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Polymer-assisted solution phase synthesis: a general method for sequestration of byproducts formed from activated acyl-transfer reactants

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Abstract

Typical amide bond-forming reactions involving amines with activated esters are purified by the use of complementary molecular reactivity/molecular recognition (CMR/R) resins, which sequester both the excess activated ester and the byproducts (leaving group) generated. It is also shown by HPLC analysis that this strategy effectively removes many of the common byproducts generated from reactions involving activated esters, carbonates, and carbamates.

Keywords: Combinatorial chemistry; Resins

Parallel synthesis and combinatorial chemistry are rapidly becoming widely used tools in discovery research. While initial reports of small molecule parallel synthesis utilized the methodology of solid-phase synthesis, several purification strategies for solution-phase combinatorial library synthesis have recently been described. [1-9] From our own laboratories, we have reported a solution-phase purification strategy based on principles of complementary molecular reactivity and molecular recognition (CMR/R) using resins with functionalities complementary to those of solution-phase reactants, reagents, and byproducts requiring resin sequestration. [3,4,5] This strategy is largely based on the use of post solution-phase sequestrative purification methods. Included in this general strategy is the use of functionalized resins to sequester byproducts away from the desired product. The most commonly encountered byproducts from bimolecular reactions are leaving groups formed as the result of reaction between nucleophiles and electrophiles. Herein we report a study to find a general byproduct sequestration resin that could be used to purify parallel solution-phase reactions where such leaving groups (nucleofuges) are formed.

Many synthetic transformations involve the reaction of an activated acyl-transfer electrophile with a nucleophile to afford the desired product with simultaneous formation of an undesired byproduct (nucleofuge). Scheme 1 illustrates the use of CMR/R resins for product purification and isolation in such cases. Nucleophile **A** and acyl-transfer electrophile **B** afford product **C** and nucleofuge byproduct **D**. Byproduct **D** possesses inherent weakly-acidic functionality to enable sequestration by a complementary base-functionalized CMR/R resin **1**. When CMR/R resin **1** is added to the reaction solution, the complementary functionalities on resin **1** and byproduct **D** interact to afford polymer-bound adduct **2**, removed from solution-phase by simple filtration. We envisioned that a judicious selection of nucleofuge-capturing resin **1** would also enable the simultaneous sequestering of excess acyl-transfer electrophile **B** (utilized to drive these reactions to completion) as adduct **3**.

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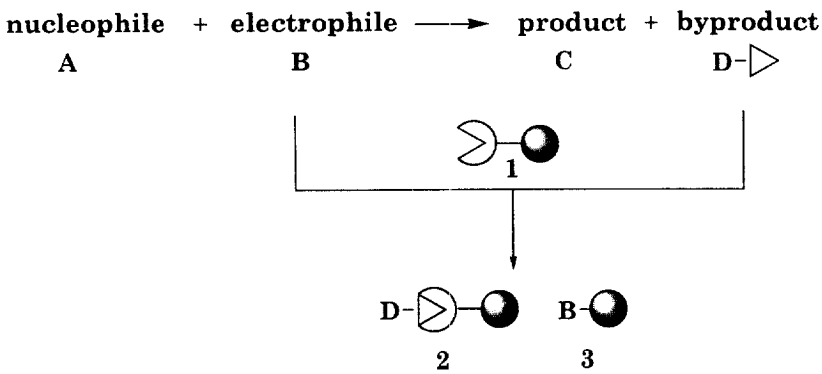
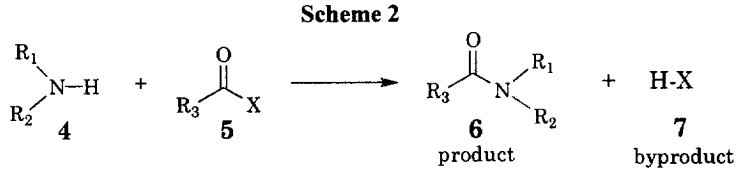
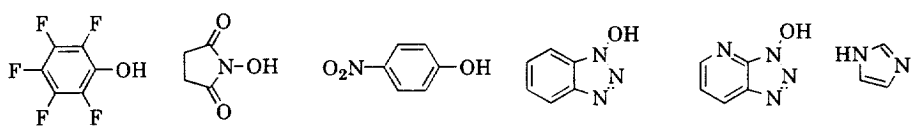
Scheme 1



Formation of carbamates, ureas, esters and amides is often accomplished by a strategy which utilizes an activated intermediate. [10] While these transformations usually proceed readily, in a library format separating the desired product from the byproduct (leaving group) of the activated intermediate can be problematic. We have found that a variety of nucleofuge sequestering resins successfully remove these byproducts from solution-phase. Scheme 2 depicts a reaction involving the addition of an amine **4** to an activated intermediate of the general structure **5** to form condensation products **6**. Typical byproducts **7** in this type of chemistry include pentafluorophenol (**7a**), hydroxysuccinimide (**7b**), 4-nitrophenol (**7c**), hydroxybenzotriazole (**7d**), 1-hydroxy-7-azabenzotriazole (**7e**), and imidazole (**7f**).

