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CHEMICALLY-TAGGED MITSUNOBU REAGENTS FOR USE IN SOLUTION-PHASE CHEMICAL LIBRARY SYNTHESIS

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Abstract: A general method for high-throughput product purification of Mitsunobu reactions is described. Tagged phosphine and azodicarboxylate reagents are used to synthesize individual library members in solution-phase. Workup and purification are easily accomplished by post-reaction sequestration of the tagged reagents and reagent byproducts by a complementary functionalized ion exchange resin. The reagents are utilized in a 3 step library synthesis.

Introduction

High throughput synthesis methodology is currently an area receiving considerable attention in the academic and industrial community. Although solid-phase organic chemistry (SPOC) was the initial focus of methodology development,[1] more recently several innovative techniques have been developed to enable solution-phase library synthesis.[2-8] We have recently reported a general methodology for parallel array solution phase synthesis based on leveraging principles of organic molecular recognition.[3] One aspect of this method utilizes chemically-tagged bifunctional reagents that can be used to affect solution phase reactions. The chemical tags attached to the reagents (and reagent byproducts) do not interfere with the performance of the reagents, yet enable their post-reaction sequestration by complementary-tagged resins. These complementary-tagged resins often are convenient and commercially available ion exchange resins. While ion exchange chromatography is well known and has been extensively employed for many years in a variety of applications,[8a] including protein,[8b] water[8c] and biological fluid[8d] purification, its utility in the rapid purification of organic chemical libraries is relatively unexplored.[3,5,7] Herein we describe the development of chemically-tagged reagents for the well-known Mitsunobu reaction.[9] The artificially-introduced reagent tags are designed to be complementary to the functionality present on readily available ion exchange resins, which mediate the post-reaction sequestration of the tagged reagents and spent tagged reagent byproducts. Filtration affords purified reaction products suitable for screening or further synthetic manipulation.

The Mitsunobu reaction activates alcohols **1** for attack by a range of nucleophiles **2** to form condensation products **3** using a combination of triphenylphosphine **4** and dialkylazocarboxylate **5** reagents (Scheme 1). A disadvantage often encountered in this reaction is the difficult removal of byproducts, namely the triphenylphosphine oxide **6** and dialkyl hydrazinedicarboxylate **7**. We have designed and utilized the

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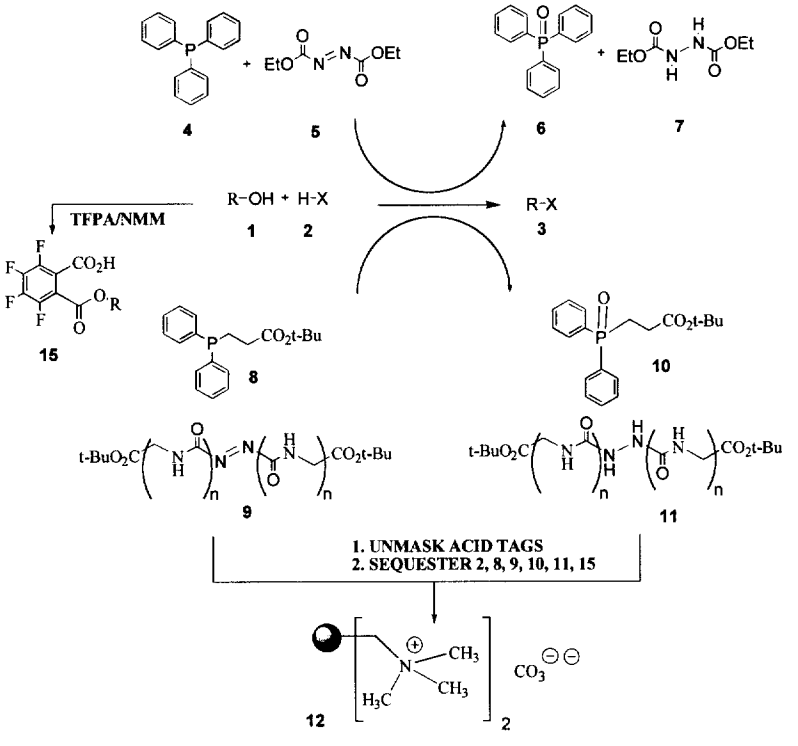
chemically-tagged bifunctional reagents **8** and **9**, which can be utilized for either manual or automated chemical library synthesis. Masked carboxylic acid tags (*t*-butyl esters) were chosen for both reagents so that upon post-reaction unmasking with trifluoroacetic acid, a singular base-functionalized ion exchange resin **12** could be used to sequester the carboxy-tagged reagents **8** and **9**, the carboxy-tagged reagent byproducts **10** and **11**, as well as any excess nucleophile **2** used to drive the solution phase reactions to completion. Purified products are easily isolated by filtration and evaporation of solvent.

