ORGANIC LETTERS

2013
Vol. 15, No. 18
4794–4797

A Concise Construction of Polycyclic Quinolines via Annulation of ω-Cyano-1-alkynes with Diaryliodonium Salts

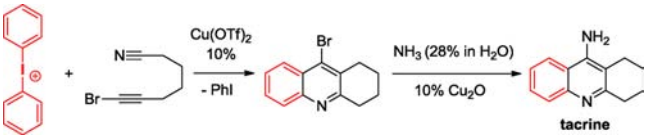
Yong Wang,[†,‡] Chao Chen,[*,†] Shu Zhang,[†,§] Zhenbang Lou,[†,‡] Xiang Su,[†] Lirong Wen,[‡] and Ming Li[‡]

Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao, Shandong 266042, China, and Department of Applied Chemistry, China Agricultural University, Beijing 100193, China

chenchao01@mails.tsinghua.edu.cn

Received July 30, 2013

ABSTRACT



A concise construction of polycyclic quinolines via intramolecular [2 + 2 + 2] annulation of ω-cyano-1-alkynes with diaryliodonium salts was realized. The process produced polycyclic quinolines in high yields with readily available staring materials and was tolerated with halogen substituents.

Polycyclic quinolines are privileged scaffolds in various bioactive natural products (especially in alkaloids) and many synthetic therapeutic agents.[1] For instance, tacrine, a tricyclic quinoline (under the trade name of Cognex, Figure 1), was the first approved drug for the treatment of Alzheimer's disease as a centrally acting anticholinesterase and indirect cholinergic agonist.[2] To date, there are already over 180 research papers related

[†] Tsinghua University
[‡] Qingdao University of Science and Technology
[§] China Agricultural University

(1) (a) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. (b) Reyes, F.; Fernández, R.; Urda, C.; Francesch, A.; Bueno, S.; de Eguilior, C.; Cuevas, C. *Tetrahedron* **2007**, *63*, 2432. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (d) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (e) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (f) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gomez, C. M. *Curr. Org. Chem* **2005**, *9*, 141. (g) Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509. (h) Dzierzbicka, K.; Kolodziejczyk, A. M. *J. Med. Chem.* **2001**, *44*, 3606. (i) Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315. (j) Gamage, S. A.; Spicer, J. A.; Atwell, G. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1999**, *42*, 2383. (k) Inman, W. D.; O'Neill-Johnson, M.; Crews, P. *J. Am. Chem. Soc.* **1990**, *112*, 1. (l) Gunawardana, G. P.; Kohmoto, S.; Gunasekara, S. P.; McConnell, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *110*, 4856. (m) Cain, B. F.; Atwell, G. J.; Denny, W. A. *J. Med. Chem.* **1975**, *18*, 1110. (n) Sanders, J. M.; Clifford, D. P.; Lutz, R. E. *J. Med. Chem.* **1971**, *14*, 1126. (o) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*, 1st ed.; Chapman and Hall: London, 1990; p 84. (p) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*, 1st ed.; Chapman and Hall: London, 1990; p 170. (q) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*, 1st ed.; Chapman and Hall: London, 1990; p 297. (r) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*, 1st ed.; Chapman and Hall: London, 1990; p 835.

(2) (a) Davis, K. L.; Powchick, P. *Lancet* **1995**, *345*, 625. (b) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. *N. Engl. J. Med.* **1986**, *315*, 1241. (c) Albert, A.; Gledhill, W. J. *J. Soc. Chem. Ind.* **1945**, *64*, 169.