Scheme 2

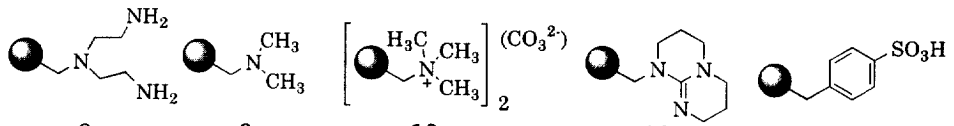




7a **7b** **7c** **7d** **7e** **7f**

We have found that certain CMR/R resins **8-12** (Scheme 3) sequester and remove byproducts **7** from solution-phase, which allows for the purification strategy illustrated in Scheme 1. [11] Solutions of the byproducts **7a-7f** were incubated with functionalized CMR/R resins **8-12** (Scheme 3). [12] After filtration and evaporation of solvents, any residue remaining was analyzed by HPLC (or ^{19}F NMR) to determine the amount of byproduct successfully removed from solution. This analysis protocol allowed for a quantitative determination of the successful removal of the various byproducts **7a-7f** from solution. The results of the analysis are summarized in Table 1. As indicated, resin **10**, an Amberlyst A-26 carbonate resin [15,16,17], and resin **11**, a polymer-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (P-TBD) [18], are the most efficient and general nucleofuge sequestering resins. When used in only 3-5 mole excess (relative to the nucleofuges), resins **10** and **11** completely remove nucleofuges **7a-7e** and surprisingly remove ~70-80% of imidazole **7f** (presumably as imidazolyl anion).

Scheme 3



8 polyamine resin | **9** A-21 | **10** A-26(CO_3^{2-}) | **11** P-TBD | **12** A-15

Table 1

HPLC (^{19}F NMR) Analysis of Residues Remaining After Sequestration of Byproducts **7a-f** by CMR/R Resins **8-12**.

Byproduct	wavelength	8 (5 eq)	8 (3 eq)	9 (5 eq)	9 (3 eq)	10 (5 eq)	10 (3 eq)	11 (5 eq)	11 (3 eq)	12 (5 eq)	12 (3 eq)
pentafluorophenol (**7a**)[a]	^{19}F NMR	100%	100%	100%	100%	100%	100%	100%	100%	--	--
hydroxysuccinimide (**7b**)	220 nm	100%	100%	100%	100%	100%	100%	100%	100%	--	--
4-nitrophenol (**7c**)	220 nm	98%	94%	94%	90%	100%	100%	100%	100%	--	--
hydroxybenzotriazole (**7d**)	310 nm	100%	100%	97%	96%	100%	100%	100%	100%	--	--
1-hydroxy-7-azabenzotriazole (**7e**)	280 nm	100%	100%	97%	94%	100%	100%	100%	100%	16%	6.8%
imidazole (**7f**)	220 nm	7.8%	6.5%	25%	21%	73%	63%	89%	70%	100%	100%

Entries indicate the percentage of byproduct 7 successfully removed from solution. An HPLC method was developed using each byproduct **7b-7f** as standards of known concentrations detected at the appropriate wavelength.

a) Experiments with pentafluorophenol (**7a**) were analyzed by ^{19}F NMR spectroscopy. No fluorine signal was detected in any of these cases.

With appropriate CMR/R resins in hand to sequester byproducts **7**, we wished to further demonstrate this purification strategy and its applicability in organic reactions. Some typical amide bond-forming reactions involving amines with activated esters were purified by this CMR/R approach. The hydroxysuccinimide and 4-nitrophenol esters of N-Boc valine (**13a** and **13b**) were reacted in excess with benzylamine (**14**) to afford amide products **15**. The reaction mixtures were then purified by incubation with resin **8** or **10**. [19] The results are summarized in Table 2. The CMR/R resins removed the byproduct H-X hydroxysuccinimide (**7b**) or 4-nitrophenol (**7c**), as well as the excess activated reactants **13**. The hydroxysuccinimide (**13a**) example afforded product **15** in excellent yield and purity after treatment of the reaction mixture with 5 mol equiv of CMR/R resin (**8** or **10**), whereas as initial treatment of the 4-nitrophenol example (**13b**) with 8 mol equiv of CMR/R resin (**8** or **10**) yielded product **15** that was about 80% pure and required a subsequent incubation with 3 mole equiv of the A-21 resin (**9**) to afford acceptable purity.

Scheme 4

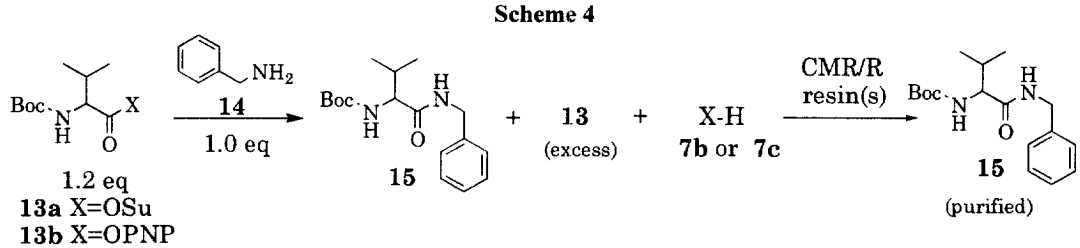


Table 2

Purification of amide bond-forming reactions with CMR/R resins.

