ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Direct 2-acetoxylation of quinoline *N*-oxides *via* copper catalyzed C–H bond activation†

Cite this: *Chem. Commun.*, 2013, **49**, 6900

Received 26th May 2013,
Accepted 11th June 2013

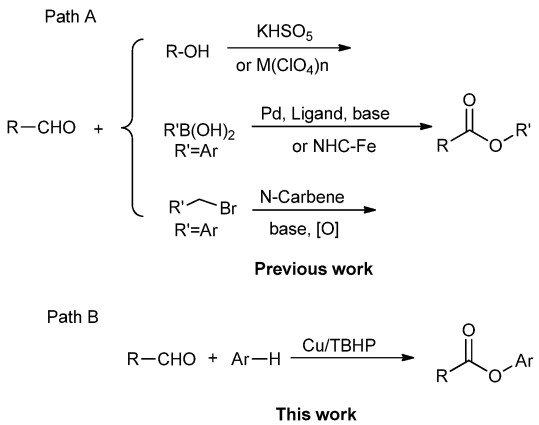
DOI: 10.1039/c3cc43947j

www.rsc.org/chemcomm

Xuan Chen,[a] Chongwei Zhu,[a] Xiuling Cui*[ab] and Yangjie Wu*[a]

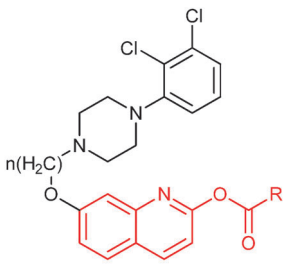
An efficient and direct 2-acetoxylation of quinoline *N*-oxides *via* copper(I) catalyzed C–H bond activation has been developed. This transformation was achieved using TBHP as an oxidant in the cross-dehydrogenative coupling (CDC) reaction of quinoline *N*-oxides with aldehydes, and provided a practical pathway to 2-acyloxyl quinolines.

Esters are ubiquitous and important functional groups, prevalent in a wide range of organic compounds: natural products, polymers, and fine chemicals.[1] Conventionally, esters were synthesized by the esterification of alcohols with carboxylic acids, acyl halides and anhydrides in the presence of a strong acid or base, which results in a multistep transformation accompanied by pollution and waste.[2] In the past decade, transition-metal catalyzed oxidative esterification of aldehydes with alcohols, boronic acids and aryl halides has provided a convenient alternative approach to prepare esters (Scheme 1, path A).[3] However, stoichiometric amounts of metal salt as an oxidant, complicate ligand and excess Lewis acid or base as additives are required, which make these transformations environmentally unfriendly. Recently, the cross-dehydrogenative coupling (CDC) reaction has emerged as a powerful protocol for C–C, C–heteroatom bond formation.[4] Such a strategy is attractive because it avoids pre-functionalization and provides a more direct approach to build a carbogenic core of complicated molecules. Several examples of constructing esters using this strategy have emerged.[5] For example, Wang[6] and Patel[7] groups have reported pioneering work on the benzylic C–H acyloxylation of alkylarenes catalyzed by copper and Bu_4NI. However, this procedure is only limited to benzylic C–H bond activation.



Scheme 1 Different approaches for synthesizing esters.

On the other hand, 2-acyloxyl quinoline is an important skeleton in drugs used in the treatment of neurological and psychiatric disorders including schizophrenia, mania, anxiety and bipolar disorder (Scheme 2).[8] Building such skeletons still relies on prefunctionalized quinoline derivatives and acyl chloride or lactams, and gives up to only 37% yield.[8,9] The direct and efficient catalytic transformation *via* dual C–H bond activation to 2-acyloxyl quinoline has not been exploited. Herein, we utilized quinoline *N*-oxides and aldehydes as the substrates, *tert*-butyl hydroperoxide (TBHP) as an oxidant and Cu(I) as a catalyst to



R=aryl, substituted aryl, alkyl, etc.

