ORGANIC LETTERS

2010
Vol. 12, No. 21
4716−4719

Enamides Accessed from Aminothioesters via a Pd(0)-Catalyzed Decarbonylative/β-Hydride Elimination Sequence

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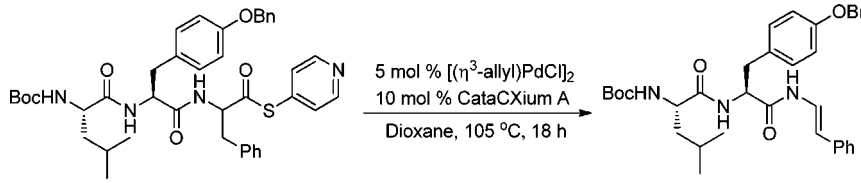
Received July 14, 2010

ABSTRACT



A facile synthesis of various enamides from aminothioesters via a palladium(0)-catalyzed decarbonylation/β-hydride elimination is reported. This protocol was applied to mercaptopyridyl C-terminal modified peptides for the generation of enamides without epimerization at stereogenic centers.

Generation of enamides has been a long-standing interest to the biological and chemical community as these motifs are contained in several bioactive natural products (Figure 1).[1] Enamides have also been used extensively as a building block for further transformations.[2] Several standard methods have been reported in the literature for the synthesis of enamides including Curtius rearrangement of α,β-unsaturated acyl azides[3] and amide Petersen olefination,[4] copper-mediated amidation of vinylic halides,[5] Horner Wittig and Wadsworth Emmons reactions,[6] and others[7] as shown in Scheme 1.

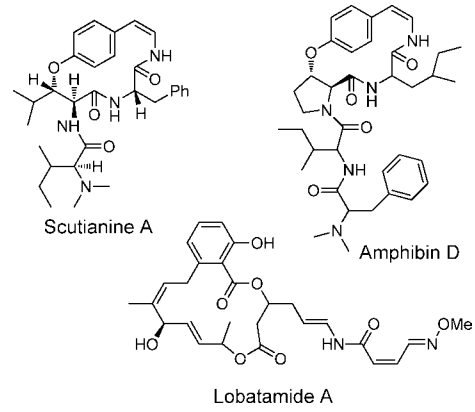
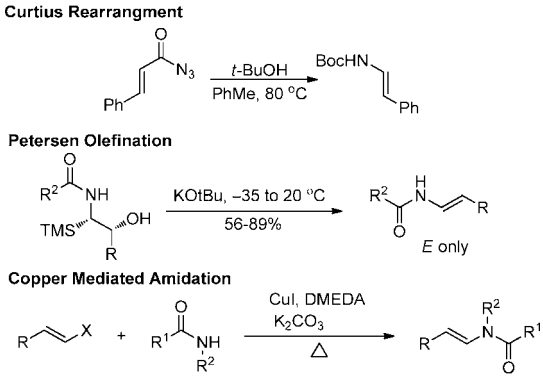


Figure 1. Natural products possessing the enamide functional unit.

(1) (a) Galinis, D.; McKee, T.; Pannell, L.; Cardellina, J.; Boyd, M. *J. Org. Chem.* **1997**, *62*, 8968. (b) Suzumura, K.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantioamodjo, R.; Suzuki, K.; Nagano, N. *Tetradron Lett.* **1997**, *38*, 7573. (c) Dekker, K.; Aiello, R.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J.; Yamuchi, Y.; Kojima, N. *J. Antiobiot.* **1998**, *51*, 14. (d) McKee, T.; Ganlanis, D.; Pannell, L.; Cardellina, J.; Laasko, J.; Ireland, C.; Murray, L.; Capon, R.; Boyd, M. *J. Org. Chem.* **1998**, *63*, 7805. (e) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antiobiot.* **1998**, *51*, 1075. (f) Kim., J.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. (g) Boyd, M.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J.; Hayakawa, Y.; Beutler, J.; McKee, T.; Bowman, B.; Bowman, E. *J. Pharmacol. Exp. Ther.* **2000**, *297*, 114. (h) Sugie, Y.; Dekker, K. A.; Hirai, H.; Ichiba, T.; Ishiguro, M.; Shiomi, Y.; Sugiura, A.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, Y. *J. Antibiot.* **2001**, *54*, 1060. (i) Gournelif, D. C.; Laskarisb, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, *14*, 75. (j) Tschesche, R.; Kauβmann, Fehlhaber, H. *Chem. Ber.* **1972**, *105*, 3094.

