ORGANIC LETTERS

2013
Vol. 15, No. 7
1626–1629

Synthesis of Functionalized Allenamides from Ynamides by Enolate Claisen Rearrangement

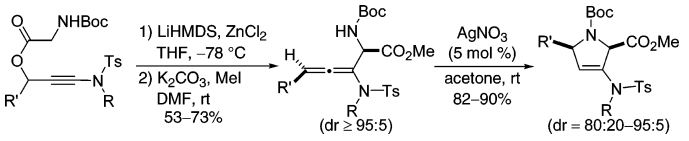
Julien Brioche, Christophe Meyer,* and Janine Cossy*

Laboratoire de Chimie Organique, ESPCI Paris Tech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

christophe.meyer@espci.fr; janine.cossy@espci.fr

Received February 11, 2013

ABSTRACT



The Claisen rearrangement of *N*-Boc glycinates derived from ynamido-alcohols affords an efficient and stereoselective access to highly functionalized allenamides. These compounds undergo silver-catalyzed cyclization to 3-pyrrolines which are useful precursors for the synthesis of substituted pyrrolidines.

Over the past decade, the chemistry of allenamides has elicited considerable interest.[1] These compounds, which are more stable than allenamines, have emerged as useful building blocks in a wide variety of transformations cleverly exploiting their greater nucleophilic character compared to nonheterosubstituted allenes and their ability to introduce valuable nitrogen-based functionalities into the resulting products.[1,2] Several methods have been developed for the synthesis of allenamides (Scheme 1) and the most popular route involves the base-catalyzed isomerization of *N*-propargyl amides **A** which only affords terminal allenamides (Scheme 1, path a).[3] Allenamides have been prepared from other nitrogen-containing precursors by β-elimination of enol triflates **B** (Scheme 1, path b)[4] or reaction of metalated chiral *N*-propargyl oxazolidinones **C** with aldehydes (Scheme 1, path c).[5] Alternatively, the nitrogen atom can be introduced by intramolecular addition to a σ-allenylPd(II) complex generated from an appropriate propargylic nucleofuge in compounds **D** (Scheme 1, path d)[6] or by copper-catalyzed cross-coupling between an amide and an allenyl halide **E** (Scheme 1, path e).[7] Another strategy involves the [3,3]-sigmatropic rearrangement of a propargyl alcohol derivative. This transformation was initially reported for propargyl imidates,[8a] propargyloxy-oxazoles,[8b] and purines,[8c] with a limited substrate scope. Recently *N*-phosphoryl allenamides have been synthesized by

(1) For a review, see: Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773–782.

(2) For selected recent contributions, see: (a) Braun, M.-G.; Katcher, M. H.; Doyle, A. G. *Chem. Sci.* **2013**, *4*, 1216–1220. (b) Hayashi, R.; Ma, Z.-X.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 252–255. (c) Li, X.-X.; Zhu, L.-L.; Zhou, W.; Chen, Z. *Org. Lett.* **2012**, *14*, 436–439. (d) Singh, S.; Elsegood, M. R. J.; Kimber, M. C. *Synlett* **2012**, 565–568. (e) Briggini, G.; Borsini, E.; Fasana, A.; Poli, G.; Liron, F. *Eur. J. Org. Chem.* **2012**, 3617–3624. (f) Suárez-Pantiga, S.; Hernández-Díaz, C.; Piedrafita, M.; Rubio, E.; González, J. M. *Adv. Synth. Catal.* **2012**, *354*, 1651–1657. (g) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1658–1664. (h) Wu, Y.-K.; Niu, T.; West, F. G. *Chem. Commun.* **2012**, *48*, 9186–9188. (i) Francos, J.; Grande-Carmona, F.; Faustino, H.; Iglesias-Sigüenza, J.; Díez, E.; Alonso, I.; Fernández, R.; Lassaletta, J. M.; López, F.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 14322–14325. (j) Suárez-Pantiga, S.; Hernández-Díaz, C.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11552–11555. (k) Ma, Z.-X.; He, S.; Song, W.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 5736–5739.

