Palladium-Catalyzed Carbonylative Cyclization/Arylation Cascade for 2-Aroylindolizine Synthesis

ORGANIC LETTERS XXXX Vol. XX, No. XX 000–000

Zhou Li, Dmitri Chernyak, and Vladimir Gevorgyan*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, United States

vlad@uic.edu

Received October 25, 2012





An efficient synthesis of densely substituted 2-aroylindolizines via the palladium-catalyzed carbonylative cyclization/arylation is reported. This transformation proceeds via the *5-endo-dig* cyclization of 2-propargylpyridine triggered by an aroyl Pd complex. It produced diversely substituted 2-aroylindolizines in good to excellent yields.

Indolizines have attracted noteworthy attention in recent years because of their profound biological effects.¹ Both naturally occurring and synthetic indolizines have shown great potential in pharmaceutical research as cytotoxins,² anti-inflammatory agents,³ and 5-HT3 receptor antagonists.⁴ In this regard, transformations that utilize readily available substrates to provide access to diversely substituted indolizines, especially those bearing an electronwithdrawing group at the C-2 postion,⁵ are in high demand. The classic Tschichibabin reaction provides straightforward access to C-2-substituted indolizines via the condensation of picolines and α -bromoacetophenone derivatives. However, the limited availability of starting materials restricts the substitution pattern of the product.⁶ The [3 + 2] cycloaddition of pyridinium ylides with alkynes provides another viable route to the indolizine core. However, the regioselectivity issue, as well as the moderate yields caused by necessary oxidation of the formed intermediate, limit its synthetic application.⁷ The Morita–Baylis–Hillman reaction can also be utilized for the preparation of indolizin-2-yl ketone from an appropriate Michael acceptor. However, it suffers from the narrow range of starting materials that can be used and the usually low reactivity of the substrates.⁸ In addition to the traditional condensation methods, transition-metal catalysis has been widely used for the

^{(1) (}a) Flitsch, W. *Comprehensive Heterocyclic Chemistry, II*; Pergamon Press: Oxford, 1984; Vol. 8, 237–248. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

^{(2) (}a) Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao, M. *J. Nat. Prod.* **2002**, *65*, 500. (b) Pla, D.; Marchal, A.; Olsen, C. A.; Francesch, A.; Cuevas, C.; Albericio, F.; Alvarez, M. *J. Med. Chem.* **2006**, *49*, 3257. (c) Chittchang, M.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *ChemMedChem* **2009**, *4*, 457.

⁽³⁾ Oslund, R. C.; Cermak, N.; Gelb, M. H. J. Med. Chem. 2008, 51, 4708.

⁽⁴⁾ Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. J. Med. Chem. **1990**, *33*, 1924.

⁽⁵⁾ For biological activity of indolizines bearing an electron-withdrawing group at the C-2 position, see: (a) Shen, Y.-M.; Lv, P.-C.; Chen, W.; Liu, P.-G.; Zhu, H.-L.; Zhang, M.-Z. *Eur. J. Med. Chem.* **2010**, *45*, 3184–3190. (b) Wu, X.-W.; Wu, Z.-P.; Chen, J.-W.; Zhang, W.; Gu, L.-Q.; Huang, Z.-S.; An, L.-K.; Wang, L.-X.; Zhang, H.-B. *Eur. J. Med. Chem.* **2011**, *46*, 4625. (c) Warui, D. M.; Baranger, A. M. *J. Med. Chem.* **2009**, *52*, 5462.

^{(6) (}a) Tschitschibabin, A. E. Ber. Dtsch. Chem. Ges. 1927, 60, 1607.
(b) Kostik, E. L.; Abiko, A.; Oku, A. J. Org. Chem. 2001, 66, 2618.
(c) Liu, Y.; Sun, J.-W. J. Org. Chem. 2012, 77, 1191.

^{(7) (}a) Katritzky, A. R.; Qiou, G.; Yang, B.; He, H.-Y. J. Org. Chem. 1999, 64, 7618. (b) Bora, U.; Saikia, A.; Boruah, R. C. Org. Lett. 2003, 5, 435. (c) Rotaru, A. V.; Druta, I. D.; Oeser, T.; Müller, T. J. J. Helv. Chim. Acta 2005, 88, 1798.

^{(8) (}a) Bode, M. L.; Kaye, P. T. J. Chem. Soc., Perkin Trans. 1 1990, 2612.
(b) Basavaiah, D.; Rao, A. J. Chem. Commun. 2003, 604.
(c) Specowius, V.; Bendrath, F.; Winterberg, M.; Khurshid, A.; Langer, P. Adv. Synth. Catal. 2012, 354, 1163.

