ORGANIC LETTERS

2011
Vol. 13, No. 16
4371–4373

Enantiospecific Synthesis of Pyridinones as Versatile Intermediates toward Asymmetric Piperidines

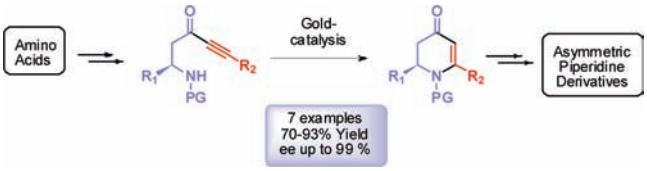
Nicolas Gouault,* Myriam Le Roch, Adèle Cheignon, Philippe Uriac, and Michèle David

Equipe Produits Naturels, Synthèse et Chimie Médicinale, UMR 6226 Sciences Chimiques de Rennes, Université de Rennes 1, 2 Avenue du Pr Léon Bernard 35043 Rennes Cedex, France

nicolas.gouault@univ-rennes1.fr

Received June 24, 2011

ABSTRACT



The enantiospecific syntheses of pyridinones from amino acids via a gold-catalyzed strategy are reported. Excellent stereocontrol was observed during the cyclization. This approach provides a straightforward tool for further synthetic applications toward piperidines.

The piperidine ring is an important structural pattern present in natural and/or synthetic products that display a broad range of biological activities.[1] Therefore, much effort has been devoted to the development of new approaches for its preparation.[2] The use of pyridinones (2,3-dihydropyridin-4(1*H*)-ones) as versatile intermediates for piperidine synthesis synthesis has attracted significant attention.[3] Many synthetic methods are reported in the literature to obtain asymmetric pyridinones including the hetero-Diels–Alder reaction, the nucleophilic addition to pyridinium salts utilizing chiral auxiliaries or chiral catalysts.[3,4] The search for more efficient, convenient, functional groups that are compatible and highly stereoselective alternative synthetic routes is of interest. Thus two approaches were recently developed from amino acids using amino ynone[5] or diazoketone[6] intermediates (Scheme 1).

The amino ynone strategy developed by Georg[5a] (Scheme 1a) involves the *in situ* deprotection of the amine function to permit cyclization by Michael addition. However in some instances partial racemization of the reaction products was observed during these reactions as pointed out by the authors.[6]

Previously we have reported a gold-catalyzed approach for the synthesis of pyrrolidinones from amino ynones. In some instances, however, moderate stereocontrol during

(1) For reviews, see: Struntz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, p 89. (b) Schneider, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, p 155.

(2) Synthesis of piperidines. Reviews: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (f) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.

(3) For reviews, see: (a) Comins, D. L.; Joseph, S. P. *Adv. Nitrogen Heterocycl.* **1996**, *2*, 251. (b) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870. (c) Comins, D. L.; O'Connor, S.; Al-awar, R. S. In *Comprehensive Heterocyclic Chemistry III*; Alan, R. K., Christopher, A. R., Eric, F. V. S., Richard, J. K. T., Eds.; Elsevier: Oxford, 2008; p 41.

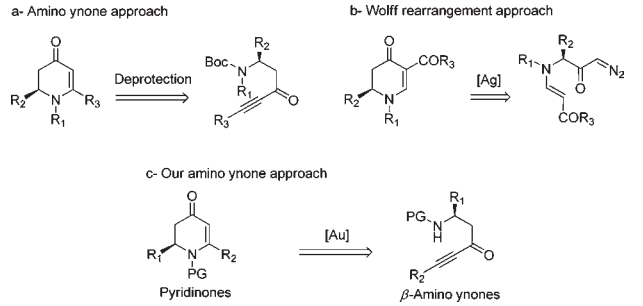
(4) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (d) Kobayashi, S.; Kusakabe, K.-I.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (e) Yao, S.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem.—Eur. J.* **2000**, *6*, 2435. (f) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (g) Mancheno, O. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. (h) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803. (i) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (j) Keller Friedman, R.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775. (k) Stoye, A. S.; Quandt, G.; Brunnhöfer, B.; Kapatsina, E.; Baron, J.; Fischer, A.; Weymann, M.; Kunz, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2228.

(5) (a) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702. (b) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793. (c) Acharya, H. P.; Clive, D. L. J. *J. Org. Chem.* **2010**, *75*, 5223.

