RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 32835

Received 16th March 2015
Accepted 31st March 2015

DOI: 10.1039/c5ra04632g

www.rsc.org/advances

Metal-free regioselective C-3 nitration of quinoline *N*-oxides with *tert*-butyl nitrite†

Jingjing Zhao,[ab] Pan Li,[a] Chungu Xia[a] and Fuwei Li*[a]

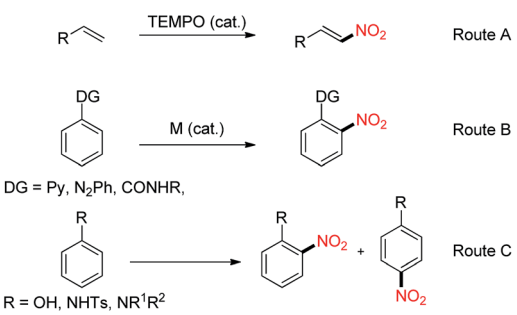
A direct and eco-friendly nitration methodology to synthesize 3-nitroquinoline *N*-oxides from quinoline *N*-oxides using *tert*-butyl nitrite as both the nitro source and oxidant has been developed. Although this reaction undergoes a free radical process, it exhibits high regioselectivity and can be smoothly scaled up to gram scale.

Aromatic nitro compounds are important and versatile building blocks in synthetic organic chemistry, and their derivatives are widely utilized in various fields such as pharmaceuticals, dyes, explosives, plastics, and materials.[1,2] Traditional nitration methods often use an excess of nitric acid or its mixture with sulfuric acid or dinitrogen pentoxide, which then result in limited functional group tolerance under such harsh conditions. Moreover, undesirable by-products and acidic waste are generated by these procedures. Recently, nitro reactions have developed rapidly with the emergence of new nitrating agents such as nitrate,[3] nitrite salts[4] and *tert*-butyl nitrite (TBN).[5]

Recently, direct C–H nitration of olefins and arenes has been developed rapidly. Accordingly, various nitroolefins were synthesized from olefins with different nitrating agents (Scheme 1, Route A).[6] Besides, direct C–H nitration of arenes could also be realized through the following two pathways: (1) Pd, Cu or Rh-catalyzed aromatic C–H nitration with the necessary assistance of directing groups (Scheme 1, Route B);[7] (2) nitration at the *ortho*- and *para*-position of phenol or amines (Scheme 1, Route C).[8] Although these nitration methods have gained significant developments, the direct nitration of heterocycles has rarely been reported.

Quinoline *N*-oxides and quinoline derivatives exist widely in natural products, pharmaceuticals and functional materials. Generally, quinoline *N*-oxides[9] were used as a typical substrate to realize C-2 functionalization *via* C–H bond activation.[10] Meanwhile, the nitration of quinoline *N*-oxides usually proceed at the 4 or 8-position in the presence of mixed acid (Scheme 2).[11,12] Comparing with the above mentioned C2- and C4-functionalization of quinoline *N*-oxide, the direct C3-functionalization including the nitration has rarely been achieved. Considering that the electron density of C3 position is slightly higher than that of C2 and C4 sites, it is speculated to provide a way to develop selective C3-functionalization method through electrophilic radical coupling strategy. As part of our continuing interest in free radical and the heterocyclic chemistry,[13] we herein disclose our investigation on the direct C3 nitration of quinoline *N*-oxide using TBN as an eco-friendly nitration source under metal free conditions. Although it is known that the selectivity of free-radical transformation is difficult to control, our methodology displays excellent C3 selectivity and can be smoothly scaled up.

Quinoline *N*-oxide **1a** was initially chosen as the model substrate to screen the various reaction parameters (Table 1). The 3-nitroquinoline *N*-oxide **2a** was isolated in 50% yield using $NaNO_2$ as NO_2 source with the assistance of $Pd(OAc)_2$ and $K_2S_2O_8$ in MeCN (entry 1). However, only trace amount of **2a** was observed in the absence of $Pd(OAc)_2$ (entry 2). Surprisingly, when TBN was employed as the nitro source and oxidant, the

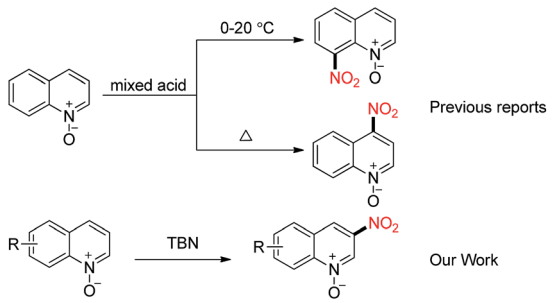


Scheme 1 Direct C–H nitration of olefins and arenes.