(3) (a) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541. (b) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1999**, *51*, 1883. (c) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Phytochemistry* **2000**, *53*, 1075. (d) Wall, M. E.; Wani, M. C. In *Anticancer Agents Based on Natural Product Models*; Cassadt, J. M., Donuros, J. D., Eds.; Academic Press: New York, 1980; p 417. (e) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(4) Selected recent examples: (a) Halim, R.; Aurelio, L.; Scammells, P. J.; Flynn, B. L. *J. Org. Chem.* **2013**, *78*, 4708. (b) Hasaninejad, A.; Shekouhy, M.; Zare, A. *Catal. Sci. Technol.* **2012**, *2*, 201. (c) Hasaninejad, A.; Zare, A.; Shekouhy, M.; Ameri-Rad, J. *Green Chem.* **2011**, *13*, 958. (d) Tajik, H.; Niknam, K.; Sarrafan, M. *Synth. Commun.* **2011**, *41*, 2103. (e) Piechowska, J.; Gryko, D. T. *J. Org. Chem.* **2011**, *76*, 10220. (f) Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S. *Tetrahedron Lett.* **2010**, *51*, 2342. (g) Yamuna, E.; Jayarampillai, K.; Prasad, R. *J. Chem. Res* **2010**, *34*, 385. (h) Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menendez, J. C. *J. Org. Chem.* **2009**, *74*, 5715. (i) Yang, D.; Guo, W.; Cai, Y.; Jiang, L.; Jiang, K.; Wu, X. *Heteroat. Chem.* **2008**, *19*, 229. (j) Some, S.; Ray, J. K. *Tetrahedron Lett.* **2007**, *48*, 5013. (k) Khalilzadeh, M. A.; Hosseini, A.; Tajbakhsh, M. *J. Heterocycl. Chem.* **2007**, *44*, 535. (l) Ma, Z.; Xiang, Z.; Luo, T.; Lu, K.; Xu, Z.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2006**, *8*, 696. (m) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379. (n) Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509. (o) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765. (p) Rossi, E.; Abbiati, G.; Arcadi, A.; Marinelli, F. *Tetrahedron Lett.* **2001**, *42*, 3705.

10.1021/ol402164s
Published on Web 09/09/2013

to tacrine published in *J. Med. Chem.*; most of them are based on the development of new tacrine derivatives and hybrids. Besides, luotonin A and camptothecin were found as natural topoisomerases with structures typical of pentacyclic quinoline (Figure 1).[3] Therefore, a long-term and strong demand exists for the chemistry community to develop approaches toward polycyclic quinolines.[4] Among the traditional name reactions for the construction of quinolines, probably only Niementowski[5] and Friedländer[6] reactions are generally suitable for the synthesis of polycyclic quinolines. However, these methods require toxic, unstable, and often inaccessible 2-aminoaryl aldehydes, ketones, or carboxylate derivatives as starting materials. Furthermore, these name reactions mostly proceed via condensation, substitution, and addition reactions under harsh conditions with a low tolerance of functional groups. Consequently, the development of new methods to conviniently construct polycyclic quinolines with readily available starting materials is of great importance.

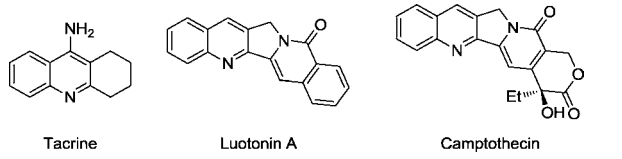
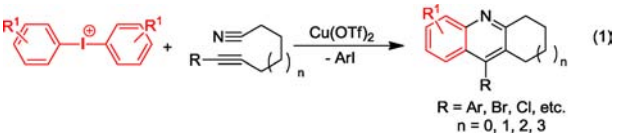


Figure 1. Some representative polycyclic quinolines.

As part of our study on heterocycle synthesis, we have reported an efficient method to synthesize multisubstituted quinolines from three readily available components, including alkynes, nitriles, and diaryliodoniums.[7] We envisaged that if ω-cyano-1-alkynes (i.e., alkynes linearly tethered with nitriles) are used to react with diaryliodoniums,[8] polycyclic quinolines would be produced. Herein, we would like to report this new strategy to prepare 5-, 6-, 7-, and 8-member ring-fused quinolines from readily available starting materials and catalyst in one step (eq 1). The process features electrophilic annulation in the mode of formal intramolecular [2 + 2 + 2] cycloaddition and is capable of directly synthesizing chloro- and bromo-quinolines, which are applied to a two-step synthesis of tacrine derivatives.