(6) (a) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512. (b) Seki, H.; Georg, G. I. *Org. Lett.* **2011**, *13*, 2147.

10.1021/ol201698m
Published on Web 07/26/2011

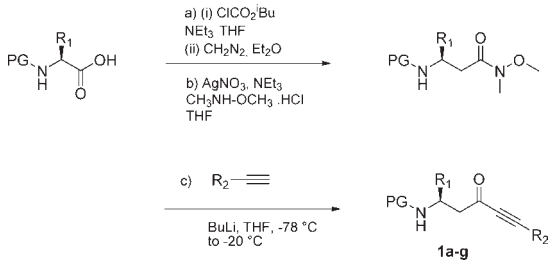
Scheme 1. Previously Reported Approaches for the Synthesis of Pyridinones from Amino Acids and Our Work



these reactions was observed.[7] In this paper we reported the cyclization of *N*-protected *β*-amino ynones into pyridinones under mild conditions. The use of a gold catalyst,[8] acting as a soft Lewis acid, allows cyclization to proceed through a triple bond electrophilic activation pathway and subsequent nucleophilic attack of *N*-protected amines. Thus, our approach is revealed to be complementary to the Georg approach since *N*-protected compounds are obtained which may be useful for further transformations. Moreover, we illustrate the synthetic utility of such compounds for the synthesis of asymmetric polysubstituted piperidines.

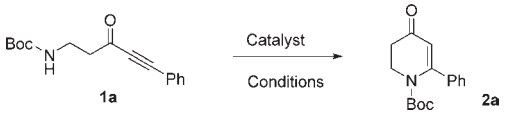
Initially, a series of *β*-amino ynones derivatives **1a**–**g** were easily prepared from commercially available amino acids *via* Arndt–Eistert homologation,[9] Weinreb amide formation, and subsequent addition of various lithium acetylides (Scheme 2). Thus, amino ynones **1a**–**g** could be produced in two steps with moderate to excellent overall yields (50–97%) from the corresponding enantiopure L-amino acids. Data were reported in the Supporting Information.

Scheme 2. Synthesis of *β*-Amino Ynones **1a**–**g**



To optimize the cyclization reaction conditions, various gold sources, the presence or absence of cocatalyst, and different solvents were evaluated. The results are reported in Table 1. We performed a catalyst screening to optimize the cyclization conditions (Table 1). Thus, reactions were conveniently performed under an inert atmosphere with the substrate **1** and a variety of gold catalysts. We found that the use of PPh_3AuCl in the presence of a silver salt in dichloroethane (DCE) at room temperature afforded in 0.5 h the desired product **2a** in good yield (entry 5) whereas ring closure was not efficient in the presence of AuCl or $AuCl_3$ (entries 1–2).

Table 1. Optimization Studies



entry	catalysts (mol %)	conditions	yield (%)[a]
1	AuCl (5)	THF, rt, 24 h	<20
2	$AuCl_3$ (5)	THF, rt, 24 h	<20
3	PPh_3AuCl (10)/$AgSbF_6$ (30)	THF, rt, 5 h	84
4	PPh_3AuCl (10)/$AgSbF_6$ (30)	THF, 60 °C, 1 h	82
5	PPh_3AuCl (10)/$AgSbF_6$ (30)	DCE, rt, 0.5 h	85
6	PPh_3AuCl (5)/$AgSbF_6$ (5)	DCE, rt, 1 h	85
7	PPh_3AuCl (5)	DCE, rt, 1 h	nr[b]
8	$AgSbF_6$ (5)	DCE, rt, 1 h	nr[b]

[a] Isolated yield. [b] No reaction.

A complementary study on solvents prompted us to choose DCE that proved more efficient than THF (entries 3–4). A lower catalyst loading (5 mol %) did not affect the yield but delayed the accomplishment of this reaction (entry 6). As expected, no reaction was observed when we used a [Ag] or [Au] catalyst independently (entries 7 and 8). These results emphasize the importance of the anion exchange to obtain catalytic activity. Finally, similar results were obtained when we varied the silver source (AgOTf), but the less hygroscopic $AgSbF_6$ was preferred.

