Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7649–7651

Phenylsilane as an active amidation reagent for the preparation of carboxamides and peptides

Zheming Ruan,* R. Michael Lawrence and Christopher B. Cooper

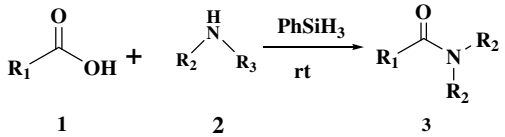
Early Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA

Received 3 July 2006; revised 2 August 2006; accepted 9 August 2006
Available online 7 September 2006

Abstract—The use of phenylsilane as a mild coupling reagent for amidation reactions is reported. Applicability to both solution- and solid-phase chemistry has been demonstrated for a variety of amines and carboxylic acids.

1. Introduction

There are multiple routes to prepare carboxamides and peptides from carboxylic acids and amines, many of which (e.g., BOP, DCC, HOBt, and PyBOP) have been used for more than 20 years.[1] In general, these agents act in situ as activating reagents and convert the carboxylic acids to more reactive intermediates. Silanes are well-recognized as good hydride donors, and as such, they are widely used.[2] They are also commonly used in silylations to form silyl ethers, aminosilanes, and especially vinylsilanes which are considered important building blocks in organic synthesis.[3] Silanes are also used in the synthesis of silicon containing polymers.[4] Phenylsilane, in particular, 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.[5] We have recently determined that phenylsilane can also act as an in situ carboxylic acid activating agent, and as such can be effectively used as a coupling reagent to prepare carboxamides and peptides (Scheme 1). In order to explore the generality and scope of this coupling reaction, a set of structurally diverse carboxylic acids and amines (primary, secondary, and anilines) was examined in a high-throughput manner in both solution and on solid-phase.



1 2 3

Scheme 1.

2. Results and discussion

The scope of this reaction was first examined with a series of diverse carboxylic acids and amines. A 77 compound array was constructed from a matrix of 7 carboxylic acids crossed with 11 amines and anilines in solution (Table 1).

The array was prepared with equimolar acids and amines (0.25 mmol scale) in anhydrous DMF at room temperature overnight.[6] An excess of $PhSiH_3$ (3 equiv)

Table 1. Acids and amines used in the study

Acid		Amine	
1a	2-Phenylpropionic acid	**2a**	Pyrrolidine
1b	(D)-(+)-2-Phenylpropionic acid	**2b**	Glycine *tert*-butyl ester
1c	Benzoic acid	**2c**	Morpholine
1d	4-Nitrobenzoic acid	**2d**	2-Phenylethylamine
1e	Pivalic acid	**2e**	Cyclohexylamine
1f	Hydrocinnamic acid	**2f**	*N*-(3-Aminopropyl)imidazole
1g	*trans*-Cinnamic acid	**2g**	Benzylamine
		2h	4-Picolylamine
		2i	Diethylamine
		2j	*N*-Propyl-cyclopropane methylamine
		2k	Aniline

* Corresponding author. Tel.: +1 609 252 3752; e-mail: zheming.ruan@bms.com

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.08.024

Table 2. Representative yields of amide **3**

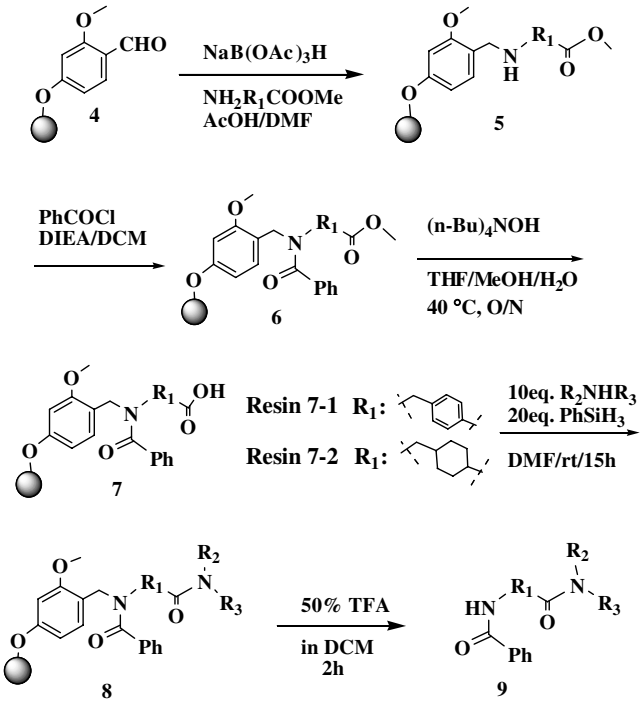
Entry	Acid	Amine	Yield (%)
1	**1a**	**2a**	95
2	**1a**	**2c**	88
3	**1a**	**2d**	88
4	**1a**	**2e**	89
5	**1a**	**2f**	94
6	**1b**	**2d**	71
7	**1b**	**2g**	86
8	**1c**	**2b**	70
9	**1c**	**2a**	76
10	**1c**	**2d**	85
11	**1c**	**2e**	98
12	**1c**	**2g**	65
13	**1c**	**2j**	0
14	**1c**	**2k**	0
15	**1d**	**2b**	77
16	**1d**	**2a**	65
17	**1d**	**2c**	89
18	**1d**	**2d**	80
19	**1d**	**2f**	95
20	**1d**	**2g**	65
21	**1d**	**2h**	40
22	**1e**	**2d**	66
23	**1e**	**2g**	76
24	**1e**	**2h**	89
25	**1f**	**2e**	71
26	**1f**	**2f**	92
27	**1f**	**2g**	62
28	**1g**	**2d**	78
29	**1g**	**2g**	88
30	**1g**	**2i**	94

