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$CuCl_2$-Promoted 6-*endo-dig* Chlorocyclization and Oxidative Aromatization Cascade: Efficient Construction of 1-Azaanthraquinones from *N*-Propargylaminoquinones

Na Fei,[†] Hao Yin,[†] Shaozhong Wang,*[,†] Huaqin Wang,[‡] and Zhu-Jun Yao[†]

State Key Laboratory of Coordination Chemistry, Institute of Chemical Biology and Drug Innovation, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China, and Modern Analytical Center of Nanjing University, Nanjing 210093, P. R. China

wangsz@nju.edu.cn

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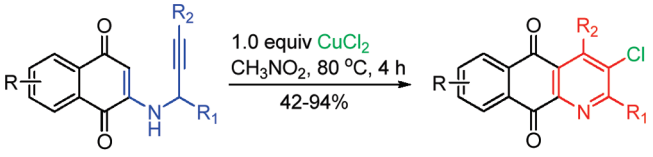
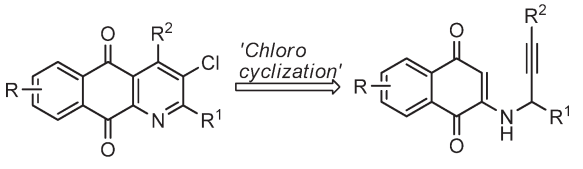
ABSTRACT



An efficient synthetic methodology was developed to assemble 1-azaanthraquinones from *N*-propargylaminoquinones by copper(II)-promoted sequential 6-*endo-dig* chlorocyclization and oxidative aromatization. The approach can be extended to preprare chlorinated alkaloids such as cleistophine and sampangine. A possible mechanism involving carbon−carbon bond formation triggered by regioselective electrophilic activation and carbon−chlorine bond formation via reductive elimination was proposed.

1-Azaanthraquinone belongs to a featured scaffold embedded in naturally occurring alkaloids such as cleistophine, sampangine, and amphimedine.[1] The pronounced biological activities of these alkaloids together with their analogs have attracted considerable attention, and different methodologies have been developed to elaborate the tricyclic skeleton. To date, a strategy based on an aza-Diels−Alder reaction starting from 1-azabutadiene and quinone has been generally employed even though intrinsic limitations are still encountered.[2] Our recent exploration in electrophilic cyclization made us recognize the benign nucleophilicity of aminoquinones.[3] Since the incorporation of a chlorine atom on the azaanthraquinone ring should potentially expand the scope of a structure−activity relationship investigation,[4] a strategy involving chlorocyclization of *N*-propargylaminoquinone was envisioned to assemble a 1-azaanthraquinone framework (Scheme 1).

Scheme 1. Chlorocyclization Strategy



[†] State Key Laboratory of Coordination Chemistry, Institute of Chemical Biology and Drug Innovation, School of Chemistry and Chemical Engineering, Nanjing University.

[‡] Modern Analytical Center of Nanjing University.

(1) (a) Chaves, M. H.; Santos, L. A.; Lago, J. H. G.; Roque, N. F. *J. Nat. Prod.* **2001**, *64*, 240. (b) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825. (c) Marshall, K. M.; Barrows, L. R. *Nat. Prod. Rep.* **2004**, *21*, 731.

(2) For reviews, see: (a) Pautet, F.; Nebois, P.; Bouaziz, Z.; Fillion, H. *Heterocycles* **2001**, *54*, 1095. (b) Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386.

(3) (a) Jiang, C.; Xu, M.; Wang, S.; Wang, H.; Yao, Z.-J. *J. Org. Chem.* **2010**, *75*, 4323. (b) Fei, N.; Hou, Q.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Biomol. Chem.* **2010**, *8*, 4096.

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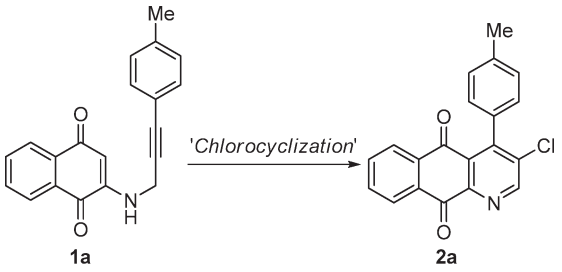
Chlorocyclization has emerged as a powerful tool for the construction of carbocycles and heterocycles. A combination of a divalent palladium catalyst with superstoichiometric amounts of lithium chloride or cupric chloride has been predominantly employed.[5,6] The process is proposed to start from a chloropalladation of carbon−carbon multiple bonds followed by an insertion to a C−Pd bond and end with β-elimination or oxidative cleavage. However, recent studies demonstrate that some chlorocyclization involving allene and alkyne substrates tethered with *O*-, *N*-nucleophiles can be implemented on treatment with cupric chloride without any palladium catalyst, delivering chlorinated heterocycles such as butenolides,[7] isobenzofuran-1-ones,[8] isochromen-1-ones,[9] 1,3-oxazines,[10] indoles,[11] and isoquinolines.[12] The documented examples encourage us to investigate the chlorocyclization of *N*-propargylaminoquinones, a class of 1,5-enyne bearing an enamine nucleophile.

