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Research Letter

A Novel, One-Step Palladium and Phenylsilane Activated Amidation from Allyl Ester on Solid Support

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The direct conversion of solid-supported carboxylic acid allyl esters to carboxamides through the use of phenylsilane and catalytic $Pd(PPh_3)_4$ under mild reaction conditions is reported. The use of this methodology for the generation of a 48 compound solid-phase array is described herein.

1. Introduction

The synthesis of large combinatorial libraries of low molecular weight, drug-like molecules requires robust chemistry employing a wide variety of diversity elements on solid support. The carboxylic acid functional group has been widely used in solid-phase chemistry, especially when protected as an ester. An allyl ester is a commonly used protecting group that can be used with many acid or base-labile linkers, and is removed easily with $Pd(PPh_3)_4$ in various solvent systems with the aid of a scavenger reagent [1–3]. Phenylsilane, acting as a hydride donor, has been reported to be an excellent scavenger when used in conjunction with $Pd(PPh_3)_4$ in the removal of the allyl ester group [4]. Recently, it was also reported from our laboratory that phenylsilane could be directly used as an active amidation reagent of carboxylic acids like other coupling agents [5]. Based on this finding, a novel, one-step to convert allyl ester to amide, using palladium and phenylsilane as activating agents, has been developed on solid support (Scheme 1). In an effort to explore the generality and scope of this method, this reaction was examined using various structurally diverse carboxylic acids and amines (primary, secondary, or anilines) on solid support. A general method to protect carboxylic acids with an allyl ester group on solid support is also reported.

2. Results and Discussion

(1) Three representative allyl ester resins (Scheme 2, **4**–**6**) were initially prepared from the resin-bound N-benzoyl carboxylic acids 1–3, which could be easily prepared through standard procedures. Resin bound allylation proceeds well under optimized reaction conditions (5 equivalents of allylbromide, 5 equivalents of CsF, DMF, room temperature).

Typical Procedure

(a) The acid resin **1**–**3** (2 g, ~1.0 mmol/g loading) was swollen with ~15 mL DMF at room temperature and then 5 equiv of allybromide and 5 equiv of CsF were added into the resin mixture. The reaction was allowed to agitate overnight. After that, the reaction was washed with DMF(2x), THF(3x), DCM(4x). The resin **4**–**6** was dried under high vacuum pump. The resin was checked by TFA cleavage, and the product **7**–**9** had 90~96% of purity and 96~100% of yield.

(b) A 48-compound array was constructed from a matrix of these three R_2 allyl esters crossed with 16 R_3 amines and anilines. The process was carried out using IRORI MicroKans, which is Rf-encoded split pool synthesis technology. The reactions were performed on a 0.02 mmol scale (0.02 mmol/one microkan) in anhydrous CH_2Cl_2 at room temperature for 24 hours with 10 equivalents of amines

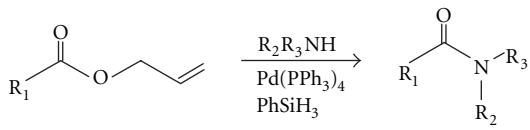
Table 1: Purity and yield data for 48-compound automation library.

Entry	Resin **4**-**5**	Amines or anilines	Product characterization (**10**)[(c)]		
			MH^+	Purity (%)	Yield (%)
1	**4**	Pyrrolidine	309.20	90	73
2	**4**	Morpholine	325.17	99	72
3	**4**	Diethylamine	311.25	27(53[(a)])	74
4	**4**	Tetrahydrofurylamine	339.24	90	68
5	**4**	N-Acetylethylenediamine	340.20	72	68
6	**4**	Phenethylamine	359.26	95	64
7	**4**	1-(3-aminopropyl)imidazole	363.30	77	65
8	**4**	4-(2-aminoethyl)morpholine	368.30	84	49
9	**4**	Tyramine	375.30	86	61
10	**4**	Cyclohexylamine	337.25	20(67[(a)])	67
11	**4**	Benzylamine	345.22	85	50
12	**4**	4-(Aminomethyl)pyridine	346.23	87	62
13	**4**	4-Bromobenzylamine	424.14	95	55
14	**4**	Aniline		Only acid	0
15	**4**	p-Anisidine		Only acid	0
16	**4**	4-Nitroaniline		Only acid	0
17	**5**	Pyrroline	315.20	86	71
18	**5**	Morpholine	331.23	94	47
19	**5**	Diethylamine	317.37	7 (14[(a)])	56
20	**5**	Tetrahydrofurylamine	345.40	97	43
21	**5**	N-Acetylethylenediamine	346.10	98	42
22	**5**	Phenethylamine	365.33	86	61
23	**5**	1-(3-Aminopropyl)imidazole	369.35	94	54
24	**5**	4-(2-Aminoethyl)morpholine	374.10	97	55
25	**5**	Tyramine	381.33	86	35
26	**5**	Cyclohexylamine	343.32	52(73[(a)])	64
27	**5**	Benzylamine	351.29	85	64
28	**5**	4-(Aminomethyl)pyridine	352.29	89	38
29	**5**	4-Bromobenzylamine	430.13	85	51
30	**5**	Aniline		Only acid	0
31	**5**	p-Anisidine		Only acid	0
32	**5**	4-Nitroaniline		Only acid	0
33	**6**	4-Nitroaniline	247.10	100	56
34	**6**	Pyrroline	263.20	97	83
35	**6**	Morpholine	249.24	37(67[(a)])	71
36	**6**	Diethylamine	277.29	99	69
37	**6**	Tetrahydrofurylamine	278.10	100	54
38	6	N-Acetylethylenediamine	297.10	98 (0[(b)])	92 (0[(b)])
39	**6**	Phenethylamine	301.26	99	91
40	**6**	1-(3-Aminopropyl)imidazole	306.10	99	80
41	**6**	4-(2-Aminoethyl)morpholine	313.10	98	58
42	**6**	Tyramine	275.32	92	56
43	**6**	Cyclohexylamine	283.26	99	72
44	**6**	Benzylamine	284.27	100	66
45	**6**	4-(Aminomethyl)pyridine	362.17	99	52

