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Revolutionizing Resin Handling for Combinatorial Synthesis

Butrus Atrash, Mark Bradley,* Ryzard Kobylecki,*
Dan Cowell, and John Reader

The last decade has seen rapid growth both in combinatorial methodology and technology development.[1] Traditionally, resin beads have been handled as a free-flowing material, which although relatively simple for the synthesis of single compounds, does complicate the handling issues for large numbers of single compounds in multiple parallel synthesis. The major advances in this area; tea-bags,[2] crowns,[3] and Irori Kans[4] methodology permit the production and handling of discrete packets of resin materials for multiple parallel synthesis, although even here the filling, sealing, labeling of the units and the recovery of tagging devices complicates handling and have cost implications. More recent innovations include the monolithic polymer discs of Sherrington et al.,[5] which were then used by a number of other workers.[6]

We now report a fundamentally new approach to resin handling. The method is applicable to various resin types (polystyrene (PS), polystyrene–polyethyleneglycol graft polymer (PS-PEG)), either pre- or postloaded with virtually any linker or linker-scaffold combinations. The method is applicable to all routinely used resin bead sizes and substitutions. The approach can be used to generate individual resin-based supports in virtually any shape or form desired, and makes resin much more convenient to handle, yet maintains the original chemical properties of the resin.

The basis of this new method is resin sintering within an inert polymer matrix.[7] This was achieved by blending appropriate proportions, in this case 1:1, of ultra-high molecular weight polyethylene and the synthesis resin, to a homogeneous mix. This was then loaded into polytetrafluoroethylene(PTFE)-lined moulds and passed through a sintering oven under a nitrogen atmosphere. The temperature of the mixture was gradually increased as it passed through the oven, just to the point where the polyolefin matrix began to soften (determined experimentally). The moulds were then gradually cooled and the formed plugs ejected from the mould. The plugs were made in a cylindrical form, as this shape fitted nicely into the wells of a 96-well plate. This shape also combines ease of preparation of the mould with the physical strength of the plug. Plugs could however be made in a variety of different shapes or sizes, with an upper limit determined by the necessity for reasonably low-temperature gradients between the inside and outside of the plug during the sintering process. Various structural features such as handles, holes, or struts can be in-built for improving the ease of handling or increasing the strength of the shape by changing the mould. The cylindrical plugs made were 9 mm long, 7.5 mm diameter and had a mass of (170 ± 6) mg resulting in a very defined loading per plug. A typical plug contained 50 % synthesis resin, which approximates to 85 mg of Merrifield resin (initially 0.96 mmol g^{-1}) thereby giving an initial loading of 81.6 μmol per plug. The plugs are porous, with solvent able to freely access through the pores of the matrix of the plug and into the synthesis resin held therein. This was demonstrated by soaking a plug in a solution of bromophenol blue in dichloromethane and then slicing the plug to ascertain the loading of the dye. Within one minute the dye had entered the polyethylene (PE) plug although presumably it would take longer to reach all the reactive sites. The plugs produced are solid devices in which the beads are intact and are physically attached to the polyethylene filler by a small amount of polymer flow onto the beads (Figure 1). Clearly, a proportion of resin bead is physically prevented from reacting freely, but this is small and only on the surface and thus insignificant. These plugs in effect function as minireactors.

A feature of these devices is the relative freedom from the well-known swelling properties of all manner of gel based resins. We attribute this to the void volume within the plug, and the flexibility of the internal structure allowing an

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[*] Prof. M. Bradley, Dr. B. Atrash
Department of Chemistry
University of Southampton
Southampton, SO17 1BJ (UK)
Fax: (+44) 23-8059-3781
E-mail: MB14@soton.ac.uk

Dr. R. Kobylecki, D. Cowell, Dr. J. Reader
Millennium Pharmaceuticals (Formerly, Cambridge Discovery Chemistry)
The Merrifield Centre
Rosemary Lane, Cambridge CB1 3LQ (UK)
Fax: (+44) 01223-722401
E-mail: john.reader@mpi.com

