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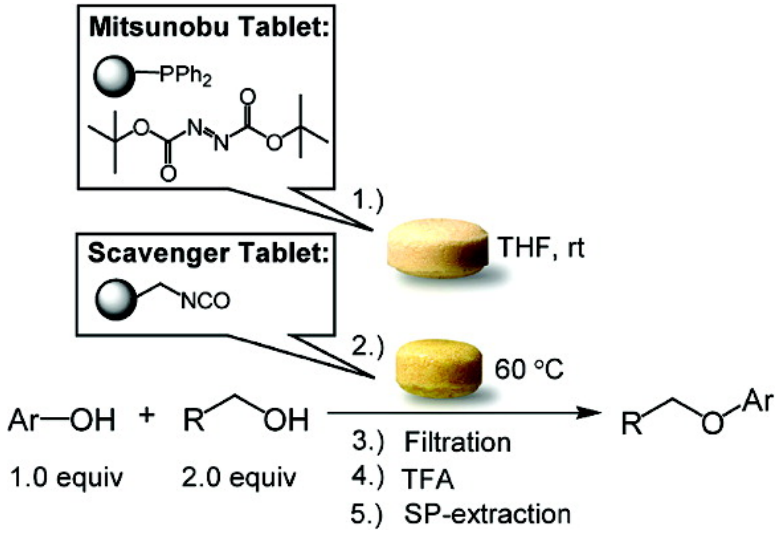

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Tablets of Functionalized Polystyrene Beads Alone and in Combination with Solid Reagents or Catalysts. Preparation and Applications in Parallel Solution and Solid Phase Synthesis†

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Pretreatment of polystyrene beads with a nonpolar organic solvent is the key for the generation of mechanically robust tablets consisting of neat functionalized polystyrene beads, both alone and in combination with solid reagents or catalysts. The novel dosing methodology provides accurately preweighed tablets in virtually any shape and size and with excellent disintegration properties, speeding up parallel solution and solid phase synthesis. The use of tablets is demonstrated in parallel Mitsunobu and acylation reactions.

Introduction

During the past decade, the intensive investigation in solid phase synthesis of small organic molecules, as well as the use of polymer-supported reagents and catalysts for solution phase organic synthesis, has led to paradigm shifts in many areas of chemistry.[1] This has particularly been the case within the fields of biological and medicinal chemistry where the parallel synthesis of discrete molecules (in series or larger libraries), by either manual or automated methods, has been implemented as a key technology/methodology in the preparation of compounds for biological evaluation.[2]

A prerequisite for the efficient synthesis of compound series and libraries is precise, rapid, and safe dosing of functionalized polymer beads, solid reagents, and catalysts. Numerous technical achievements addressing the dosing problem of polymer supports have been developed. Discrete packages of polymers in the form of tea bags,[3] Irori-Kans and Tubes,[4] resin plugs,[5] crowns and pins,[6] as well as polymer disks and monoliths,[7] and related technologies[8] have been reported, in which the polymers remain addressable during the entire solid phase synthesis. Another approach is the dosing of preweighed and free-flowing polymer beads in soluble polycarbonate capsules.[9] In addition, several methods for the automated and semiautomated dosing of polymer supports as dry powders and as suspensions have been developed.[10]

Results and Discussion

In the present paper, we describe the formulation of functionalized polystyrene beads alone and in combination with other solid reagents or catalysts as tablets (Figure 1).

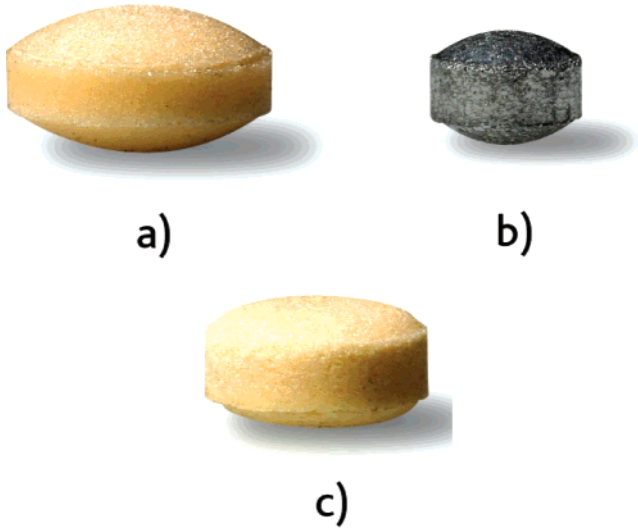

Figure 1. (a) Merrifield tablet (∅ = 10 mm, 275 mg) consisting of neat chloromethyl polystyrene beads (1.10 mmol/g; 100−200 mesh) (Table 1, entry 5). (b) Sm tablet (∅ = 6 mm, 100 mg) consisting of samarium powder (approximately 325 mesh) and polystyrene beads (100−200 mesh) in a w/w ratio of 3:10 (Table 1, entry 13). (c) Mitsunobu tablet (∅ = 8 mm, 195 mg) consisting of diphenylphosphine polystyrene beads (1.69 mmol/g, 200−400 mesh) and a mixture of di-*tert*-butyl azodicarboxylate (DBAD) and polystyrene beads (100−200 mesh) in a w/w/w ratio of 10:3:12, respectively (Table 1, entry 8). Further details in Tables 1 and 2.

In addition, we describe the application of such tablets in solid phase and solution phase synthesis.

The preparation of tablets from commercially available starting materials involved three steps. First, the functionalized polystyrene beads were pretreated by suspending the beads in an organic solvent such as dichloromethane (DCM) with subsequent filtration and drying. Second, the pretreated polystyrene beads were screened through a sieve and finally compressed to tablets using a single-punch tableting machine.

