Dehydrogenative etherification homocoupling of heterocyclic *N*-oxides

Dong Zhang, Kai Qiao, Xin Yuan, Mingwei Zheng, Zheng Fang, Li Wan, Kai Guo

PII: S0040-4039(18)30400-3
DOI: https://doi.org/10.1016/j.tetlet.2018.03.071
Reference: TETL 49840

To appear in: *Tetrahedron Letters*

Received Date: 13 February 2018
Revised Date: 20 March 2018
Accepted Date: 23 March 2018

Please cite this article as: Zhang, D., Qiao, K., Yuan, X., Zheng, M., Fang, Z., Wan, L., Guo, K., Dehydrogenative etherification homocoupling of heterocyclic *N*-oxides, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.03.071

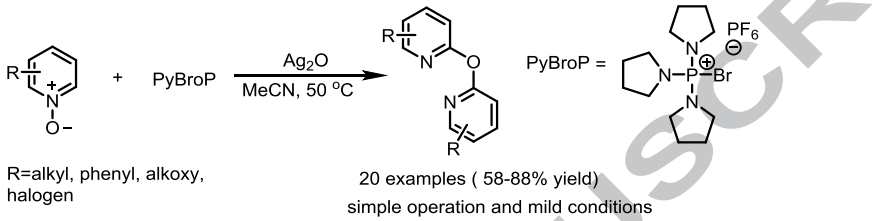
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Dehydrogenative etherification homocoupling of heterocyclic *N*-oxides

Leave this area blank for abstract info.

Dong Zhang, Kai Qiao, Xin Yuan, Mingwei Zheng, Zheng Fang, Li Wan and Kai Guo



Tetrahedron Letters
journal homepage: www.elsevier.com

Dehydrogenative etherification homocoupling of heterocyclic *N*-oxides

Dong Zhang [a] , Kai Qiao [a], Xin Yuan [a], Mingwei Zheng [a], Zheng Fang [a], Li Wan [a, b, *], and Kai Guo [a, b, *]

[a] *College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University 30 Puzhu South Road, Nanjing211816, P. R. China*
[b] *State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University 30 Puzhu South Road, Nanjing 211816, China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
regioselective
homocoupling
quinoline
PyBroP
O-tethered

ABSTRACT

A novel approach was developed for the dehydrogenative etherification homocoupling of heterocyclic *N*-oxides in the presence of silver oxide and PyBroP. Various substrates were well tolerated and the desired products were obtained in moderate to good yields. Generally, this reaction features excellent functional group compatibility, broad substrate scope and good regioselectivity.

Quinoline heterocycles are ubiquitous core structures in medicinal chemistry, the agrochemical industry, and materials science.[1] As an important class of *N*-heterocycle, the direct functionalization of quinolines has attracted extensive attention from synthetic chemists,[2] and in recent years, there have been many attempts regarding their direct functionalization. Various modifications have been reported at the C2-position of quinolines, such as halogenation, amination, alkylation, arylation, alkenylation, cyanation, and acylation.[3] Among quinoline derivatives, the homodimers of electron-deficient *N*-heterocycles are important and useful compounds. They are widely used in light-emitting materials,[4] for marking biomacromolecules in bioanalysis,[5] as ligands in transition metal catalyzed synthesis,[6] and as substructures in a wide variety of biologically active compounds.[7] Remarkably, a series of quinoline derivatives with potential anti-prostate cancer biological activities have been reported by Li and co-workers, which have similar structures to *O*-tethered dimeric quinolines (Fig. 1).[8] Malathi,[9] Małgorzata,[10] and Zhao[11] have reported the synthesis of *O*-tethered dimeric quinolines using quinolin-2 (1 *H*)-ones as precursors, but which suffers from relatively low yields, requires multiple steps, and utilises strong bases (Scheme 1). Additionally, there are few literature reports regarding the direct synthesis of homodimers of electron- deficient *N*-heterocycles *via* homocoupling of the corresponding *N*-heterocycles. Herein, we report the reaction of quinoline *N*-oxides with silver oxide in acetonitrile to afford the corresponding homodimers which are connected by an ether bond at the C2 position. The phosphonium salt PyBroP (bromotri (1-pyrrolidinyl) phosphonium hexafluorophosphate)[12] is utilised as a nucleophile to activate the homocoupling reaction.

