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Mitsunobu reaction modifications allowing product isolation without chromatography: application to a small parallel library

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Abstract

Readily available reagents, triphenylphosphine resin and di-*t*-butylazodicarboxylate, were used in Mitsunobu reactions and the byproducts were removed without chromatography. The new modification was utilized to prepare a small, parallel, solution phase library. © 2000 Elsevier Science Ltd. All rights reserved.

The process of simultaneously preparing numerous compounds either as mixtures or as discrete sets (combinatorial chemistry) has rapidly become a powerful tool for industrial and academic applications that require screening of large sets of molecules to identify subsets that possess desired properties. The procedure has gained widespread application in pharmaceutical, agricultural and materials science sectors.[1] Coupled with the normal synthetic problems associated with combinatorial chemistry (side reactions, incomplete reactions, etc.) is the tedious procedure of purification. This has been partially overcome through the use of solid phase synthesis where reactions are driven to completion by the utilization of excess reagents and starting materials.[2] Improvements in automated chromatographic techniques have also increased the ability to provide moderately large libraries of pure discrete compounds. Recently, the use of 'reagent' and 'scavenger' resins in solution phase parallel library synthesis has reduced the need for classical post-reaction purification.[3] Removal of the reagent and/or scavenger resins is done through filtration which can be readily performed on hundreds or thousands of samples. Other purification techniques may be as simple as aqueous–organic extraction followed by evaporation.[4] A recent communication describes the post-reaction destruction of reagents followed by their removal via nonchromatographic techniques.[5] These methods can also be applied simultaneously to multiple samples.

The Mitsunobu reaction has frequently been used as a reliable method for the alkylation of moderately acidic heteroatoms.[6] Excess reagents and byproducts, however, are nonvolatile and soluble in organic solvents necessitating chromatographic purification of products in almost all instances. The procedure has been applied to solid phase synthesis making it ideal for use in combinatorial chemistry where resin techniques are employed.[7] Recently, Flynn and co-workers reported a solution phase Mitsunobu reaction

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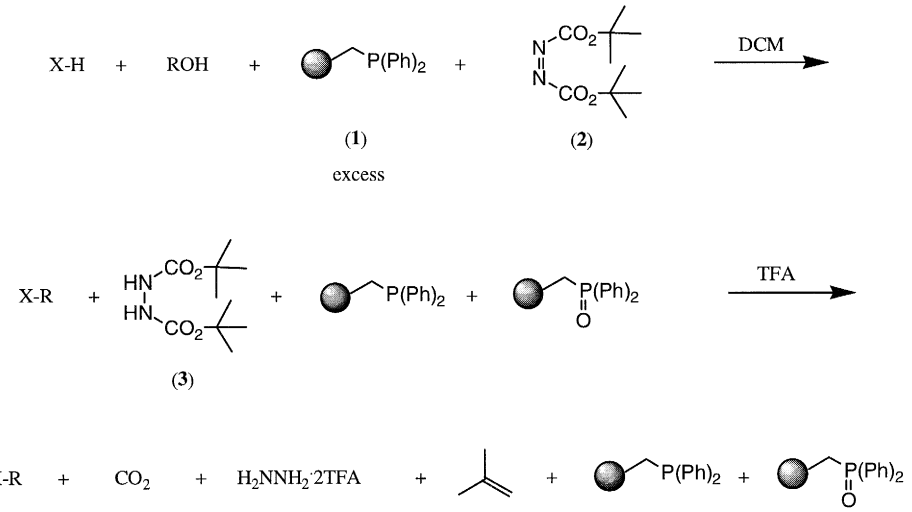
employing solid phase scavengers and reagents.[8] Byproducts were removed by filtration with the product residing in the filtrate. However, some of the necessary reagents are not readily available and must be prepared. A related communication described Mitsunobu reagents that were destroyed or removed by aqueous workup.[9] These latest disclosures have prompted us to report our results on a reliable solution phase version of the Mitsunobu reaction that employs purification techniques readily adaptable to parallel synthesis.

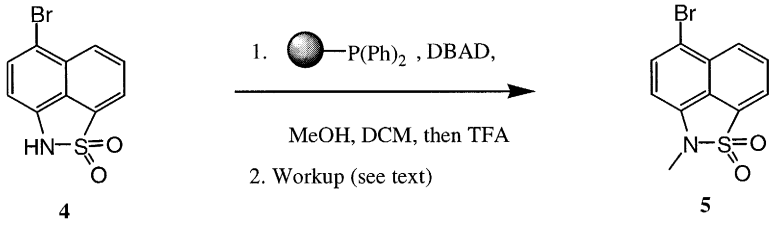
Resin bound triphenylphosphine (**1**) was prepared by Ford[10] and is now available commercially. Its use in the Mitsunobu reaction has been previously documented to enable excess phosphine and phosphine oxide removal via filtration.[10,11] A survey of commercially available azodicarboxylates revealed that the di-*t*-butyl derivative (**2**) can be readily obtained. Furthermore, both this material and the expected hydrazide byproduct (**3**) should provide volatile and water soluble products after decomposition following acid treatment (Eq. (1)). Filtration, evaporation and aqueous wash remove excess phosphine/phosphine oxide, gaseous byproducts and hydrazine ditrifluoroacetate, respectively. At this stage the product should be isolated free of phosphine and hydrazine byproducts.



