for resin attachment and cleavage steps. Recently, a number of strategies for utilizing the benefits of solution-phase synthesis in combinatorial chemistry have been reported.[5]

In our experience, the reasons for choosing to prepare combinatorial libraries (with or without automation) can generally be divided by two purposes. The first is the preparation of lead generation libraries for high volume screening. In this case, the time investment required to develop a robust solid-phase synthesis (several months) can be recouped if one makes thousands of compounds via mix and split synthesis strategies.

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(1) Recently reviewed: (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (c) Czarnik, A. *Chemtracts: Org. Chem.* **1995**, *8*, 13.

(2) Geysen, M. H.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acac. Sci. U.S.A.* **1984**, *81*, 3998.

(3) Houghten, R. A. *Proc. Natl. Acac. Sci. U.S.A.* **1985**, *82*, 5131.

(4) Recently reviewed: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki R. J.; Steele, J. *Tetrahedron* **1995** *51*, 8135. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(5) (a) Carrell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, Jr., J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059. (b) Boger, D. L.; Tarby, D. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109. (c) Curran, D. P. *Chemtracts: Organic Chemistry* **1996**, *9*, 75. (d) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480. (e) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.

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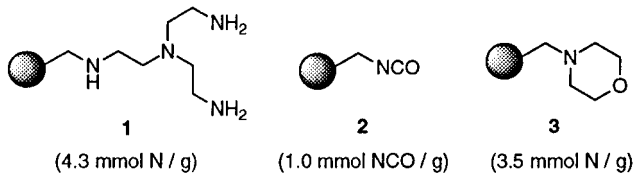

Figure 1. Polymeric reagents.

The second purpose is the optimization of an existing lead. If the existing lead came from a library that was prepared by solid-phase synthesis, there is good reason to try and optimize its properties by making analogous compounds with the same synthesis. On the other hand, many leads are found by screening historical collections of compounds. In such circumstances, parallel solution-phase synthesis becomes the method of choice for two reasons: (1) A solid-phase synthetic route is not available and the time necessary to devise one is inconsistent with the relatively small number of compounds (hundreds) one generally needs to transform a mass screening lead to a drug candidate. (2) The purpose for any individual synthetic array is typically unidimensional, *i.e.* a single starting material is modified with a collection of synthons to derive a structure−activity relationship at one position of the molecule. In such a unidimensional array, mix and split synthesis strategies cannot be used to reduce the number of reactions.

Results and Discussion

Recognizing two major advantages of solid-phase synthesis, we set out to devise a method whereby (1) excess reagent could be similarly employed to drive solution-phase reactions to completion and (2) the reaction workup would be simplified to a single filtration and evaporation of solvent at each synthetic step. We have found that polystyrene beads bearing reactive groups which mimic the limiting reagent of a reaction can be used to remove the remainder of excess reagent(s) from crude product solutions and are thereby convenient and effective tools for performing rapid purifications.[6] The resulting products may or may not meet conventional purity standards by elemental analysis. However their purity, as determined by HPLC and ^{1}H-NMR, is sufficient for routine *in vitro* biological testing. Described below are polymeric reagents and reactions which illustrate the polymer-supported quench (PSQ) method of purification.