(1)

We first examined the reaction of diphenyliodonium hexafluorophosphate **1a** with ω-cyano-1-phenyl-1-pentyne **2a**, which was easily prepared by a Sonogashira coupling reaction of ω-cyano-1-pentyne (see Supporting Information). The reaction proceeded smoothly, catalyzed by $Cu(OTf)_2$ (10 mol %) in DCE to give five-member ring-fused quinoline **3aa** in 95% isolated yield, where these conditions were used in our previous study. Diphenyliodoniums **1** with a range of substituents involving 4-methyl, 4-trifluoromethyl, 2-fluoro, and 2,5-dimethyl groups all worked well to give expected fused quinolines **3ba**–**3ea** (Scheme 1). There certainly existed lots of choices for R group in cyano-pentyne **2** to be alternated to other substituents, but we attempted to use ω-cyano-1-bromo-pentyne **2b** to prepare bromoquinoline, since it is important and useful quinoline building block. To our delight, ω-cyano-1-bromo-pentyne **2b** reacted with diaryliodonium salts[9] **1a**–**1c** to give bromoquinoline **3ab**–**3cb** in good yields.[10] The structure **3cb** of was further confirmed by XRD (Figure 2).

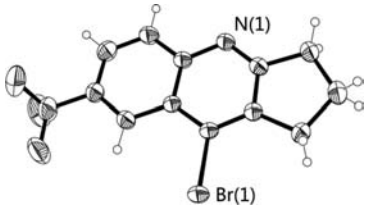


Figure 2. ORTEP drawing of **3cb** (C13H9BrF3N) with 35% probability ellipsoids.

Inspired by the successful preparation of five-member ring-fused quinolines, we next prepared six-member ring-fused quinolines using diaryliodonium salts and ω-cyano-1-hexyne **2**. Diphenyliodonium **1a** reacted with ω-cyano-1-phenyl-1-hexyne **2c** to give fused quinoline **3ac** in 90% isolated yield. A range of substituents involving 4-methyl, 4-trifluoromethyl, 2-fluoro, 4-fluoro, 4-chloro, and 2,4-dimethyl groups on the phenyl ring were well tolerated to produce desired six-member ring-fused quinoline in excellent yields (Scheme 2).

(5) (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, N. D.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140. (b) Niementowski, S. *J. Prakt. Chem.* **1895**, *51*, 564.

(6) (a) Bañón-Caballero, A.; Guillena, G.; Nájera, C. *J. Org. Chem.* **2013**, *78*, 5349. (b) Shiri, M.; Zolgigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Adv. Heterocycl. Chem.* **2011**, *102*, 139. (c) Contelles, J. M.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.

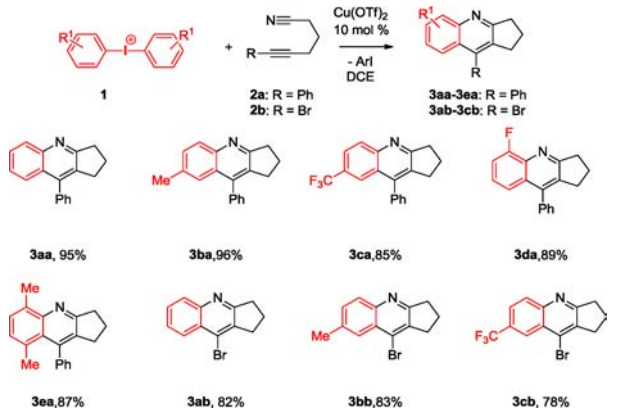
(7) (a) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323. (b) Su, X.; Chen, C.; Wang, Y.; Peng, J.; Lou, Z.; Li, M. *Chem. Commun.* **2013**, *49*, 6752. (c) Peng, J.; Chen, C.; Wang, Y.; Lou, Z.; Li, M.; Xi, C.; Chen, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7574. (d) Wang, F.; Chen, C.; Deng, G.; Xi, C. *J. Org. Chem.* **2012**, *77*, 4148.