(3) Wie, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459–466 and references therein.

(4) Farina, V.; Kant, J. *Tetrahedron Lett.* **1992**, *33*, 3559–3562.

(5) (a) Gaul, C.; Seebach, D. *Helv. Chem. Acta* **2002**, *85*, 963–978. (b) Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2004**, *69*, 105–111. (c) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 8628–8630.

(6) Kimura, M.; Wakamiya, Y.; Horino, Y.; Tamaru, Y. *Tetrahedron Lett.* **1997**, *38*, 3963–3966.

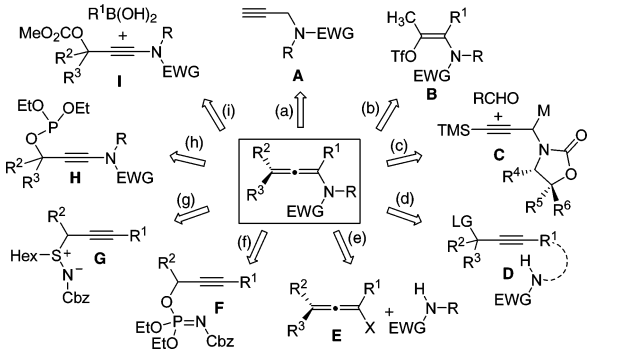
(7) (a) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117–2120. (b) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081–3084. (c) Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E. *Org. Lett.* **2009**, *11*, 3814–3817.

(8) (a) Overman, L. E.; Marlowe, C. K.; Clizbe, L. A. *Tetrahedron Lett.* **1979**, *7*, 599–600. (b) Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399–406. (c) Ranganathan, D.; Rathi, R.; Kevasan, K.; Singh, P. W. *Tetrahedron* **1986**, *42*, 4873–4878.

10.1021/ol400402n © 2013 American Chemical Society
Published on Web 03/15/2013

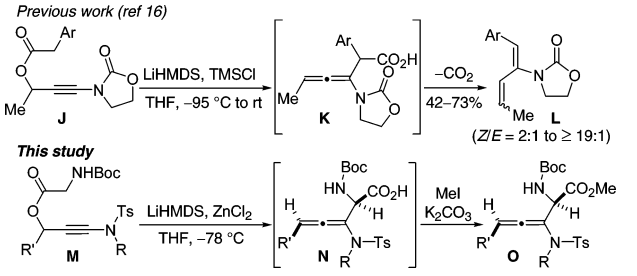
Pd(II)-catalyzed rearrangement of propargyl phosphorimidates **F** (Scheme 1, path f).[9] A complementary strategy relies on the [2,3]-sigmatropic rearrangement of propargyl sulfimides **G** leading to *N*-allenylsulfenimides (Scheme 1, path g).[10] Another recently investigated class of precursors are ynamides[11] possessing a propargylic alcohol (hereafter referred to as "ynamido-alcohols"), as illustrated with the [2,3]-sigmatropic rearrangement of phosphites **H** leading to α-aminoallenylphosphonates (Scheme 1, path h)[12] and the Pd(0)-catalyzed coupling of propargylic carbonates **I** with arylboronic acids (Scheme 1, path i).[13] However, the preparation of enantiomerically enriched functionalized allenamides with respect to axial chirality has only been achieved by route (c) relying on a chiral auxiliary,[5] route (e) using enantioenriched allenyl halides whose preparation is not trivial,[7b] and routes (f) and (g) by chirality transfer.[9,10]

Scheme 1. Synthetic Routes toward Allenamides



Despite the synthetic potential of Claisen rearrangements involving derivatives of propargyl alcohols as a route to allenes,[14] the possibility to access allenamides by a [3,3]-sigmatropic rearrangement involving ynamido-alcohol derivatives has not been demonstrated yet.[15] Recently, Carbery and Heffernan reported that an Ireland−Claisen rearrangement applied to arylacetates **J** did not lead to the expected allenamide carboxylic acids **K** because these compounds underwent spontaneous decarboxylative rearrangement leading to aminodienes **L**.[16] This work prompted us to disclose our results, and we report herein the first synthesis of highly functionalized allenamides **O** using the ester-enolate Claisen rearrangement of glycinates[17] **M** derived from *N*-sulfonyl ynamido-alcohols as well as their use for the synthesis of substituted pyrrolidines (Scheme 2).