Three polymeric reagents which are readily made in one step from commercially available polymers are shown in Figure 1. Contrary to polymer-supported synthesis, it is advantageous to have as high a loading of functionality as possible in PSQ. Hence the polyamine resin **1** is prepared by heating Merrifield resin with tris(2-aminoethyl)amine (400 mol %) in DMF (65 °C, 6 h).[7] The starting loading of chloromethyl groups affects the amount of amine cross-linking that occurs in this reaction. We have found by comparing a number of commercially available resins with loadings in the range of 0.5−4.3 mmol of Cl/g, that a starting loading of 1.7 mmol of Cl/g gives a maximal loading of approximately 3.2 mmol of NH and NH_2/g of **1**. The NH/NH_2 loading is deduced from N analysis and confirmed by treatment of the resin with excess 3,4-dichlorophenyl isocyanate, followed by Cl analysis of thoroughly washed and dried product. The isocyanate resin **2** is prepared by reacting triphosgene (200 mol % equiv of phosgene) and Et_3N (500 mol %) with aminomethyl resin at rT. In this case approximately 1 mmol of NCO/g of **2** is the highest loading that is possible if one starts with commercially available aminomethyl resins (≤1.1 mmol of N/g). A strong IR absorption at 2260 cm^{-1} is observed, indicative of the resin-bound isocyanate. Loading is verified by reaction with excess 4-bromobenzylamine and Br analysis of the resulting polymer-supported urea. The polymeric base **3** is prepared by treating Merrifield resin (4.3 mmol of Cl/g) with morpholine (266 mol %) in DMF (65 °C, 6 h).[8] In this case cross-linking is not an issue, and elemental analysis is consistent with quantitative displacement of Cl by morpholine.

Figure 2 shows selected examples of reactions wherein the resins **1**−**3** are employed. The first two examples illustrate an important advantage of PSQ methods. One can choose which reagent to use in excess and adjust the quenching resin accordingly. Thus reaction of excess **4** with **5**, followed by quenching with **1**, affords **6** upon filtration and evaporation of solvent. Alternatively, excess **5** may be used, followed by quenching with **2**. Completion of both the reaction and the quenching process can be monitored by TLC. ^{1}H-NMR and HPLC analyses show **6**, produced by either method, to be of excellent purity. In a closely related reaction, **9** is prepared from **7** and excess **8**, with quenching by **1**. These means of preparation of ureas and thioureas have been widely applied to compounds of proprietary interest in our laboratories with equal results. The only complication encountered was the occasional precipitation of the desired product, in which cases a suitable solvent must be added to dissolve the product before filtration of the resin.

PSQ is also applicable to the synthesis of sulfonamide **12** and amide **15**. In these cases, **3** is employed as a base during the reaction. It is not necessary to remove **3** before adding the quenching resin. Worth noting is the synthesis of **15**, wherein excess **14** is reacted with **13** in the presence of **3**. TLC monitoring of this reaction shows a small amount of 4-methylbenzoic acid, presumably an impurity in the starting acid chloride. Therefore, both **1** and **2** were added in the quench step. The excess amine is removed by covalent reaction with **2**, and the acid impurity is removed by salt formation with **1** (**3** is insufficiently basic to completely remove the benzoic acid in addition to the HCl produced). Alternatively, one could consider using a mixture of acidic and basic resins to remove the excess amine and benzoic acid impurities, respectively. Experience has taught us, however, that removal of impurities by covalent binding to a resin is typically more reliable than an acid−base equilibrium and thus requires less experimentation to choose the amount of resin that ensures a quantitative removal of impurities. Hence we employ the isocyanate resin **2** as a first resort to remove amine starting materials so long as there are no other groups in the products that would also react inappropriately. The purification of **15** thus illustrates another important advantage of the PSQ method. A multiplicity of quenching reagents may be added concurrently to remove a multiplicity of impurities and excess reagents since reactive groups on separate polymer-supports are known not to interact.[9] In principle, so long as one understands what impurities are in the crude product, one can devise the necessary PSQ reagents to selectively remove them and still maintain a single filtration workup.

Based upon the success of these simple examples, it seems rational that the ability to do traditional multistep syntheses with

(6) During the course of review of this manuscript a similar strategy was published: Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. Kaldor, S. W.; Fritz, J. E.; Tang, J.; McKinney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041.

(7) Other polyamine resins have been reported: Yamskov, I. A.; Budanov, M. V.; Davankov, V. A. *Bioorg. Khim.* **1979**, *5*, 757.