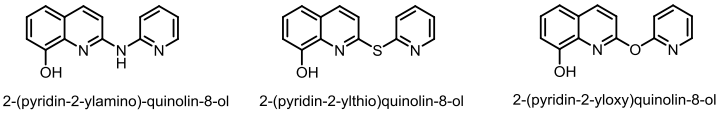
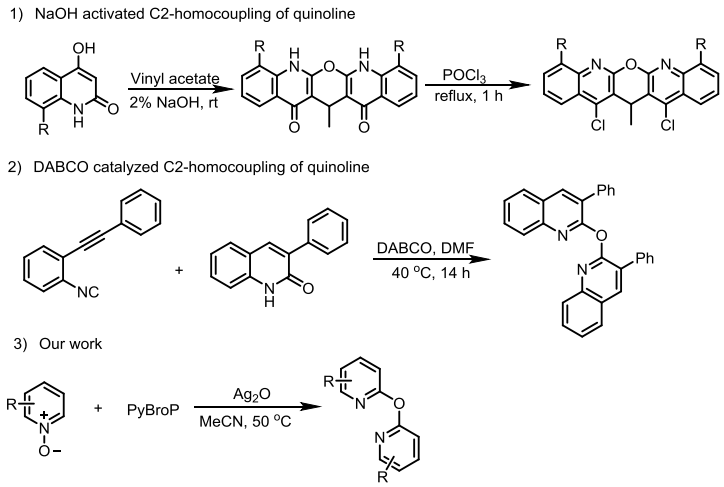


Figure 1. Structures related to *O*-tethered dimeric quinolines.



Scheme 1. Synthesis of *O*-tethered dimeric quinolines.

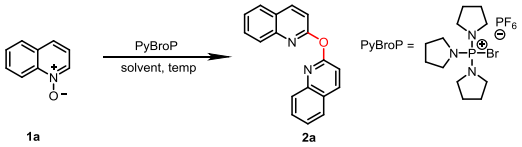
Initially, quinoline *N*-oxide **1a** was chosen as a model substrate for optimization of the reaction parameters due to its

* Corresponding author. Tel.: +86 25 5813 9926; fax: +86 25 5813 9935; e-mail: liwan126@126.com

* Corresponding author. Tel.: +86 25 5813 9926; fax: +86 25 5813 9935; e-mail: guok@njtech.edu.cn

widespread use in C–H functionalization reactions (Table 1). To our delight, excellent conversion of **1a** was achieved in the reaction utilising PyBroP (3 equiv.), potassium carbonate (2 equiv.) and acetonitrile at 25 °C for 12 h under an air atmosphere. The corresponding dimeric product **2a** was isolated in 38% yield (Entry 1). To improve the yield of the quinoline homodimer, different additives were examined. Silver oxide was demonstrated as a favorable additive, compared to potassium carbonate, sodium carbonate, cesium carbonate and silver carbonate, affording the desired product **2a** in 80% yield (Entry 5). A number of solvents such as DCE, CH_2Cl_2, THF, $CHCl_3$ and DMF were examined, however none could match the efficiency of CH_3CN (Entries 14-18). Temperatures lower or higher than 50 °C resulted in reduced yields of **2a** (Entries 7 and 13). Finally, different amounts of PyBroP and silver oxide were examined for the formation of **2a**; the optimal loading was determined as PyBroP (2 equiv.) and silver oxide (1 equiv.) (Entries 8-12).