^{(9) (}a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. J. Am. Chem. Soc. 2001, 123, 2074. (b) Seregin, I.; Gevorgyan, V. J. Am. Chem. Soc. 2006, 128, 12050. (c) Liu, Y.; Song, Z.; Yan, B. Org. Lett. 2007, 9, 409. (d) Chuprakov, S.; Gevorgyan, V. Org. Lett. 2007, 9, 4463. (e) Hardin, A. R.; Sarpong, R. Org. Lett. 2007, 9, 4547. (f) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. J. Am. Chem. Soc. 2010, 132, 13200and refs 11 and 15.

construction of diversely functionalized, especially heteroatom-substituted indolizines, under mild conditions.⁹ Nonetheless, the selective introduction of functionality at the C-2 position is still a challenging task.¹⁰ Along this line, our group has recently reported a synthesis of 2-aryl indolizines via the palladium catalyzed arylative 5-*endo-dig* cyclization of 2-propargylpyridine (Scheme 1, eq 1).¹¹ Herein, we report a Pd-catalyzed cascade carbonylative cyclization/arylation approach to densely substituted 2-aroylindolizines that proceeds in good to excellent yields (Scheme 1, eq 2).

Scheme 1. Indolizine Synthesis via Palladium-Catalyzed Cyclization



Continuing with our efforts in the synthesis of diversely functionalized indolizines, we thought that the employment of benzoyl chloride instead of an aryl halide as electrophile in this cascade cyclization would provide 2-benzoylindolizine.¹² However, the reaction of pivaloate **1a** with benzoyl chloride in the presence of a Pd catalyst failed to produce even a trace amount of **2a** (eq 3).

Thus, we thought of alternative methods to introduce the benzoyl function at the C-2 position of indolizine. Since (1) an acylpalladium species can be formed via a migratory insertion of carbon monoxide into an aryl– palladium bond and (2) there have been reported examples on synthesis of diaryl ketones via the palladium-catalyzed carbonylative cyclization/arylation cascades,¹³ we anticipated that under a CO atmosphere the in situ formed acyl palladium species might trigger

(12) For palladium-catalyzed acylation reactions using acyl chlorides as the electrophile, see: (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. Synthsis 1977, 777. (b) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* 1983, 24, 5181.
(c) Renaldo, A. F.; Labadie, J. W.; Stille, J. K. Org. Synth. 1989, 67, 86. (d) Kabalka, G. W.; Malladi, R. R.; Tejedor, D.; Kelley, S. *Tetrahedron Lett.* 2000, 41, 999.

(13) For selected reports on the palladium-catalyzed carbonylative cyclization/arylation cascade, see: (a) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* 1994, 50, 437. (b) Dai, G.; Larock, R. C. Org. Lett. 2001, 4, 193. (c) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. J. Org. Chem. 2002, 67, 2365. (d) Dai, D.; Larock, R. C. Org. Lett. 2002, 4, 193. (14) See the Supporting Information for details.

the expected carbonylative cyclization/arylation cascade to obtain **2**.



To test this idea, we examined the carbonylative cyclization of pivaloate 1a and different aryl halides under continuous 10 psi CO supply. Initially, we found that the carbonylative cyclization of 1a and iodobenzene in the presence of $Pd(PPh_3)Cl_2$ catalyst vielded 2a in quantitative yield (Table 1, entry 1). However, aryl halides bearing electron-withdrawing groups, such as methyl p-iodobenzoate, were not competent reactants under these conditions (entry 2).¹⁴ On the contrary, the combination of Pd(OAc)₂ catalyst, PCy₃ ligand, and triethylamine base afforded benzoate 2f in 90% yield (entry 3). Under the same conditions, the yield of 2a was only 19% along with a substantial amount of palladium black produced, which implied decomposition of an excessively reactive catalyst (entry 4). The yield of 2a was improved to 51% by switching ligand to PPh₃ (entry 5). The reaction that was performed in a sealed Schlenk tube, which simplified the reaction setup and allowed a higher pressure (20 psi and above), provided 2a in 86% yield at 20 psi CO pressure (entry 6). Finally, the screening of different solvents under a reduced temperature revealed that acetonitrile was the optimal choice over DMF and toluene (entries 7-9).