We initiated the study by choosing *N*-propargylaminoquinone **1a** as substrate (Table 1). After establishing palladium acetate as a catalyst, a variety of conditions were screened. No anticipated chlorocyclization was observed in the presence of excess lithium chloride either at room temperature or under heating conditions (Table 1, entries 1−2). When cupric chloride was used instead, the desired azaanthraquinone **2a** was achieved in 51% yield (Table 1, entry 3). The structure of **2a** was confirmed by X-ray crystallographic analysis[13] (Figure 1). The yield changed little when the amount of cupric chloride decreased from 4 to 3 equiv (Table 1, entry 4). To probe the solvent effect, several solvents including DMA, acetonitrile, 1,2-dichloroethane, and nitromethane were tested, and it was found that the best yield was accessed in nitromethane (Table 1, entries 5−8). Switching the catalyst to palladium chloride was almost not detrimental to the yield (Table 1, entry 9). A combination of palladium chloride and ferric chloride proved to be futile, which drove us to further examine the role of cupric chloride (Table 1, entry 10). Control experiments showed that the transformation can be accomplished in higher efficiency only by cupric chloride (Table 1, entry 11), and the amount of cupric chloride can be reduced to 1 equiv without compromising the yield under a prolonged reaction time (Table 1, entry 12). A parallel experiment revealed that ferric chloride did not promote the transformation (Table 1, entry 13).

Table 1. Optimization of Reaction Conditions



1a **2a**

entry	condition[a]	yield (%)[b]
1	5 mol % $Pd(OAc)_2$, 4.0 equiv of LiCl, HOAc, rt, 4 h	0
2	5 mol % $Pd(OAc)_2$, 4.0 equiv of LiCl, HOAc, 80 °C, 4 h	0[c]
3	5 mol % $Pd(OAc)_2$, 4.0 equiv of $CuCl_2$, HOAc, 80 °C, 1 h	51
4	5 mol % $Pd(OAc)_2$, 3.0 equiv of $CuCl_2$, HOAc, 80 °C, 1 h	50
5	5 mol % $Pd(OAc)_2$, 3.0 equiv of $CuCl_2$, DMA, 80 °C, 4 h	17
6	5 mol % $Pd(OAc)_2$, 3.0 equiv of $CuCl_2$, CH_3CN, 80 °C, 1 h	60
7	5 mol % $Pd(OAc)_2$, 3.0 equiv of $CuCl_2$, $(CH_2Cl)_2$, 80 °C, 1 h	60
8	5 mol % $Pd(OAc)_2$, 3.0 equiv of $CuCl_2$, CH_3NO_2, 80 °C, 1 h	66
9	5 mol % $PdCl_2$, 3.0 equiv of $CuCl_2$, CH_3NO_2, 80 °C, 1 h	62
10	5 mol % $PdCl_2$, 3.0 equiv of $FeCl_3$, CH_3NO_2, 80 °C, 4 h	0
11	3.0 equiv of $CuCl_2$, CH_3NO_2, 80 °C, 1 h	85
12	1.0 equiv of $CuCl_2$, CH_3NO_2, 80 °C, 4 h	86
13	3.0 equiv of $FeCl_3$, CH_3NO_2, 80 °C, 4 h	0

[a] The reaction concentration is 0.05 M. [b] Isolated yield. [c] Consumption of the substrate happened.

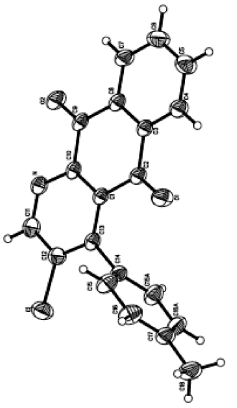


Figure 1. X-ray crystal structure of 1-azaanthraquinone **2a**.

