Impurity annihilation; a strategy for solution phase combinatorial chemistry with minimal purification

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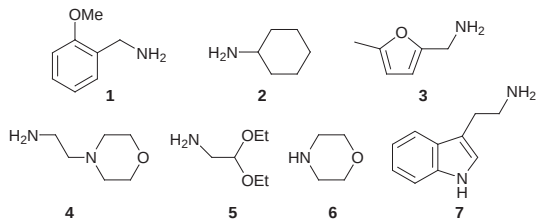
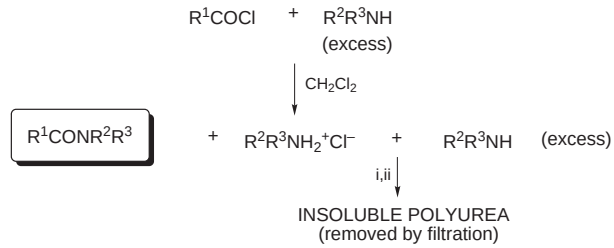
Received (in Cambridge, UK) 26th August 1998, Accepted 7th September 1998

The selective annihilation of all contaminants in the solution phase formation of amides or sulfonamides is accomplished by their incorporation into a polyurea and removal by filtration.

Combinatorial chemistry has received much attention of late as an engine for the discovery of new pharmaceuticals, catalysts and materials. Library generation may be accomplished using solid phase organic synthesis or by using conventional solution phase chemistry.[1] There is, however, an unending controversy as to which of the major synthetic strategies for library synthesis is superior. Polymer supported synthesis has the clear advantages of ease of manipulation, the ability to drive reactions to completion by use of excess reagent and isolation of the product by filtration alone. However, many synthetic transformations on solid phase encounter difficulties of analysis and reaction tracking. The development of new reactions on a solid phase is frequently time consuming although once developed they may be used in rapid automated production of libraries. In contrast, the primary advantage of solution phase chemistry is its familiarity to the synthetic chemist. Additionally reactions are generally amenable to easy tracking and analysis. Nonetheless the complicated work-up procedures usually associated with such reactions in solution have been a major hurdle to automation and the use of multi-step sequences. Recently the use of polymer supported scavengers has been described as a method to overcome these problems.[2] Disadvantages include the often slow removal of contaminants and variable quality of the libraries produced. Other strategies include the use of fluorous phase chemistry. Disadvantages here include the lack of fluorinated reagents which often need to be prepared by highly specialised syntheses.[3]



Herein we report a novel method which readily addresses the problem of solution phase library clean-up discussed above. Our approach is based upon the selective annihilation of all contaminants which are then removed by simple filtration as an insoluble product. The procedure is exemplified by the synthesis of amides from the condensation reaction of acid chlorides with amines. Reaction of an acid chloride with excess amine may be used to prepare pure amides in the solution phase without chromatography simply by the polymerisation of the excess amine and filtration (Scheme 1). Co-polymerisation of 1,4-phenylene diisocyanate and pentaethylenehexamine was used to effectively remove the excess amine as a highly insoluble easily filtered polyurea (Table 1).‡ The procedure appears widely applicable with both primary and secondary amines affording the corresponding amides in excellent yield and purity. One caveat is the presence of a second unprotected indole NH function (entry 7, Table 1) which affords none of the desired amide due to its propensity to undergo reaction with 1,4-phenylene diisocyanate and thence to polymer. Sulfonamides may be prepared by the reaction of a sulfonyl chloride with excess amine (Scheme 2 and Table 2).‡ The use of an arenesulfonyl chloride generally gave superior results, both in terms of yield and purity, compared with an alkanesulfonyl chloride.



Scheme 1 *Reagents*: i, 1,4-phenylene diisocyanate (excess); ii, pentaethylenehexamine.

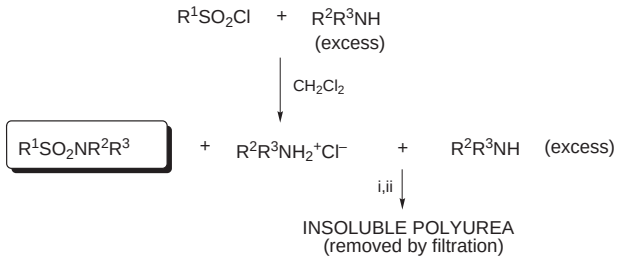
Table 1 Formation of amides using impurity annihilation[a]

3,5-$Cl_2C_6H_3COCl$ —(i–iii)→ 3,5-$Cl_2C_6H_3CONR^2R^3$

Entry	Amine	Yield (%)	Purity (%)[b]
1	**1**	92	92
2	**2**	96	99
3	**3**	93	93
4	**4**	90	95
5	**5**	85	98
6	**6**	90	99
7	**7**	0	—

[a] *Reagents*: i, amine (3 equiv.); ii, 1,4-phenylene diisocyanate (6 equiv.); iii, pentaethylenehexamine (2.5 equiv.). [b] Determined by GC–MS and ^{1}H NMR spectroscopy.