By this procedure, tablets of functionalized polystyrene

† Dedicated to Prof. R. W. Hoffmann on the occasion of his 70th birthday.

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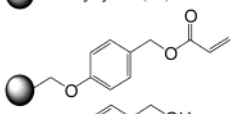
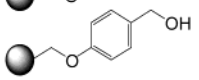
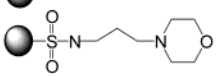
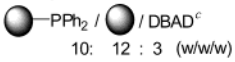
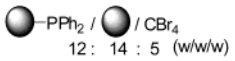
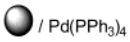
Table 1. Tablet Characteristics

Entry	Tablet composition	PS in %	Weight mg	Size mm	Strength[a] N	Tablet content[b] µmol/tablet
1	= Polystyrene (PS)	100	100	6	20	-
2		0	100	6	15	100
3		0	100	6	20	110
4		0	35	5	15	59
5		0	65	6	8	72
6		0	80	6	20	80
7		0	200	8	25	164
8	 10: 12 : 3 (w/w/w)	48	195	8	8	130/ - /100
9	 12 : 14 : 5 (w/w/w)	45	220	8	8	140/ - /110
10		86	100	6	15	12
11		67	100	6	15	239
12		77	250	8	15	64
13		77	100	6	15	153
14		77	100	6	15	284
15		80	100	6	15	666

[a] Crushing strength of tablet in Newtons (N). [b] Content of reactive functional group and/or embedded reagent. [c] DBAD = di-*tert*-butyl azodicarboxylate.

beads, useful as scavengers, reagents, or catalysts for solution phase synthesis as well as supports for solid phase synthesis, were prepared (Table 1, entries 1−7).

Nonpolymer-bound solid reagents or catalysts are often noncompressible and therefore not suitable for the manufacture of tablets. However, admixing polystyrene beads with solid reagents or catalysts provided suitable compressibility and flowability for the rapid preparation of robust tablets. Such tablets were prepared as described in the three step procedure outlined above, except that the constituents were mixed in the first step. For solids with reasonable solubility in the solvent applied, the solid was dissolved prior to the suspension of the polystyrene beads, and the solvent was evaporated subsequently in vacuo. For solids with limited solubility, a homogeneous suspension of polystyrene beads and the solid were formed prior to filtration and drying (Table 1, entries 10−15).

For tablets containing a mixture of functionalized polystyrene beads and a solid reagent or catalyst, the functionalized polystyrene beads were pretreated separately from the other components. The solid reagent or catalyst was pretreated with neat polystyrene beads and then mixed with the pretreated functionalized polystyrene beads prior to tablet compression (Table 1, entries 8 and 9).

To the best of our knowledge, we report herein the first compression of neat polystyrene beads to give mechanically robust tablets. The formation of agglomerates of polystyrene beads was found to be essential for the compression of polystyrene beads to tablets. We observed that the agglomeration of polystyrene beads took place after pretreatment with organic solvents. In particular, a high degree of agglomeration was associated with a high degree of swelling of the beads in solvents such as DCM and tetrahydrofuran (THF). The agglomerates of polystyrene beads were analyzed by scanning electron microscope (SEM). Figure 2a,b show polystyrene beads before and after pretreatment with DCM, respectively. The SEM micrographs of polystyrene beads after pretreatment with DCM indicate that the agglomeration is probably caused by bead−bead interaction. The origin of this interaction is difficult to unambiguously define but is

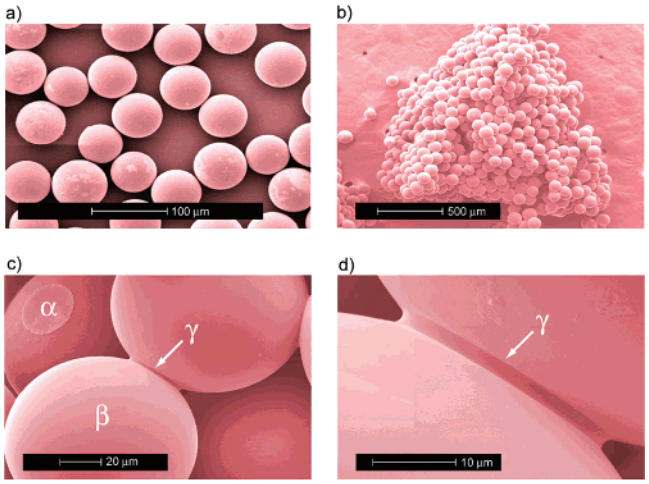
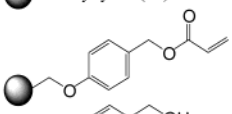
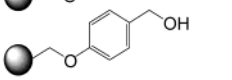
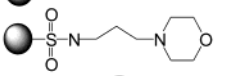
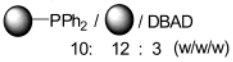
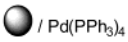


Figure 2. (a) Distinct polystyrene beads (200−400 mesh) after pretreatment with methanol. (b) Agglomerated polystyrene beads after pretreatment with DCM. (c, d) Bead−bead interaction via polymer bridges; α = former contact area after disruption of polymer bridge; β = bead surface; γ = polymer bridge.