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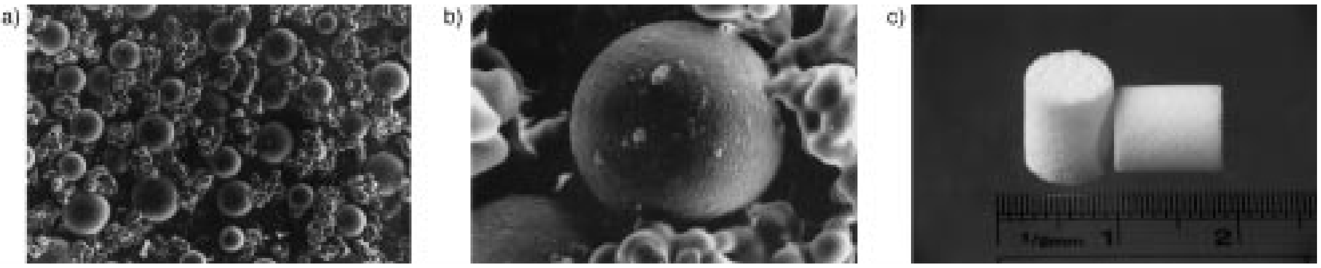
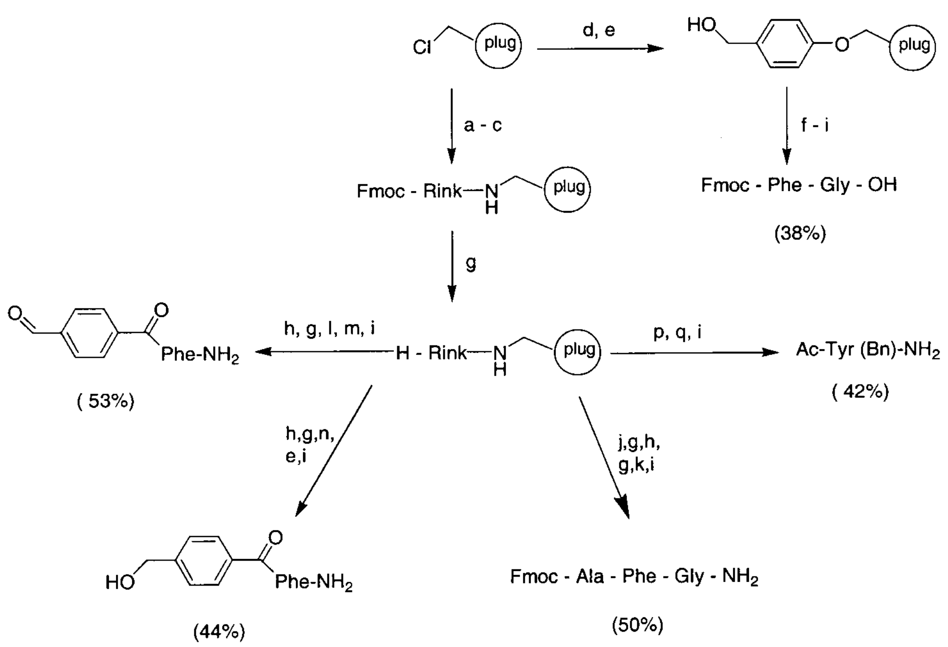


Figure 1. a) Cross-section of resin plug (100 × magnification). b) Single bead within the matrix of resin plug (270 × magnification). c) Illustration of dimensions of resin plug (9 mm long, 7.5 mm diamater).

element of "breathing" which accommodates within the device framework any swelling that occurs. There was only an approximately 20% increase in the volume of a plug when swollen in DMF. The structural integrity of the new support was checked in a wide range of organic solvents normally used in solid-phase organic synthesis (SPOS), both at room temperature and with heating. They were stable in all solvents with the exception of hot toluene (which is known to soften polyethylene) and maintained both their original shape and size. The plugs were also treated for two hours at room temperature with a variety of acids (trifluoroacetic acid (TFA), 2 M HCl) and bases (piperidine, triethylamine, 2 M NaOH) and were perfectly stable. The plugs were robust towards magnetic stirring, mechanical shaking, centrifugation, and the application of a vacuum. Washing the plugs to release a dye, did require a slightly longer time than loose resin (1.5 times), although like Irori Kans the process was accelerated by the application of a vacuum. Mechanical losses from the surface were negligible and only noticeable at the first swelling/reaction of the plugs. The resin plugs were found to require longer reaction times than loose resin (double the time). They also took longer to wash than loose resin.