10.1021/ol101620r
Published on Web 09/24/2010

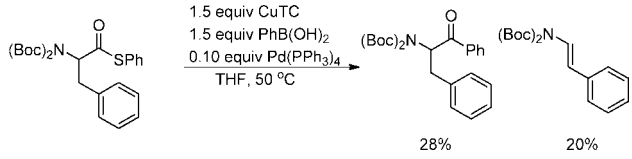
Scheme 1. Previous Enamide Syntheses



However, some of these protocols require several steps to generate the desired compounds, harsh conditions for enamide formation, or the synthesis of unstable precursors.

In 2007, Liebeskind and co-workers reported a palladium/copper facilitated cross coupling between aminothioesters and organoboronic reagents.[8] When using $Pd(PPh_3)_4$ and copper thiocarboxylate at elevated temperatures, they reported the formation of the desired cross coupled product with the enamide obtained as the byproduct in Scheme 2.

Scheme 2. Liebeskind's Previous Studies

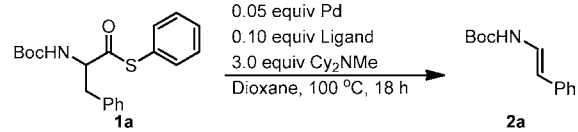


Crisp and Bubner also have reported enamide formation when attempting to cross couple aminothioesters with organotin reagents using $Pd(dppf)Cl_2$.[9] These observations led us to speculate whether the formation of enamides could be promoted by a Pd(0)-catalyzed decarbonylative/β-hydride sequence.

Herein, we report the study leading to this method for the preparation of enamides. Not only does this developed method provide easy access to substituted enamides starting from simple protected amino acid derivatives, but it also allows the introduction of the possibility of C-terminal modification of peptides.

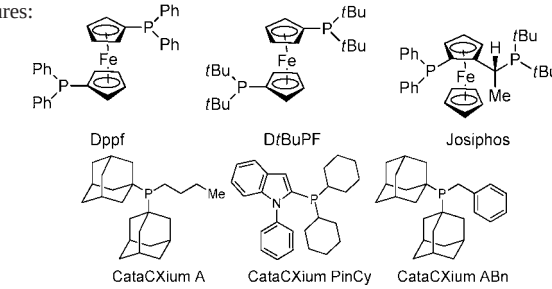
Applying the conditions developed by Liebeskind without the copper additive failed to yield enamide formation. Various solvents, bases, and temperatures were screened with these catalysts, and the reactions yielded only starting material or decomposed material. Other palladium complexes were investigated (Table 1). The allyl palladium chloride dimer and dppf (entry 3) achieved 14% isolated yield of the desired enamide product **2a**. Various other ligands, monodentate and bidentate, were screened with the same palladium(II) complex. Using CataCXium A (entry 6) provided a 70% NMR yield. After screening solvents (THF, PhMe, and dioxane) with allylpalladium chloride dimer and CataCXium A at various temperatures with various bases, using diisopropylethylamine at 100 °C in dioxane for 18 h was determined as the optimal conditions for this system.

Table 1. Initial Screening Experiments



entry	Pd source	ligand[a]	NMR yield, %
1	$PdCl_2$	PCy_3	13
2	$Pd(dba)_2$	PCy_3	0
3	$[(\eta^3\text{-allyl})PdCl]_2$	Dppf	14
4	$[(\eta^3\text{-allyl})PdCl]_2$	D*t*BuPF	28
5	$[(\eta^3\text{-allyl})PdCl]_2$	P*t*Bu_3[a]	21
6	$[(\eta^3\text{-allyl})PdCl]_2$	CataCXium A	70
7	$[(\eta^3\text{-allyl})PdCl]_2$	Josiphos	41
8	$[(\eta^3\text{-allyl})PdCl]_2$	CataCXium PinCy	29
9	$[(\eta^3\text{-allyl})PdCl]_2$	CataCXium ABn	56
10	$[(\eta^3\text{-allyl})PdCl]_2$	PCy_3[a,b]	42

[a] 0.20 equiv phosphine. [b] 3.0 equiv DIPEA instead of Cy_2NMe. [a] Ligand structures:



(2) (a) Savarin, C.; Murray, J.; Dormer, P. *Org. Lett.* **2002**, *4*, 2071. (b) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley-VCH: New York, 1999. (c) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.—Eur. J.* **2001**, *7*, 5286.