Scheme 2. Claisen Rearrangement of Ynamido-Alcohol Derivatives



Propargylic glycinate **2a** was selected as the test substrate and was readily prepared by copper-catalyzed cross-coupling between bromoalkyne **1a**, derived from but-3-yn-2-ol, and *N*-benzyl sulfonamide.[18] As reported recently,[12] this coupling reaction could be carried out with the free alcohol, but to avoid long reactions times and obtain satisfactory yields of the coupling products in all the investigated cases, we found that a 3-fold increase of the copper salt and ligand loadings was beneficial. Subsequent esterification of the intermediate ynamido-alcohol with *N*-Boc glycine provided glycinate **2a** (63%, two steps from **1a**). The chelated α-amino zinc enolate **P** was generated from glycinate **2a** by treatment with LiHMDS (THF, −78 °C) followed by the addition of $ZnCl_2$.[17b,c] Subsequent enolate-Claisen rearrangement proceeded smoothly (−78 °C, 2 h) and led to the corresponding stable carboxylic acid **3a** which did not undergo decarboxylation, by contrast with the behavior of compounds **J**.[19] Carboxylic acid **3a** was converted to the corresponding methyl ester (MeI, K_2CO_3, DMF, rt) to afford allenamide **4a**, but the diastereoselectivity of the rearrangement was difficult to evaluate due to the presence of rotamers (Boc group). Cyclization of the crude allenamide **4a** could be accomplished under remarkably mild conditions by treatment

(9) Danowitz, A. M.; Taylor, C. E.; Shrikian, T. M.; Mapp, A. K. *Org. Lett.* **2010**, *12*, 2574–2577.

(10) (a) Armstrong, A.; Cooke, R. S.; Shanahan, S. E. *Org. Biomol. Chem.* **2003**, *1*, 3142–3143. (b) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547–1550.

(11) For reviews on ynamides, see: (a) DeKorver, K. A; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064–5106. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840–2859.

(12) Gomes, F.; Fadel, A.; Rabasso, N. *J. Org. Chem.* **2012**, *77*, 5439–5444.

(13) Cao, J.; Kong, Y.; Deng, Y.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Biomol. Chem.* **2012**, *10*, 9556–9561.

(14) (a) *The Claisen Rearrangement. Methods and Applications*; Nubbenmeyer, U., Hiersemann, M., Eds.; Wiley-VCH: Wienheim, 2007. (b) For a recent review, see: Trejedor, D.; Méndez-Abt, G.; Cotos, L.; Garcķa-Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458–471.

(15) For sigmatropic rearrangements of the related enamido allylic alcohols, see: (a) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111–1114. (b) Barbazanges, M.; Meyer, C.; Cossy, J.; Turner, P. *Chem.—Eur. J.* **2011**, *17*, 4480–4495.

(16) Heffernan, S. J.; Carbery, D. R. *Tetrahedron Lett.* **2012**, *53*, 5180–5182. Rearrangement of a propionate derived from an ynamido-alcohol also led to an aminodiene instead of an allenamide.

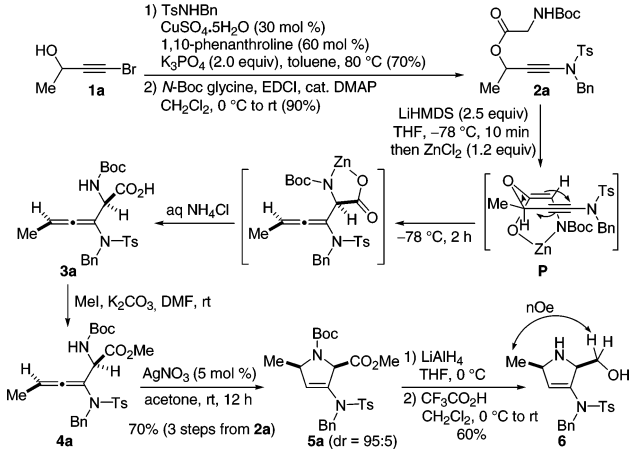
(17) (a) Castelhano, A. L.; Horne, S.; Taylor, G. J.; Billedeau, R.; Krantz, A. *Tetrahedron* **1988**, *44*, 5451–5466. (b) Kazmaier, U.; Görbitz, C. H. *Synthesis* **1996**, 1489–1493. (c) Zumpe, F. L.; Kazmaier, U. *Synlett* **1998**, 434–436. (d) Mitasev, B.; Brummond, K. M. *Synlett* **2006**, 3100–3104.