(8) Previously prepared at 110 °C. Metelko, M.; Zupan, M. *Synth. Commun.* **1988**, *18*, 1821.

(9) For selected references on compatibility of polymer-supported reactants, see Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620. Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395.

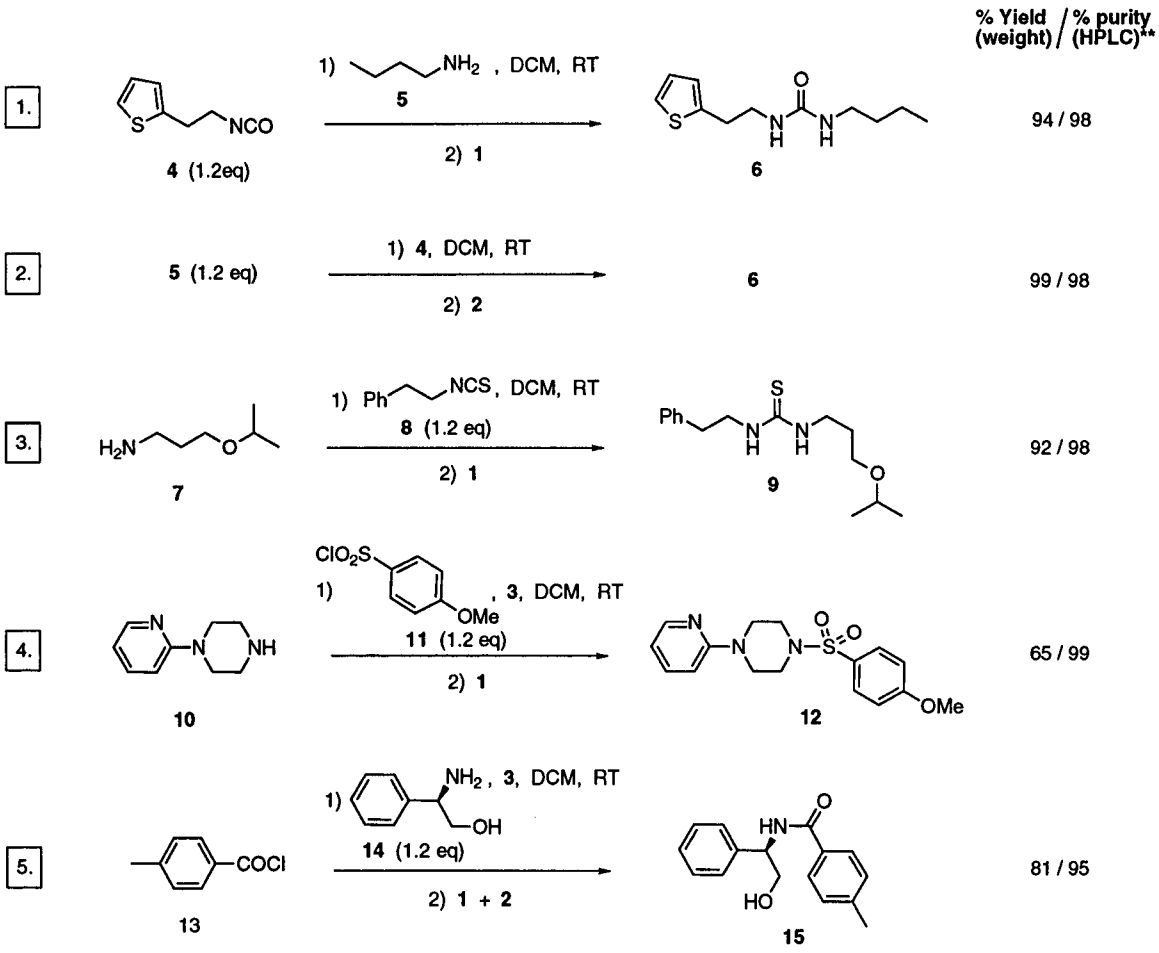

Figure 2. Polymer-supported quench-examples.