With these results in hand, the scope of this gold-catalyzed cyclization was further examined. We turned our attention to the synthesis of enantiopure pyridinones since our strategy was developed from chiral amino acids. As shown in Table 2, the intermediates **1a**–**g** were efficiently converted under mild conditions to the corresponding pyridinones **2a**–**g** in good to excellent yield. The enantiomeric purity of **2b**–**g** was confirmed by chiral HPLC to be >99% ee, with the assessment that no epimerization occurs during this process. Therefore, we investigated the synthetic utility of such chiral pyridinones for the obtention of asymmetric piperidines focusing on the stereocontrol of the reactions during these transformations. For this purpose, substrates **2b** and **2c** possessing variously hindered substituents, methyl and isobutyl respectively, served as models.

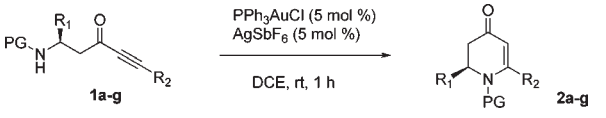
We first examined reduction reactions. Hydrogenation of substrates **2b**–**c** over 10% Pd/C in MeOH was carried

(7) Gouault, N.; Le Roch, M.; Cornée, C.; David, M.; Uriac, P. *J. Org. Chem.* **2009**, *74*, 5614.

(8) For recent reviews on gold catalysis, see: (a) Rudolph, M.; Hashmi, S. K. *Chem. Commun.* **2011**, *47*, 6536. (b) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063. (c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (d) Shen, C. *Tetrahedron* **2008**, *64*, 7847. (e) Das, A.; Sohel, S.; Md., A.; Liu, R.-S. *Org. Biomol. Chem.* **2010**, *8*, 960. Cossy, J. *Pure Appl. Chem.* **2010**, *82*, 1365. (f) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

(9) Arndt, F.; Eistert, B. *Ber.* **1935**, *68B*, 200.

Table 2. Substrate Scope of the Reaction



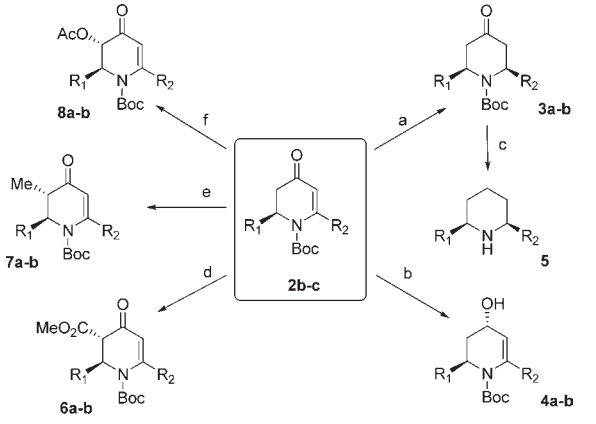
substrate	R^1	R^2	PG	product	yield (%)[a]	*ee* (%)[b]
1a	H	Ph	Boc	**2a**	85	–
1b[c]	Me	*n*Pr	Boc	**2b**	70	>98
1c	*i*Bu	*n*Pr	Boc	**2c**	73	>98
1d	*i*Bu	Ph	Boc	**2d**	87	>98
1e	$BnO-CH_2$	Ph	Boc	**2e**	93	>98
1f	Bn	*n*Pr	Cbz	**2f**	86	>98
1g	secBu	Ph	Boc	**2g**	85	>98

[a] Isolated yield. [b] Determined by chiral HPLC. [c] *R*-Enantiomer was also synthesized from D-alanine for HPLC conditions optimization.

out, and **3a**–**b** were obtained as single diastereoisomers (Table 3). The *cis*-stereochemistry was easily demonstrated by NOE experiment and is in accordance with results previously reported by Ma et al.[10] Reduction of **2b**–**c** under Luche conditions gave the corresponding allylic alcohols **4a**–**b** with a 15/85 and 12/88 diastereoisomeric ratio respectively.[11] The trans configuration of the major isomer was confirmed by NOESY experiment. Finally, 2,6-disubstituted piperidine **5** was obtained from **3b** by its conversion into the corresponding enol triflate under standard conditions, hydrogenation, and then removal of the Boc protecting group by using HCl (3 N) in MeOH. The piperidine **5** was obtained with an overall yield of 61%. The existence of **5** as a single enantiomer was confirmed by ^{13}C NMR spectroscopy analysis of diastereomeric salts utilizing (*S*)- and (*R,S*)-*tert*-butylphenylphosphinothioic acid as a chiral solvating agent.[12] Data were reported in the Supporting Information.