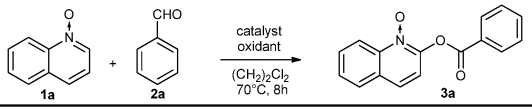
Scheme 2 Examples illustrating the importance of 2-carboxyl quinoline.

[a] *Department of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou, 450052, P. R. China. E-mail: cuixl@zzu.edu.cn, wyj@zzu.edu.cn; Tel: +86 371-67767753*

[b] *School of Biomedical Sciences, Engineering Research Center of Molecular Medicine of Chinese Education Ministry, Xiamen Key Laboratory of Ocean and Gene Drugs, Institute of Molecular Medicine of Huaqiao University, Huaqiao University, Xiamen, 361021, P. R. China*

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/c3cc43947j

Table 1 Screening reaction parameters for the reaction of quinoline *N*-oxide **1a** with benzaldehyde **2a**[a]



Entry	Catalyst	Oxidant	Solvent	T/°C	t/h	Yield[b]
1	CuBr	TBHP[c]	DCM	40	48	57
2	—	H_2O_2	DCM	40	60	n.r.
3	CuBr	H_2O_2	DCM	40	60	n.r.
4	CuI	TBHP[c]	DCM	40	48	30
5	$CuBr_2$	TBHP[c]	DCM	40	48	47
6	$Cu(OAc)_2$	TBHP[c]	DCM	40	48	39
7	CuBr	TBHP[d]	DCM	40	48	67
8	CuBr	TBHP[d]	DCE	70	24	69
9[e]	CuBr	TBHP[d]	DCE	70	24	11
10[f]	CuBr	TBHP[d]	DCE	70	24	52
11	CuBr	TBHP[d]	Dioxane	70	24	n.r.
12	CuBr	TBHP[d]	DMSO	70	24	n.r.
13	CuBr	TBHP[d]	MeOH	70	24	n.r.
14	CuOTf	TBHP[d]	DCE	70	24	77
15	CuOTf	TBHP[d]	DCE	70	12	72
16	CuOTf	TBHP[d]	DCE	70	8	84
17	CuOTf	TBHP[d]	DCE	70	4	71

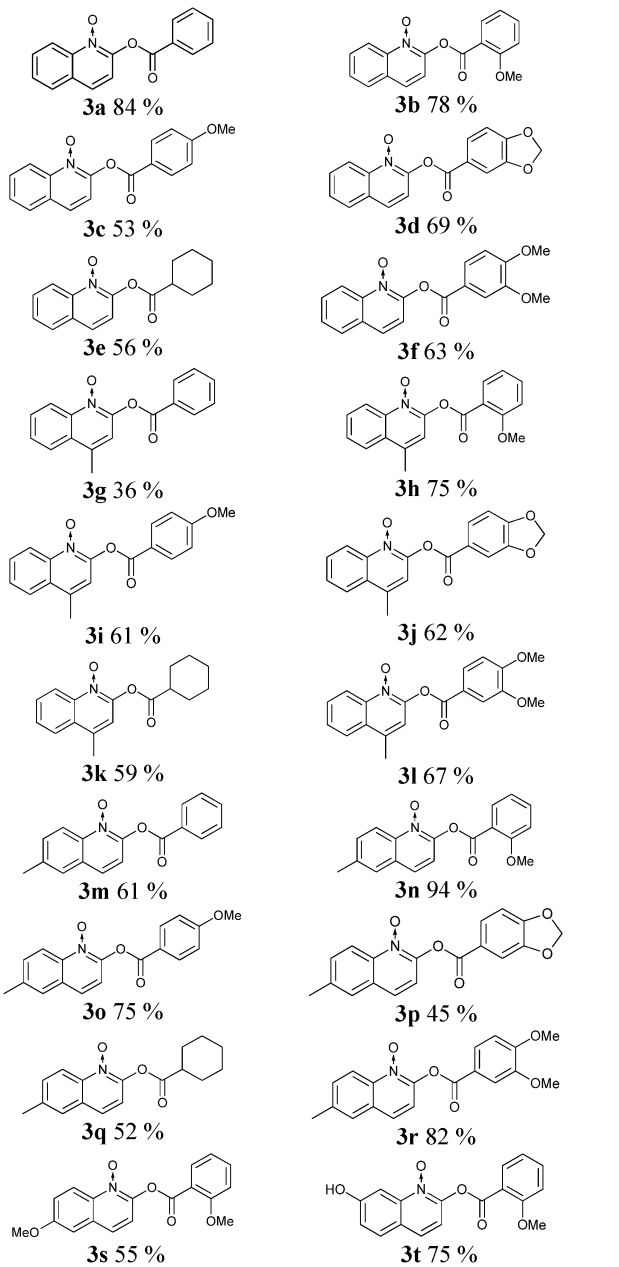
[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), oxidant (0.6 mmol), solvent (2 mL), catalyst (5 mol%). [b] Isolated yields. [c] TBHP (70 aq.%). [d] TBHP (5–6 M in decane). [e] 3 mol% CuBr. [f] 10 mol% CuBr. n.r. = no reaction.