Table 2. Disintegration Times of Tablets in Different Solvents

Entry	Tablet composition	CH_2Cl_2 min	THF min	DMF min	Toluene min	CH_3CN min	DMSO h	Ethanol h
1	= Polystyrene (PS)	<2.5	<5.0	<24.0	<7.0	[a]	<12.0	[a]
2		<1.0	<2.0	<3.0	<2.0	<2.0	<0.083	[a]
3		<7.0	<13.0	<30.0	<27.0	<35.0	<2.0	[a]
4		<5.0	<9.0	<10.0	<10.0	<45	<12.0	[a]
5		<3.0	<4.5	<1.0	<4.0	<45	<12.0	[a]
6		<2.5	<16.0	<17.0	<45.0	[a]	<0.08	[a]
7		<2.5	<3.0	<3.0	<720	<5.0	<2.0	[a]
8	 10: 12 : 3 (w/w/w)	<3.0	<3.0	<2.0	<4.0	<2.0	<0.16	<0.16
9	 12 : 14 : 5 (w/w/w)	<2.5	<1.5	<0.2	<0.2	<10.0	<0.10	[a]
10		<0.2	<2.0	<1.0	<4.0	<3.0	<12	[a]
11		<1.0	<4.0	<1.0	<1.0	<20.0	[a]	[a]
12		<0.2	<1.0	<1.0	<0.2	<15.0	<0.06	<3.0
13		<1.5	<1.0	<1.0	<1.0	<420	[a]	[a]
14		<0.5	<1.0	<1.0	<1.0	<420	[a]	[a]
15		<0.5	<2.0	<1.0	<1.0	<35.0	[a]	[a]

[a] Not disintegrated within 24 h.

probably the result of noncovalent interactions (van der Waals and/or mechanical entanglement) between loosely bound polymer chains on the surfaces of adjacent beads, in a manner analogous to Velcro fastenings (Figure 2c,d). If this were the case, it would also explain why solvents with good swelling properties are required for this agglomeration, because the "freeing" of these surface chains could only take place when the resin is efficiently swollen. To provide evidence for this hypothesis and to exclude the possibility that agglomeration is caused by traces of impurities, the elemental composition of the bridging material between the beads was analyzed by environmental scanning electron microscopy (ESEM) using X-ray energy dispersive analysis (EDX).[11] The analysis clearly indicates that polystyrene beads and polymer bridges have identical elemental compositions, which thereby strengthens the "Velcro/entaglement" hypothesis.

Physical properties relevant for the application of the tablets in the organic chemistry laboratory were evaluated and are summarized in Tables 1 and 2. The disintegration time for the tablets in the most frequently used organic solvents was determined by gentle shaking (Table 2). A plausible mechanism for tablet disintegration is that the bead−bead interactions and the bead packing within the tablet (Figure 3a,b) are disrupted due to swelling of the individual polystyrene beads. All tablet types have disintegration times shorter than 7 and 16 min in DCM and THF, respectively. Tablets consisting of polystyrene beads and a solid reagent or catalyst have even shorter disintegration times, less than 4 min in DCM and THF. A similar overall pattern is observed for DMF and toluene, except that

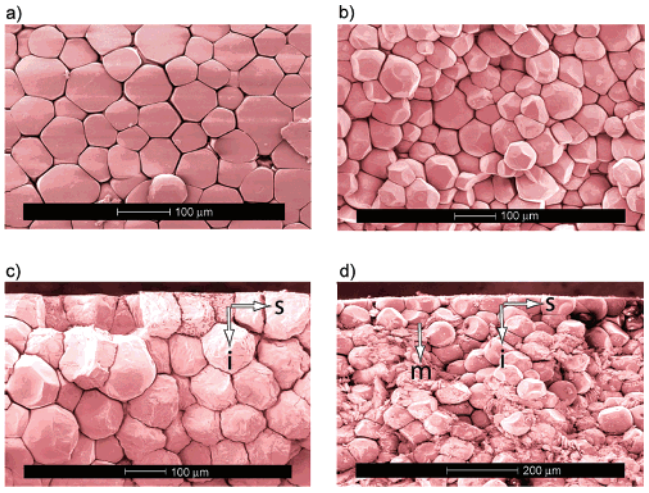
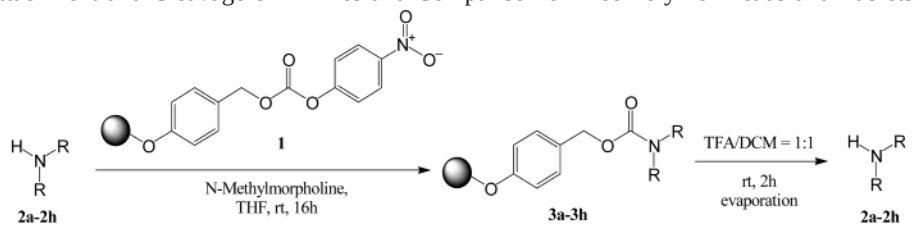
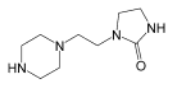
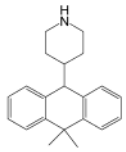
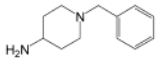
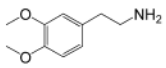
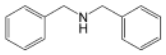
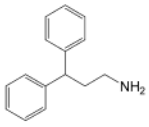
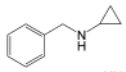
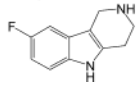


Figure 3. (a) Tablet surface of compressed polystyrene beads (Merrifield resin). (b) Inner tablet cross-section (Merrifield resin). (c) Tablet cross-section of a mixture of DBAD, polymer-bound triphenylphosphine, and polystyrene beads in a w/w/w ratio of 3:10:12; *s* = beads on the tablet surface and *i* = beads underneath the tablet surface. (d) Tablet cross-section of a mixture of samarium powder and polystyrene beads in a w/w ratio of 3:10; *s* = beads on the tablet surface, *i* = beads underneath the tablet surface, and *m* = embedded Sm particles.

disintegration times for functionalized polymer beads are much longer than for DCM or THF (generally less than 30 or 40 min for DMF and toluene, respectively). In particular, it is noticeable that toluene is a poor solvent for the disintegration of functionalized polymer tablets containing polar groups. Although this observation is unsurprising, it is consistent with the suggested mechanism of tablet disrup-