(18) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154.

(19) The different reactivity seems to be due to the nature of the electron-withdrawing group on the nitrogen atom since the Ireland−Claisen rearrangement of an arylacetate derived from a *N*-tosyl ynamido-alcohol was not followed by decarboxylation; see Supporting Information for a comparison of the reactivity.

with $AgNO_3$ (5 mol %) (acetone, rt)[20] to afford the corresponding 3-pyrroline **5a** which, as indicated by analysis of its ^1H NMR spectrum recorded at 395 K, was obtained with high diastereoselectivity (dr = 95:5) and isolated in excellent overall yield (70%, three steps from glycinate **2a**). After reduction of the ester moiety and cleavage of the Boc group, the 2,5-*cis* relative configuration of pyrroline **6** was established by NMR (NOESY). The observed stereochemical outcome was consistent with a chairlike transition state for the [3,3]-sigmatropic rearrangement of the zinc enolate **P** in which the methyl substituent preferentially occupies a pseudoequatorial position (Scheme 3).[17b−d]

Scheme 3. Preliminary Results with Glycinate **2a**



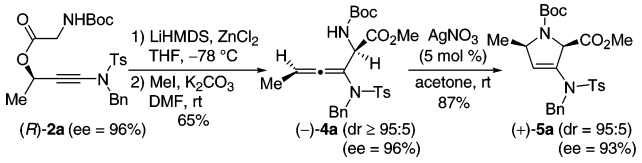
The presence of the nitrogen substituent on the alkyne had no adverse effect on the stereochemical outcome of the [3,3]-sigmatropic Claisen rearrangement by contrast with previous observations with derivatives of the related enamido allylic alcohols.[15] Due the high diastereoselectivity observed in the rearrangement of **2a**, the absolute chirality transfer was evaluated with glycinate (*R*)-**2a** (ee = 96%). The enolate-Claisen rearrangement of this latter substrate led to the enantioenriched allenamide **4a** whose optical purity confirmed that complete chirality transfer took place, as previously observed with nonheterosubstituted alkynes.[17] Subsequent silver-catalyzed cyclization also proceeded with chirality transfer though a slight erosion of the measured optical purity (ee = 93%) was observed for the corresponding 3-pyrroline **5a** (Scheme 4).[21]

The scope of the enolate-Claisen rearrangement was explored with a variety of substituted ynamido-propargylic glycinates **2b**−**i**, and the corresponding allenamides **4b**−**i** were isolated in satisfactory overall yields (53−73%, two steps from **2b**−**i**). For glycinates possessing a *N*-benzyl *N*-sulfonylamino group on the alkyne, the substituent at the propargylic position could be a benzyloxymethyl group (R′ = CH_2OBn) or an isopropyl group (R′ = *i*-Pr) and

(20) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855–3858.