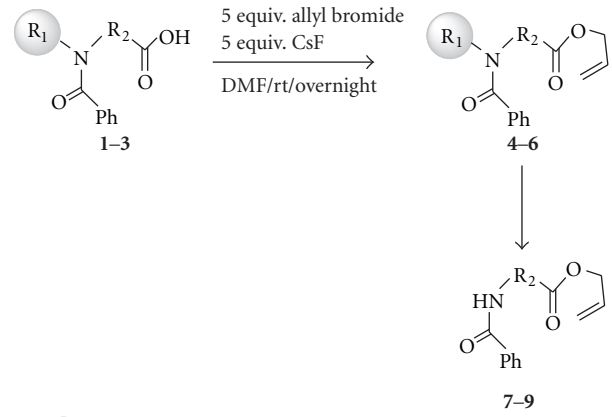
Table 1: Continued.

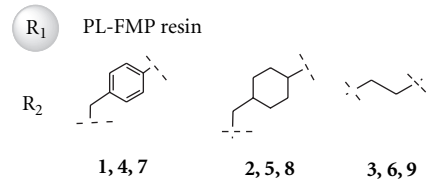
Entry	Resin **4**-**5**	Amines or anilines	Product characterization (**10**)[(c)]		
			MH^+	Purity (%)	Yield (%)
46	**6**	4-Bromobenzylamine		Only acid	0
47	**6**	Aniline		Only acid	0
48	**6**	p-Anisidine		Only acid	0

[(a)]60°C in DMF for 24 hours. [(b)]Without the addition of both $PhSiH_3$ and $Pd(Ph_3P)_4$, or one of them. [(c)]Overall isolated yield after cleavage. All products were analyzed by LC-MS and flow ^1H NMR spectroscopy.

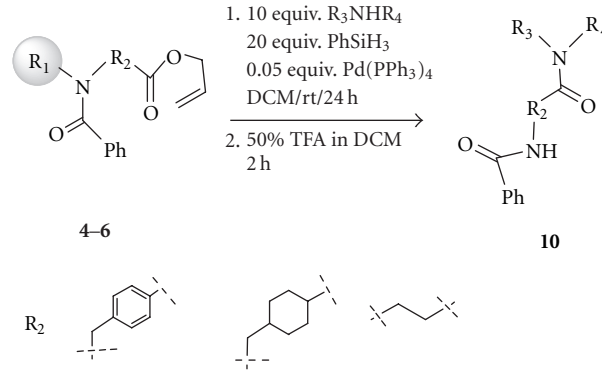


Scheme 1





Scheme 2



Scheme 3

or anilines, 20 equiv of $PhSiH_3$ and 0.05 equiv of $Pd(PPh_3)_4$. After that, all microkans were pooled together and then washed with DMF(2x), THF(3x), DCM(4x). All microkans were dried under high vacuum pump and then sorted into IRORI cleavage station. The final products **10** were cleaved into 96 well-format plate with 30% of TFA solution in DCM. The solvent was removed and the products were directly analyzed with flow NMR and LC-MS. Overall yield was calculated based on the initial loading of resins.

Following cleavage from the resin with TFA, nearly quantitative yields of the allyl ester products **7–9** (based on the initial loading of resin **1–3**) were obtained with high purity (>90%) (Scheme 2).

Using resins **4–6**, a 48 compound array was constructed from a matrix of these three R_2 allyl esters crossed with 16 R_3R_4NH amines and anilines (see Typical Procedures above). The reactions were performed on a 0.02 mmol scale in anhydrous CH_2Cl_2 at room temperature for 24 hours with 10 equivalents of amines or anilines, 20 equiv of $PhSiH_3$ and 0.05 equiv of $Pd(PPh_3)_4$. The final products **10** were obtained after cleavage from the resins. This entire process was carried out using commercially available IRORI MicroKans [6] (Scheme 3).

Solid-phase array results are provided in Table 1 below. The general reaction conditions employed worked equally well for both primary and secondary amines with the various allyl esters. Additional experiments have indicated that the best solvents for this method are DMF or NMP and the reaction could be carried out with 5 equivalents of amines and 10 equiv of $PhSiH_3$.

Direct analyses of the cleaved products (HPLC and LC/MS) indicated high purity and yields in most cases. All calculations were based on the initial loading of resin 1–3. All reactions were clean with the major side product being the unprotected carboxylic acid. With an increase in steric congestion of the amine component (entries 3, 10, 19, 26, and 35), more severe conditions were required to drive reactions to completion (i.e., higher reaction temperatures and the use of additional equivalents of amines). Reactions with anilines were disappointing with few amide products obtained and high recovery of the unprotected acids observed even under more forcing reaction conditions. No product was formed in the reaction without addition of both $PhSiH_3$ and catalytic $Pd(Ph_3P)_4$ reagents. It was shown in our controlling experiments, entry 38.

3. Conclusion

In summary, a Pd(0)/$PhSiH_3$ system has been successfully applied to convert resin-bond allyl esters to amides. The reaction can typically be carried out in a single step at room temperature. A systematic investigation of amine and aniline inputs has demonstrated that in general, primary amines and unhindered secondary amines give excellent yields of amides with high purity. Higher reaction temperatures and additional equivalents of amines can be used to push reactions to completion. This methodology has been recently used in a solid-phase sequence to prepare a 10000-compound library directed at the identification of protease inhibitors.

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