Scheme 1. Chemistries done on resin plugs (figures shown represent yields of isolated products). a) Potassium phthalimide (5 equiv), DMF, 120°C, 16 h; b) H_2NNH_2 (10 equiv), EtOH, reflux, 5 h; c) Fmoc-Rink-OH (1.5 equiv), DIC (1.5 equiv), HOBt (1.5 equiv), CH_2Cl_2, 24 h; d) 4-hydroxybenzaldehyde (10 equiv), K_2CO_3 (10 equiv), MeCN, reflux, 48 h; e) $NaBH_3CN$, MeOH, 6 h; f) Fmoc-Gly-OH (5 equiv), DIC (5 equiv), DMAP (0.2 equiv); g) 20% piperidine/DMF, 20 min; h) Fmoc-Phe-OH (5 equiv), DIC (5 equiv), HOBt (5 equiv); i) 95% TFA; j) Fmoc-Gly-OH (5 equiv), DIC (5 equiv), HOBt (5 equiv); k) Fmoc-Ala-OH (5 equiv), DIC (5 equiv), HOBt (5 equiv); l) 4-hydroxymethylbenzoic acid (5 equiv), DIC (5 equiv), HOBt (5 equiv); m) $PySO_3$/DMSO (10 equiv), Et_3N (10 equiv); n) 4-formylbenzoic acid (5 equiv), DIC (5 equiv), HOBt (5 equiv), 16 h; p) Ac-Tyr-OH (5 equiv), DIC (5 equiv), HOBt (5 equiv), 6 h; q) $PhCH_2OH$ (10 equiv), PPh_3 (5 equiv), DEAD (5 equiv), THF, 2 h. DIC = diisopropylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, Py = Pyridine, TFA = trifluoroacetic acid, DEAD = diethylazodicarboxylate, Bn = benzyl.

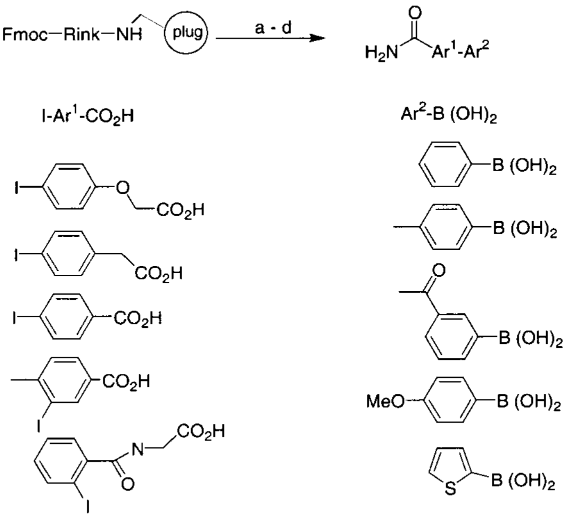
Applications: Initially, resin plugs were prepared with Merrifield Resin and were converted into the aminomethylated form by using potassium phthalimide followed by hydrazine to give a measured loading[8] of 56 μmol per plug. The plugs were then loaded with the Fmoc–Rink–amide linker[9] and a number of standard chemistries/cleavages (Scheme 1) performed on this new material in parallel with identical chemistry carried out on loose resin. These initial chemistries included: oxidation, reduction, Mitsunobu's, and peptide synthesis. The results of these chemistries were very similar to those obtained on loose resin carried out in parallel. The resin plugs were also derivatized with a Wang linker and used to synthesize a dipeptide in the standard manner (Scheme 1).

To test the general applicability of the method, nine different resin types were sintered and a number of different chemistries carried out on the plugs and compared with identical loose resin. The results are summarized in Table 1. In all cases, the results were virtually identical, and considering our limited experience of handling the plugs at this stage, very encouraging.

Synthesis of three small libraries: A number of small libraries was then prepared on the resin plugs. Initially a small library of biaryl derivatives was constructed (Scheme 2).

Table 1. Comparison of co-sintered resin with loose resin.

Entry	Type of resin	Yield [%] on plugs/loose resin	Reaction type
1	NovaSyn TG resin	74/81	Rink linker loading,
2	NovaSyn TG amino resin	60/67	acylation,
3	aminomethyl-NovaGel HL	64/73	cleavage
4	Merrifield resin LL	70/70	aminomethylation
5	3,5-dimethoxy-4-formylphenoxyethoxymethylpolystyrene	60/66	reductive amination, acylation, cleavage
6	2-chlorotrityl chloride resin	55/63	diamine loading, derivatization, cleavage
7	Rink acid resin	62/70	hydroxamic acid synthesis
8	Wang-derivatized resin	92/96	esterification, cleavage
9	*p*-nitrophenyl carbonate Wang resin	64/72	amidine attachment, cleavage