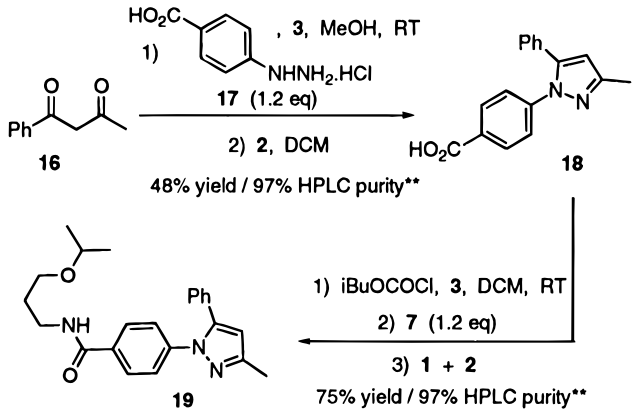

Figure 3. Pyrazole synthesis with PSQ-purification.

a quick PSQ purification after each step would make possible the application of combinatorial synthesis paradigms to many known solutionphase syntheses. As such, PSQ methods would apply to preparation of both lead optimization and lead generation libraries. An example of the application of PSQ purification to a traditional synthesis of pyrazoles[10] is illustrated by the conversion of **16** to **19** (Figure 3). In the first step a 1,3-diketone (**16**) is condensed with excess phenylhydrazine-4−carboxylic acid hydrochloride (**17**) in the presence of **3**. Removal of excess **17** by quenching the reaction with **2** affords **18** which is of excellent purity as determined by ^{1}H-NMR and HPLC. The moderate yield of this reaction is poorly understood. By TLC the reaction appears to be very clean. Literature precedent[10] would appear to rule out the possibility that the alternate pyrazole regioisomer is also formed, crystallizes from the reaction mixture, and is being removed in the filtration. It is plausible that some of the desired product is retained by the weakly basic morpholino resin; however, attempts to more vigorously wash the resin gave substantially less pure product so we chose to accept the moderate yield in favor of greater purity. In the second step, **18** is converted to a mixed anhydride by treatment with isobutyl chloroformate in the presence of **3** which, in the third step, is treated *in situ* with **7** to afford **19**, also of excellent purity by ^{1}H-NMR and HPLC, following PSQ purification with a mixture of **1** and **2**.

An example of the application of PSQ in mixed synthesis is shown in Figure 4. Equimolar quantities of three unusual carboxylic acids (**20**[11], **21**[12], and **22**[13]), which were obtained from the Parke-Davis historical collection, are combined and converted to the corresponding mixed anhydrides as above. Treatment with an excess of an unusual amine from the P-D collection (**23**[14]), followed by quenching with a mixture of **2** and **1** (added for good measure to ensure that any traces of

(10) Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.

(11) Short, F. W.; Hoefle, M. L. United States Patent 3,657,270.

(12) Prepared according to the method of Gates, M.; and Dickinson, C. L. *J. Org. Chem.* **1957**, *22*, 1398. For compound **21**: mp 129−130 °C (benzene/hexane). Anal. Calcd for $C_{14}H_{16}O_3S_2$: C, 56.75; H, 5.44; S, 21.6. Found: C, 56.97; H, 5.37; S, 21.52.

(13) Prepared according to the method of Creger P. L.; Neuklis W. A. United States Patent 3,707,566. For compound **22**: mp 79−80 °C (hexane). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.54; H, 6.71. Found: C, 75.76; H, 6.71.

