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# Reporter Resins for Solid-Phase Chemistry

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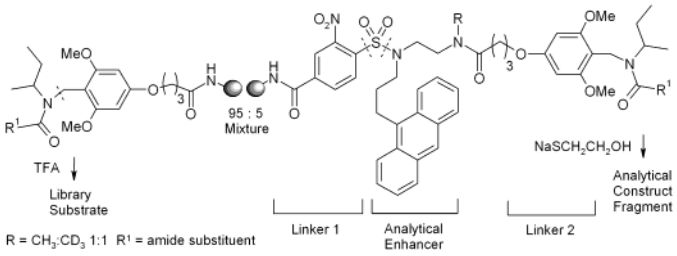
## ABSTRACT




**An analytical construct resin, designed to aid the analysis of solid-phase chemistry, has been mixed in a small proportion with a conventional resin. The analytical construct ("reporter resin") contains two orthogonal linkers that allow cleavage of either the synthetic intermediates (at linker 2) or their analytically enhanced derivatives (at linker 1). The convenient and rapid monitoring of each step in the syntheses of representative library compounds was possible using small resin aliquots.**

Development of new chemistries and synthetic sequences directly on solid supports can be a difficult and time-consuming process.[1] In particular, assessment of product mixtures formed on a resin can be problematical. Usually cleavage of the synthetic intermediates from the linking group prior to analysis is necessary because current methods, such as IR or NMR, for directly analyzing polymer-supported compounds are limited and often require expensive instrumentation.[2] Without the ability to directly monitor reactions as they proceed by HPLC or mass spectrometry, or to easily identify byproducts formed during each step, reaction optimization can be difficult. In an effort to overcome these problems we have developed a number of analytical construct resins that incorporate features which greatly simplify the analysis of materials synthesized on solid supports.[3] These constructs are multidetachable resins[4] (Figure 1) which have an additional linker that allows cleavage either of the substrates themselves (cleavage at linker 2) or of an analytically enhanced fragment (cleavage at linker 1). Typically, linker 1 will be an amine-releasing linker so that each fragment will contain an amine functionality greatly improving the ionization properties of the materials and thus allowing easy detection by electrospray mass spectrometry in the ESI+ mode (a MS sensitizer).[5] Introduction of an isotopic label between the two linkers, usually as a 1:1

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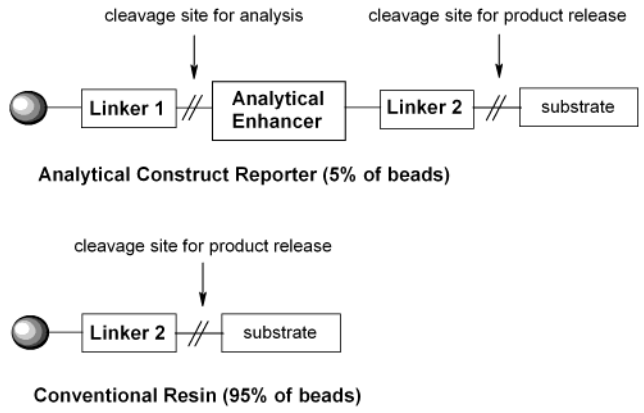


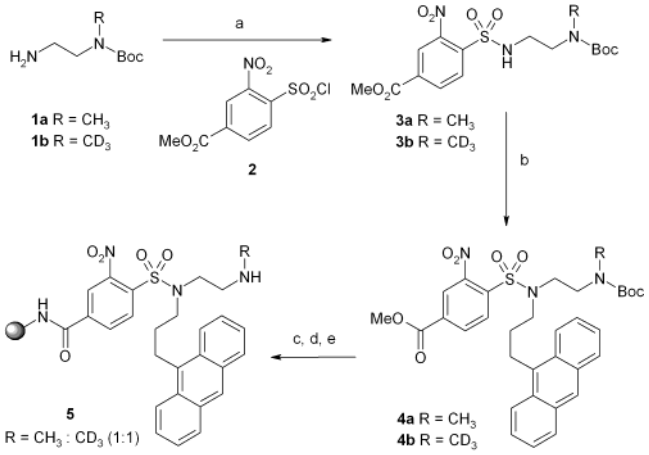

**Figure 1.** The principle of the "reporter resin". Introduction of an analytical enhancer between the linker used in the solid-phase synthesis (linker 2) and another chemically orthogonal linker (linker 1) in 5% of the beads enables monitoring of each chemical step by cleavage of linker 1 followed by LC/MS analysis.