Amide and sulfonamide formation may also be accomplished by the reaction of amine with an excess of acyl or sulfonyl chloride, respectively (Scheme 3). Under these circumstances it is necessary to add an excess of poly(vinylpyridine) to capture liberated hydrogen chloride and enable amide or sulfonamide formation to proceed to completion. The excess acyl or sulfonyl chloride is then scavenged by the addition of the polyamine (3



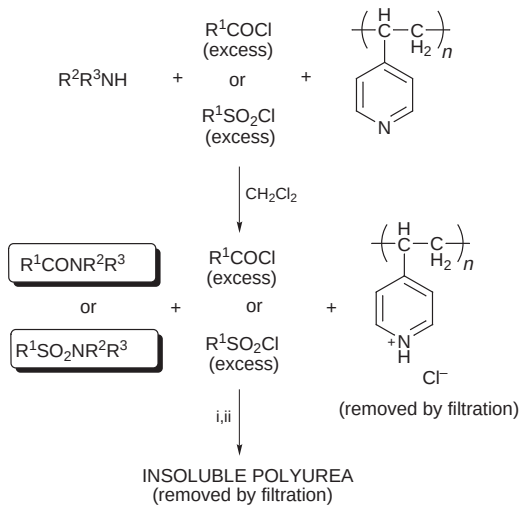
Scheme 2 *Reagents*: i, 1,4-phenylene diisocyanate (excess); ii, pentaethylenehexamine.

Table 2 Formation of sulfonamides using impurity annihilation[a]

(a) R^1 = *p*-Tol
(b) R^1 = Et

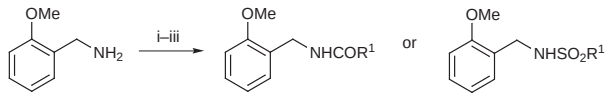
Entry	Amine	Yield (%)	Purity (%)[b]
1a	**1**	90	95
1b	**1**	74	81
2a	**2**	79	94
2b	**3**	68	80
3a	**3**	85	89
3b	**3**	64	67
4a	**4**	92	92
4b	**4**	81	57
5a	**5**	97	98
5b	**5**	92	92
6a	**6**	81	92
6b	**6**	80	61

[a] *Reagents*: i, amine (3 equiv.); ii, 1,4-phenylene diisocyanate (6 equiv.); iii, pentaethylenehexamine (2.5 equiv.). [b] Determined by GC–MS and ^{1}H NMR spectroscopy.



Scheme 3 *Reagents*: i, pentaethylenehexamine (excess); ii, 1,4-phenylene diisocyanate.

Table 3 Formation of sulfonamides and amides using impurity annihilation[a]



Entry	Chloride	Yield (%)	Purity (%)[b]
1	3,5-$Cl_2C_6H_3COCl$	90	99
2	c-$C_6H_{11}COCl$	98	97
3	2-furylCOCl	95	92
4	4-$MeC_6H_4SO_2Cl$	84	92

[a] *Reagents*: i, chloride (3 equiv.), poly(vinylpyridine); ii, pentaethylenehexamine (3 equiv.); iii, 1,4-phenylene diisocyanate (3 equiv.). [b] Determined by GC–MS and ^{1}H NMR spectroscopy.

equiv.) followed by the addition of the diisocyanate (3 equiv.) to induce polymerisation to the polyurea. Both the polyurea and poly(vinylpyridine) are then simply removed by filtration. Once again excellent yields and purities are obtained (results for various chlorides are listed in Table 3).§ Thus component annihilation is suitable for the removal of either excess electrophilic or nucleophilic components.

In summary, we have developed a method for the efficient 'clean-up' of a number of solution phase reactions that affords the desired products in excellent yields and purities in a reasonable time frame. This methodology has been successfully carried out manually and with the use of automation.¶ Extension of this methodology to the synthesis of esters and for the annihilation of other common reagents‖ will be reported in due course.

We thank RPA and the BBSRC for a studentship (F. J. Z.), Glaxo Wellcome Research Ltd. for their endowment (A. G. M. B.) and the Royal Society for a Dorothy Hodgkin fellowship (M. L. S.).

Notes and references

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‡ Typical procedure for the formation of amides or sulfonamides using an acid chloride or sulfonylchloride respectively with excess amine: To a solution of the acid chloride or sulfonamide (0.1 mmol) in CH_2Cl_2 (1 ml) was added a solution of the amine (3 equiv.) in CH_2Cl_2 (1 ml). The mixture was stirred at room temperature for 30 min and a solution of 1,4-phenylene diisocyanate (6 equiv.) in CH_2Cl_2 (4 ml) was added. The mixture was stirred at room temperature for 40 min and a solution of pentaethylenehexamine (2.5 equiv.) in CH_2Cl_2 (4 ml) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Evaporation of the solvent under reduced pressure afforded the expected amide in high yield and purity (see Tables 1 and 2 respectively).

§ Typical procedure for the formation of amides or sulfonamides using an amine with excess acid chloride or sulfonyl chloride respectively: To a solution of the amine (0.1 mmol) in CH_2Cl_2 (1 ml) was added a solution of the acid chloride or sulfonyl chloride (3 equiv.) in CH_2Cl_2 (1 ml) and poly(vinylpyridine) (100 mg). The mixture was stirred at room temperature for 30 min when a solution of pentaethylenehexamine (3 equiv.) in CH_2Cl_2 (4 ml) was added. The mixture was stirred at room temperature for 40 min. and a solution of 1,4-phenylene diisocyanate (3 equiv.) in CH_2Cl_2 (4 ml) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Evaporation of the solvent under reduced pressure afforded the expected amide or sulfonamide in high yield and purity (see Table 3).

¶ Automated synthesis was carried out using a Nautilus™ 2400 Organic Synthesizer (Argonaut Technologies, Inc.).

‖ Kurth has recently reported the use of 1,4-phenylene diisocyanate as a convenient reagent for the generation of nitrile oxides from nitroalkanes since the by product urea readily polymerises (see ref. 4).

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Communication 8/06693K