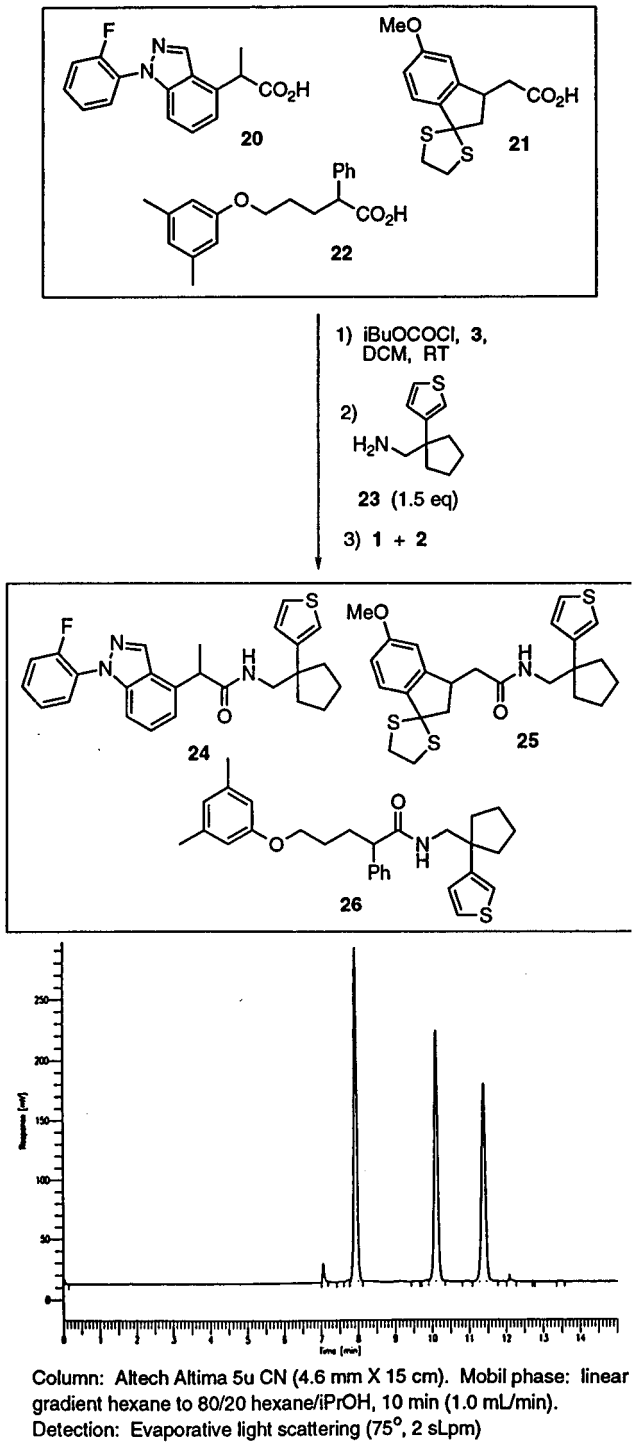

Figure 4. Amide mixture synthesis.

starting carboxylic acids are removed) affords an approximately equimolar mixture of **24**, **25**, and **26**, as confirmed by ^{1}H-NMR analysis, HPLC (Figure 4), and CI-MS. Complete removal of the excess amine is further verified by the use of a ninhydrin test. Complete removal of unreacted carboxylic acid starting materials is further verified by comparison of the ^{1}H-NMR spectrum for each of the individual starting acids with that of the amide product mixture. By inference, one could similarly use a much larger number of carboxylic acids to prepare a larger mixture of desired amides with comparable results. The ninhydrin test would still be applicable for demonstrating complete removal of the starting amine(s), but complete removal of all of the starting carboxylic acids would be much more difficult to establish conclusively by NMR. LC-MS would likely be a preferable analytical tool for this purpose. This simple example illustrates the utility of PSQ for removing multiple starting materials from a crude reaction mixture when multiple products are intentional. In such batch mode combinatorial syntheses, PSQ has an inherent advantage over traditional purification methods since it focuses on the chemical, not physical properties of the contaminants. In common practice, one would likely identify contaminants and validate PSQ purification protocols with a representative variety of starting materials in small mixture and/or single compound syntheses and assume similar success with the same PSQ protocols on a larger mixture.

