Phenanthridine Synthesis through Iron-Catalyzed Intramolecular *N*-Arylation of *O*-Acetyl Oxime

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

Indubhusan Deb and Naohiko Yoshikai*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

nyoshikai@ntu.edu.sg

Received July 19, 2013



O-Acetyl oximes derived from 2'-arylacetophenones undergo N-O bond cleavage/intramolecular N-arylation in the presence of a catalytic amount of iron(III) acetylacetonate in acetic acid. In combination with the conventional cross-coupling or directed C-H arylation, the reaction offers a convenient route to substituted phenanthridines.

Phenanthridine is an important fused heteroaromatic skeleton that occurs frequently in natural products, pharmaceutical drugs, and other functional molecules.¹ For example, nitidine and fagaronine belong to a class of phenanthridine alkaloids, which display activity against leukemia.^{1a} Consequently, methods for efficient and selective synthesis of phenanthridine derivatives could serve as important tools in medicinal chemistry and material science.² Among many possible approaches to the phenanthridine skeleton, those involving closure of the central ring through intramolecular C-C or C-N bond formation of an ortho-functionalized biaryl precursor are particularly attractive in light of the ready accessibility of the starting material by cross-coupling reactions. In this context, the classical Pictet-Hubert phenanthridine synthesis from ortho-acetaminobiphenyl derivatives remains an attractive option, while the reaction typically requires harsh conditions (Scheme 1a).³ Recent studies of the groups of Tobisu/Chatani and Chiba led to milder and modular routes to phenanthridines. The former group developed manganese-mediated oxidative cyclization of *ortho*-isocyanobiphenyls with organoboronic acids (Scheme 1b),⁴ while the latter group devised a one-pot two-step protocol involving Grignard addition to *ortho*-cyanobiphenyls followed by copper-catalyzed C–N bond formation under aerobic conditions (Scheme 1c).⁵

Besides the above-mentioned approaches, intramolecular C–N cyclization of oxime derivatives of biaryl aldehydes/ketones represents an attractive approach to phenanthridines (Scheme 1d), particularly considering the improved accessibility to the starting materials owing to the recent progress in direct arylation of aryl ketones and imines.⁶ Indeed, the feasibility of such cyclization reactions has been demonstrated by the groups of Rodríguez and Walton under photochemical conditions, which

^{(1) (}a) Cushman, M.; Mohan, P.; Smith, E. C. R. J. Med. Chem. **1984**, 27, 544. (b) Fang, S. D.; Wang, L. K.; Hecht, S. M. J. Org. Chem. **1993**, 58, 5025. (c) Lynch, M. A.; Duval, O.; Sukhanova, A.; Devy, J.; MacKay, S. P.; Waigh, R. D.; Nabiev, I. Bioorg. Med. Chem. Lett. **2001**, *11*, 2643. (d) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. J. Am. Chem. Soc. **2008**, *130*, 7182.

⁽²⁾ Keller, P. A. In *Science of Synthesis*, Vol. 15; St. Black, D. C., Ed.; Thieme: Stuttgart, 2004; p 1065.

⁽³⁾ Xi, J.; Dong, Q.-L.; Liu, G.-S.; Wang, S.; Chen, L.; Yao, Z.-J. Synlett **2010**, 1674 and references cited therein.

⁽⁴⁾ Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. Angew. Chem., Int. Ed. 2012, 51, 11363.

⁽⁵⁾ Zhang, L.; Ang, G. Y.; Chiba, S. Org. Lett. 2010, 12, 3682.

^{(6) (}a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. Org. Lett. 2002, 4, 1783.
(b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. J. Am. Chem. Soc. 2005, 127, 5936. (c) Ackermann, L. Org. Lett. 2005, 7, 3123. (d) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. Angew. Chem., Int. Ed. 2009, 48, 2925. (e) Kim, M.; Kwak, J.; Chang, S. Angew. Chem., Int. Ed. 2009, 48, 8935. (f) Tredwell, M. J.; Gulias, M.; Bremeyer, N. G.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. Angew. Chem., Int. Ed. 2011, 50, 1076. (g) Gao, K.; Lee, P. S.; Long, C.; Yoshikai, N. Org. Lett. 2012, 14, 4234.

^{(7) (}a) Alonso, R.; Campos, P. J.; Garcia, B.; Rodriguez, M. A. Org. Lett. **2006**, *8*, 3521. (b) Alonso, R.; Caballero, A.; Campos, P. J.; Rodriguez, M. A. Tetrahedron **2010**, *66*, 8828.

presumably involve iminyl radicals as reactive species.^{7–10} However, these photochemical reactions required high dilution or the use of a stoichiometric photosensitizer. We report here that the same C-N cyclization reaction can be achieved starting from O-acetyloximes under simple conditions using an iron(III) salt as a catalyst. The reaction appears mechanistically distinct from the photochemical reaction, likely proceeding through a nonradical pathway.