[a]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, China. E-mail: fuweili@licp.cas.cn; Fax: +86-931-4968129

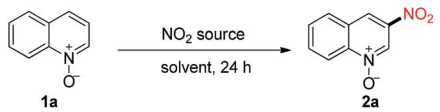
[b]Graduate University of Chinese Academy of Sciences, Beijing, 100049, China

† Electronic supplementary information (ESI) available. CCDC 1031244. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra04632g



Scheme 2 The nitration of quinoline *N*-oxides at different positions.

Table 1 Optimization of reaction conditions[a]



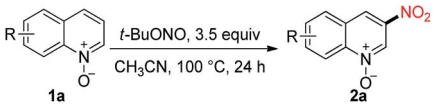
Entry	NO_2 source (equiv.)	Solvent	T (°C)	Yield (%)
1[b,c]	$NaNO_2$ (2.5)	MeCN	100	50
2[b]	$NaNO_2$ (2.5)	MeCN	100	Trace
3	*t*-BuONO (2.5)	MeCN	100	77
4[d]	*t*-BuONO (2.5)	MeCN	100	53
5[e]	*t*-BuONO (2.5)	MeCN	100	66
6	*t*-BuONO (2.5)	DCE	100	74
7	*t*-BuONO (2.5)	Toluene	100	72
8	*t*-BuONO (2.5)	H_2O	100	N.R.
9	*t*-BuONO (3.0)	MeCN	100	89
10	***t*-BuONO (3.5)**	**MeCN**	**100**	**94**
11	*t*-BuONO (3.5)	MeCN	80	74
12	*t*-BuONO (3.5)	MeCN	50	28
13	*t*-BuONO (3.5)	MeCN	25	N.R.

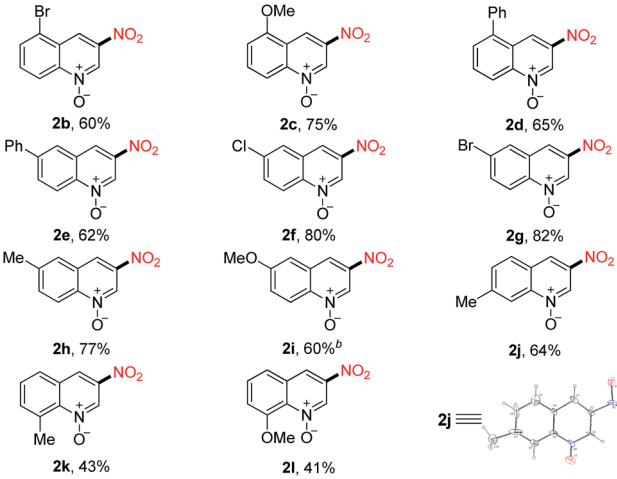
[a] All reactions were carried out on a 0.3 mmol scale in 3 mL of solvent for 24 h. Isolated yield. [b] $K_2S_2O_8$ (2.5 equiv.) was added. [c] $Pd(OAc)_2$ (10 mmol%) was added. [d] Under oxygen in pressure tubes. [e] Under argon in pressure tubes.

desired **2a** was obtained in 77% yield (entry 3). Running the reaction under oxygen or argon atmosphere made the yield decrease to 53% and 66%, respectively (entries 4 and 5). The reaction proceeded smoothly in DCE and toluene (entries 6 and 7). Unfortunately, the reaction did not work in H_2O (entry 8). To be noteworthy, 94% yield could be obtained when the loading of TBN was increased to 3.5 equivalent (entry 10). In addition, decreasing the temperature brought a distinct decrease in the yields (entries 11–13), implying such reaction is quite sensitive to temperature variation.

With these satisfactory conditions in hand, we then turned to examining the scope of quinoline *N*-oxides for this transformation (Table 2). Quinoline *N*-oxides containing electron-donating groups (OMe, Me, Ph) and electron-withdrawing groups (Br, Cl) at the 5, 6, 7, 8-positions all underwent nitration smoothly at the 3-position. 5-Bromo, 5-methoxy and 5-phenyl quinoline *N*-oxides gave the desired products (**2b**–**2d**) in 60–75% yields, respectively. Likewise, 6-substitued quinoline *N*-

Table 2 Direct C3 nitration of different quinoline *N*-oxides[a]