Table 1. Reaction Conditions Optimization.[a]



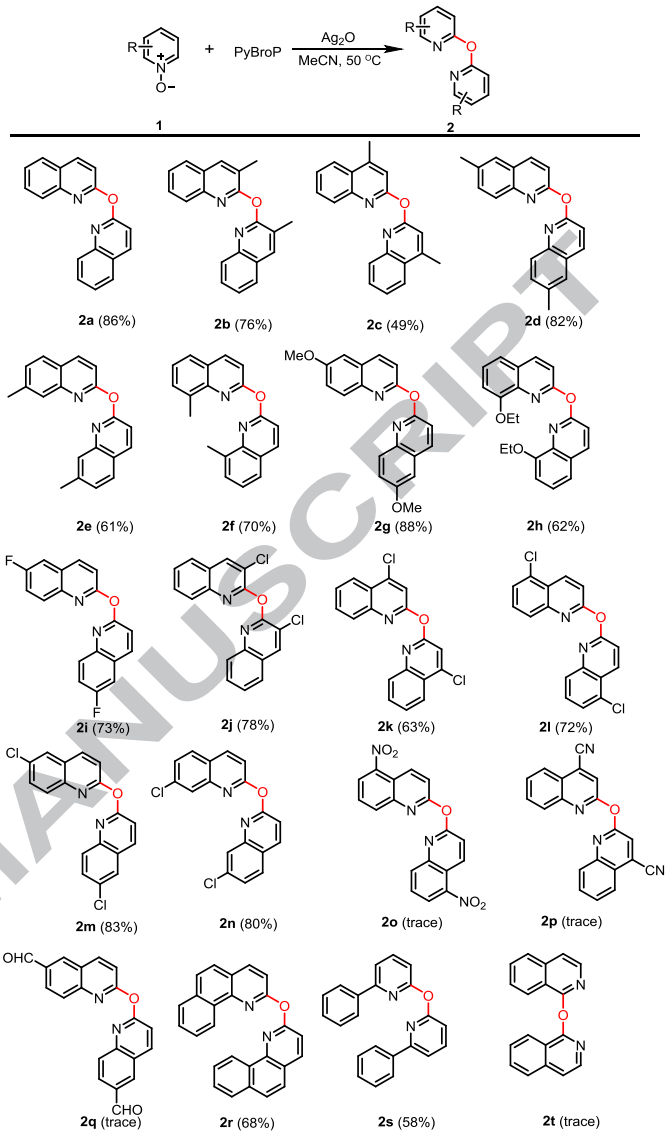
Entry	PyBroP (equiv.)	Additive (equiv.)	Temp (°C)	Solvent	Yield **2a** (%)[b]
1	3	K_2CO_3 (2)	25 °C	CH_3CN	38
2	3	Cs_2CO_3 (2)	25 °C	CH_3CN	48
3	3	Na_2CO_3 (2)	25 °C	CH_3CN	51
4	3	Ag_2CO_3 (2)	25 °C	CH_3CN	61
5	3	Ag_2O (2)	25 °C	CH_3CN	80
6	2	Ag_2O (2)	25 °C	CH_3CN	78
7	2	Ag_2O (1)	25 °C	CH_3CN	77
8	2	Ag_2O (1)	50 °C	CH_3CN	86
9	3	Ag_2O (2)	50 °C	CH_3CN	86
10	3	Ag_2O (1)	50 °C	CH_3CN	86
11	2	Ag_2O (0.5)	50 °C	CH_3CN	69
12	1	Ag_2O (1)	50 °C	CH_3CN	72
13	2	Ag_2O (1)	70 °C	CH_3CN	83
14	2	Ag_2O (1)	50 °C	CH_2Cl_2	51
15	2	Ag_2O (1)	50 °C	DCE	46
16	2	Ag_2O (1)	50 °C	THF	56
17	2	Ag_2O (1)	50 °C	$CHCl_3$	37
18	2	Ag_2O (1)	50 °C	DMF	24

[a]Reagents and conditions: quinoline *N*-oxide (0.2 mmol), PyBroP, Ag_2O, solvent (2.0 mL), under air in a sealed tube, 12 h.

[b]Isolated yield.