Table 3. Attachment and Cleavage of Amines and Comparison of Free Polymer Beads and Tablets



			Free beads of resin 1			Tablets of resin 1		
Entry	Amine		Yield (%)	Purity by LC/MS-UV (%)	Purity by LC/MS-ELSD (%)	Yield (%)[a]	Purity[a] by LC/MS-UV (%)	Purity[a] by LC/MS-ELSD (%)
1		**2a**	70	-	100	105[b]	-	100
2		**2b**	65	86	87	105[b]	95	97
3		**2c**	62	70	100	90	75	100
4		**2d**	59	44	49	86	61	70
5		**2e**	50	80	98	83	91	100
6		**2f**	62	83	94	98	89	99
7		**2g**	19	31	70	9	24	50
8		**2h**	72	56	56	89	67	70

[a] Yields and LC/MS purities after SCX purification.[16] [b] Yields greater than 100% could be due to (for example) variations in tablet weight (±5%).

tion due to bead swelling. Similarly, the shorter disintegration times observed for tablets consisting of polystyrene beads and a solid as compared to tablets consisting of neat polystyrene beads may be explained by the weaker bead−bead interactions due the embedded solid (Figure 3c,d). Both tablet types disintegrate either very slowly or remain intact in polar solvents such as dimethyl sulfoxide (DMSO) and ethanol, probably due to the poor swelling properties of the polystyrene beads in these solvents.

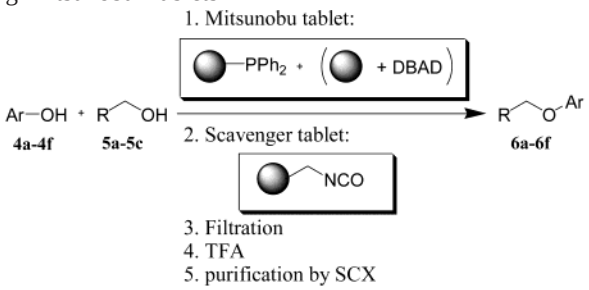
The mechanical stability of the tablets was determined as the crushing strength in a tablet hardness tester. The crushing strengths of the tablets prepared are in the range of 8−25 N (Table 1) and are therefore suitably robust for transportation and handling in automated equipment.

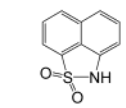
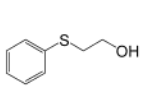
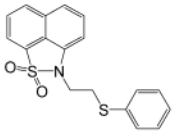
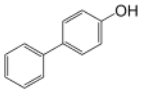
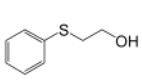
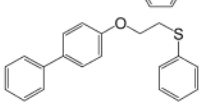
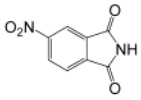
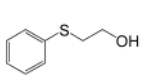
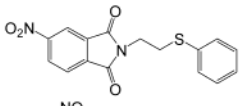
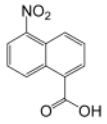
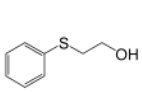
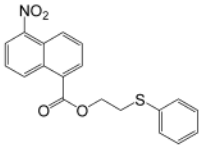
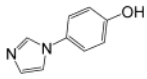
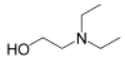
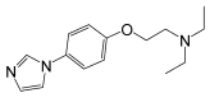
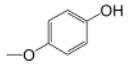
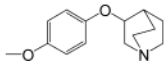
It is essential that the polystyrene beads remain intact during the entire tablet manufacturing procedure, to ensure efficient washing and filtration of the beads after disintegration of the tablets. The integrity of the beads was analyzed in a series of SEM micrographs (Figures 2 and 3). SEM micrographs of polystyrene beads located on the tablet surface plus those from the interior of the tablet clearly show that the beads are only extremely deformed but not fragmented (Figure 3). In addition, bead deformation is completely reversible and beads return to their original shape after tablet disintegration in organic solvents.

As is evident from Table 1, tablets in a variety of shapes and compositions are obtained in excellent quality, with weights in the range of 30−250 mg, and using 100−200 or 200−400 mesh polystyrene beads. Best results were obtained for polystyrenes with low cross-linking (1−2%). Highly cross-linked polystyrene beads (e.g., the macroporous Argopore) or polystyrene beads with poor swelling properties (polyethylene-grafted polystyrenes, e.g., ArgoGel and TentaGel resins) showed poor tendencies toward agglomeration, and it was difficult to obtain robust tablets. Generally, the standard deviation of tablet weights was determined to be less than 5%. In the following examples, the efficiency of this novel dosing form is demonstrated in solid phase and parallel solution phase synthesis in order to exemplify the general applicability of the methodology.

The chemical performance of tablets in solid phase synthesis was compared to the performance of loose polymer beads. The reactive resin-bound carbonate **1** was prepared from commercially available Wang resin.[12] Immediately after preparation, one part of the polymer was compressed to give tablets (51 mg, 4 mm), and the remaining portion was used

Table 4. Mitsunobu Reactions Performed Using Mitsunobu Tablets



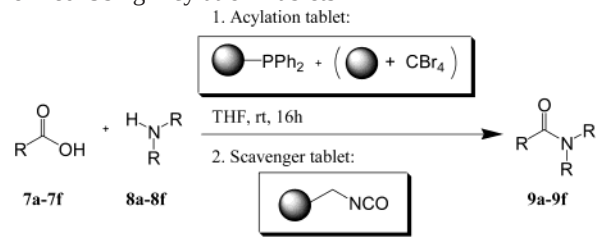
Entry	Substrates **4**	Substrates **5**	Products **6**	Yield[a] %	Purity by LC/MS-UV[a] %	Purity[a] by LC/MS-ELSD %
1	 **4a**	 **5a**	 **6a**[16]	89	98	99
2	 **4b**	 **5a**	 **6b**[16]	91	89	87
3	 **4c**	 **5a**	 **6c**[16]	100	84	80
4	 **4d**	 **5a**	 **6d**[16]	90	97	99
5	 **4e**	 **5b**	 **6e**[17]	61	100 (GC-MS)	-
6	 **4f**	 **5c**	 **6f**[17]	69	37	87