(d) Rodríguez, Walton (refs 7, 8)/This work



We came across the present cyclization reaction while studying pyridine synthesis through copper-catalyzed oxime N–O cleavage that we reported recently.¹¹ Thus, the reaction of O-acetyl oxime of 2'-phenylacetophenone (1a) in the presence of CuI (20 mol %) in DMSO at 80 °C resulted in the formation of phenanthridine 2a in 40% yield (Table 1, entry 1). The yield of 2a was improved by using Cu(OAc)₂ instead of CuI (entry 2), and further by changing the solvent to AcOH (entry 3).

While we initially thought that the ability of Cu(I) to reduce the oxime N-O bond was crucial for the cyclization reaction,^{9b} it turned out not to be true. Thus, iron(III) acetylacetonate, a simple iron salt that appears redoxinsensitive under the present conditions, promoted the reaction cleanly to afford 2a in 96% yield (entry 4). The same level of the reaction efficiency was achieved either by reducing the loading of Fe(acac)₃ to 10 mol % or by lowering the temperature to 60 °C (entries 5 and 6). The reaction at 60 °C became sluggish with a lower catalyst loading of 10 or 5 mol % (entries 7 and 8). While FeCl₃ also promoted the reaction albeit in modest yield (entry 9). acetylacetonate salts of the neighboring metal elements, that is, Mn(acac)₃, Co(acac)₃, and Ni(acac)₂, were not effective at all (entries 10-12). The reaction became very sluggish in solvents other than AcOH (entries 13–15). While the screening study was performed using a pure E-isomer of oxime 1a, a mixture of E- and Z-isomers (ca. 4:1) could also be used without problem, affording 2a in 90% yield. Note that free oxime of 2'-phenylacetophenone did not participate in the cyclization reaction.

Table 1. Screening of Reaction Conditions^a



entry	$\mathrm{ML}_n (\mathrm{mol} \%)$	solvent	temp (°C)	yield $(\%)^b$
1^c	CuI (20)	DMSO	80	40
2	$Cu(OAc)_2(20)$	DMSO	80	55
3	$Cu(OAc)_2(20)$	AcOH	80	70
4	$Fe(acac)_3(20)$	AcOH	80	$96 (93)^c$
5	$Fe(acac)_3(10)$	AcOH	80	90
6	$Fe(acac)_3(20)$	AcOH	60	92
7	$Fe(acac)_3(10)$	AcOH	60	51
8	$Fe(acac)_3(5)$	AcOH	60	8
9	$FeCl_3(20)$	AcOH	60	48
10	$Mn(acac)_3(20)$	AcOH	60	0^d
11	$Co(acac)_3(20)$	AcOH	60	0^d
12	$Ni(acac)_2(20)$	AcOH	60	0^d
13	$Fe(acac)_3(20)$	DMSO	60	5
14	$Fe(acac)_3(20)$	dioxane	60	5
15	$Fe(acac)_3(20)$	toluene	60	8

^a The reaction was performed on a 0.2 mmol scale in 1.2 mL of the solvent. ^b Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c Isolated yield is shown in the parentheses. ^d Determined by GC.

With the optimized catalytic system in hand, we explored the scope of the present cyclization reaction (Scheme 2). First, C-N cyclization of oxime derivatives of various 2'-arylacetophenones was examined. The reaction tolerated chloro, fluoro, trifluoromethyl, cyano, and methyl substituents on the *para* position of the aryl group, affording the phenanthridines 2b-2f in moderate to good yields. Blockage of one of the ortho positions was tolerable, as demonstrated by the formation of 1-fluorophenanthridine 2g and benzo[a]phenanthridine 2h in

^{(8) (}a) Portela-Cubillo, F.; Scanlan, E. M.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2008**, 4189. (b) Portela-Cubillo, F.; Lymer, J.; Scanlan, E. M.; Scott, J. S.; Walton, J. C. *Tetrahedron* **2008**, *64*, 11908. (c) McBurney, R. T.; Slawin, A. M. Z.; Smart, L. A.; Yu, Y. P.; Walton, J. C. Chem. Commun. 2011, 47, 7974.

⁽⁹⁾ For reviews on reactions involving iminyl radicals, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. (c) Kitamura, M.; Narasaka, K. Bull. Chem. Soc. Jpn. 2008, 81, 539. (d) Zard, S. Z. Chem. Soc. Rev. 2008, 37, 1603. (e) Chiba, S. Synlett 2012, 23, 21.