(8) For reviews on diaryliodonium salts, see: (a) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, 370. (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (e) Grushin, V. V. *Chem. Soc. Rev.* **2000**, *29*, 315. (f) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.

(9) The anion of diaryliodonium salts **1** is triflate except **1a** (PF_6^-). Diaryliodonium salts **1** were easily synthesized according to literature except commercially available **1a**: (a) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090. (b) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (c) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521. (d) Olofsson, Bielawski, B. *Org. Synth.* **2009**, *86*, 308.

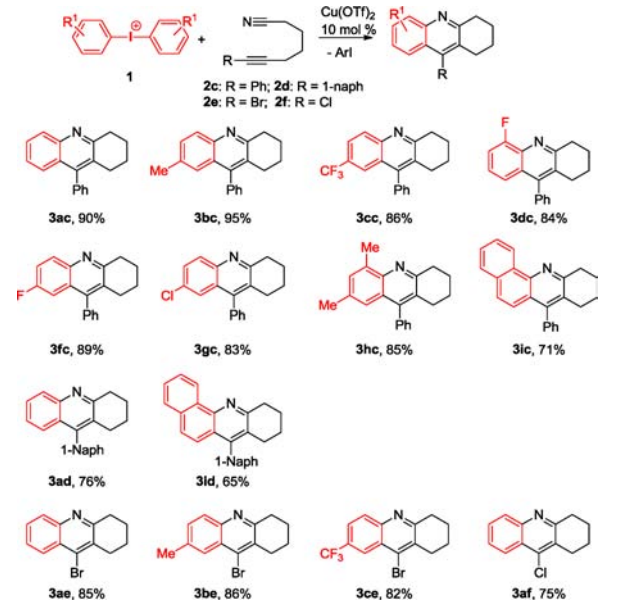
(10) Sargent, L. J.; Small, L. *J. Org. Chem.* **1946**, *11*, 359.

Scheme 1. Preparation of Dihydro-cyclopenta[b]quinoline



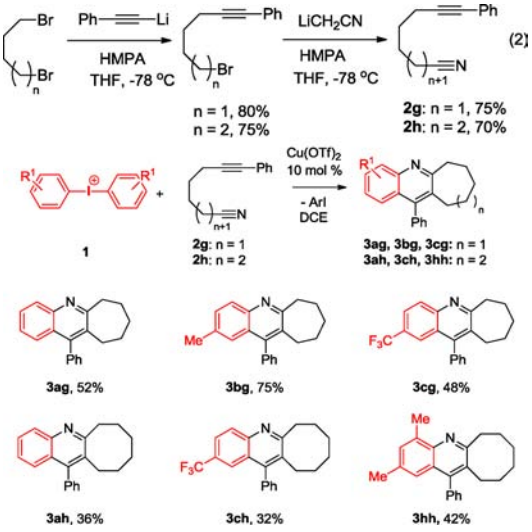
Interestingly, di(1-naphthyl)iodonium **1i** also reacted with **2c** to give tetracyclic quinoline **3ic** in 71% yield. The use of ω-cyano-1-naphthyl-1-hexyne **2d** instead of **2c** reacted with diaryliodoniums **1a** and **1i** to form **3ad** (76% yield) and **3id** (65% yield), respectively. Analogously, ω-cyano-1-bromo-hexyne **2e** reacted with diaryliodonium salts **1a**–**1c** to give bromoquinoline **3ae**–**3ce** in good yields. Furthermore, ω-cyano-1-chloro-hexyne **2f** reacted with **1a** to give chloroquinoline **3af** in 75% yield.[11]