With the optimized reaction conditions in hand, we then explored the scope of quinoline *N*-oxides amenable to the synthesis of *O*-tethered dimeric quinolones (Table 2). A series of quinoline *N*-oxides reacted smoothly to afford a diverse array of *O*-tethered dimeric quinoline (**2b**–**n**, **2r**, **2s**) in modest to high yields. Methyl-substituted quinoline *N*-oxides gave the desired dimeric quinolines in moderate to good yields (**2b**–**f**). The presence of an electron-donating methyl group at the 4-position resulted in a slightly decreased yield of the dimeric quinoline **2c**. Methoxy and ethoxy-substituted quinoline *N*-oxides underwent dimerization in 88% (2g**)** and 62% (2h**)** yield, respectively.

Table 2. Substrate scope.[a]



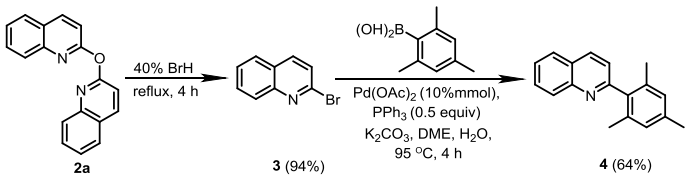
[a]Reagents conditions: quinoline *N*-oxide (0.2 mmol), PyBroP (0.4 mmol), Ag_2O (0.2 mmol), CH_3CN (2.0 mL), under air in a sealed tube, 12 h.

[b]Isolated yield.

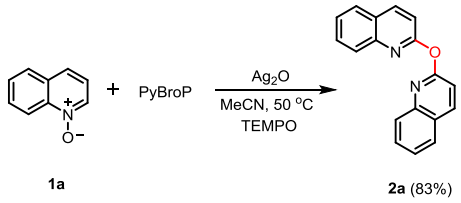
Halogenated substrates also exhibited high reactivity, affording the desired products (**2i**–**n**) in good to excellent yields, which were slightly higher than those obtained with the methyl-substituted substrates. Moreover, this methodology was effective at converting benzoquinoline and *N*-oxides of 2-phenylpyridine to their dimerized derivatives, **2r** and **2s**, respectively. A number of strongly electron withdrawing group (CN, NO_2, CHO) substituted quinoline *N*-oxides were also examined. Disappointingly, these substrates afforded the corresponding dimers in trace yields. Meanwhile in order to investigate the compatibility of this protocol with other *N*-heterocycles, isoquinoline *N*-oxides were also subjected to the optimized reaction conditions. Unfortunately, this reaction only afforded the corresponding dimer in trace yield. This discrepancy suggested that further work is required to generalize the reaction conditions.

After successful exploration of the dimerization of heterocyclic *N*-oxides, we turned our attention to the potential application of these dimeric compounds in organic synthesis. The ether linkage of **2a** is susceptible to cleavage; heating at reflux with 40% hydrobromic acid for 4 h, resulted in the formation of 2-bromoquinoline **3**.[13] Subsequent Suzuki cross-coupling reaction of 2-bromoquinoline with mesitylboronic acid afforded

compound **4** in moderate yield, which has pharmaceutically important activity as a corticotropin releasing factor (CRF) receptor antagonist.[14]



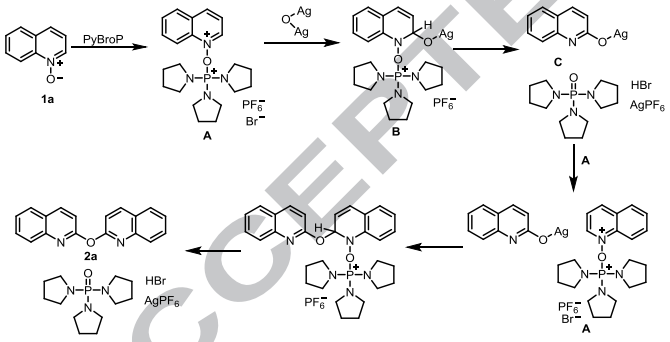
Scheme 2. Potential application of the dimeric quinolines in organic synthesis.