(1)

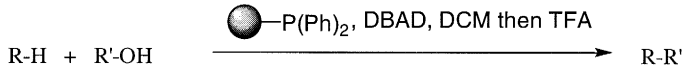
With a rationale for preparing Mitsunobu products established the alkylation of a sulfonamide was attempted (Scheme 1). Hence, a mixture of 5-bromonaphthosultam (**4**, 1.0 equiv.), methanol (2.0 equiv.) and triphenylphosphine resin (**1**, 3 mmol/g, 2.5 equiv.) was treated with di-*t*-butylazodicarboxylate (DBAD, **2**, 2.0 equiv.) at ice temperature in dichloromethane (DCM) for 30 min. Trifluoroacetic acid (TFA) was added at 20°C, stirred for an additional 60 min then filtered and evaporated to dryness. The residue was dissolved in aq. HCl-DCM and separated with the use of a hydrophobic phase separation tube.[12] After evaporation of the organic layer 2-methyl-5-bromonaphthosultam (**5**) was obtained in >95% yield and high purity.[13] A small amount of impurity (<5%) extracted from the resin was present but could be removed by dissolving the product in toluene then decanting the solvent from the insoluble extract or by filtration.

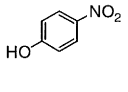
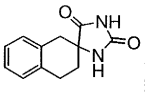
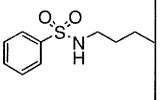
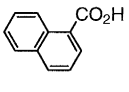
The potential application to parallel libraries was attractive since the product was reasonably pure and all work-up steps are applicable to multiple simultaneous operations. Starting materials containing several representative functional groups (i.e. hydantoin, phenol, carboxylic acid, imide and sulfonamide) were used since they are typical Mitsunobu substrates. A 5×3 parallel library was prepared using methanol, isopropanol and benzyl alcohol as alkylating agents. The results are shown in Table 1.



Scheme 1.

Table 1[a]



R-H / R'-OH					
Methanol	33, 80, 20[b,c]	100, 92, 5	78, 82, 4	88, 76, 24	70, 95, 5
Isopropanol	56, 78, 12	72, 88, 10	77, 80, 20	79, 21, 78	83, 93, 7
Benzyl Alcohol	80, 95, 5	66, 88, 12	89, 86, 6	88, 62, 38	93, 97, 3

[a] All compounds were characterized by HPLC, MS and ^{1}H-NMR.
[b] Values represent crude percent yield, percent product by HPLC and percent starting material by HPLC respectively.
[c] HPLC conditions: 2-98% acetonitrile in water, 0.05% TFA, 1.5 mL/min, 12 mins; Column; C18, 5 µm, 4.4 X 50 mm.

As can be seen in Table 1 most products were of good purity (>80%). The major impurity in all cases was the starting material. Conversion can be enhanced by repeating the reaction or, as an alternative, the mixture can be treated with resin bound carbonate.[14] The basic extraction reagent can remove acidic starting materials with the products isolated by a second filtration. Some products were also contaminated with a small amount (<5%) of material extracted from the phosphine resin. As stated earlier the resin impurity can be removed by dissolving the product in toluene followed by decanting or filtration. We have also carried products on without purification and found the resin impurity to be inert.

In summary, a modified Mitsunobu alkylation protocol that involves the destruction/removal of reagent byproducts through filtration, evaporation and aqueous wash has been developed. The method allows reasonably pure products to be obtained without the need for chromatography. It has also been successfully applied to a 3×5 parallel library where a number of compounds with different functional groups were alkylated with three different alcohols.

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13. Experimental details for **5**: A mixture of 5-bromonaphthosultam (**4**, 0.20 g, 0.70 mMol), triphenylphosphine resin (**1**, 3 mMol/g, 0.58 g, 1.8 mMol) and methanol (45 mg, 1.4 mMol) in dichloromethane (8 mL) was magnetically stirred and cooled in an ice bath. Di-*t*-butylazodicarboxylate (DBAD, **2**, 0.32 g, 1.4 mMol) was added all at once and stirring continued for 30 min. The ice bath was removed and trifluoroacetic acid (TFA, 4 mL) was added. After 60 min. The reaction mixture was filtered (Celite®), the residue washed with DCM (3×10 mL) and the combined filtrate was evaporated to dryness. The crude product was dissolved in DCM (5 mL) and 1N HCl (2 mL) and filtered through a phase separation tube (8 mL, hydrophobic). The organic layer filtrate was evaporated to leave a gray solid (0.21 g, 100%). ^{1}H NMR ($CDCl_3$); δ 8.30 (d, 1H, *J*=8.4 Hz), 8.04 (d, 1H, *J*=7.2 Hz), 7.87 (dd, 1H, *J*=8.4 Hz, *J*=7.2 Hz), 7.78 (d, 1H, *J*=8.1 Hz), 6.60 (d, 1H, *J*=8.1 Hz), 3.37 (s, 3H). Positive ESMS *m/z*=300. Experimental details for **5** using excess 5-bromonaphthosultam: Experiment was run exactly as above using MeOH as the limiting reagent (20 mg, 0.63 mMol). The gray solid residue obtained after solvent evaporation was dissolved in DCM (4 mL), placed in a 20 mL scintillation vial, carbonate resin (3.0 mMol/g, 0.12 g, 0.35 mMol) was added, the vial was capped and shaken 16 h. After filtration through a polypropylene frit and DCM wash the solvent was evaporated to leave a gray solid (0.18 g). Physical data were identical to the sample above. No starting material was present (^{1}H NMR, HPLC and ESMS).
14. Available from Argonaut Technologies, Inc., 887 Industrial Rd., Ste G, San Carlos, CA 94070.