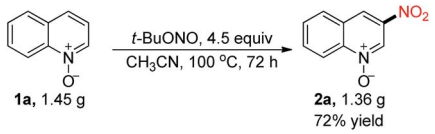
[a] A mixture of quinoline *N*-oxides (0.3 mmol), *t*-BuONO (1.05 mmol), in 3 mL of MeCN was stirred in 15 mL pressure tubes at 100 °C for 24 h. Isolated yields. [b] DCM instead of MeCN owing to poor solubility of **1i**.

oxides yielded 60–82% products (**2e**–**2i**). Meanwhile, 7-methyl quinoline *N*-oxide afforded **2j** in 64% yield. Besides, 8-substituted quinoline *N*-oxides still gave the desired products (**2k** and **2l**) in moderate yields. Unfortunately, the 2,4-substituted quinoline *N*-oxides were not suitable for this transformation.[14] No products were afforded when isoquinoline *N*-oxide and pyridine *N*-oxide were utilized as the substrates. The structure of the nitroquinoline *N*-oxide **2j** was further confirmed by X-ray crystallography (XRD) (CCDC 1031244).

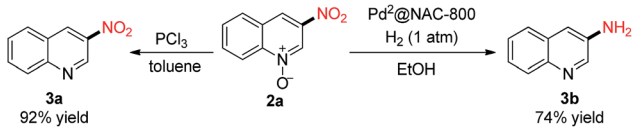
In order to prove the practicality of this approach, a gram-scale synthesis of the 3-nitroquinoline *N*-oxides **2a** (1.36 g, 72% yield) was performed, which suggested that such methodology could also be efficiently scaled up (Scheme 3).

Furthermore, 3-nitroquinoline *N*-oxides **2a** could be selectively reduced by PCl_3 to give the corresponding 3-nitroquinoline **3a** in 92% yield. Compound **2a** could be hydrogenated to 3-aminoquinoline **3b** in 74% yield using Pd^2@NAC-800 catalyst[15] under 1 atm H_2 at room temperature (Scheme 4).

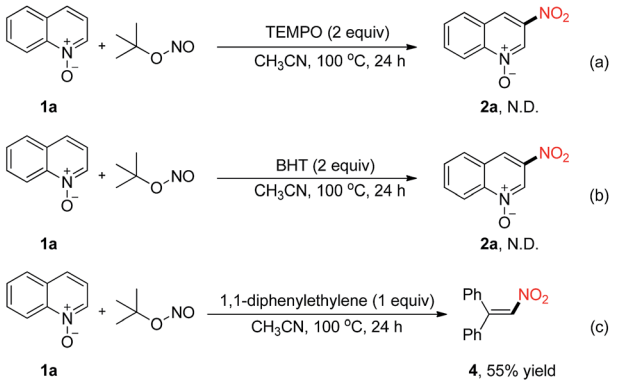
In order to deeply understand the mechanism, a series of control experiments were carried out (Scheme 5). The addition of either TEMPO (2,2,6,6-tetramethylpiperidinooxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol) could stop such nitration reaction



Scheme 3 Gram scale synthesis of **2a**.



Scheme 4 Transformations of 3-nitroquinoline *N*-oxide.

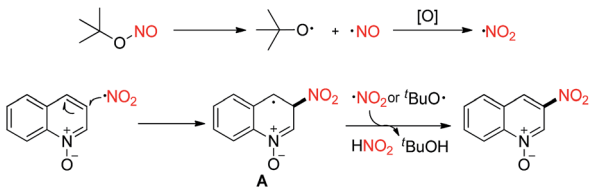


Scheme 5 Radical trapping experiments.

(Scheme 5, eqn (a) and (b)). The reaction was also inhibited by 1,1-diphenylethylene, and 1,1-diphenyl-2-nitroethylene was isolated in 55% yield (Scheme 5, eqn (c)).[6b] These results may suggest that the reaction undergo a free radical process and NO_2 radical was involved in present transformation. After the reaction, tertiary butanol was detected by GC-MS, which showed that *t*-BuONO may generate ^{t}BuO radical and NO radical, and the latter could be easily oxidized to NO_2 radical *via* a SET process.[16]

Based on the above control experiments, a plausible mechanism was proposed as shown in Scheme 6. Initially, TBN generates NO radical, which could be oxidized to NO_2 radical *via* a SET process.[5c,16] Then the NO_2 radical and quinoline *N*-oxides generated radical **A** through an electrophilic radical addition process. Eventually, the desired product was generated *via* a single-electron oxidation process with the assistance of NO_2 or ^{t}BuO radical.