Activated ester	Resin 8		Resin 10	
	yield of 15	purity of 15	yield of 15	purity of 15
Hydroxysuccinimide (**13a**) (5 eq resin)	85%	96%	98%	98%
4-nitrophenol (**13b**) (8 eq resin)	75%	80%	105%	78%
*4-nitrophenol (**13b**)(subsequent treatment with 3 eq resin **9**)*	57%	97%	73%	94%

Yields based on mass recovery. Purity based on HPLC. All compounds exhibited satisfactory ^{1}H NMR spectra.

In conclusion, a method for sequestering the byproducts of activated intermediates with nucleofuge sequestering resins has been demonstrated. Resins **8-12** also effectively sequester the excess activated ester electrophiles used to drive these reactions to completion. Synthetic transformations such as that outlined in Scheme 2 have not been very amenable to a library format, primarily due to the requirement for extractive work-up and chromatographic purification. The resin sequestering methodology presented here provides a convenient and readily-automatable means of purifying such reactions.

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References and Notes

1. Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567-2573.
2. Studer, A.; Hadida, S.; Ferritto, R.; Kim, S. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823-826.
3. a) Flynn, D. L.; Crich J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881. b) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. *Curr. Opin. Drug Disc. Dev.* **1998**, *1*, 41-50.
4. Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, *38*, 7959-7962.
5. Parlow, J. J.; Mischke, D. A.; Woodard, S. S. *J. Org. Chem.* **1997**, *62*, 5908-5919.
6. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886.
7. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513-516.
8. Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196.
9. Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525-530.
10. Carey, F. A.; Sundbergh, R.J. *Advanced Organic Chemistry, second edition* Plenum Press: New York, 1983; pp. 121-122.
11. Sequestration of byproduct **7c** after amide formation has been reported. Lawrence, R. M.; Biller, A. S.; Fryszman, M. O.; Poss, A. M. *Synthesis* **1997**, *5*, 553-558.
12. A solution of 0.10 mmol of byproduct (**7a-7f**) in 3 mL of dichloromethane [13] was incubated with the indicated theoretical equivalents [14] of resin **8**, **9**, **10**, **11**, or **12** for 2 hours. The solutions were filtered, the resins washed with dichloromethane, and the filtrates evaporated. Any residue remaining was taken up in 3 mL acetonitrile [13] and analyzed by HPLC.
13. 1-Hydroxy-7-azabenzotriazole (**7e**) proved to be insoluble in dichloromethane or acetonitrile. This compound was treated with resin as a solution in 5:1 DCM:DMF and the resulting residue after evaporation dissolved in 3 mL DMF. An injection of DMF on the HPLC showed no absorbance in the range of interest for this byproduct.
14. Resins **8** [5] and **10** [15,16] were synthesized in our laboratories. The elemental analysis results for resin **8** were 4.51% N and 0.0 % Cl, resulting in a calculated loading of 3.2 meq N/g polymer. The elemental analysis results for resin **10** were 4.22% N, 0.0% Cl and 0.0% K, resulting in a calculated loading of 3.0 meq N/g polymer or 1.5 meq CO_3^{2-}/g polymer. The loadings of resins **9**, **11**, and **12** are quoted by the supplier as 4.8 meq/g polymer, 2.2 meq/g polymer, and 4.7 meq/g polymer respectively.
15. Ruddick, C. L.; Hodge, P.; Houghton, M. P. *Synthesis* **1996**, 1359-1362.
16. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Synthesis* **1981**, 793-794.
17. A macroporous triethylammonium methylpolystyrene carbonate resin is available through Argonaut Technologies.
18. Polymer-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**11**) and Amberlyst A-21 (**9**) were purchased from Fluka/Aldrich Chemical Company.
19. Experimental: A solution of benzylamine (**14**) in DCM (2.0 mL, 0.20 mmol) and a solution of the activated intermediate **13** in DCM (2.2 mL, 0.22 mmol) were combined and stirred overnight. The reaction mixtures were then incubated with the appropriate resin (**8** or **10**) for 2 hours. The reaction mixtures were filtered, the resins washed with DCM (3 x 2 mL) and the filtrates evaporated under a stream of nitrogen. The mass recovery was recorded, the residue taken up in CD_3CN, and analyzed by ^{1}H NMR and HPLC. For reactions involving **13b**, the CD_3CN was evaporated under a stream of nitrogen, the residue taken up in DCM (2 mL) and incubated with resin **9** for 2 hours. The reaction mixtures were filtered, the resins washed with DCM (3 x 2 mL), and the filtrates evaporated under a stream of nitrogen. The mass recovery was recorded, the residue taken up in CD_3CN, and analyzed by ^{1}H NMR and HPLC. The results are summarized in Table 2.