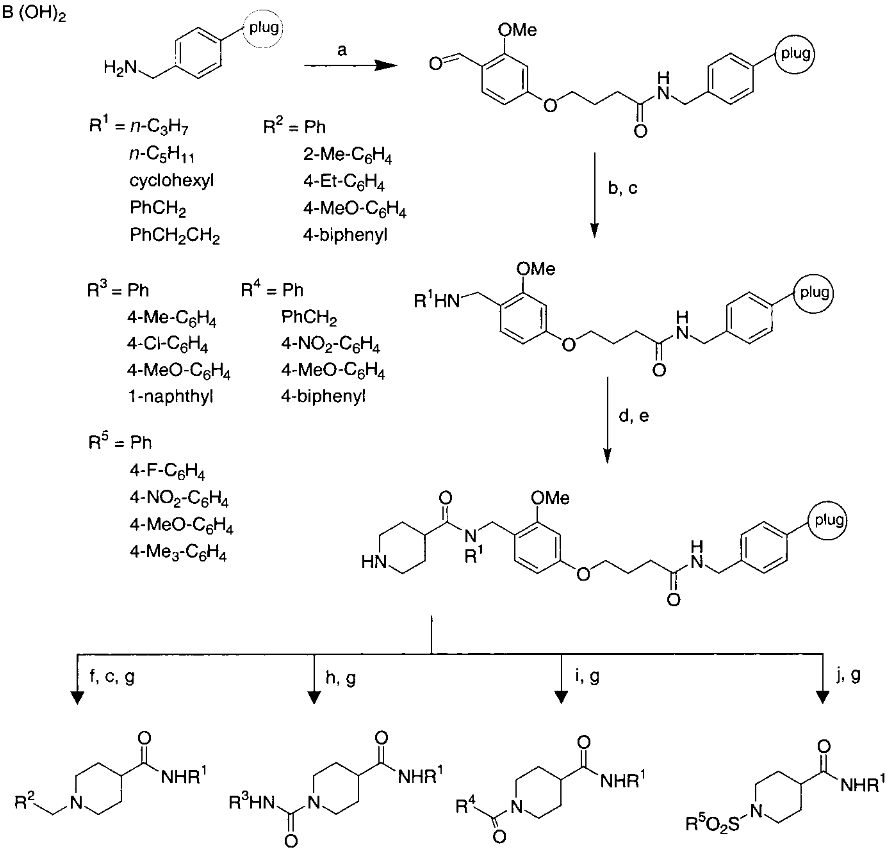
Scheme 2. Library of biaryl derivatives. a) 20% piperidine/DMF, 20 min; b) I-Ar^1-CO$_2$H (5 equiv), DIC (5 equiv), HOBt (5 equiv); c) Ar$_2$-B(OH)$_2$ (1.5 equiv), K_2CO_3 (2 equiv), [Pd(PPh$_3$)$_4$] (0.1 equiv), DMF, 100 °C, 24 h; d) 95% TFA.

Table 2. Library of biaryl derivatives.

Entry	Ar^1	Ar^2	HPLC Purity [%]
1	p-C_6H_4	Ph	81
2	p-C_6H_4	4-Me-C_6H_4	92
3	CH_2-p-C_6H_4	Ph	95
4	CH_2-p-C_6H_4	4-Me-C_6H_4	83
5	CH_2O-p-C_6H_4	Ph	68
6	CH_2O-p-C_6H_4	4-Me-C_6H_4	65
7	m-(4-Me-C_6H_4)	Ph	98
8	m-(4-Me-C_6H_4)	4-Me-C_6H_4	98
9	CH_2NHCO-o-C_6H_4	Ph	87
10	CH_2NHCO-o-C_6H_4	4-Me-C_6H_4	86

It was based on the Suzuki coupling reaction. A representative compound (Table 2, entry 4) was isolated with an overall yield of 58%. The average crude product purity of the library was shown by HPLC to be 85%.

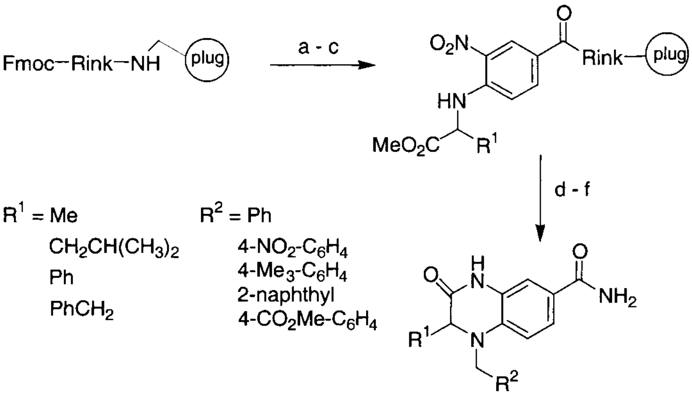
A second library was prepared, this time encoded. 100 resin plugs were fitted with commercially available radiofrequency (RF) transponders through a hole in the center of the plug which provides an alternative to chemical tagging.[10] The transponders used were glass-encoded microchip devices pretuned to emit a unique binary code when pulsed with a radiofrequency. The inert nature of the RF transponder construction renders this tagging strategy compatible with virtually all synthetic methods. Also, the noninvasive transmission or retrieval of information from any plug is unambiguous and instantaneous. The 100 RF transponder encoded resin plugs were used to synthesize a 100 compound library of sulfonamides, tertiary amines, ureas, and amides (Scheme 3). Again, the synthesis was successful, and all plugs remained intact. An