(14) Trivedi, B. K.; Holmes, A.; Stoeber, T. L.; Blankley, C. J.; Roark, W. H.; Picard, J. A.; Shaw, M. K.; Essenburg, A. D.; Stanfield, R. L.; Krause, B. R. *J. Med Chem.* **1993**, *36*, 3300.

Summary

In summary, PSQ purification offers an efficient and readily automated means for obtaining organic molecules of suitable purity for routine *in vitro* biological testing. Relative to traditional chromatography, PSQ uses less solvent, requires less solid support, and eliminates the need to collect multiple fractions. Thus it is amenable to parallel application and automation. Furthermore, when applied to batch mode synthesis, mixtures of desired products can be separated from mixtures of starting materials, a process that would be cumbersome, if not impossible, by traditional methods of purification. Although the PSQ resins described are expensive relative to silica gel on a per gram basis, the small quantity of resin and solvent employed, combined with labor savings, actually make PSQ purification significantly cheaper than flash chromatography in most cases. Additionally, the PSQ reagents described are easily made in large quantity from some of the least expensive resin starting materials, and each PSQ reagent has many possible applications in the selective removal of excess reagents and identified impurities from crude product mixtures. The combination of solution synthesis and PSQ purification provides a convenient alternative to solid-phase synthesis in the practice of combinatorial chemistry.

Experimental Section

General. Unless otherwise indicated, all reactions were run in capped glass vials and were shaken on an orbital shaker. Reagents and solvent were commercially available and used without further purification. In order to represent the purity of compounds as they would be found following a solution-phase synthesis of a combinatorial library, all characterization listed before the term "Recrystallized mp" is derived from compounds as they are obtained following filtration of PSQ resins and evaporation of solvent. HPLC analysis was achieved using a Perkin Elmer, reduced activity, C18 column (4.6 mm ID, 8 cm length). The mobile phase (acetonitrile/25 mM phosphate buffer pH 3, 1.0 mL/min) was used as a linear gradient of 20−90% acetonitrile over 7 min; detection was at 210 nm. Unless otherwise stated, NMR spectra were obtained at a field strength of 400 MHz with samples dissolved in $CDCl_3$. Coupling constants (J) are reported in hertz. IR spectra were taken as KBr pellets, and absorptions are reported in cm^{-1}. High resolution mass spectra were obtained by chemical ionization with methane or by electrospray ionization from a soluton in MeOH/H_2O (2:1) with 2.5% HOAc. Melting points are uncorrected.

Polymer-Supported Tris(2-aminoethyl)amine (1). A suspension of Merrifield resin (Fluka, 50 g, 1.7 mmol of Cl/g resin, 85 mmol) in DMF (500 mL) was treated with tris(2-aminoethyl)amine (50 mL, 342 mmol). The resulting mixture was shaken at 65 °C for 6 h under N_2 atmosphere. After cooling to room temperature, the resin was filtered and washed successively with MeOH, DMF, Et_3N, MeOH, DCM, Et_3N, MeOH, DCM, MeOH, DCM, and MeOH. The resulting amine resin was dried at 45−50 °C, 20 mmHg for 24 h, and stored in tightly sealed

bottles. Calcd: N, 8.02; Cl, 0.00. Found: N, 5.96; Cl, 0.42 (indicates approximately 25% cross-linking). A small sample reacted with excess 3,4-dichlorophenyl isocyanate in DCM indicates a quenching capacity of 3.18 mmol/g resin, consistent with 3/4 of the N content in the amine resin. Anal. Calcd: N, 6.51; Cl, 14.15. Found: N, 6.25; Cl, 13.99.