Scheme 3. Control experiment.

In order to shed light on the mechanism, a control experiment was carried out with the radical inhibitor TEMPO (Scheme 3). The addition of TEMPO (2 equiv.) did not suppress the formation of **2a**, suggesting that a radical reaction is not involved.

A possible mechanism for this reaction is shown in Scheme 4. In the first step, under the activation of PyBroP, compound **A** is obtained from **1a** as reported by Wang and co-workers.[15] Nucleophilic attack of Ag_2O at the C2-position of the quinoline affords compound **B**, which with the assistance of the bromide anion furnishes intermediate **C**. Next, intermediate **C** reacts as a nucleophile with compound **A**. Finally, upon the precipitation of silver ions, the desired product **2a** was obtained in high yield.



Scheme 4. Proposed mechanism.

In summary, we report a practical and mild method for the synthesis of *O*-tethered dimeric quinolines. The dimerization is operationally simple and exhibits a wide substrate scope, especially using substrates which contain electron donating groups.

Acknowledgments

This study was supported by the National Key Research and Development Program of China (2016YFB0301501), the National Natural Science Foundation of China (21502090，21522604 and 21776130), Natural Science Foundation of Jiangsu Province (BK20150942 and BK20150031).

References and notes

1. (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.*, 2003, **103**, 893–930; (b) Vieth, M.; Siegel, M. G.; Higgs, R. E.; Watson, I. A.; Robertson, D. H.; Savin, K. A.; Durst, G. L.; Hipskind, P. A. *J. Med. Chem.*, 2004, **47**, 224–232; (c) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361; (d) Carey, J. S.; Laffan, D.; Thomson, C.; Williams. M. T. *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.
2. (a) Markham, A.; Faulds. D. *Drugs*, 1998, **56**, 251–256; (b) Fournier, C.; Hamon, M.; Wannebroucq, J.; Petiprez, S.; Pruvo. J.; Hecquet, B. *Int. J. Pharm.*, 1994, **106**, 41–49; (c) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.*, 1996, **68**, 131–138; (d) Liu, J. K.; Couldwell, W. T. *Neurocrit. Care*, 2005, **2**, 124–132.
3. (a) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature*, 2012, **492**, 95–99; (b) Liu, B.; Huang, Y. M.; Lan, J. B.; Songa, F. J.; You, J. S. *Chem. Sci.*, 2013, **4**, 2163–2167; (c) Ren,X. Y.; Wen,P.; Shi,X. K.; Wang,Y. L.; Li,J.; Yang,S. Z.; Yan, H.; Huang, G. S. *Org. Lett.*, 2013, **15**, 5194–5197.
4. (a) Su, H. C.; Chen, H. F.; F. Fang, C.; Liu, C. C.; C. Wu, C.; Wong, K. T.; Liu, Y. H.; Peng, S.M. *J. Am. Chem. Soc.*, 2008, **130**, 3413–3419; (b) Moon, H. C.; Lodge, T. P.; Frisbie, C. D. *J. Am. Chem. Soc.*, 2014, **136**, 3705–3712; (c) Coe, B. J.; Curati, N. R. M.; Fitzgerald, E. C.; Coles,S. J.; Horton,P. N.; Light, M. E.; Hursthouse, M. B. *Organometallics*, 2007, **26**, 2318–2329; (d) Zhang, S.; Dokko, K.; Watanabe, M. *Chem. Mater.*, 2014, **26**, 2915–2926.