⁽¹⁰⁾ Microwave-assisted, thermal cyclization was also reported: Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. J. Org. Chem. 2009, 74, 4934.

⁽¹¹⁾ Wei, Y.; Yoshikai, N. J. Am. Chem. Soc. 2013, 135, 3756.

moderate yields. Interestingly, no regioselectivity was observed for cyclization reactions of substrates bearing *m*-tolyl and *m*-methoxyphenyl groups (see products 2i/2i' and 2j/2j').

The reaction tolerated variation of the aromatic ring of the acetophenone moiety (see products **2k** and **2l**), and oximes derived from 2'-phenylpropiophenone and 2'-phenylbenzophenone (see products **2m** and **2n**). On the other hand, oxime derived from 2'-phenylbenzaldehyde failed to undergo the desired C-N cyclization but produced 2-cyanobiphenyl through elimination of acetic acid. Note again that the stereochemistry of the oxime C=N bond did not have a significant influence on the reactivity. For example, the products **2m** and **2n** were obtained in good yields from 1:1 mixtures of *E*- and *Z*-isomers of the respective oximes.

Scheme 2. Cyclization of Various Biaryl Oximes^a OAc Fe(acac)₃ (20 mol %) AcOH 80 °C 24 h 2 1 Me Me Me **2a**, 93% **2h** 90% 2c. 87% M **2f**, 77% 2d, 74% 2e, 56% Me(H) H(Me **2i + 2i**', 82% (1:1) **2g**, 55% **2h**, 51% OMe(H) H(OMe) MaC 2j + 2j', 80% (1:1) 2k. 77% 2I. 77%

^{*a*} Unless otherwise noted, the reaction was performed on a 0.2 mmol scale in 1.2 mL of AcOH. Yields refer to isolated yields.

2n. 75%

During the exploration of the substrate scope, we found that oximes bearing *p*- and *o*-methoxyphenyl groups, upon exposure to the catalytic conditions, immediately decomposed to give black, tarry materials of unknown identity

2m. 84%



Scheme 4. Proposed Reaction Mechanism



(Scheme 3a). This observation is in sharp contrast to the reaction of similar substrates under photochemical conditions, which afforded the desired phenanthridine derivatives without problem.^{7,8} In another experiment, we noted that the addition of TEMPO (1 equiv) did not interfere with the cyclization of **1a** to **2a** (Scheme 3b). Finally, comparison of individual reactions of the parent substrate **1a** and its pentadeuterated analogue **1a**- d_5 showed that initial conversion of **1a**- d_5 takes place much more sluggishly than that of **1a**, curiously with an induction period of ca. 20 min (Scheme 3c). While the presence of the induction

period makes it difficult to derive a quantitative kinetic isotope effect, these observations strongly suggest that the C-H bond cleavage is involved in the rate-determining step of the reaction.

On the basis of the above observations, we consider that the present reaction is mechanistically distinct from the photochemical cyclization and does not involve formation of an iminyl radical. We speculate that the reaction proceeds through a Friedel–Crafts type mechanism with Lewis acid activation of the acetoxy group (Scheme 4a). Alternatively, it is possible to draw a mechanism involving 6π -electrocyclization and subsequent elimination of acetic acid (Scheme 4b). At this moment, we prefer the Friedel– Crafts type pathway, because such a mechanism involving electrophilic attack on the aromatic ring appears to better account for the failure of the reaction of the substrate bearing *p*-methoxyphenyl group (Scheme 4c). In summary, we have developed a convenient iron(III)catalyzed protocol for the cyclization of 2-biarylketone *O*-acetyl oximes to phenanthridine derivatives. The reaction likely proceeds through a nonradical mechanism with activation of the acetoxy leaving group by the iron catalyst. Further studies on the development of new transition-metal-catalyzed condensation methods for carboand heterocycles are ongoing.^{11,12}

Acknowledgment. This work was supported by the National Research Foundation Singapore (NRF-RF2009-05 to N.Y.) and Nanyang Technological University. We thank Boon-Hong Tan (Nanyang Technological University) for technical assistance.

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

^{(12) (}a) Wei, Y.; Deb, I.; Yoshikai, N. J. Am. Chem. Soc. **2012**, 134, 9098. (b) Hajra, A.; Wei, Y.; Yoshikai, N. Org. Lett. **2012**, 14, 5488. (c) Yamakawa, T.; Yoshikai, N. Org. Lett. **2013**, 15, 196.

The authors declare no competing financial interest.