(3) (a) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185. (b) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. (c) Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649.

(4) (a) Cuevas, J. C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841. (b) Palomo, C.; Aizpurua, J. Md.; Legido, M.; Picard, J. P.; Dunogues, J.; Constantieux, T. *Tetrahedron Lett.* **1992**, *33*, 3903. (c) Furstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955.

(5) (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, *8*, 1443. (b) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333. (c) Han, C.; Shen, R.; Shun, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (d) Jiang, L.; Job, G.; Klapars, A.; Buchwald, S. *Org. Lett.* **2003**, *5*, 3667.

(6) (a) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (b) Paterson, I.; Cowden, C.; Watson, C. *Synlett* **1995**, 2009.

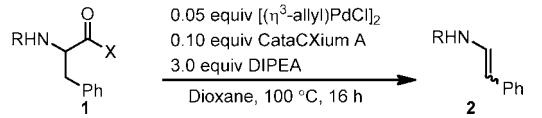
(7) (a) Gooβen, L.; Blanchot, M.; Salih, K.; Gooβen, K. *Synthesis* **2009**, 2283. (b) Gooβen, L.; Blanchot, M.; Salih, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492. (c) Couladouros, E.; Moutsos, V. *Tetrahedron Lett.* **1990**, *40*, 7027. (d) Matusmura, Y.; Ohishi, T.; Sonoda, C.; Maki, T.; Watanabe, M. *Tetrahedron* **1997**, *53*, 4579. (e) Kimber, M. *Org. Lett.* **2010**, *12*, 1128. (f) Klapars, A.; Campos, K.; Cheng-yi, C.; Volante, R. *Org. Lett.* **2005**, *7*, 1185.

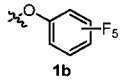
(8) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. *J. Am. Chem. Soc.* **2007**, *129*, 1132.

(9) Crisp, G. T.; Bubner, T. P. *Synth. Commun.* **1990**, *20*, 1665.

Various leaving groups were also screened as shown in Table 2. When subjected to the palladium decarbonylative

Table 2. Varying the Nature of the Leaving Group



entry	R	X	isolated yield
1	Boc	 **1a**	51%
2	Cbz	 **1b**	0%
3	Cbz	 **1c**	73% (59%, 14%)[a]
4	Boc	 **1d**	77% (70%, 7%)[a,b]

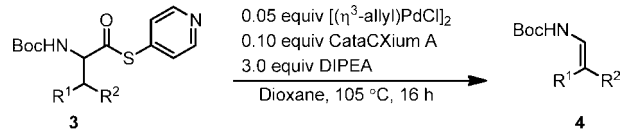
[a] Isolated yields of the trans- and cis-isomers. [b] The cis-isomer was inseparable from the phosphine ligand on silica flash chromatography.

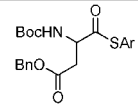
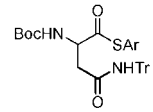
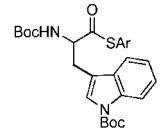
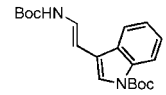
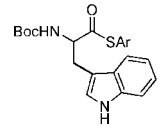
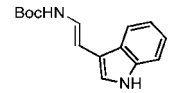
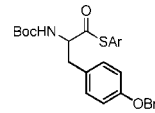
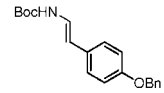
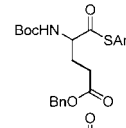
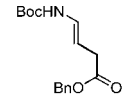
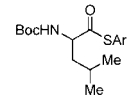
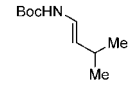
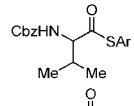
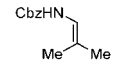
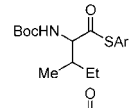
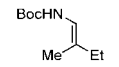
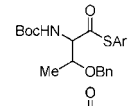
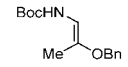
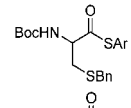
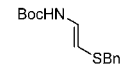
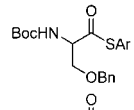
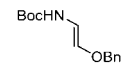
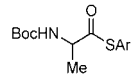
conditions, 2-mercaptopyridine **1c** (entry 3) and 4-mercaptopyridine **1d** (entry 4) showed complete consumption of starting material after 18 h and yielded the enamide product in good yields. 4-Mercaptopyridine aminothioester **1d** provided a more stable starting material, and when subjected to the palladium decarbonylative conditions, a good 77% isolated yield of **2** was obtained.