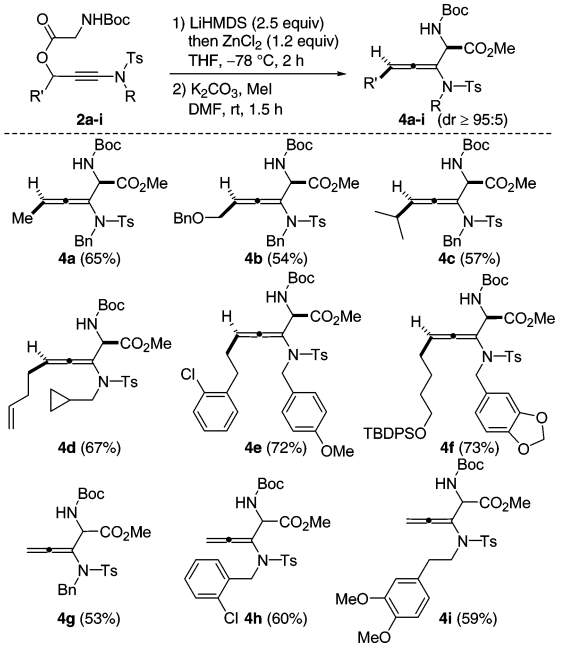
(21) This difference may be due to the presence of the 2,5-*trans*-diastereomer of pyrroline **5a** which is at the limit of detection by ^1H NMR spectroscopy (dr = 95:5).

Scheme 4. Chirality Transfer in the Rearrangement of **2a**



allenamides **4b** (54%) or **4c** (57%), respectively, were isolated in overall yields comparable to the one obtained for **4a** (65%). The substituents were then varied at the propargylic position and at the nitrogen atom to provide functionalized allenamides **4d**−**f** in good overall yields (67−73%) (Scheme 5).

Scheme 5. Scope of the [3,3]-Claisen Rearrangement



We also checked that glycinates **2g**−**i**, derived from primary ynamido-alcohols, were viable substrates that led to the corresponding terminal allenamides **4g**−**i** in similar yields (53−60%) without competing deprotonation at the unsubstituted propargylic position (R′ = H) (Scheme 5).

The cyclization of α-amino allenes to 3-pyrrolines can be catalyzed by $AgNO_3$[20] or $AgBF_4$.[22] When the nitrogen

(22) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand. B* **1979**, *33*, 309–310.

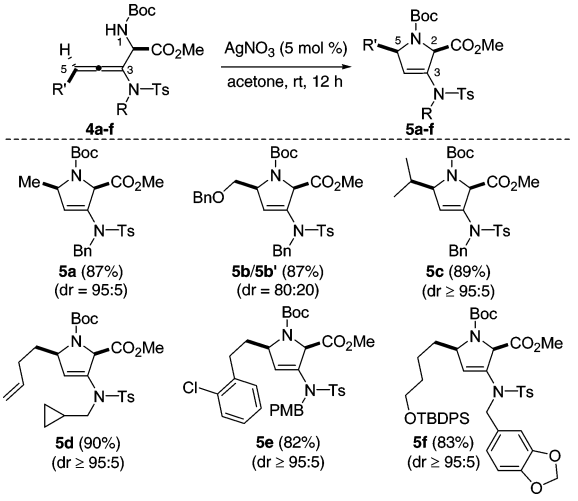
(23) (a) Billet, M.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2002**, *43*, 1453–1456. (b) Scherle, K.; Vahle, R.; Stechan, E. *Eur. J. Org. Chem.* **1998**, 509–514.

(24) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253–4256.

(25) For the cyclization of *N*-sulfonyl α-amino allenes, see: (a) Okala Amombo, M.; Hausherr, A.; Reissing, H.-U. *Synlett* **1999**, 1871–1874. (b) Ohni, H.; Toda, A.; Miwa, Y.; Taga, T.; Oswa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992–2993. (c) Cai, S.; Gorityala, B. K.; Ma, J.; Leow, M. L.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 1072–1075.