[a] Yield and LC/MS purities after chromatography.[16]

as loose resin. Eight different amines **2a**−**h** were attached to resin **1** and were subsequently cleaved under acidic conditions from the intermediate resins **3a**−**h**, purified by ion exchange chromatography (SCX columns[13]), and analyzed by liquid chromatography/mass spectroscopy (LC/MS), using evaporative light scattering detection (ELSD) and UV ($\lambda = 254$ nm) detection (Table 3). Reactions carried out with tablets provided amines in excellent yields (83−105%) and LC/MS−UV purities (61−95%). The only exception was benzyl-cyclopropylamine **2g**, which gave low yields probably due to degradation under the strong acidic cleavage conditions (Table 3, entry 7). In contrast, experiments carried out with loose resin gave amines in significantly lower yields (50−86%) and LC/MS−UV purities (44−86%). These results were unexpected, since polymer from the same batch was used. However, both the loose resin beads and the tablets were stored at room temperature for approximately 8 weeks prior to use and were equally exposed to air and humidity. Our results suggest tentatively that the tablets may act as sealed packages protecting embedded, sensitive functional groups against humidity. Figure 3a shows the tight assembly of beads on the tablet surface, which presumably provides an effective seal. Another significant advantage is that the distribution of tablets is much faster than weighing out comparable amounts of loose resin. The manual distribution of tablets into 48 reaction vessels took approximately 3 min, whereas the weighing of loose resin and its distribution into 48 reaction vessels required more than 30 min.

In a second test of this methodology, the Mitsunobu reaction was investigated in solution by the use of a Mitsunobu tablet and a scavenger tablet (Table 4). The Mitsunobu tablet (195 mg, 8 mm) contained a full set of reagents required for the Mitsunobu reaction [0.13 mmol of polymer-bound triphenylphosphine and 0.10 mmol of di-*tert*-butyl azodicarboxylate (DBAD)].[14] The scavenger tablet containing neat isocyanatomethyl polystyrene (150 mg, 0.15 mmol, 8 mm) was used to scavenge excess alcohol. Representative Mitsunobu transformations were carried out on a 0.1 mmol scale in conventional glass flasks. The crude products were purified by solid phase extraction over silica gel and were analyzed by LC/MS and NMR. Generally, Mitsunobu products **6a**−**f** were obtained in good to excellent yields (61−100%) and LC/MS−UV purities (84−98%). The best coupling results were obtained with 2-phenylsulfanyl-ethanol **5a** and 5-nitro-isoindole-1,3-dione **4c** (Table 4, entry 3). The coupling product was obtained in 100% yield after solid phase extraction and high LC/MS−UV purity (84%). Only the Mitsunobu coupling of the sterically hindered

Table 5. Acylation of Amines Performed Using Acylation Tablets



Entry	Substrates **7**	Substrates **8**	Products **9**	Yield[a] %	Purity[a] by LC/MS-UV %	Purity[a] by LC/MS-ELSD %
1	**7a**	**8a**	**9a**[17]	29	66	81
2	**7b**	**8b**	**9b**[17]	45	98	99
3	**7c**	**8c**	**9c**[18]	72	-	99
4	**7d**	**8d**	**9d**[18]	66	43	72
5	**7e**	**8e**	**9e**[18]	75	65	92
6	**7f**	**8e**	**9f**[18]	45	98	99

[a] Yield and LC/MS purification after chromatography.[16]

secondary alcohol 1-azabicyclo[2.2.2]octan-3-ol **5c** with 4-methoxy-phenol **4f** (Table 4, entry 6) gave modest yield (69%) and low LC/MS−UV purity (37%).

In a third test of this methodology, the acylation of amines with carboxylic acids in solution by the use of an acylation tablet and a scavenger tablet was investigated (Table 5). The acylation tablet (220 mg, 8 mm) contained a full set of reagents required for the acylation of amines (0.14 mmol of polymer-bound triphenylphosphine and 0.11 mmol of tetrabromomethane).[15] The scavenger tablet contained neat isocyanatomethyl polystyrene (150 mg, 0.15 mmol, 8 mm) and was used to scavenge excess amine. Representative acylations were carried out on a 0.1 mmol scale in conventional glass flasks. Crude products were purified by solid phase extraction over silica gel and were analyzed by LC/MS and NMR. Generally, amides **9a**−**f** were obtained in modest to good yields (29−75%) and good to excellent LC/MS−UV purities (43−98%). Best coupling results were obtained for the acylation of morpholine with 4-phenyl-butyric acid **7e** (Table 5, entry 5). After solid phase extraction, the amide **9e** was obtained in good yield (75%) and LS/MS−UV purity (65%). The acylation of the sterically hindered 2,6-dimethyl aniline **8a** with 4-methoxybenzoic acid **7a** (Table 5, entry 1) gave a low yield (29%) but good LC/MS−UV purity (66%).