Using these optimized conditions, other aminothioesters were then investigated, the results of which are depicted in Table 3. The palladium decarbonylative method was applied to a number of aminothioesters that contain aromatic chains, heterogroups, and alkyl groups, furnishing the enamides in moderate to good yields. In most cases, the trans-isomer was isolated as the major product except in the case of entries 1 and 2, which favored the cis-product. In these cases, the cis isomers were preferred presumably due to product stabilization gained from hydrogen bonding between the amide and the carbonyl substituent. The aminothioesters **3c**−**e** (entries 3−5), in which R^1 or R^2 was aromatic, provided product yields in the range of 74−77%. With R^1 or R^2 as an alkyl chain, the yields dropped slightly to 51−64% with the formation of the more highly substituted enamides furnishing the better isolated yields, while the least substituted example (entry 13) provided a 29% isolated yield of the vinyl amide. Interestingly, in the case of the glutamic thioester (entry 6), when presented with the possibility of double bond migration in order to be in conjugation with the carboxylate group, the reaction yielded only the desired enamide product.

This method was also applied to small peptide chains with an aminothioester at the C-terminal end, providing 58−72% yields of the desired enamides **5**−**7** depicted in Figure 2. The method also works with nonstandard amino acids, such as one containing a 2,2,2-trifluoroethyl side-chain, yielding the volatile enamide **8** in a 21% yield.

Table 3. Enamide Synthesis from Amino Acids



entry	aminothioester[a]	enamide product		yield[b]
1			**4a**	67% (37:63)
2			**4b**	64% (0:100)
3			**4c**	74% (90:10)
4			**4d**	76% (90:10)
5			**4e**	76% (90:10)
6			**4f**	51% (60:40)
7			**4g**	51% (75:25)
8			**4h**	64%
9			**4i**	61% (86:14)
10			**4j**	62% (90:10)
11			**4k**	47% (72:28)
12			**4l**	60% (70:30)
13			**4m**	29%

[a] SAr = 4-mercaptopyridine. [b] All trans:cis ratios in parentheses were determined by isolated yield of each by flash chromatography except for isoleucine and unprotected tryptophan. For isoleucine and unprotected tryptophan derivatives, the trans/cis-isomers were inseparable.

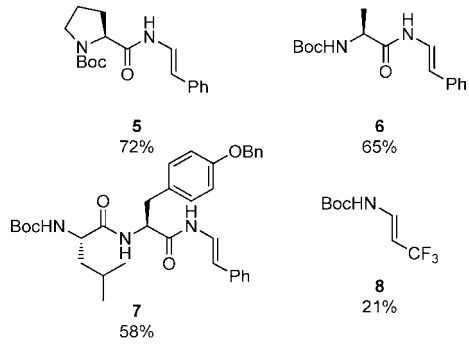


Figure 2. Peptide and unconventional amino acid functionalization.

In summary, we have demonstrated a facile way of synthesizing enamides from aminothioesters via a palladium-catalyzed decarbonylative/β-hydride elimination process in moderate to good yields. This method is applicable to various aminothioesters and can potentially be further applied toward the synthesis of various bioactive natural products that exhibit this motif.

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, the Danish Council for Independent Research/Natural Sciences, the Lundbeck Foundation, the Carlsberg Foundation, and Aarthus University. D.H. thanks the Gobierno de España (MICINN) for a posdoctoral contract (Programa Nacional de Movilidad de Recursos Humanos del Plan nacional de I+D+I 2009−2011). We also thank Solvias for a generous gift of ligands.

Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101620R