Next, we envisioned a series of transformations aiming at functionalization of the C-3 position. In this case, formation of enolate intermediates was achieved by using LHMDS as base followed by condensation of two electrophiles (methyl chloroformate or iodomethane).[13] Corresponding compounds **6a**–**b** and **7a**–**b** were obtained in good yields and excellent diastereoselection (in all cases, a single diastereoisomer could be detected in ^1H NMR).

Table 3. Synthesis of Piperidine Derivatives[a]



product	**3a**	**3b**	**4a**	**4b**	**5**
R^1	Me	*i*Bu	Me	*i*Bu	*i*Bu
R^2	*n*Pr	*n*Pr	*n*Pr	*n*Pr	*n*Pr
yield (%)[b]	65	83	83	94	61
dr (cis/trans)[c]	>98/2	>98/2	15/85	12/88	>98/2

product	**6a**	**6b**	**7a**	**7b**	**8a**	**8b**
R^1	Me	*i*Bu	Me	*i*Bu	Me	*i*Bu
R^2	*n*Pr	*n*Pr	*n*Pr	*n*Pr	*n*Pr	*n*Pr
yield (%)[b]	82	85	60	73	65	70
dr (cis/trans)[c]	<2/98	<2/98	<2/98	<2/98	<2/98	<2/98

[a] Conditions: (a) H_2 4.5 bar, Pd/C 10%, MeOH, rt, 16 h; (b) $NaBH_4$, $CeCl_3$. $7H_2O$, −40 °C, MeOH, 2 h; (c) (i) KHMDS, $PhNTf_2$, THF, −78 °C to rt, 2 h, 18 h, (ii) H_2 4 bar, Pd/C 40%, Li_2CO_3, EtOAc, 3 h; (iii) HCl (3 N)/MeOH, rt, 24 h then K_2CO_3; (d) LiHMDS, Methyl chloroformate, −78 °C to rt, 18 h, THF; (e) LiHMDS, MeI, −78 °C to rt, 18 h, THF; (f) $Pb(OAc)_4$, Toluene, reflux, 4 h. [b] Isolated yield. [c] ^1H NMR of the crude material.

Finally, **3b**–**c** were subjected to oxidation, C-3 acetoxylation, with $Pb(OAc)_4$ in refluxing toluene.[14] This reaction was regio- and stereoselective[15] providing the *trans*-2,3-disubstituted products **8a**–**b** in good yields. These results are noteworthy since piperidine compounds are obtained with very good control of the stereochemistry during these reduction reactions and allow an application toward natural products.

In summary, we have developed a novel enantiospecific synthetic method to obtain pyridinones from the chiral pool of amino acids. Moreover, the use of gold catalysis in this process allows an excellent stereocontrol during the cyclization. This approach provides a straightforward tool for further synthetic applications toward piperidines. Further investigation regarding the synthetic utility of this methodology toward natural products is ongoing.

Acknowledgment. The authors thank Prof. J.-P. Hurvois (University of Rennes 1) for helpful discussions and providing phosphinothioic acid.

Supporting Information Available. Preparative methods and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Ma, D.; Zhu, W. *Tetrahedron Lett*. **2003**, *44*, 8609.
(11) (a) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc*. **1981**, *103*, 5454. (b) Liu, D.; Acharya, H. P.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S.; Chiruta, C.; Jachak, S. M.; Clive, D. L. J. *J. Org. Chem*. **2009**, *74*, 7414.
(12) Wang, F.; Polavarapu, P. L. *J. Org. Chem*. **2001**, *66*, 9015.
(13) (a) Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett*. **1995**, *36*, 9141. (b) Kranke, B.; Kunz, H. *Org. Biomol. Chem*. **2007**, *5*, 349. (c) Etayo, P.; Badorrey, R.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Eur. J. Org. Chem*. **2008**, 6008.
(14) Comins, D. L.; Stolze, D. A.; Thakker, P.; McArdle, C. L. *Tetrahedron Lett*. **1998**, *39*, 5693.
(15) The use of $Pb(OAc)_4$ (99% purity) afforded a single diastereoisomer. When the same reaction was conducted using $Pb(OAc)_4$, (96%, stabilized with acetic acid), two diastereoisomers were detected by ^1H NMR in a ratio of 85/15.