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Use of Solid Supported Nucleophiles and Electrophiles for the Purification of Non-Peptide Small Molecule Libraries

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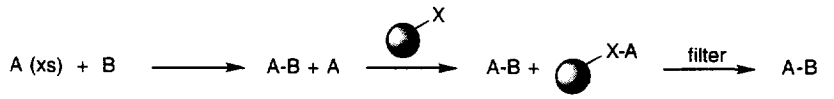
Abstract: Solid supported nucleophiles and electrophiles are employed to expedite the work-up and purification of a variety of amine alkylations and acylations. These solid suported scavengers are particularly advantageous for the construction of non-peptide libraries in a parallel array format.

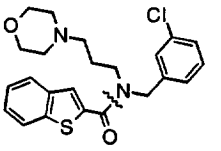
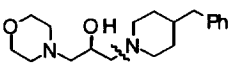
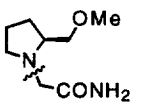
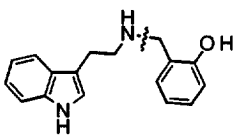
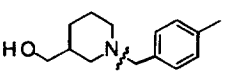
Combinatorial chemistry has become the focus of intense interest as a tool for expedited synthesis and drug discovery.[1-3] Most recent research in this area has exploited the advantages of solid phase organic synthesis (SPOS)[4,5] to form large libraries of small molecules. A key strength of SPOS is the ease with which reaction work-up and purification can be conducted: simple filtration allows separation of reagents, starting materials, and solvents from the desired product, and permits the chemist to use the principle of excess with impunity to drive reactions to completion. We wish to report on a complementary *solution phase* approach for expedited amine alkylation and acylation employing solid phase scavenging agents which retains this advantage of solid supported chemistry while greatly reducing or eliminating some of its disadvantages. In this approach, the reaction product is formed in a solution phase reaction,[6] and unreacted excess starting material is selectively removed from solution in a subsequent "quenching" step involving covalent bond formation to a solid supported electrophile or nucleophile (Scheme 1).[7-10] Filtration and evaporation then provide products of high purity in an operationally simple manner which lends itself to parallel processing and automation. As with SPOS, an excess of one starting material can be utilized to drive a reaction to completion without fear of complicating the isolation and purification of the final product.

Scheme 1



We chose to examine amine acylation as a "proof of concept" reaction, as an acylating agent (electrophile) should be readily differentiated from either the starting amine (nucleophile) or product acylated amine by a nucleophilic scavenging agent. Thus, we reacted benzylamine with an excess of *p*-methoxyphenyl isocyanate in $CDCl_3$. After 1 h, excess aminomethylpolystyrene (0.8 mequiv/gm) was added as a scavenger for unreacted isocyanate, the reaction was filtered, and the resulting $CDCl_3$ solution was analyzed by ^1H NMR. Within the limits of detection, we observed only the desired urea product, with no evidence of excess isocyanate. We have since found this protocol to be quite general in scope, and have utilized it to prepare thousands of ureas and thioureas. This chemistry can also be applied to the construction of amides, sulfonamides, and carbamates if one incorporates the use of a basic resin in the initial reaction step (Table 1, entry 1).

Table 1. Selective Scavenging Of Excess Reagents

entry	limiting reagent	excess reagent[a]	scavenger	solvent/ temp.	representative product[11]	yield	purity (HPLC)
1	R_1R_2NH	R_3NCO R_3COCl[b,c] R_3SO_2Cl[b]		$CHCl_3$/ RT		67%	94%
2		R_1R_2NH		MeOH[d]/ RT-65°C		94%	93%
3	R_3X[b,e]	R_1R_2NH		CH_3CN[d]/ 30-60°C		96%	>95%[f]
4		R_1NH_2		(see text)		73%	90%
5		R_1R_2NH		10% HOAc-$C_2H_4Cl_2$/ RT		62%	>95%[f]

a) typically 1.25-2 fold excess. b) piperidinomethyl polystyrene or other solid-supported base is added as an acid scavenger. c) acid chlorides or chloroformates. d) reaction was diluted with 2 volumes of CH_2Cl_2 prior to scavenging at room temperature. e) X=halide, sulfonate ester. f) purity estimated by ^1H NMR.

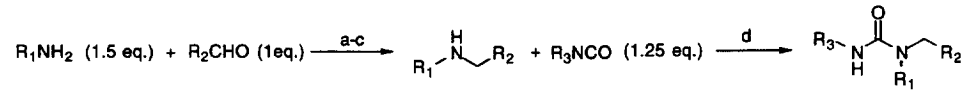
We next examined amine alkylation chemistry. In order to apply the scavenger concept to amine alkylations, we developed two complementary procedures. For the alkylation of secondary amines with alkylating agents (i.e. alkyl halides and epoxides), we elected to use an excess of secondary amine relative to electrophile, and to then scavenge excess starting amine from the relatively non-nucleophilic tertiary amine product using a polymer supported isocyanate[12] as an electrophilic scavenger (Table 1, entries 2 and 3).[13]