Scheme 3. Synthesis of a transponder encoded library. a) 4-(4-Formyl-3-methoxyphenoxy)butyric acid (2 equiv), DIC (2 equiv), HOBt (2 equiv) 24 h; b) R^{1}NH$_2$ (5 equiv), 5% AcOH/DMF, 2 h; c) NaBH$_3$CN (5 equiv), 1% AcOH/DMF, 24 h; d) Fmoc-isonipecotyl chloride (5 equiv), DIPEA (5 equiv), 5 h; e) 20% piperidine/DMF, 20 min; f) R^{2}CHO (5 equiv), 5% AcOH/DMF, 5 h; g) 20% TFA/DCM, 1 h; h) R^{3}NCO (5 equiv), CH_2Cl_2, 24 h; i) R^{4}COCl (5 equiv), DIPEA (5 equiv), DCM, 5 h; j) R^{5}SO$_2$Cl (5 equiv), DIPEA (5 equiv), DCM, 24 h.

average purity of 90–95% (HPLC) was observed for the sulfonamides, amides, and ureas, falling to 80–90% for the tertiary amines. The weight recovery per plug for each purified compound was good and ranged between 5–12 mg. Based on the starting plug loading, the overall yields of cleaved purified materials were 36–86%.

A third small library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones was prepared on the resin plugs. The synthesis (Scheme 4) was adapted from the literature.[11] A representative compound (Table 3, entry 9) was isolated with an overall yield of 40% (literature, 48%). The average crude product purity by HPLC was 52%.



Scheme 4. Library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones. a) 20% piperidine/DMF, 20 min; b) (4-F,3-NO_2)PhCOCl (5 equiv), DIPEA (5 equiv); c) $H_2NCH(R^1)CO_2Me$ (10 equiv), DIPEA (10 equiv), DMF, 3 days; d) $SnCl_2 \cdot H_2O$ (20 equiv), DMF, 3 days; e) R^2CH_2Br (25 equiv), K_2CO_3 (25 equiv), $(CH_3)_2CO$, reflux, 48 h; f) 95% TFA.

Table 3. Library of 3,4-disubstituted 7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones.

Entry	R^1	R^2	HPLC purity [%]
1	Me	Ph	69
2	Me	4-Me-C_6H_4	43
3	Me	2-naphthyl	39
4	$CH_2CH(CH_3)_2$	Ph	42
5	$CH_2CH(CH_3)_2$	2-naphthyl	52
6	$CH_2CH(CH_3)_2$	4-CO_2Me-C_6H_4	59
7	Ph	Ph	44
8	Ph	4-Me-C_6H_4	75
9	CH_2Ph	4-Me-C_6H_4	40
10	CH_2Ph	2-naphthyl	57

In summary, we have developed a new method of resin handling. Considering the huge effort in the area of solid-phase synthesis and solution chemistry using resin scavengers/reagents, the approach of resin sintering offers a cheap and readily available method of preparing discrete, easy to handle, encoded materials for multiple parallel synthesis, defined mix and split synthesis and scavenging/immobilized reagents, in whatever formats are deemed appropriate, and with any resin desired. We are currently investigating the use of resin plugs in further reactions and their use as scavengers, supported reagents and catalysts and will communicate our results in due course.

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Adsorption-Mediated Electrochemical Sensing of Halides[**]

Richard Michalitsch and Paul E. Laibinis[*]

Measurements of halide concentrations are crucial in many clinical and environmental analyses and in many areas of industrial chemistry.[1] Ion-selective electrodes (ISEs) have been increasingly used for monitoring the concentrations of many ions such as halides.[2, 3] These electrodes incorporate a solid membrane that allows the selective diffusion of one ion to its surface to produce an electrochemical potential that is proportional to the concentration of the ion in solution.

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[*] Prof. P. E. Laibinis, Dr. R. Michalitsch
Department of Chemical Engineering
Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-5042
E-mail: pel@mit.edu

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