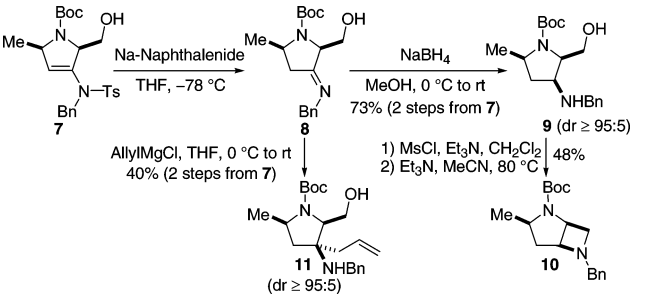
atom is substituted by an electron-withdrawing carbonyl group, $AgBF_4$ has often been used in large if not stoichiometric quantities and the cyclization worked well with terminal allenes;[23] otherwise side reactions were also observed.[17d,24,25] Although gold-catalyzed cyclizations have also been developed,[26,27] the mild conditions observed for the silver-catalyzed cyclization of *N*-Boc α-amino allenamide **4a** to **5a** were noteworthy and thus applied to the other allenamides **4b**–**f**. In the case of allenamide **4b**, substituted by a benzyloxymethyl group at C5, a 80:20 mixture of diastereomeric pyrrolines **5b**/**5b′** was obtained. In the particular case of **4b**, anchimeric assistance by the oxygen atom of the benzyl ether may partially occur leading to the opposite configuration at C5 after intramolecular nucleophilic attack of the nitrogen atom. The other 2,5-disubstituted 3-pyrrolines **5c**–**f** were obtained in excellent yields (82–90%) and with high diastereoselectivities (dr ≥95:5) (Scheme 6).

Scheme 6. Silver-Catalyzed Cyclization of Allenamides **4a**–**f**



To highlight the interest of the Claisen rearrangement of glycinates derived from ynamido-alcohols and the subsequent silver-catalyzed cyclization, we briefly examined its application to the preparation of substituted pyrrolidines. One important issue was cleavage of the tosyl substituent on the nitrogen atom of the enamide moiety. As illustrated for pyrroline **7** (generated from **5a** by reduction with $LiAlH_4$), this operation could be cleanly accomplished by treatment with sodium naphthalenide (THF, −78 °C)[28] and

Scheme 7. Synthesis of Substituted Pyrrolidines



was accompanied by isomerization to the corresponding *N*-benzyl ketimine **8** which was not purified. Subsequent reduction with $NaBH_4$ led to the 2,3,5-*cis*-trisubstituted pyrrolidine **9** (73%, two steps from **7**) with high diastereoselectivity (dr ≥95:5). By intramolecular nucleophilic substitution of the mesylate derived from the primary alcohol, compound **9** was converted to the substituted 2,6-diazabicyclo[3.2.0]heptane **10** (48%), a scaffold of interest in medicinal chemistry.[29] The addition of allylmagnesium chloride to ketimine **8** also proceeded with high diastereoselectivity (dr ≥95:5) and provided the tetrasubstituted pyrrolidine **11** possessing a quaternary stereocenter in 40% yield (unoptimized, two steps from **7**) (Scheme 7).

In conclusion, we have reported that the Claisen rearrangement of *N*-Boc glycinates derived from ynamido-alcohols offers an efficient and stereoselective access to functionalized allenamides. These compounds underwent silver-catalyzed cyclization to 3-pyrrolines which are useful building blocks for the synthesis of substituted pyrrolidines. Further work is in progress to expand the scope of sigmatropic rearrangements involving ynamido-alcohol derivatives.

Acknowledgment. The authors thank the ANR (DYNAMITE ANR-2010-BLAN-704 project) for financial support.

Note Added after ASAP Publication. The uncorrected version of this paper was published ASAP on March 15, 2013 the corrected version reposted later on March 15, 2013.

Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) For a review, see: Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009.

(27) The gold-catalyzed cyclization of allenamides bearing a remote hydroxy group leads to dihydrofurans bearing a *N*,*O*-acetal; see: Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658–8660.

(28) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A. J.; Bank, S.; Closson, W. D.; Wriede, P. A. *J. Am. Chem. Soc.* **1967**, *20*, 5311–5312.

(29) (a) Basha, A.; Bunnelle, W. H.; Dart, M. J.; Gallagher, M. E.; Ji, J.; Li, T.; Pace, J. M.; Ryther, K. B.; Tietje, K. R.; Mortell, K. H.; Nersesian, D. L.; Schrimpf, M. R. U.S. Patent 2005/101602 A1, May 12,

The authors declare no competing financial interest.