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Ion-Exchange Resins for Solution Phase Parallel Synthesis of Chemical Libraries

Leah M. Gayo, Mark J. Suto*

Department of Medicinal Chemistry
Signal Pharmaceuticals, Inc.
5555 Oberlin Drive, San Diego, CA 92121

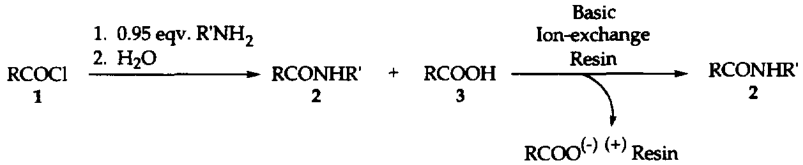
Abstract. Described are various techniques that employ ion-exchange resins for the solution-phase synthesis of chemical libraries. We have found these resins to be useful as reagents and/or scavengers in a variety of reactions. Nine basic ion-exchange resins were evaluated for the catalysis and purification of an amide synthesized from an acid chloride. A number of the resins examined provided products in >95% purity. Acidic ion-exchange resins were also useful as scavengers in the synthesis of ureas. A demonstration of the utility of these resins for the preparation of amide, ester and urea libraries is also described. © 1997, Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry is a rapid and efficient approach for the preparation of large numbers of compounds or libraries to accelerate the drug discovery process. Using solid-phase combinatorial chemistry, we have generated libraries of small organic molecules for both discovery and lead optimization. In addition to the solid-phase synthesis of libraries, we are developing solution-phase[1] techniques that facilitate the parallel synthesis of chemical libraries for lead optimization. These techniques would be applicable to a variety of reactions that are acid or base catalyzed and/or require an aqueous workup, and therefore, would be generally useful in combinatorial chemistry.

There are advantages to solution-phase combinatorial chemistry such as cost effectiveness (for example, the large excess of reagents and solvents, typical of solid-phase chemistry, is not needed) and the greater quantities of final products. However, the chemistry for a solution-phase parallel synthesis requires complete conversion of reactants to product with little or no formation of byproducts or impurities. In addition, many reactions require an aqueous workup, which is tedious if manually preparing large libraries.

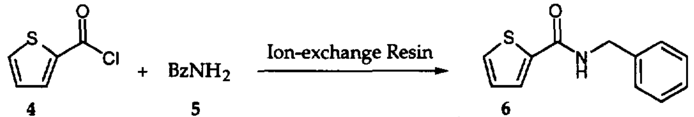
We have been exploring the use of ion-exchange resins[2] as reagents to remove reaction byproducts and eliminate aqueous workups in the solution-phase synthesis of combinatorial libraries. Scheme 1 illustrates the use of an ion-exchange resin to purify an amide product without the typical aqeuous extraction. The amine is reacted with a slight excess of the acid chloride to provide the amide **2**. Following the reaction, a small amount of water is added to quench any unreacted acid chloride. The carboxylic acid **3** and associated HCl is then

SCHEME 1



absorbed by the resin, leaving only clean product in solution. To quickly optimize the conditions for this reaction, we ran 60 reactions in parallel in a 96-well format.[3] Nine ion-exchange resins (weakly to strongly basic), three solvents (EtOAc, CH_2Cl_2, and THF) and two different addition regimens (prior to reaction and following reaction) were evaluated. The purities and relative yields of product were determined by HPLC and