We also explored reductive amination as an alternative amine alkylation protocol. For the synthesis of secondary amines from primary amines, we chose to use an excess of primary amine relative to carbonyl component. After preformation of the corresponding imine adduct in methanol, reduction was performed using polymer supported borohydride.[14] Excess primary amine was readily separated from the desired secondary amine product by selective imine formation using a polymer supported aldehyde[15] (Table 1, entry 4). The resin bound borohydride and resin bound aldehyde can be added simultaneously; polymer site isolation and the relative kinetics of imine formation on- and off-polymer allow for this convenient experimental procedure. Filtration and evaporation provided secondary amines with only trace quantities of impurities.[16]

Reductive amination was also utilized to form tertiary amines by the reaction of an aldehyde with an excess of secondary amine and polymer supported cyanoborohydride in acetic acid/dichloroethane, followed by scavenging of excess secondary amine with polymer supported benzoyl chloride (Table 1, entry 5).[17,18]

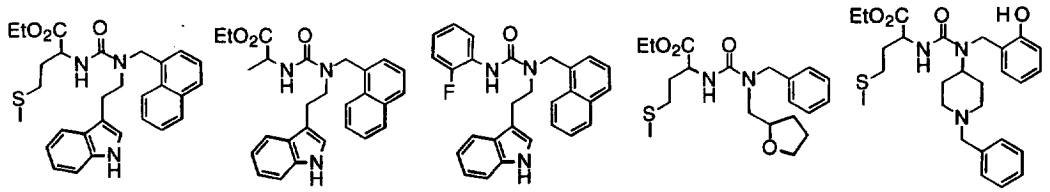
In a significant extension of these methods, we have found it possible to conduct multi-step sequences (Scheme 2). In a representative example, *N*-benzyl-tetrahydrofurfurylamine, 4-(2-hydroxybenzylamino)-1-benzylpiperidine, and *N*-naphthyltryptamine were synthesized in high purity and 87%, 84%, and 89% yield respectively utilizing our reductive amination procedure with polymer supported benzaldehyde scavenger. These three amines were then acylated with (±)-ethyl 2-isocyanato-4-methylthiobutyrate. *N*-naphthyl tryptamine was also acylated with (±)-ethyl 2-isocyanatopropionate and 4-fluorophenyl isocyanate, giving a total of five trisubstituted ureas (Figure 1). All five compounds were obtained in good yield and purity.

Scheme 2



a) MeOH, r.t., 1 hr; b) Amberlite IRA-400 borohydride resin, r.t.; c) 1. polystyrene carboxaldehyde, CH_2Cl_2, overnight, 2. filter; d) 1. ethanol-free chloroform, 1 hr; 2. aminomethylated polystyrene, 1 hr, 3. filter

This two step sequence leads to products with an extremely small invariant region and three diversification points which can be varied independently. In contrast to most SPOS, this method does not yield products containing a vestigial linker (typically an acid or amide in SPOS),[19] does not require the additional steps of attachment to and cleavage from a resin,[20] and is readily amenable to standard analytical techniques for reaction monitoring. The protocol is highly general in scope and has been exploited to produce thousands of amides, sulfonamides, ureas, and thioureas for biological evaluation.



(100/93) (89/95) (95/95) (87/81) (100/97)

Figure 1. Products of two step protocol (% yield/% HPLC purity)

A typical procedure for the reductive amination of primary amines: To a 4 mL screw cap glass vial is added 1 mL methanol, 0.5 mmol of a primary aliphatic amine, and 0.33 mmol of an aldehyde. The vial is sealed with a Teflon® backed cap and the solution is then shaken for 2-3 hours to allow for imine formation, then treated with approximately 250 mg (2.5 mmol BH_4^-/g resin, 0.63 mmol) of Amberlite® IRA-400 borohydride resin (Aldrich Chemicals). The slurry is then shaken an additional 24 hours to effect reduction to the secondary amine, then 1 mL methylene chloride and approximately 350 mg (1 mmol/g resin, 0.35 mmol) polystyrene-linked benzaldehyde resin is added to the vial, and the mixture is shaken overnight, then filtered through a cotton plug, and the residual solids are rinsed with methanol. Evaporation yields a product of typically 90-95% purity in yields ranging from 50-99%.

In summary, we have demonstrated the utility of a family of solid supported covalent scavengers in amine acylation and alkylation chemistry. Electrophilic and nucleophilic scavengers have been employed successfully, and hybrid protocols coupling these scavengers with solid supported reagents and/or solid phase extraction have also been exemplified. Extension of these concepts to other reaction classes (e.g. O- and S-alkylation) will be the subject of future reports.

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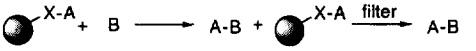

see: *Preparative Chemistry Using Supported Reagents*; Laszlo, P. ed.; Academic Press, Inc.: San Diego, 1987; Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, 81, 557-587.
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