mixture of hydrogen and deuterium isotopes, produces a doublet in the mass spectrum of the analytical fragment (peak splitter).[6] This ensures that all analytical fragments cleaved from the resin can be easily recognized in the mass spectrum. Such construct systems have been successfully applied to detection of materials by MS after "split-mix-pool" synthesis from single beads.[7] We recently reported a construct system that additionally includes an anthracene moiety. The chromophore enables the direct monitoring of resin-derived products by HPLC−UV at a wavelength that is remote from extraneous reagents and reaction substrates (386 nm) with single bead sensitivity.[8]

In this Letter we now describe how such a construct can be used as a "reporter resin" to predict the course of reactions occurring on conventional resins when mixed in the same chemical reaction. This is achieved simply by mixing the analytical construct resin in a small proportion, typically 5% weight for weight, with the conventional resin before commencing the synthetic sequence (Figure 1).[9] In order for an analytical construct resin (the "reporter") to be generally predictive of the chemistry occurring on the conventional resin we considered that it must be derived from the same polymeric support to minimize differences in the chemistry due to variations in resin solvation. We then sought to determine whether the reporter resin, possessing construct functionality that might potentially modify the properties of the material, was indeed predictive of the chemistry of a conventional resin throughout a sequence of reactions.

The reporter resin was synthesized as illustrated in Scheme 1. The amines **1a** and **1b**[10] were reacted with sulfonyl

**Scheme 1.** Synthesis of the Reporter Resin[a]




[a] (a) **2** (1 equiv), DIPEA (1.5 equiv), $CH_2Cl_2$, 0 to 20 °C, 17 h, **3a** 69%, **3b** 63%; (b) PS-BEMP[12] (1.3 equiv), 9-(3-bromopropyl) anthracene (1.1 equiv), DMF, 20 °C, 14 h, **4a** 98%, **4b** 86%; (c) aqueous sodium hydroxide (1.2 equiv), methanol:THF (1:1), 20 °C, 3 h, 90%; (d) ArgoGel-$NH_2$ (0.75 equiv), DIC (2 equiv), HOBt (2 equiv), DMF, 20 °C, 16 h; (e) TFA: $CH_2Cl_2$ (1:1), 20 °C, 2 × 30 min.

chloride **2**[11] to give sulfonamides **3a** and **3b**. *N*-Alkylation with 9-(3-bromopropyl)anthracene, saponification of an equimolar mixture of the methyl esters **4a** and **4b**, coupling to ArgoGel-$NH_2$ resin, and treatment with trifluoroacetic acid (TFA) to remove the Boc-protecting group gave amino-resin **5**.

The reporter resin **5** was then mixed 1 part in 20 with commercial ArgoGel-$NH_2$ resin (0.4 mmol $g^{-1}$ initial loading). The mixture of resins was then used to synthesize model combinatorial library products (Scheme 2). At each stage the progress of the reactions was monitored by HPLC and LC/MS analysis of the secondary amine-containing analytical fragments. Selective cleavage at the sulfonamide linker was achieved by treatment with a thiol,[13] and the results are displayed in Table 1. A 10% solution of the sodium salt of mercaptoethanol in methanol was found to be a suitable protocol, effecting very rapid cleavage (5−10 min) and giving a good signal-to-noise ratio using 2 mg of resin (which equates to approximately 50 reporter beads).[14] The amide coupling of the mixed resins with linker **6**[15] gave the dimethoxyaldehyde resins **7**. These were subjected to reduc-