In summary, we have successfully developed a direct and eco-friendly methodology for the regioselective synthesis of 3-nitroquinoline *N*-oxides in the absence of any metal catalyst and external oxidant. This transformation is realized due to the higher electron density of C3 position and the electrophilic property of NO_2 radical. Furthermore, it is worth noting that such transformation could also be smoothly scaled up. The



Scheme 6 Plausible reaction mechanism.

reactions of free radicals with other coupling partners are under investigation in our laboratory.

Acknowledgements

We gratefully acknowledge the Chinese Academy of Sciences and the National Natural Science Foundation of China (21133011 and 21373246) and the "Strategic Priority Research Program" of the Chinese Academy of Sciences (XDA09030104) for generous financial support.

Notes and references

1 For an excellent review on aromatic nitro compounds, see: G. Yan and M. Yang, *Org. Biomol. Chem.*, 2013, **11**, 2554.

2 (*a*) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, 2001; (*b*) K. Schofield, *Aromatic Nitrations*, Cambridge University Press, Cambridge, 1980; (*c*) H. Feuer and A. T. Nielson, *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, Weinheim, 1990; (*d*) G. A. Olah, R. Malhotra and S. C. Narang, *Nitration: Methods and Mechanisms*, VCH, Weinheim, 1989.

3 For selected reports on nitrate salts as the nitro source, see: (*a*) S. Manna, S. Maity, S. Rana, S. Agasti and D. Maiti, *Org. Lett.*, 2012, **14**, 1736; (*b*) N. Nowrouzi, A. M. Mehranpour, E. Bashiri and Z. Shayan, *Tetrahedron Lett.*, 2012, **53**, 4841; (*c*) M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, A. Zare, H. G. Kruger, Z. Asgari, V. Khakyzadeh and M. Kazem-Rostami, *J. Org. Chem.*, 2012, **77**, 3640; (*d*) J. Jacoway, G. G. K. S. N. Kumar and K. K. Laali, *Tetrahedron Lett.*, 2012, **53**, 6782.

4 For selected reports on nitrite salts as the nitro source, see: (*a*) Y.-M. Li, X.-H. Wei, X.-A. Li and S.-D. Yang, *Chem. Commun.*, 2013, **49**, 11701; (*b*) B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 12898; (*c*) P. J. A. Joseph, S. Priyadarshini, M. L. Kantam and H. Maheswaran, *Tetrahedron Lett.*, 2012, **53**, 1511; (*d*) G. Yan, L. Zhang and J. Yu, *Lett. Org. Chem.*, 2012, **9**, 133; (*e*) H. J. Yang, Y. Li, M. Jiang, J. M. Wang and H. Fu, *Chem.–Eur. J.*, 2011, **17**, 5652.

5 (*a*) X. Wu, J. Schranck, H. Neumann and M. Beller, *Chem. Commun.*, 2011, **47**, 12462; (*b*) X. Wu, H. Neumann and M. Beller, *Chem. Commun.*, 2011, **47**, 7959; (*c*) T. Shen, Y. Yuan and N. Jiao, *Chem. Commun.*, 2014, **50**, 554; (*d*) S. Wang, C. Shu, T. Wang, J. Yu and G. Yan, *Chin. Chem. Lett.*, 2012, **23**, 643.

6 (*a*) S. Maity, S. Manna, S. Rana, N. Togati, A. Mallick and D. Maiti, *J. Am. Chem. Soc.*, 2013, **135**, 3355; (*b*) S. Maity, N. Togati, U. Sharma and D. Maiti, *Org. Lett.*, 2013, **15**, 3384; (*c*) S. Manna, S. Jana, T. Saboo, A. Maji and D. Maiti, *Chem. Commun.*, 2013, **49**, 5286; (*d*) N. Togati, S. Maity, U. Sharma and D. Maiti, *J. Org. Chem.*, 2013, **78**, 5949; (*e*) I. Jovel, S. Prateeptongkum, R. Jackstell, N. Vogl, C. Weckbecker and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2493.

7 (*a*) Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng and N. Jiao, *ACS Catal.*, 2015, **5**, 1956; (*b*) F. Xie, Z. Qi and X. Li, *Angew.*

Chem., Int. Ed., 2013, **52**, 11862; (*c*) L. Zhang, Z. Liu, H. Li, G. Fang, B.-D. Barry, T. A. Belay, X. Bi and Q. Liu, *Org. Lett.*, 2011, **13**, 6536; (*d*) Y.-K. Liu, S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Chem.–Eur. J.*, 2010, **16**, 13590; (*e*) D. Katayev, K. F. Pfister, T. Wendling and L. J. Gooßen, *Chem.–Eur. J.*, 2014, **20**, 9902; (*f*) B. Majhi, D. Kundu, S. Ahammed and B. C. Ranu, *Chem.–Eur. J.*, 2014, **20**, 9862; (*g*) W. Zhang, S. Lou, Y. Liu and Z. Xu, *J. Org. Chem.*, 2013, **78**, 5932; (*h*) P. Sadhu, S. K. Alla and T. Punniyamurthy, *J. Org. Chem.*, 2014, **79**, 8541.