Scheme 2. Preparation of 1,2,3,4-Tetrahydroacridine

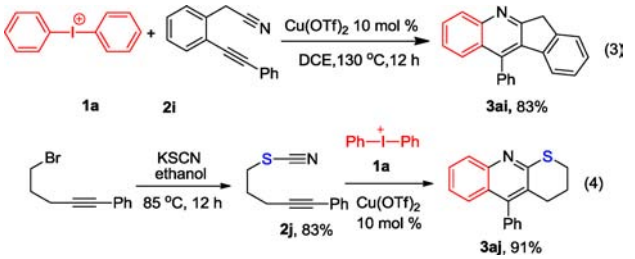


Inspired by the results above, we attempted to prepare 7- and 8-member ring-fused quinolines using ω-cyano-1-heptyne **2g** and ω-cyano-1-octyne **2h**. These two starting materials were easily prepared via a linear process from dibromoalkane and lithium phenylacetylide followed by treatment with cyanomethyl lithium (eq 2). The reaction of diphenyliodonium **1a**–**1c** with **2g** produced 7-member ring-fused quinolines **3ag**–**3cg** in synthetically useful yields. Eight-member ring-fused quinolines **3ah**, **3ch**, and **3hh** were made analogously from ω-cyano-1-octyne **2h**, albeit in lower yields.[12]

Scheme 3. Preparation of Tetrahydrocyclohepta[b]quinoline and Hexahydrocycloocta[b]quinoline



As shown above, we demonstrated that regular tricyclic quinolines were facilely synthesized from diaryliodonium salts and ω-cyano-1-alkynes. This strategy was extended to prepare tetracyclic quinolines. For this goal, diphenyliodonium **1a** was chosen to react with cyclic ω-cyano-1-alkyne **2i**, and excitingly, tetracyclic quinoline **3ai** was obtained in 83% yield (eq 3). Sulfur-containing tacrines have also received much attention and attracted us to prepare using our method. For this target, Sulfur-containing ω-cyano-1-alkyne **2j** was prepared from dibromopropane and lithium phenylacetylide followed by treatment with KSCN. The reaction of diphenyliodonium **1a** with **2j** worked very well to supply product **3aj** in 91% yield (eq 4).

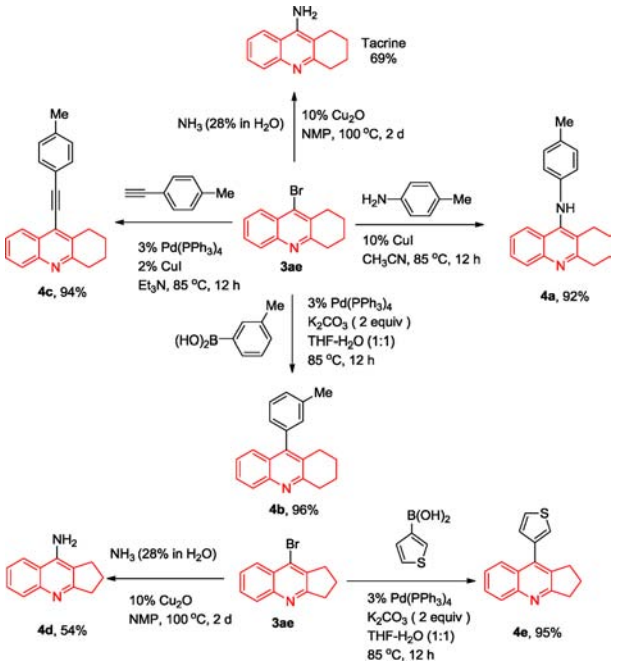


We recognized that many of the products were important building blocks toward other quinolines. For example, bromoquinoline **3ae** was transferred into tacrine in 69%

(11) (a) Wang, Y.; Guan, X. L.; Wu, P. F.; Wang, C. M.; Cao, H.; Li, L.; Guo, X. J.; Wang, F.; Xie, N.; Jiang, F. C.; Chen, J. G. *J. Med. Chem.* **2012**, *55*, 3588. (b) Szymanski, P.; Karpiński, A.; Mikiciuk-Olasik, E. *Eur. J. Med. Chem.* **2011**, *46*, 3250.