was necessary to drive the coupling reaction to completion. Reaction mixtures were dried in vacuo, and purified by reverse phase preparative HPLC with micromass detection. Representative results produced by this synthesis are listed in Table 2.

In the majority of cases, reactions proceeded cleanly and the desired carboxylic amides were obtained in high yields. However, virtually no amide products were obtained with sterically-hindered amines or aniline (see entry 13 with amine **2j** and entry 14 with amine **2k**). Phenylsilane-promoted couplings did not appear to lead to any appreciable racemization as indicated by entry 7.[7]

In order to explore the extension of these coupling conditions to solid-phase, two representative acid resins (**7-1** and **7-2** in Scheme 2) were prepared from 4-formyl-3-methoxyphenoxy methyl resin **4** and amino methyl esters, (NH_2R_1COOMe) by reductive amidation, acylation, and deprotection. The acid resins were then tested with the representative amines described in Table 1. The chemistry was performed on a 0.02 mmol scale of resin in DMF at room temperature for 15 h with 10 equiv of amines and 20 equiv of $PhSiH_3$. Typical results are summarized in Table 3.

Direct analyzes of the cleaved products **9** (HPLC and LC/MS) indicated high purity and yields in most cases based on the initial acid resin loadings. The major impurity was unreacted carboxylic acid, which can be easily separated by passing crude products through SAX



Scheme 2. Solid-phase phenylsilane-mediated amidation couplings.

Table 3. Purity and yield data of amide **9**

Entry	Resin	Amine	Purity (%)	Yield (%)
31	**7-1**	**2a**	92.8	87
32	**7-1**	**2c**	97	90
33	**7-1**	**2d**	70	81
34	**7-1**	**2g**	89	84
35	**7-1**	**2i**	14	75
36	**7-1**	**2k**	0	
37	**7-2**	**2a**	86	82
38	**7-2**	**2c**	83	86
39	**7-2**	**2d**	85	75
40	**7-2**	**2g**	86	79
41	**7-2**	**2i**	0	
42	**7-2**	**2k**	0	

SPE resin.[8] Also, as observed in the solution-phase library, very few amides were obtained from sterically-hindered amines or aniline (see entries 36, 41, and 42).

In summary, an effective method for the preparation of carboxamides from carboxylic acids, amines, and phenylsilane has been established. The method may be applied for both solution and solid-phase applications. Further investigations to explore the scope and limitations of this transformation are ongoing.

References and notes

1. (a) Jones, J. *The Chemical Synthesis of Peptides*; Oxford University Press: Oxford, 1991; (b) Bodanszky, M. *Principles of Peptide Synthesis*; Springer: Berlin, 1984.
2. (a) Molander, G.; Schmitt, M. *J. Org. Chem.* **2000**, *65*, 3767–3770; (b) Lipshutz, B.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J.; Vivian, R.; Keith, J. *Tetrahedron*

2000, *56*, 2779–2788; (c) Onozawa, S.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1994**, *35*, 8177–8180.
3. (a) Onozawa, S.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1995**, *36*, 5741–5744; (b) Wang, J.; Dash, A.; Berthet, J.; Ephritikhine, M. *J. Organomet. Chem.* **2002**, *610*, 49–57; (c) Molander, G.; Schmitt, M. *J. Org. Chem.* **2000**, *65*, 3767–3770.
4. (a) Reddy, P.; Chauhan, B.; Hayashi, T.; Tanaka, M. *Chem. Lett.* **2002**, 250–251; (b) Yamashita, H.; Uchimaru, Y. *Chem. Commun.* **1999**, 1763–1764.
5. Dessolin, M.; Guillerez, M.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741–5744.
6. A representative experimental procedure is described for the reaction of (D)-(+)-2-phenylpropanoic acid with benzylamine: To a solution of 2-phenylpropanoic acid (37.6 mg, 0.25 mmol) and benzylamine (27.1 mg, 0.25 mmol) in DMF (2 mL) was added phenylsilane (92.4 uL, 0.75 mmol) slowly. The reaction mixture was stirred for 5 h at room temperature under an argon atmosphere and then the solvent was evaporated. The resulting mixture was purified preparative HPLC to afford (2*S*)-*N*-benzyl-2-phenylpropanamide (**7**) (51.4 mg, 86%) as a white solid (Table 2, entry 7).
7. Entry 7: [α] 27.2 (*c* 0.82, EtOH), lit. [α] 27.4 (*c* 1.01, EtOH).[9]
8. Lawrence, R. M.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553–557.
9. Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, 2811–2818.