(4) For a review on naturally occurring organohalogen compounds, see: Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141.

(5) (a) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (b) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *Chem. Commun.* **1995**, 271. (c) Lee, C.-Y.; Wu, M.-J. *Eur. J. Org. Chem.* **2007**, 3463. (d) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442. (e) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 5406. (f) Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 784.

(6) For an account on chloropalladation, see: Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115.

(7) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701.

(8) Jithunsa, M.; Ueda, M.; Miyata, O. *Org. Lett.* **2011**, *13*, 518.

(9) Liang, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2007**, 400.

(10) Hashmi, A. S. K.; Schuster, A. M.; Zimmer, M.; Rominger, F. *Chem.—Eur. J.* **2011**, *17*, 5511.

(11) (a) Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107. (b) Chen, C.-C.; Chin, L.-Y.; Yang, S.-C.; Wu, M.-J. *Org. Lett.* **2010**, *12*, 5652.

(12) Yu, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 895.

(13) CCDC 780630 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www. Ccdc.cam.ac.uk/data_request/cif.

Table 2. Copper(II)-Promoted Chlorocyclization and Oxidative Aromatization of *N*-Propargylaminoquinones[a]

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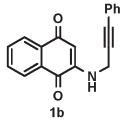
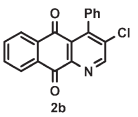
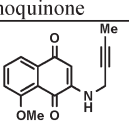
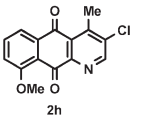
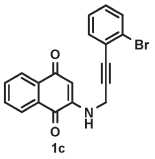
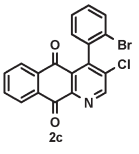
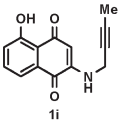
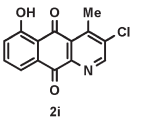
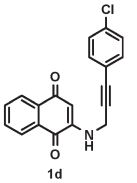
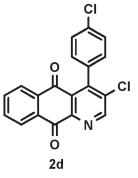
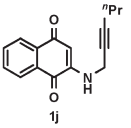
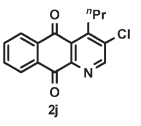
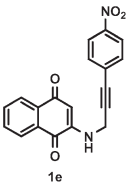
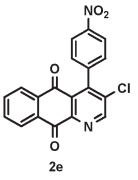
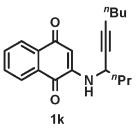
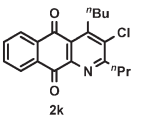
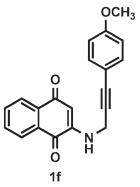
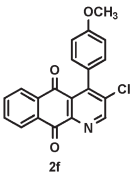
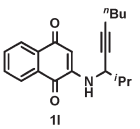
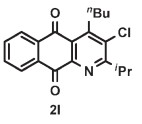
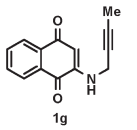
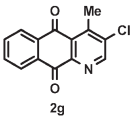
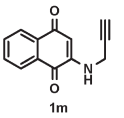
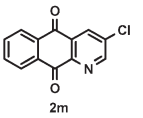
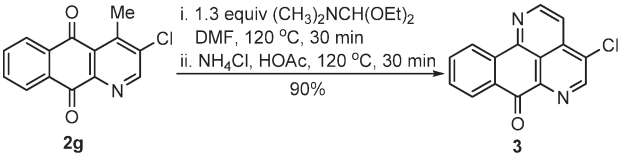
1	 1b	 2b	83	7	 1h	 2h	94
2	 1c	 2c	60	8	 1i	 2i	70
3	 1d	 2d	66	9	 1j	 2j	92
4	 1e	 2e	42	10	 1k	 2k	91
5[b]	 1f	 2f	60	11	 1l	 2l	64
6	 1g	 2g	80	12	 1m	 2m	58

[a] The concentration is 0.05 M. [b] 3-Unsubstituted azaanthraquinone was isolated.