Conclusions

We have developed a novel methodology for the preparation of tablets consisting of neat functionalized polystyrene beads and for tablets of nonpolymer-bound solid reagents or catalysts in combination with polystyrene beads. The methodology described produces mechanically robust tablets without requiring the use of other additives. The agglomeration of polystyrene beads by pretreatment of the beads in solvents providing a high degree of swelling is essential for the formulation of tablets. The efficiency of the tablets in both solution and solid phase synthesis has been demonstrated. The novel methodology provides accurately preweighed tablets in virtually any shape and size, combined with sufficient mechanical stability and excellent disintegration properties in organic solvents. Furthermore, our results suggest tentatively that the tablets can act as sealed packages, embedding sensitive functional groups/reagents and protecting them against moisture and oxygen. Dosing and distribution of reagents and catalysts as tablets is more convenient and faster as compared to conventional methods and is also compatible with automation. Application of tablets, especially in parallel synthesis, significantly reduces the exposure of toxic, hazardous, and dusty materials to the working environment. This novel methodology has a significant potential to speed up parallel solution and solid phase synthesis but is also applicable to traditional synthesis.

Experimental Section

All reactions were carried out under positive pressure of nitrogen. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. THF was distilled under N_2 from sodium/benzophenone immediately prior to use. DMF was dried over molecular sieve (4 Å) prior to use. Parallel reactions were carried out in a microblock with 96 reactors (1 mL) equipped with polyethylene frits. The reactors were flushed with

nitrogen prior to the reaction. For solid phase extraction, Scharlau 60 (230−400 mesh) silica gel (sorbil) was used. Ion exchange chromatography was performed on a Gilson ASPEC XL instrument using SCX columns (1 g) from Varian Mega Elut, Chrompack. Prior to use, the SCX columns were preconditioned with a 10% solution of acetic acid in methanol (3 mL). Thin-layer chromatography was performed on Merck 60 F_{254} 0.25 μm silica gel plates. ^{1}H NMR and ^{1}H-decoupled ^{13}C NMR spectra were recorded at 500.13 and 125.67 MHz, respectively, on a Bruker Avance DRX 500 instrument. Unless otherwise noted, compounds were measured in deuterated chloroform (99.8%). Chemical shifts for ^{1}H NMR are reported in ppm with TMS as internal reference. Chemical shifts for ^{13}C NMR are reported in ppm relative to chemical shifts of deuterated solvents. Coupling constants (*J* values) are in Hertz. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, dd = double doublet, and m = multiplet. LC/MS data were obtained on a PE Sciex API150EX equipped with a Heated Nebulizer source operating at 425 °C. The LC pumps were Shimadzu 8A series running with a Waters C-18 4.6 mm × 50 mm, 3.5 μm column; solvent A, 100% water + 0.05% trifluoroacetic acid; solvent B 95% acetonitrile, 5% water + 0.035% trifluoroacetic acid; gradient (2 mL/min), 10% B−100% B in 4 min, 10% B for 1 min; total time including equilibration, 5 min; injection volume, 10 μL from a Gilson 215 Liquid Handler. Purities of compounds were determined by UV detection at 254 nm and by ELSD. GC/MS data were obtained on a Varian CP-3800/Saturn 2000 instrument. The column was Varian CP-Sil8 CB-MS Rapid-MS (10 mm × 0.53 mm) with He flow of 1.1 mL/min. The temperature gradient was 60−300 °C in 15 min. The mass detector was operated in the EI mode. The compression of tablets was performed at a Korsch EK0 single punch machine. The crushing strength was measured at a Schleuniger 6D tablet hardness tester. Disintegration times of tablets were measured in a glass tube (16 mm × 100 mm) with 2 mL of solvent by vortex mixing at a speed of approximately 500 Hz with an IKA shaker (KS 125 basic). The process of tablet disintegration was monitored visually, and tablets were deemed to be fully disintegrated when dispersion was formed and no more lumps were present. For SEM pictures, the resin samples were sputter coated in a Microtech, Polaron SC 7640 using a gold/platinum electrode, and SEM analysis was performed using a Philips electron microscope XL30. Elemental analyses were performed at the University of Vienna, Department of Physical Chemistry (Vienna, Austria), with a Perkin-Elmer 2.400 CHN elemental analyzer. Neat polystyrene resin (100−200 mesh, 1% DVB), resin-bound diphenylphosphin (1.69 mmol/g; 100−200 mesh, 1% DVB), Wang resin (1.0 mmol/g; 100−200 mesh, 1% DVB), (vinylcarbonyloxymethyl)-phenoxymethyl polystyrene (0.9 mmol/g; 200−400 mesh, 1% DVB), Merrifield resin (1.0 mmol/g; 200−400 mesh, 1% DVB), and 3-(morpholino)propyl polystyrene sulfonamide (2.0 mmol/g; 100−200 mesh, 1% DVB) were commercially available. 4-[(4-Nitrophenoxy)carbonyloxymethyl)-phenoxymethyl polystyrene[1] (approximately 0.82 mmol/g; 100−200 mesh, 1% DVB) and isocyanatomethyl polystyrene[2] (approximately 1.00 mmol/g; 200−400 mesh) were prepared according to procedures known from the literature. Metals were commercially available as follows: samarium powder (approximately 325 mesh, Avocado), selenium poweder (approximately 100 mesh, Aldrich), and aluminum powder (bronze, E. Merck).

Tablet Formulation. Representative examples for the pretreatment and compression of polystyrene beads alone and in combination with solid reagents are presented.

Functionalized Polystyrene Beads (Resin 1). Resin **1** (25.0 g; 0.82 mmol/g; 100−200 mesh) was suspended in DCM (500 mL) at room temperature for 15 min. The resin was filtered on a D3-frit by gravity and was dried on the frit at room temperature in vacuo.

Polystyrene Beads and a Soluble Solid Reagent (DBAD). To a solution of DBAD (2.45 g) in DCM (200 mL) was added neat polystyrene beads (10.0 g, 100−200 mesh) under gentle stirring. After 15 min, the solvent was slowly and carefully evaporated under reduced pressure (35 °C).