(12) In the reaction mixture of **1a** and **2h**, no starting materials remained after the completion of the reaction. Analyzing the reaction mixture by ESI-MS, a few byproducts were observed, and most of them could be assigned to the dimers of **3ah** (for details see Supporting Information, page S63).

Scheme 4. Derivation of Polycyclic Bromoquinolines



yield via amination with ammonium catalyzed by Cu_2O.[13] Other transformation involving amination with toluidine,[14] ethynylation with tolyl acetylene (Sonogashira coupling reaction),[15] and arylation with *m*-tolyl boronic acid (Suzuki coupling reaction) worked also well under classic conditions and provided quinoline derivatives **4a**–**4c**.[16] Analogously, bromoquinoline **3ab** was aminated into **4d** in 54% yield and arylated into **4e** in 95% yield. (Scheme 4)

On the basis of the previous reports[7] and our findings, we proposed a mechanism for this reaction with Ar–Cu(III) species involved. Initially, oxidative addition to the Cu(I) species (generated in situ from $Cu(OTf)_2$ via reduction or disproportion) by the diaryliodonium salt (as exemplified by Ph_2I^+) gives a Ph–Cu(III) species that

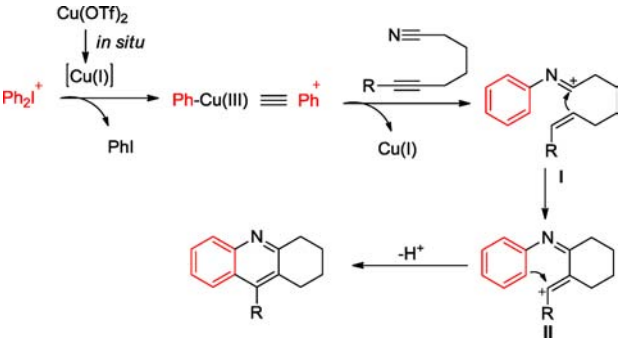
(13) Xu, H. H.; Wolf, C. *Chem. Commun.* **2009**, 3035.

(14) (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Thomas, A. W.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Girgis, N. S.; Pedersen, E. B. *Synthesis* **1985**, *5*, 547.

(15) Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.

(16) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866.

Scheme 5. Mechanism Proposed



transfers the phenyl group to the cyano of the ω-cyano-1-alkyne (as exemplified by ω-cyano-1-hexyne) to give intermediate **I**. Intermediate **I** is a highly reactive species and is quickly attacked by intramolecular acetylene moiety of the same ω-cyano-1-alkyne to give intermediate **II**. Intermediate **II** undergoes an electrophilic annulation on the phenyl ring to give the polycyclic quinoline product (Scheme 5).

In summary, we have described a concise construction of polycyclic quinolines via intramolecular [2 + 2 + 2] annulation of ω-cyano-1-alkynes with diaryliodonium salts. The process produced polycyclic quinolines in high yield with readily available staring materials and catalyst and was well tolerated with halogen substituents. Our work proved that this method was suitable for the preparation of a variety of tacrine analogues. Further design and synthesis of a bioactive complex and natural molecules are in progress.

Acknowledgment. This work was supported by National Natural Science Foundation of China (21102080) and Tsinghua University Initiative Scientific Research Program (2011Z02150).

Supporting Information Available. Full experimental details, analytical and spectroscopic data (copies of ^1H and ^{13}CNMR for new compounds). X-ray structures and crystallographic information files (CIF) for compound **3cb**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.