synthesize a series of 2-acyloxyl quinoline *N*-oxides under mild, operationally simple and environmentally friendly conditions (Scheme 1, path B).

The condensation of quinoline *N*-oxide **1a** with benzaldehyde **2a** was initially chosen as a model reaction to screen the reaction parameters. The results are listed in Table 1. To our delight, the desired product **3a** was observed with an isolated yield of 57% in CH_2Cl_2 (DCM), using 5 mol% CuBr as a catalyst and 70% TBHP in water as an oxidant (entry 1, Table 1). Product **3a** was not detected with or without a catalyst using H_2O_2 as an oxidant instead of TBHP (entries 2–3, Table 1). CuBr provided a higher yield compared to other Cu salts tested, such as CuI, $CuBr_2$ and $Cu(OAc)_2$ (entry 1 *vs.* 4–6, Table 1). TBHP in decane (5–6 M) could improve this transformation and give the desired product **3a** in 67% yield (entry 7, Table 1). The yield could be increased slightly to 69% when the temperature was increased up to 70 °C (entry 8, Table 1). Changing the amount of the catalyst loading to 3 mol% or 10 mol% disfavoured this reaction and gave 11% and 52% yields, respectively (entries 9 and 10, Table 1). The solvent also played a crucial role. The desired product was not observed using other solvents, such as 1,4-dioxane, DMSO and MeOH (entries 11–13, Table 1). As is well known, the acidity of the C(2)–H bond in the heteroaromatic ring can be enhanced by using a Lewis acid (LA) catalyst.[10] To improve this transformation, the catalyst was switched from CuBr to more Lewis acidic CuOTf and afforded 77% yield (entry 14, Table 1). 84% yield could be achieved by shortening the reaction time to 8 h (entry 16, Table 1). However, the yield decreased to 71% when the reaction time was 4 h (entry 17, Table 1). The optimized reaction conditions were identified as 3 equiv. of benzaldehyde in the presence of 3 equiv. TBHP in $(CH_2)_2Cl_2$ and 5 mol% CuOTf as a catalyst at 70 °C for 8 h (entry 16, Table 1).

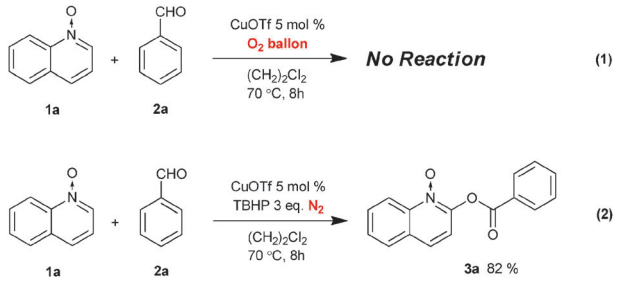
With the optimized reaction conditions in hand, the scope and generality of substrates were investigated. Acetoxylation occurred at

Table 2 2-Acetoxylation of quinoline *N*-oxides with aldehydes[a]