TABLE 1



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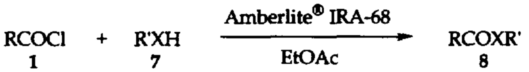
Ion-exchange Resin	Solvent	EXPERIMENT 1[A] HPLC Area (10^7)[B]	EXPERIMENT 1[A] Purity (%)	EXPERIMENT 2 HPLC Area (10^7)	EXPERIMENT 2 Purity (%)
Amberlyst 21	EtOAc	15	84	20	84
(weakly basic)	THF	16	91	30	68
	DCM	6	93	10	70
Amberlyst 27	EtOAc	13	77	18	88
(strongly basic)	THF	8	35	10	58
	DCM	11	57	18	74
Dowex® 66	EtOAc	20	94	16	94
(weakly basic)	THF	8	69	6	68
	DCM	36	96	14	80
Dowex® 1X8-50	EtOAc	13	91	12	79
(strongly basic)	THF	12	95	17	62
	DCM	34	93	13	82
Dowex® 1X2-100	EtOAc	21	99	30	95
(strongly basic)	THF	19	60	20	59
	DCM	33	84	31	65
Amberlite® IRA-68	EtOAc	31	99	30	>99
(weakly basic)	THF	19	>99	20	76
	DCM	33	99	31	93
Amberlite® IRA-900	EtOAc	15	89	14	87
(strongly basic)	THF	15	63	12	58
	DCM	21	68	20	77
Amberlite® IRA-904	EtOAc	10	99	16	99
(strongly basic)	THF	14	72	13	63
	DCM	9	78	19	85
AmberJet™ 4200	EtOAc	12	90	15	92
(strongly basic)	THF	10	65	11	59
	DCM	11	84	10	65
No Resin[C]	EtOAc	15	57	17	60
	THF	13	62	20	61
	DCM	19	63	13	62

[A] Experiment 1 is addition of ion-exchange resin *before* reaction with acid chloride. Experiment 2 is addition of ion-exchange resin *after* reaction with acid chloride; see experimental.

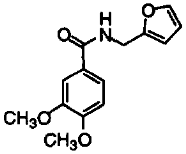
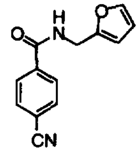
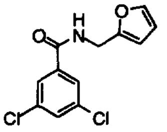
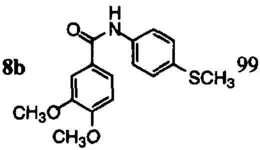
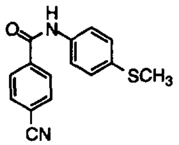
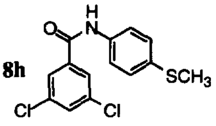
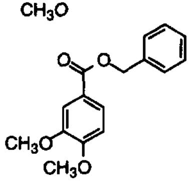
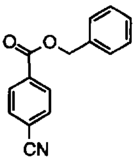
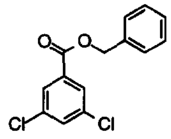
[B] Product areas and purities were determined using HPLC [Isocratic, CH_3CN/H_2O, 65:35 (1% TFA)].

[C] As a control, two reactions without resin were run for a given solvent; see experimental.

TABLE 2



$$\underset{1}{RCOCl} + \underset{7}{R'XH} \xrightarrow[EtOAc]{Amberlite^{®}\ IRA\text{-}68} \underset{8}{RCOXR'}$$

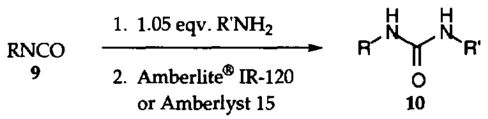
Compound	Yield, Purity	Compound	Yield, Purity	Compound	Yield, Purity
8a 	94, >99	**8d** 	93, >99	**8g** 	100, >99
8b 	99, 99	**8e** 	94, >99	**8h** 	96, 99
8c 	99, 99	**8f** 	97, 99	**8i** 	84, 98

were indicative of the optimum reaction conditions (Table 1). Several of the conditions provided products in high yield and in >95% purity. In reactions that did not contain resin, the products averaged 61% purity. As revealed in Table 1, the use of Amberlite® IRA-68, a weakly basic resin, provided products in highest purity (>99%) and was therefore selected for further evaluation.

A variety of amines and alcohols were then reacted with acid chlorides under the optimum conditions (Amberlite® IRA-68, EtOAc) and found to provide products in high yield and in >97% purity (Table 2).[4]

In addition to these applications, we have recently found that acidic ion-exchange resins (Amberlite® IR-120 and Amberlyst 15) can also be used as amine scavengers in the preparation of ureas (Scheme 2).[5]

SCHEME 2



In summary, ion-exchange resins are useful reagents for solution-phase combinatorial chemistry. We have generated several libraries for lead optimization as part of our inflammation program using the techniques described herein. Studies are continuing in an effort to further develop these techniques as well as the use of more classical solid-phase resins (such as an aminomethyl resin) as scavengers in solution-phase library synthesis.[6]