Polymer-Supported Isocyanate 2. A suspension of aminomethyl resin (Fluka, 1.1 mmol of N/g resin, 15 g, 16.5 mmol) in DCM (150 mL) was treated with Et_3N (11.5 mL, 83 mmol) and triphosgene (3.25 g, 2 mmol equiv of phosgene) and shaken 5 h at room temperature. The resulting isocyanate resin was filtered and washed with DCM (2 × 200 mL), $CHCl_3$ (2 × 200 mL), Et_2O (1 × 200 mL), THF (1 × 200 mL), Et_2O (1 × 200 mL), THF (1 × 200 mL), and Et_2O (1 × 200 mL). The resin was then dried at 35−40 °C, 25 mmHg, for 24 h. IR (KBr) 2260. Anal. Calcd: N, 1.50. Found: N, 1.45.

Polymer-Supported Morpholine 3. A suspension of Merrifield resin (Fluka, 20 g, 4.3 mmol of Cl/g resin, 86 mmol) in DMF (100 mL) was treated with morpholine (20 mL, 229 mmol). The resulting mixture was shaken at 65 °C for 6 h under N_2 atmosphere and then allowed to stand at room temperature 24 h. After cooling to room temperature, the resin was filtered and washed successively with MeOH, DMF, MeOH, Et_3N, DCM, MeOH, Et_3N, DCM, MeOH, EtOAc, and hexanes. The resulting polymer-supported morpholine, **3**, was dried at 45−50 °C, 20 mmHg, for 48 h and stored in tightly sealed bottles. Anal. Calcd: N, 4.83; Cl, 0.00. Found: N, 4.98; Cl, 0.21.

1-Butyl-3-(2-thiophen-2-yl-ethyl)urea (6). Method 1: To a solution of 2-(thieny-2-yl)ethyl isocyanate (**4**, 47 mg, 0.3 mmol) in DCM (2 mL) was added *n*-butylamine (**5**, 25 μl, 0.25 mmol). The reaction mixture was shaken for 1 h, and then polymer-supported tris(2-aminoethyl)amine (**1**, 50 mg) was added. After 2 h the resin was filtered and washed with DCM (2 × 1.5 mL). The combined organic phases, when concentrated to dryness, gave the title compound (53 mg, 94%) as an oil that crystallizes upon prolonged standing: mp 46−50 °C; t_R = 5.92; IR (KBr) 1626; ^{1}H NMR δ 0.9 (3H, t, J = 8), 1.33 (2H, m), 1.42 (2H, m), 3.0 (2H, t, J = 7), 3.11 (2H, m), 3.44 (2H, m), 4.61 (1H, brs), 4.77 (1H, brs), 6.81 (1H, dd, J = 3, 1), 6.92 (1H, dd, J = 5, 3), 7.13 (1H, dd, J = 5, 1); ^{13}C NMR δ 13.8, 20.0, 30.7, 32.3, 40.2, 41.8, 123.7, 125.2, 126.9, 141.7, 158.22; predicted mass for $(C_{11}H_{18}N_2OS + H)^+$, 227.1218; found by HRMS (CI), 227.1210. Anal. Calcd for $C_{11}H_{18}N_2OS$: C, 58.40; H, 8.02; N, 12.38. Found: C, 58.69; H, 8.22; N, 12.06. Attempted recrystallization from a variety of solvents gave at best an amorphous solid from hexanes: mp 42−46 °C.

Method 2: To a solution of **4** (30 mg, 0.2 mmol) in DCM (2 mL) was added **5** (25 μl, 0.25 mmol). The reaction mixture was shaken for 1 h, and then polymer-supported isocyanate (**2**, 50 mg) was added. After 2 h the resin was filtered and washed with DCM (2 × 1.5 mL). The combined organic phases, when concentrated to dryness, gave the title compound (44 mg, 99%) as an oil that solidifies upon prolonged standing: mp 40−42 °C. Spectral and HPLC data are identical to those from method 1 above.