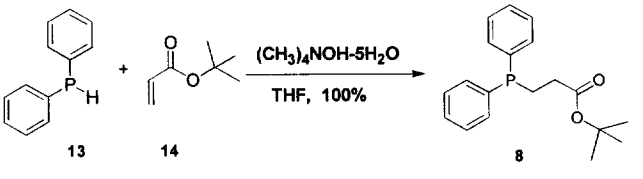
Scheme 1



Reagent Synthesis

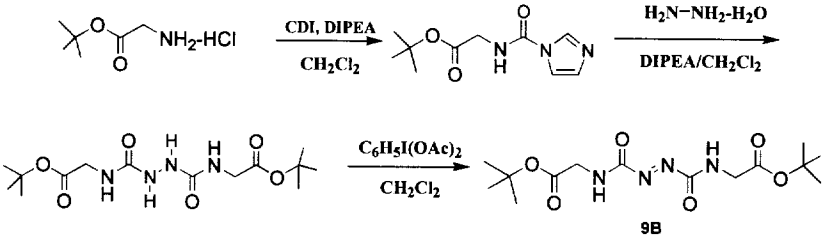
The *t*-butyl ester tagged phosphine **8** was easily prepared by conjugate addition of diphenylphosphine to *t*-butyl acrylate as shown in Scheme 2. Tagged phosphine **8** was formed in essentially quantitative yield and required no further purification.

Scheme 2



Two different azodicarboxylates were evaluated. Di-*t*-butylazodicarboxylate **9A** (n = 0) was purchased from Aldrich Chemical Company. In addition to this tagged DEAD equivalent, the tagged azodicarboxamide reagent **9B** (n = 1) was envisioned as being useful, based on the disclosure from Tsunoda et al, who reported that azodicarboxamides enable a broader range of nucleophiles to be utilized in the Mitsunobu reaction.[10] **9B** was prepared from glycine *t*-butyl ester according to the straightforward procedure illustrated in Scheme 3. Purified **9B** was obtained in 38% overall yield by recrystallization from diethyl ether/hexanes.

Scheme 3



Initial Mitsunobu Studies

The tagged reagents were next utilized in parallel array reactions involving benzylic-like alcohols or aliphatic primary alcohols and carboxylic acid or phenol nucleophiles. Table 1 illustrates the results obtained by using the tagged phosphine **8** and the tagged DEAD carboxamide equivalent **9B**. Condensations between alcohols **1A–D** and carboxylic acids **2A–C** afforded Mitsunobu reaction products in moderate to excellent mass yields (50–95%) with very good purities (75–96%) as determined by both proton NMR and HPLC analysis. The post-reaction purification protocol simply involved exposure of the reagent and reagent byproduct carboxy tags by treatment with trifluoroacetic acid, concentration, and subsequent sequestration with the quaternary ammonium carbonate resin **12**. The *meta*-chlorophenol **2D** did not afford Mitsunobu products in high purity using the combination of tagged phosphine **8** and tagged diazocarboxamide **9B**. Major contaminants in these reactions were the unreacted alcohols **1A–D**.

Replacement of **9B** by di-*t*-butyl azodicarboxylate **9A** and the addition of the alcohol-sequestering reagent TFPA (tetra-fluorophthalic anhydride)[11] during workup led to a dramatic improvement in the scope of useful nucleophiles and afforded products free from alcohol impurities. Table 1 illustrates the mass yields and purities obtained by utilizing **9A** in conjunction with the tagged phosphine **8**, and concomitant use of TFPA during the purification process. Phthalimide **2E**, *t*-butyloxycarbonyl benzenesulfonamide **2F**, and *para*-cyanophenol **2G** reacted quite well with the same training set of alcohols, affording products in moderate to excellent mass yield (13–94%) and good to excellent purities (76–98%). The additional use of TFPA allows even poorly reactive alcohol/nucleophile combinations to be used in the Mitsunobu reaction. The post-reaction