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1. Selway, C. N.; Terett, N. K. *Bioorg. Med. Chem. Lett.*, **1996**, *4*, 645.
2. Parlow, J. J. *Tetrahedron Lett.*, **1996**, *37*, 5257; Parlow, J. J. *Tetrahedron Lett.*, **1995**, *36*, 1395; Cainelli, G.; Contento, M.; Manescachi, F.; Regnoli, R. *J. Chem. Soc., Perkin Trans.*, **1980**, *11*, 2516.
3. **Procedure for the Evaluation of Ion-exchange Resins:** Using a 96-well plate (2mL capacity), approximately 25 mg of resin were placed into each well: Amberlyst 21 (wells A-C of column 1), Amberlyst 27 (A-C of 2), Dowex® 66 (A-C of 3), Dowex® 1X8-50 (A-C of 4), Dowex® 1X2-100 (A-C of 5), Amberlite® IRA-68 (A-C of 6), Amberlite® IRA-900 (A-C of 7), Amberlite® IRA-904 (A-C of 8), and AmberJet$^{\text{TM}}$ 4200 (A-C of 9). No resin was placed in column 10. Columns 11 and 12 were not used. Six solutions were prepared: benzylamine (0.049 mL, 0.45 mmol) in EtOAc (4 mL), in THF, and in CH_2Cl_2; 2-thiophenecarbonyl chloride (0.069 g, 0.47 mmol) in EtOAc (4 mL), in THF, and in CH_2Cl_2. Into each well of rows A and D was placed 0.20 mL of benzylamine in EtOAc. Benzylamine/THF (0.20 mL) was placed into rows B and E, and benzylamine/CH_2Cl_2 into rows C and F. The corresponding thiophenecarbonyl chloride solutions (0.20 mL) were then added. The plate was covered and sonicated for 45 min. Water (0.05 mL) was added to each well, and the reactions sonicated for another 30 min. The solutions in rows 1-3 were then transferred to tared test tubes using the same solvent (0.60 mL) employed in the reaction. Approximately 25 mg of resin were placed into wells D-F: Amberlyst 21 (column 1), Amberlyst 27 (2), Dowex® 66 (3), Dowex® 1X8-50 (4), Dowex® 1X2-100 (5), Amberlite® IRA-68 (6), Amberlite® IRA-900 (7), Amberlite® IRA-904 (8), and AmberJet$^{\text{TM}}$ 4200 (9). After sonicating 30 min., the solutions were transferred to tared test tubes as described above. All 60 reaction mixtures were evaporated to dryness. 3 mL of CH_3CN (0.1% TFA) was added to each, and the products were evaluated by HPLC [isocratic, CH_3CN/H_2O, 65:35 (1% TFA)]. Results are summarized in Table 1. Products prepared using Amberlite® 68 and Dowex® 1X8-50 were also analyzed by ^{1}H NMR and GCMS, and yields were determined.
4. **General Procedure for the Preparation of 8:** To Amberlite 68 (approximately 0.05 g dried under vaccum ovenight) was added the amine or alcohol (0.0475 mmol) in EtOAc (0.6 mL) followed by the acid chloride (0.050 mmol) in EtOAc (0.6 mL). The reaction mixture was then shaken overnight. Water (0.1 mL) was added, and the reaction shaken for an additional 30 minutes. Filtration and concentration of the filtrate provided **8** in high purities and yields as summarized in Table 2.
5. **Example Procedure for the Preparation of 10**; 1-Benzyl-3-(m-tolyl)urea: To m-toluidine (0.005 mL, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added benzylisocyanate (0.006 mL, 0.0475 mmol) in CH_2Cl_2 (0.5 mL). After sonication for 1 hour, Amberlyst 15 (approximately 0.05 g) or Amberlite IRA®120 (plus) (approximately 0.05 g rinsed with EtOAc and dried under vaccum) was added, and the reaction mixture was sonicated for an additional 10 min. Filtration and concentration of the filtrate provided the title compound (0.0108 g, 92% yield) in 98% purity with all spectra in agreement with literature.
6. A paper describing the use of resins as scavengers was recently published: Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.*, **1996**, *37*, 7193.

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