4-(3-Methyl-5-phenylpyrazol-1-yl)benzoic Acid (18).[10,15] A suspension of polymer-supported morpholine (**3**, 170 mg), 1-phenyl-1,3-butanedione (**16**, 81.5 mg, 0.5 mmol) and (4-carboxyphenyl)hydrazine hydrochloride (**17**, 113 mg, 0.6 mmol) in MeOH (2 mL) was shaken for 2.5 h. The methanol was blown off under a stream of N_2. DCM (4 mL) and polymer-supported isocyanate **2** (350 mg) were added, and the reaction mixture was shaken for 16 h. An additional portion of polymer-supported isocyanate **2** (120 mg) was added. After 4 h the resin was filtered and washed with DCM (2 × 1.5 mL). The combined organic phases, when concentrated to dryness, gave the title compound (67 mg, 48%) as an orange solid: mp 159−162 °C; t_R = 6.12; IR (KBr) 1699; ^{1}H NMR δ 2.36 (3H, s), 6.3 (1H, s), 7.2 (2H, m), 7.33 (3H, m), 7.35 (2H, d, J = 7), 8.0 (2H, d, J = 7); predicted mass for $(C_{17}H_{14}N_2O_2 + H)^+$, 278.1055; found by HRMS (CI), 278.1055. Recrystallization from EtOAc/hexane gives the hydrate:[15] recrystallized mp 169−170 °C. Anal. Calcd for $C_{17}H_{14}N_2O_2 \cdot H_2O$: C, 68.90; H, 5.45; N, 9.45. Found: C, 68.75; H, 5.46; N, 9.38.

***N*-(3-Isopropoxypropyl)-4-(3-methyl-5-phenylpyrazol-1-yl)benzamide (19).** A solution of 4-(3-methyl-5-phenylpyrazol-1-yl)benzoic acid (**18**, 20 mg, 70 μmol) in DCM (0.7 mL) was treated with polymer-supported morpholine (**3**, 100 mg) and 0.1 M isobutyl chloroformate in DCM (0.75 mL, 75 μmol). The resulting slurry was shaken under N_2, at rT, for 35 min and then treated with a solution of (3-isopropoxypropyl)amine (**7**, 100 mg, 85 μmol) in DCM (0.5 mL). The reaction was shaken at rT for 2.5 h. Polymer-supported isocyanate (**2**, 75 mg) and polymer-supported tris(2−aminoethyl)amine (**1**, 100 mg) were added, and the mixture was shaken an additional 2 h. Resins were removed by filtration and rinsed with DCM (2 × 2.5 mL). Combined filtrate and washings were evaporated to a solid and dried at 0.25 mmHg, rT, overnight to afford **19** as a pale orange solid (19.7 mg, 75%): mp 109−111 °C; t_R = 6.90; IR (KBr) 1629; ^{1}H NMR δ 1.15 (6H, d, J = 6), 1.87 (2H, m), 2.39 (3H, s), 3.55−3.64 (5H, complex), 6.32 (1H, s), 7.2 (2H, m), 7.3 (6H, m), 7.71 (2H, d, J = 9); predicted mass for $(C_{23}H_{27}N_3O_2 + H)^+$, 378.2181; found by HRMS (CI), 378.2166. Recrystallization from EtOAc/hexanes gives a nearly colorless solid: recrystallized mp 126−127 °C. Anal. Calcd for $C_{23}H_{27}N_3O_2 \cdot 0.3H_2O$: C, 72.14; H, 7.27; N, 10.97. Found: C, 72.15; H, 6.97; N, 10.94. Found by HRMS (CI) 378.2170.

Supporting Information Available: Complete experimental procedures and data for compounds **9**, **12**, **15**, **24**, **25**, and **26** plus photoreductions of actual ^{1}H NMR spectra and HPLC chromatograms, for **6**, **9**, **12**, **15**, **18**, **19**, and the mixture of **24**−**26** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered online from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) The hydrate of **18** has previously been described, mp 159−160 °C (EtOH).