Polystyrene Beads and an Insoluble Solid Reagent (Sm Metal). Polystyrene (10.0 g, 100−200 mesh) was suspended in DCM (250 mL). Samarium powder (3.0 g, approximately 325 mesh) was added. The suspension was filtered under continuous stirring on a D3-frit by gravity and was dried on the frit at room temperature in vacuo.

Compression of Tablets. The above prepared materials were gently crushed using a mortar and pestle, screened through a screen size of 710 μm, and then transferred to the filling device of a single-punch tableting machine. The tableting was performed either manually or automatically with a tableting speed of 50−90 tablets per min. The punch diameters used were in the range of 4−10 mm with a compound cup shape.

Typical Procedures for Tablet Testing. Test 1 (Tablets of Resin 1 in Solid Phase Synthesis). The reactions were performed in a 96 reactor microblock. Resin **1** (51 mg, 0.042 mmol) was added as tablets to the reactors in the first half (6 × 8) of the microblock and as free resin to the reactors (6 × 8) in the second part of the microblock. To each of the eight rows of 12 reactors, a solution of one of the eight amines **2a**−**h** (0.23 mmol, 5.5 equivalents) and *N*-methylmorpholine (NMM) (107.0 mg; 1.05 mmol; 25.0 equivalents) in DMF (0.7 mL) was added. The reaction mixtures were agitated by shaking at room temperature for 16 h. The resin was filtered and washed with DMF (2 × 1 mL), MeOH (1 × 1 mL), THF (1 × 1 mL), MeOH (1 × 1 mL), THF (1 × 1 mL), MeOH (1 × 1 mL), and DCM (5 × 1 mL). The resin was treated with a solution of DCM/trifluoroacetic acid (1:1) (0.65 mL) at room temperature for 2 h, then filtered, and washed with DCM (1 × 1 mL), MeOH (1 × 1 mL), and DCM (1 × 1 mL). The filtrates were combined, and the volatile solvents were evaporated. The residue was dissolved in MeOH (2 mL) and purified by ion exchange (SCX ion exchange columns). After the solvents were evaporated, the remaining residue was weighed, redissolved in DMSO, and analyzed by LC/MS using ELSD and UV detection. Yields and purities that are reported in Table 3 are average values of the six simultaneous reactions in one row of the reactor block.

Test 2 (Mitsunobu Tablets in Solution Phase Synthesis, Representative Example 6a). Two tablets containing in total 0.20 mmol of DBAD and 0.26 mmol of resin-bound diphenylphosphine (1.69 mmol/g; 200−400 mesh) were added at room temperature to a solution of 2*H*-naphtho-[1,8-*cd*]isothiazole 1,1-dioxide **4a** (21.0 mg, 0.10 mmol) and 2-phenylsulfanyl-ethanol **5a** (29.9 mg, 0.20 mmol) in THF (3 mL). After the mixture was stirred for 16 h, THF (2 mL) and one tablet containing isocyanatomethyl polystyrene (150 mg, 0.15 mmol) were added. The mixture was stirred for 2 h at 60 °C. The resin was filtered and washed with DCM (1 × 1 mL), methanol (1 × 1 mL), and DCM (1 × 2 mL). Trifluoroacetic acid (0.4 mL) was added to the combined filtrates, and the mixture was stirred for 1.5 h. After the solvents were evaporated in vacuo, the residue was purified by solid phase extraction over silica gel (Kiesel gel 60, 230−400 mesh) (eluent, heptane/ethyl acetate = 5:1) to furnish 31.5 mg (89%) of the desired product **6a** as a solid (LC/MS: 98% UV purity and 99% ELSD purity). An analytical sample was obtained as slight yellow needles by recrystallization from diethyl ether (mp 94 °C). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.93 (t, 2H, J = 8.0), 4.03 (t, 2H, J = 7.8), 6.53 (d, 1H, J = 6.6), 7.27 (t, 1H, J = 6.6), 7.36 (t, 2H, J = 7.8), 7.47 (m, 4H), 7.74 (t, 1H, J = 7.8), 7.94 (d, 1H, J = 7.1), 8.05 (d, 1H, J = 8.0). MS (*m*/*e*) 341 (M^+). Anal. calcd for $C_{18}H_{15}NO_2S_2$: C, 63.32; H, 4.43; N, 4.10; S, 18.78. Found: C, 63.30; H, 4.42; N, 4.28; S, 18.88. Compounds **6b**−**f** were prepared analogously according to the procedure described above.[16]

Test 3 (Acylation Tablet in Solution Phase Synthesis, Representative Example 9f).[17] One tablet containing 0.11 mmol of tetrabromomethane and 0.14 mmol of resin-bound diphenylphosphine (1.69 mmol/g; 200−400 mesh) was added at 0 °C to a solution of ferrocenecarboxylic acid **7f** (23.3 mg, 0.10 mmol), morpholine **8e** (10.7 mg, 0.12 mmol), and triethylamine (22.6 mg, 0.22 mmol) in dry THF (1.5 mL). After the mixture was stirred for 16 h at room temperature, THF (2 mL) and one tablet containing isocyanatomethyl polystyrene (150 mg, 0.15 mmol) were added. The mixture was stirred for 2 h at 60 °C. The resin was filtered and washed with DCM (1 × 1 mL), methanol (1 × 1 mL), and DCM (1 × 2 mL). The solvents were evaporated in vacuo, and the residue was purified by solid phase extraction (Kieselgel 60, 230−400 mesh) (eluent, heptane/ethyl acetate = 1:1) to furnish 13.6 mg (45%) of **9f**[17] as an orange solid (LC/MS, 98% UV purity and 99% ELSD purity). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.69 (m, 4H), 3.74 (m, 4H), 4.24 (s, 5H), 4.32 (t, 2H, J = 1.7), 4.55 (t, 2H, J = 1.9). MS (*m*/*e*) 300 (M^+ + 1). Compounds **9a**−**e** were prepared analogously according to the procedure described above.[16]

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

References and Notes

(1) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3815−4195. (b) Lam, K. S.; Lebl, M.; Krchnák, V. *Chem. Rev.* **1997**, *97*, 411−448.