5. (a) Wachter, E.; Heidary,D. K.; Howerton, B. S.; Parkin, S.; Glazer, E. C. *Chem. Commun.*, 2012, **48**, 9649–9651; (b) Adamson, K.; Dolan, C.; Moran, N.; Forster, R. J.; Keyes, T. E. *Bioconjugate Chem.*, 2014, **25**, 928–944; (c) Chouai, A.; Wicke, S. E.; Turro, C.; Bacsa, J.; Dunbar, K. R.; Wang, D.; Thummel, R. P. *Inorg. Chem.*, 2005, **44**, 5996–6003; (d) Suntharalingam, K. T.; Johnstone, C.; Bruno, P. M.; Lin, W.; Hemann, M. T.; Lippard, S. J. *J. Am. Chem. Soc.*, 2013, **135**, 14060–14063; (e) Zhao, Q.; Yu, M.; Shi, L.; Liu, S.; Li, C.; Shi, M.; Zhou, Z.; Huang, C.; Li, F. *Organometallics*, 2010, **29**, 1085–1091; (f) Huang, H.; Zhang, P.; Yu, B.; Chen, Y.; Wang, J.; Ji, L.; Chao, H. *J. Med. Chem.*, 2014, **57**, 8971–8983.
6. (a) Toh, K. K.; Biswas, A.; Wang, Y.-F.; Tan, Y. Y.; Chiba, S. *J. Am. Chem. Soc.* 2014, **136**, 6011–6020; (b) Mi, X.; Huang, M.; Zhang, J.; Wang, C.; Wu, Y. *Org. Lett.* 2013, **15**, 6266–6269. (c) Hayashi, Y.; Santoro, S.; Azuma, Y.; Himo, F.; Ohshima, T.; Mashima, K. *J. Am. Chem. Soc.*2013, **135**, 6192–6199;
7. (a) Cao, R.; Jia, J.; Ma, X.; Zhou, M.; Fei, H. *J. Med. Chem.* 2013, **56**, 3636–3644; (b) Gandin, V.; Porchia, M.; Tisato, F.; Zanella, A.; Severin, E.; Dolmella, A.; Marzano, C. *J. Med. Chem.* 2013, **56**, 7416–7430; (c) Fukuuchi, T.; Doh-ura, K.; Yoshiharab, S.; Ohta, S. *Bioorg. Med. Chem. Lett.* 2006, **16**, 5982–5987.
8. Kun, L.; Ying, L.; Di, Z.; Yinbo, F.; Hongyue, G.; Tianyi, M.; Jiachen, W.; Dan, L.; Linxiang, Z. *Bioorg. Med. Chem.*, 2016, **24**, 1889–1897.
9. Mahalingam, M.; Shankar, R.; Butcher, R. J.; Mohan, P. S.; Kolandaivel, P. *J. Molstruc.*, 2010, **979**, 1–11.
10. Nowak, M.; Pluta, K.; Suwińska, K. *New J. Chem.*, 2002, **26**, 1216–1220.
11. Zhao, J. J.; Peng, C. L.; Liu, L. Y.; Wang, Y.; Zhu, Q. *J. Org. Chem.*, 2010, **75**, 7502–7504.
12. (a) Lian, Y. J.; Coffey, S. B.; Li, Q. F.; Londregan, A. T. *Org. Lett.*, 2016, **18**, 1362−1365; (b) Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. *Org. Lett.*, 2014, **16**, 3336−3339; (c) Castro, B.; Coste, J. *PCT Int. Appl.*, 1990, **90**, 10009.
13. Shicmri, K.; Funakoshi, K.; Saeki, S.; Hamana, M. *chem. Pharm. Bull.*, 1980, **28**, 424−430.
14. Takeda, K.; Terauchi, T.; Hashizume, M.; Shikata, K.; Taguchi, R.; Murata-Tai, K.; Fujisawa, M.; Takahashi, Y.; Shin, K.; Ino, M.; Shibata, H.; Yonaga, M.; *Bioorg. Med. Chem.*, 2012, **20**, 6559–6578.
15. Wang, D.; Zhao, J.; Wang, Y.; Hu, J.; Li, L.; Miao, L.; Feng, H.; Yu, P. *Asian J. Org. Chem.*, 2016, **5**, 1442−1446.

Highlights:

- Regioselective homocoupling of quinolines via electrophilically activated was developed.
- Eighteen examples of *O*-tethered dimeric quinolines were synthesized in good to excellent yields.
- The homodimers of electron-deficient *N*-heterocycles are important and useful compounds.