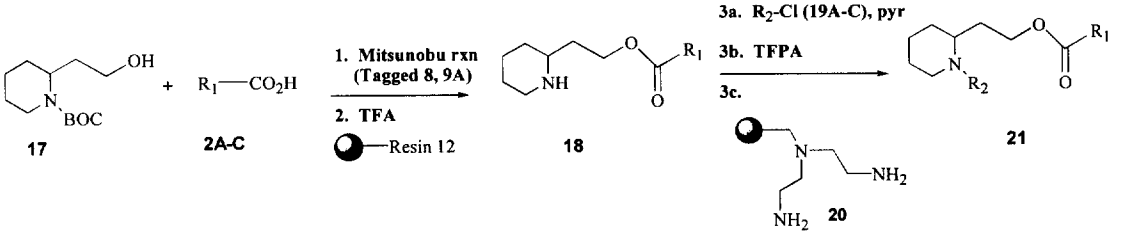
derivatized alcohols **15** (Scheme 1) and excess nucleophiles **2** are both efficiently sequestered, along with the tagged reagents, by simple incubation with the basic ion exchange resin **12**.

Table 1. Tagged DEAD reagent 9B used for 2A-D. Reagent 9A used for 2E-G. Tagged phosphine 8 used throughout.

Alcohol inputs (1)	Nucleophile inputs (2)						
	2A	2B	2C	2D	2E	2F	2G
	Yield/Purity	Yield/Purity	Yield/Purity	Yield/Purity	Yield/Purity	Yield/Purity	Yield/Purity
1A	75% 84%	92% 75%	56% 84%	33% 17%	67% 86%	55% 76%	37% 60%
1B	59% 96%	95% 95%	89% 87%	53% 41%	95% 92%	81% 93%	51% 98%
1C	50% 93%	87% 88%	82% 93%	65% 72%	28% 93%	13% 78%	42% 94%
1D	67% 92%	94% 87%	89% 96%	71% 48%	62% 85%	73% 66%	38% 95%

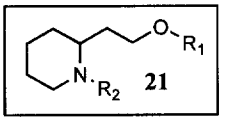
Finally, the utility of these tagged Mitsunobu reagents in multistep solution phase library synthesis was demonstrated by the derivatization of template **17** according to the three step sequence: (1) Mitsunobu reaction (2) amine deprotection and (3) amine acylation (Scheme 4). The only purification methods used in this multistep sequence were those based on sequestration of either inherently functionalized reactants or chemically-tagged reagents by complementary-functionalized resins. Steps one and two were conducted in parallel reaction chambers using the tagged Mitsunobu reagents **8** and **9A**, substrate **17**, and the three carboxylic acid inputs 2**A–C**. Unmasking of the reagent tags and concomitant removal of the N-BOC protecting groups with TFA afforded purified amines **18** after incubation with the basic sequestration resin **12** and filtration. Step three utilized a slight excess of each of three acylating agents **19A–C**. Purification and workup were affected by treatment of the reaction mixtures with TFPA (to derivatize any free alcohol impurites from Step 1) and subsequent incubation with the electrophile scavenging polyamine resin **20** for purification.[3,11] Purified products **21** were isolated by simple filtration and evaporation.

Scheme 4



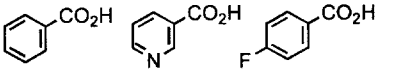
As Table 2 illustrates, good mass yields (47–60%) were obtained using the tagged Mitsunobu reagents in this three step array synthesis. Purities, as determined by proton NMR and HPLC, were exceptional (95–100%). In particular, proton NMR showed no sign of contamination of the final products **21** with any of the tagged reagents or reagent byproducts. Moreover, the concomitant use of TFPA allowed products to be obtained free from starting alcohol impurities.

Table 2

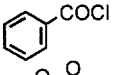
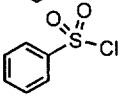
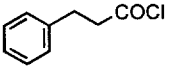


R_1 acid input

2A **2B** **2C**



R_2 acyl halide input

	Yield/Purity	Yield/Purity	Yield/Purity
19A 	48% >99%	62% 95%	59% >99%
19B 	50% >99%	47% >99%	48% >99%
19C 	60% >99%	57% >99%	56% >99%

In conclusion, conveniently tagged Mitsunobu reagents **8** and **9** have been developed for use in parallel array chemical library synthesis. Reaction purifications are easily accomplished by sequestration of carboxy-tagged reagents and reagent byproducts by a complementary base-functionalized ion exchange resin **12**. In cases involving relatively unreactive alcohol and nucleophile combinations, the additional in situ use of the sequestration-enabling-reagent tetrafluorophthalic anhydride allows for the sequestration of unreacted alcohols as their carboxy-tagged derivatives **15**. These tagged reagents are currently being used in other parallel array library syntheses.

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