With the optimal conditions in hand, the scope of the chlorocyclization was next explored. A variety of *N*-propargylaminoquinones with aryl groups attached to the alkyne moiety were first examined. Aminoquinone **1b** underwent the sequential chlorocyclization and oxidative aromatization similarly to afford the 4-phenyl substituted azaanthraquinone in 83% yield (Table 2, entry 1). In comparison, electron-withdrawing groups (2-Br, 4-Cl, 4-NO_2) on the phenyl ring were disadvantageous to the conversion; the corresponding 1-azaanthraquinones **2c**−**2e** were isolated in decreased yields ranging from 42% to 66% (Table 2, entries 2−4). An electron-donating group (4-MeO) on the ring did not facilate the transformation due to a competitive formation of 3-unsubstituted azaanthraquinone (Table 2, entry 5). On the other hand, when *N*-propargylaminoquinones derived from aliphatic propargylamines were performed, the 4-methyl, 4-propyl, and 4-butyl substituted 3-chloro-1-azaanthraquinones were obtained in relatively higher yields (Table 2, entries 6−11). It is worth mentioning that the approach not only can be extended to prepare tricyclic alkaloid derivatives such as 3-chlorocleistophine **2g**, 8-methoxy-3-chlorocleistophine **2h**, and 5-hydroxy-3-chlorocleistophine **2i** but also serves as a key step to synthesize 3-chlorosampangine (Scheme 2). Furthermore, the protocol can be applied to generate 2-alkylated 1-azaanthraquinones **2k**−**2l**, which are difficult to obtain in the aza-Diels−Alder annulation. In addition, when aminoquinone **1m** containing a terminal alkyne moiety was employed, the yield dropped to 58% (Table 2, entry 12).

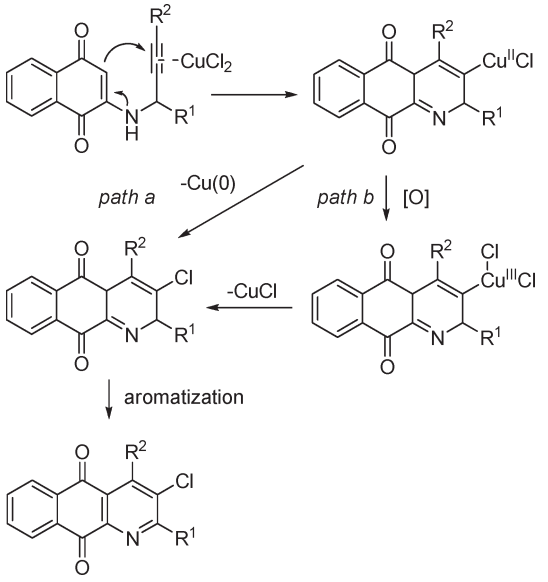
Scheme 2. Sampangine Assembly from Methylated 1-Azaanthraquinone



A possible mechanism is outlined as follows (Scheme 3). Cupric chloride selectively activates the triple bond by

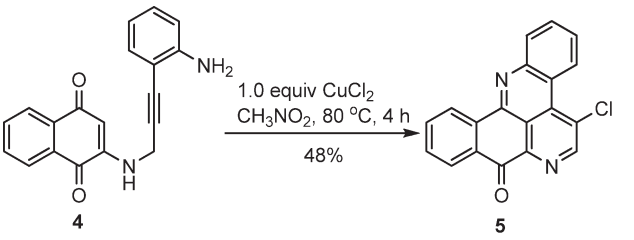
coordination, and then an intramolecular nucleophilic attack takes place in a 6-*endo* manner accompanied by the formation of a carbon−carbon bond. The organocopper(II) intermediate undergoes a reductive elimination to afford the chlorinated dihydroazaanthraquinone, which transforms to the azaanthraquinone by oxidative aromatization (path a). An alternative reductive elimination pathway to generate the dihydroazaanthraquinone from an organocopper(III) intermediate cannot be excluded since the conversion from Cu(II) species to Cu(III) has been detected under certain oxidative conditions (path b).[14]

Scheme 3. Proposed Mechanism



A domino process involving 6-*endo-dig* chlorocyclization and intramolecular condensation to construct 8*H*-benzo[*c*]pyrido[4,3,2-*mn*]acridin-8-one proved to be practical. As exemplified in Scheme 4, the pentacyclic heterocycle was obtained in moderate yield starting from *N*-propargylaminoquinone **4**.

Scheme 4. Domino Cyclization of *N*-Propargylaminoquinone **4**



In conclusion, an efficient approach has been developed to assemble 1-azaanthraquinones by employing a cupric chloride promoted 6-*endo-dig* chlorocyclization followed by oxidative aromatization. The protocol features mild conditions and benign functional group compatibility, which also allows for the construction of tetracyclic and pentacyclic heterocycles. Further applications of this transformation especially in the preparation of pyridoacridine alkaloids are underway.

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

(14) (a) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. (b) Castitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326.