8 (*a*) Y.-X. Li, L.-H. Li, Y.-F. Yang, H.-L. Hua, X.-B. Yan, L.-B. Zhao, J.-B. Zhang, F.-J. Ji and Y.-M. Liang, *Chem. Commun.*, 2014, **50**, 9936; (*b*) D. Koley, O. C. Colón and S. N. Savinov, *Org. Lett.*, 2009, **11**, 4172; (*c*) B. Kilpatrick, M. Heller and S. Arns, *Chem. Commun.*, 2013, **49**, 514; (*d*) A. K. Bose, S. N. Ganguly, M. S. Manhas, S. Rao, J. Speck, U. Pekelny and E. Pombo-Villars, *Tetrahedron Lett.*, 2006, **47**, 1885.

9 The quinoline *N*-oxides were easily prepared from quinoline with *m*-CPBA, see: G. Li, C. Jia and K. Sun, *Org. Lett.*, 2013, **15**, 5198.

10 (*a*) G. Yan and M. Yang, *Adv. Synth. Catal.*, 2014, **356**, 2375; (*b*) J. Wu, X. Cui, L. Chen, G. Jiang and Y. Wu, *J. Am. Chem. Soc.*, 2009, **131**, 13888; (*c*) X. Chen, C. Zhu, X. Cui and Y. Wu, *Chem. Commun.*, 2013, **49**, 6900; (*d*) Z. Wu, C. Pi, X. Cui, J. Bai and Y. Wu, *Adv. Synth. Catal.*, 2013, **355**, 1971; (*e*) G. Li, C. Jia and K. Sun, *Org. Lett.*, 2013, **15**, 5198; (*f*) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254; (*g*) X. Gong, G.-Y. Song, H. Zhang and X.-W. Li, *Org. Lett.*, 2011, **13**, 1766; (*h*) Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *Chem. Commun.*, 2014, **50**, 4292; (*i*) Z. Wu, H. Song, X. Cui, C. Pi, W. Du and Y. Wu, *Org. Lett.*, 2013, **15**, 1270.

11 (*a*) T. Kaiya, N. Shirai and Y. Kawazoe, *Chem. Pharm. Bull.*, 1986, **34**, 881; (*b*) L. H. Heitman, A. Goblyos, A. M. Zweemer, R. Bakker, T. Mulder-Krieger, J. P. D. Veldhoven, H. Veies, J. Brussee and A. P. IJzerman, *J. Med. Chem.*, 2009, **52**, 926.

12 Only one example of 3-nitroquinoline *N*-oxides was reported, using stoichiometric $AgNO_3$ as the nitrating agent, but only in 33% yield, see: K. S. Sharma, S. Kumari and R. P. Singh, *Synthesis*, 1981, 316.

13 (*a*) J. Zhao, P. Li, C. Xia and F. Li, *Chem. Commun.*, 2014, **50**, 4751; (*b*) P. Li, J. Zhao, C. Xia and F. Li, *Org. Lett.*, 2014, **16**, 5992; (*c*) P. Li, J. Zhao, R. Lang, C. Xia and F. Li, *Tetrahedron Lett.*, 2014, **55**, 390; (*d*) Q. Xing, P. Li, H. Lv, R. Lang, C. Xia and F. Li, *Chem. Commun.*, 2014, **50**, 12181.

14 Possibly owing to the steric effect of 2 or 4-position, quinoline *N*-oxide derivatives (such as 2-Cl, 2-Me, 4-Me, 4-NO_2) were not suitable for this transformation.

15 The synthesis of Pd^2@NAC-800, see: Z. Li, J. Li, J. Liu, Z. Zhao, C. Xia and F. Li, *ChemCatChem*, 2014, **6**, 1333.

16 The NO radical was easily oxidized to NO_2 radical in the presence of trace amount of O_2 and H_2O, see: (*a*) T. Taniguchi, A. Yajima and H. Ishibashi, *Adv. Synth. Catal.*, 2011, **353**, 2643; (*b*) I. Jovel, S. Prateeptongkum, R. Jackstell, N. Vogl, C. Weckbecker and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2493.