(2) (a) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144−154. (b) Czarnik, A. W. *Chemtracts: Org. Chem.* **1995**, *8*, 13−18. (c) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251.

(3) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5135.

(4) (a) Andres, C. J.; Swann, R. T.; Grant-Young, K.; D'Andrea, S. V.; Deshpande, M. S. *Comb. Chem. High Throughput Screening* **1999**, *2*, 29−32. (b) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289−2291.

(5) Atrash, B.; Bradley, M.; Kobylecki, R.; Cowell, D.; Reader, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 938−941.

(6) (a) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *New J. Chem.* **1997**, *21*, 125−130. (b) Valerio, R. M.; Bray, A. M.; Maeji, N. J. *Int. J. Pept. Protein Res.* **1994**, *44*, 158−165. (c) Geysen, H. M.; Rodda, S. J.; Mason, T. J.; Tribbick, G.; Schoofs, P. G. *J. Immunol. Methods* **1987**, *102*, 259−274.

(7) (a) Tripp, J. A.; Stein, J. A.; Svec, F.; Frechet, J. M. J. *Org. Lett.* **2000**, *2*, 195−198. (b) Hird, N.; Hughes, I.; Hunter, D.; Morrison, M. G. J. T.; Sherrington, D. C.; Stevenson, L. *Tetrahedron* **1999**, *55*, 9575−9584.

(8) (a) Kirschning, A.; Altwicker, C.; Dräger, G.; Harders, J.; Hoffmann, N.; Hoffmann, U.; Schönfeld, H.; Solodenko, W.; Kunz, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 3995−3998. (b) Vaino, A. R.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7692−7696. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985−2986.

(9) (a) Devonport, W.; Labadie, J. W.; Porco, J. A., Jr.; van Eikeren, P. Argonaut Technologies, Inc., WO 99/04895, 1999 (*Chem. Abstr.* **1999**, *130*, 155663). (b) Argonaut Technologies, Inc. Preweighed resin capsules for solid phase synthesis. *Lab Products International*; Reed Elsevier: New York, 1999; Vol. 13.

(10) Automated dispension of solid materials is currently available from (a) AutoDose SA, Geneva, Switzerland and (b) Chemspeed Ltd., Augst, Switzerland.

(11) ESEM measurements were made at the Force Technology (Copenhagen, Denmark). Pretreated beads of neat polystyrene and of Merrifield resin have been investigated by ESEM. The elemental composition of the bead surface was determined by EDX. In both cases, the elemental composition of the bead surface is identical with the elemental composition of the bridging material between the contact points of adjacent beads (Figure 2c,d). Elemental composition determined (by EDX) of neat polystyrene (bead surface, wt % C 97.5; binding area, wt % C 97.7) and of Merrifield resin (bead surface, wt % C 94.1; Cl 2.2; binding area, wt % C 93.6; Cl 2.6.

(12) (a) Zaragoza, F. *Tetrahedron Lett.* **1995**, *36*, 8677−8678. (b) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798−799.

(13) Cork, D.; Hird, N. *Drug Discovery Today* **2002**, *7*, 56−63.

(14) Pelletier, J. C.; Kincaid, S. *Tetrahedron Lett.* **2000**, *41*, 797−800.

(15) Appel, R. *Angew. Chem.* **1975**, *87*, 863−866.

(16) Experimental/analytical details are given in the Supporting Information.

(17) **6e**: (a) Groutas, W. C.; Hoidal, J. R.; Brubaker, M. J.; Stanga, M. A.; Venkataraman, R.; Gray, B. H.; Rao, N. V. *J. Med. Chem.* **1990**, *33*, 1087−1090. (b) Greenberg, S. S.; Lis, R. E.; Lumma, W. C., Jr.; Nickisch, K.; Wohl, R. A. (Schering, A.-G., Fed. Rep. Ger.), EP 306440, 1989 (*Chem. Abstr.* **1989**, *111*, 153801). **6f**: Wieringa, J. H.; van Aelst, S. F.; Plate, R. (AKZO N. V., Netherlands), EP 497415, 1992 (*Chem. Abstr.* **1992**, *117*, 212340).

(18) **9a**: (a) Clark, C. R.; McMillian, C. L. *J. Pharm. Sci.* **1990**, *79*, 220−222. (b) Beedle, E. E.; Robertson, D. W. (Lilly, Eli, and Co., U.S.A.), EP 279633, 1988 (*Chem. Abstr.* **1989**, *110*, 7875). **9b**: Ghanbarpour, A.; Hadizadeh, F.; Piri, F.; Rashidi-Ranjbar, P. *Pharm. Acta Helv.* **1997**, *72*, 119−122. **9c**: McGovern, T. P.; Bodenstein, O. F.; Fales, J. H.; Beroza, M. *J. Med. Entomol.* **1975**, *12*, 259−260. **9d**: Isozaki, M.; Nakazawa, K.; Kasukawa, H. (Terumo Corp, Japan), JP 09003019, 1997 (*Chem. Abstr.* **1997**, *126*, 181358). **9e**: Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* **2000**, *41*, 9997−10001. **9f**: Galow, T. H.; Rodrigo, J.; Cleary, K.; Cooke, G.; Rotello, V. M. *J. Org. Chem.* **1999**, *64*, 3745−3746.

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