Table 1. Optimization of Conditions



	· · · · · ·						
4	$Pd(OAc)_2/PCy_3$	NEt_3	DMF	80	Α	2a , 19	
5	Pd(OAc) ₂ /PPh ₃	NEt_3	DMF	80	Α	2a , 51	
6	Pd(OAc) ₂ /PPh ₃	NEt_3	DMF	80	В	2a , 86	
7	Pd(OAc) ₂ /PPh ₃	NEt_3	DMF	70	В	2a , 65	
8	Pd(OAc) ₂ /PPh ₃	NEt_3	toluene	70	В	2a , 45	
9	Pd(OAc) ₂ /PPh ₃	NEt_3	MeCN	70	В	2a , 95	

 a (A) Reactions were conducted in flask with continuous 10 psi CO supply. (B) Reactions were conducted in a sealed Schlenk tube with 20 psi CO. b Isolated yields of 0.5 mmol reactions. c 1 equiv of TBAI was added.

With the optimized conditions in hand, the scope of reaction was examined. It was found that a series of iodoarenes bearing different substituents at various

⁽¹⁰⁾ For the regioselectivity of the direct C-H functionalization of indolizine, see: (a) Renard, M.; Gubin, J. *Tetrahedron Lett.* **1992**, *33*, 4433. (b) Shipman, M. *Science of Synthesis* **2000**, *10*, 777. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. Org. Lett. **2004**, *6*, 1159. (d) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. J. Am. Chem. Soc. **2007**, *129*, 7742. (e) Petit, A.; Flygare, J.; Miller, A. T.; Winkel, G.; Ess, D. H. Org. Lett. **2012**, *14*, 3680.

^{(11) (}a) Chernyak, D.; Skontos, C.; Gevorgyan, V. Org. Lett. 2010, 12, 3242. (b) Chernyak, D.; Gevorgyan, V. Org. Lett. 2010, 12, 5558.

Table 2. Reaction Scope of Carbonylative Cyclization



^{*a*} Conditions: Pd(OAc)₂ (5 mol %), PPh₃ (10 mol %), Ar–I (1.5 equiv), triethylamine (2 equiv), MeCN (0.2 M), 70 °C, CO 20 psi in a sealed Schlenk tube, 12 h. ^{*b*} Isolated yields of 0.5 mmol reactions.

positions smoothly underwent this carbonylative cyclization with **1a**, yielding indolizines **2a** to **2i** in moderate to excellent yields (Table 2, entries 1–9). The cyclization of 3-*n*-hexyl-, *n*-butyl-, and cyclohexenyl-substituted pivaloates also provided the expected products in good yield (entries 10–15). Substrates possessing a functionalized pyridine ring at C-5 produced indolizines **2p** and **2q** and pyrrolo[1,2-*a*]quinoline **2r** in moderate to good yields (entries 16–18). On the contrary, cyclization of 3-methylsubstituted pyridine provided 8-methyl **2s** in a relative low yield (entry 19). In addition to various pivaloates, a TBDMS ether was equally effective in this reaction, yielding **2t** in 80% yield (entry 20). More interestingly, the cyclization of 1-(1-pyridin-2-ylpropargyl)morpholine resulted in the 1-morpholin-1-ylindolizine 2u in 71% yield, which provided a convenient access to the C-2 substituted 1-aminoindolizines.¹⁵

Presumably, this palladium-catalyzed carbonylative cyclization starts with the formation of the aroylpalladium species **3** (Scheme 2) via a migratory insertion of CO into the aryl-palladium bond, followed by its coordination of the triple bond of **1** to the palladium center. The 5-*endo-dig* cyclization leads to the formation of indolizinium intermediate **4**, which after a proton loss-aromatization sequence produces heteroaryl palladium species **5**. The reductive elimination of **5** releases the product 2-benzoylindolizine **2** to regenerate the Pd catalyst.

In summary, a Pd-catalyzed carbonylative cyclization/ arylation approach to 2-aroylindolizines has been developed. This new method allows for the efficient and selective synthesis of important⁵ 2-aroylindolizines from readily

⁽¹⁵⁾ For synthesis of 2-nonsubstituted 1-aminoindolizine via the A³ coupling reaction, see: (a) Yan, B.; Liu, Y. Org. Lett. 2007, 9, 4323.
(b) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X.-W. J. Comb. Chem. 2010, 12, 696.

Scheme 2. Proposed Mechanism



available propargylpyridines and iodoarenes under a carbon monoxide atmosphere.

Acknowledgment. The support of the National Institutes of Health (GM-64444 and 1P50 GM-086145) is gratefully acknowledged.

Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.