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(9) The concept of using one resin as an analytical tool to predict the course of chemical reactions on another conventional resin is protected in an unpublished US patent application by H. M. Geysen.
(10) The monoprotected diamines were purchased from AstaTech, Inc., Philadelphia.
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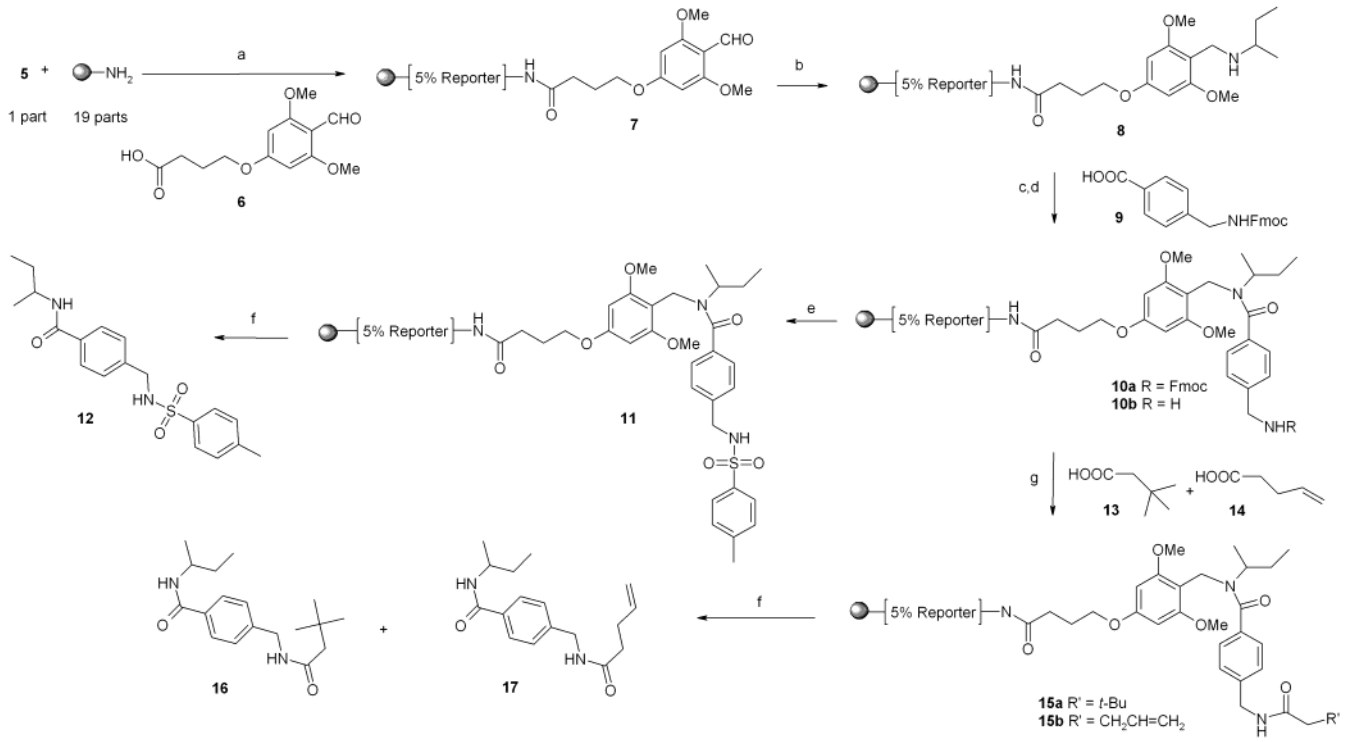
(12) 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazophosphorine on polystyrene resin from Fluka.
(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373.
(14) ArgoGel is reported as 130-230 $\mu$m diameter beads, which equates to approximately 500 beads per mg of resin.
(15) Commercially available from Peakdale Fine Chemicals, Glossop, U.K. Khehyong, N.; Patel, D. V. *J. Org. Chem*. **1997**, *62*, 7088.

**Scheme 2.** Synthesis of Model Library Compounds[a]




[a] (a) **6** (5 equiv), PyBOP (5 equiv), DIPEA (10 equiv), $CH_2Cl_2$:DMF (1:4), 20 °C, 8 h; (b) (i) *sec*-$BuNH_2$ (5 equiv), AcOH (5 equiv), NMP, 20 °C, 1.5 h, (ii) $Bu_4NBH_4$ (5 equiv), AcOH (5 equiv), NMP, 20 °C, 2 h; (c) **9** (10 equiv), PyBOP (10 equiv), DIPEA (20 equiv), $CH_2Cl_2$: DMF (1:4), 20 °C, 30 min; (d) piperidine:DMF (1:4), 20 °C, 30 min; (e) *p*-toluenesulfonyl chloride (2 equiv), $Et_3N$ (4 equiv), MeCN, 20 °C, 2 h; (f) TFA:$CH_2Cl_2$ (1:1), 20 °C, 1 h; (g) **13** (6 equiv) **14** (3 equiv), PyBOP (10 equiv), DIPEA (20 equiv), $CH_2Cl_2$: DMF (1:4), 20 °C, 3 h.

tive amination with *sec*-butylamine to give the resin-bound secondary amines **8**. Analytical cleavage of **8** indicated that the reaction had gone to completion in less than 4 h. Next, monitoring of the amide coupling of resins **8** with amino acid **9** indicated that the reaction was complete after only 30 min, as assessed by disappearance of the starting material analytical fragment by HPLC. Typically a hindered coupling of this type would be left for at least 18 h, but the reporter indicated that this was unnecessary in this case. Fmoc deprotection of resins **10a** using a mixture of piperidine in DMF gave the amino-resins **10b**. Fmoc quantification[16] indicated a loading of 0.21 mmol $g^{-1}$.

Reaction of **10b** with tosyl chloride gave the resins **11** in good conversion with minimal formation of resin-bound byproducts. Using the reporter it was possible to make a quantitative assessment by HPLC of the purity of the final resin-bound product before cleavage and isolation as being 89% (at 386 nm). Treatment of the resins **11** with TFA in $CH_2Cl_2$ gave the expected product **12** in a purity that was consistent with that predicted by the reporter (90−95% by $^1$H NMR). This indicated that the chemistry monitored on the 5% of beads bearing the reporter was representative of the course of the reactions on the commercial ArgoGel support. The yield of the isolated product **12** was 94% based upon the observed loading of **10a** (0.21 mmol $g^{-1}$).

To further assess the predictive nature of the reporter, the resin system **10b** was condensed with a mixture of carboxylic acids to give the resin-bound secondary carboxamides **15a** and **15b.** The ratio of the products formed was assessed by HPLC analysis of the amine fragments following sulfonamide linker cleavage (Table 1). The mixture of resins **15a** and **15b** was then cleaved with TFA and the ratio of the products **16** and **17** determined by $^1$H NMR. In both cases close to a 1:1 ratio was obtained. This again indicated that the reporter had been predictive of the chemistry taking place on the conventional resin (HPLC ratio 48:52; $^1$H NMR ratio 49:51).

Throughout the syntheses described above, analysis of the resins using magic angle spinning (MAS) NMR was also undertaken.[17] Due to the small quantity of reporter resin present in each sample, resonances from these resins were not clearly visible using the MAS NMR technique, and it was, therefore, possible to assess the products present on the conventional resin at each synthetic step. The NMR data were fully consistent with the expected products in each case, again indicating a good correlation of the chemistry occurring on the ArgoGel support with that on the reporter resin. Trace impurities that were obvious by use of the reporter analyses could not be assessed by MAS NMR, as it is not a sufficiently sensitive or quantitative technique.

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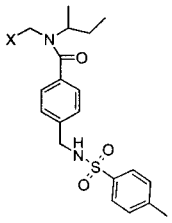
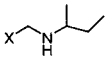
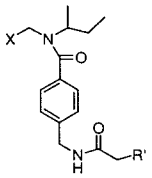
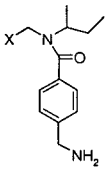
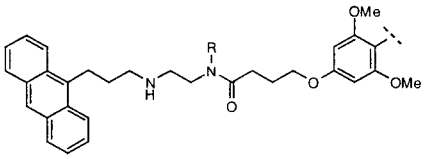
**Table 1.** Analysis of Resins after Each Synthetic Step

| Resins | Analytical Fragment[a] | HPLC Area (%)[b] | Molecular Ions Detected[c] | Resins | Analytical Fragment[a] | HPLC Area (%)[b] | Molecular Ions Detected[c] |
|---|---|---|---|---|---|---|---|
| **7** | X—CHO | 100 | 543, 546 | **11** |  | 89 | 887, 890 |
| **8** |  | 95 | 301, 302.5[d] (major)<br>600, 603 (minor) | **15a,b**[g] |  | **15a**: 49<br>**15b**: 45 | **15a**: 831, 834<br>**15b**: 815, 818 |
| **10b**[e] |  | 94 | 756, 759[f] (major)<br>734, 737 (minor) | | | | |

X = 

R = $CH_3$ : $CD_3$ 1:1

[a] Analytical fragments are the result of cleavage of the sulfonamide linker with the sodium salt of mercaptoethanol in methanol to give derivatives for analysis by LC/MS and by HPLC. [b] HPLC area was measured at 386 nm, the remote absorption of the anthracene chromophore; each peak at this wavelength will be derived from a resin-bound intermediate and can be quantified by peak area. A selected region of the spectrum in each case is illustrated to indicate the major product and observed byproducts and to give an indication of the signal-to-noise ratio. [c] Product molecular ions are indicated (MH+) and were measured using an LC-MS instrument (Thermoquest LCQ in ESI+ mode). [d] Doubly charged ions from the diamine product. [e] Cleavage of resin **10a** also causes some removal of the Fmoc protecting group. [f] Sodium adducts. [g] **15a** R′ = *t*-Bu **15b**, R′ = $CH_2CH{=}CH_2$.

In summary, by the use of a mixture of a conventional resin and a resin bearing an analytical construct as a reporter, it has been possible to conveniently monitor each step in the syntheses of model library products without the need to cleave large quantities of resin at each stage for analysis. In addition, it was possible to indirectly assess the purity of the final products before cleavage and isolation with TFA. This powerful analytical method will greatly assist the development of new chemistry on solid supports and allow for the facile and rapid assessment of the success of a given library synthesis. The use of a small quantity of the reporter resin in the synthesis maximizes the cost effectiveness of the analytical resin without compromising the compound loading and enables quality control of library products prior to cleavage and isolation of the target molecules.

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**Supporting Information Available:** Experimental procedures for the synthesis of 9-(3-bromopropyl) anthracene, compounds **3a**, **3b**, **4a**, **4b**, **5**, and **7** and general conditions for analytical cleavage of the reporter. This material is available free of charge via the Internet at http:/www.pubs.acs.org.

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