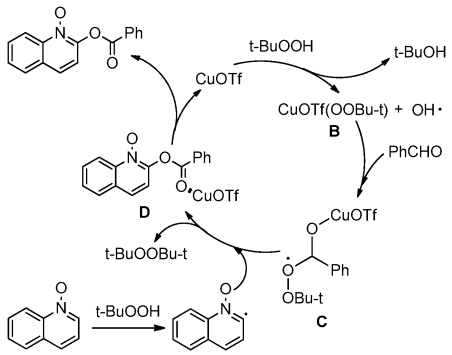


[a] Conditions: **1** (0.2 mmol), **2** (0.6 mmol), CuOTf (5 mol%), TBHP (0.6 mmol, 5–6 M in decane), $(CH_2)_2Cl_2$ (2 mL), 70 °C, 8 h.

C_2 of quinoline *N*-oxides in all cases (Table 2). When quinoline *N*-oxide (**1a**) was subjected to the optimized reaction conditions various electron-rich arylaldehydes could be converted into 2-acyloxyl quinoline *N*-oxides in moderate to good yields (**3a–3f**, Table 2). Benzaldehyde and 2-methoxybenzaldehyde provided the desired products in 84% and 78% yields, respectively (**3a** and **3b**, Table 2). Different quinoline *N*-oxides were tested for this transformation with electron-rich arylaldehydes. 4-Methylquinoline *N*-oxide



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism for the oxidative esterification.

gave the corresponding desired products in 36–75% yield (**3g–l**, Table 2). 6-Methylquinoline *N*-oxide reacted smoothly with 2-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde, affording the desired products in 94% and 82% yields, respectively (**3n** and **3r**, Table 2). 6-Methoxyquinoline *N*-oxide and 7-hydroxyquinoline *N*-oxide provided the desired products in 55% and 75% yields, respectively (**3s** and **3t**, Table 2). Notably, cyclohexylaldehyde could also be used as a substrate in this catalytic system and gave 2-(cyclohexylcarboxy)quinoline *N*-oxides in 56%, 59% and 52% yields, respectively (**3e**, **3k** and **3q**, Table 2), which made the present transformation attractive for future applications. However, this reaction was limited to the electron-withdrawing aldehydes and heterocyclic aldehydes. No desired product was detected for the 2-pyridinecarboxylaldehyde. And furfural only gave the desired product in 10% yield.

To clarify the reaction mechanism and the oxygen source, control experiments were performed (Scheme 3). When the reaction of quinoline *N*-oxide **1a** with benzaldehyde **2a** was carried out under an oxygen atmosphere in the absence of TBHP, no desired product was detected (Scheme 3, eqn (1)). Whereas, the above reaction proceeded smoothly under a nitrogen atmosphere using 3 equiv. TBHP as an oxidant and provided the desired product **3a** in 82% yield, which is close to the result obtained under the optimal reaction conditions (84% yield, **3a**, Table 2) (Scheme 3, eqn (2)). These results indicate that TBHP served as a terminal oxygen source.

The reaction mechanism was proposed according to the literature[11] and results obtained are shown in Scheme 4 and eqn (1) and (2). Copper(I) was oxidized to copper(II) by TBHP, generating a Cu(II) species **A** and a hydroxyl radical (eqn (1)). Then Cu(II) species **A** reacted with the second molecule of TBHP to give a *tert*-butylperoxy complex **B** and *t*-BuOH (eqn (2)). **B** and the hydroxyl radical could react with benzaldehyde to form intermediate **C**. Then **C** was attacked by the quinoline *N*-oxide radical which was formed by TBHP to form species D. Finally, **D** released the desired product and CuOTf as well (Scheme 4).

$$\mathrm{CuOTf} + t\text{-BuOOH} \rightarrow \underset{\mathbf{A}}{\mathrm{CuOTf(OBu\text{-}}t)} + \mathrm{HO}^{\bullet} \qquad (1)$$

$$t\text{-BuOOH} + \mathbf{A} \rightarrow \underset{\mathbf{B}}{\mathrm{CuOTf(OOBu\text{-}}t)} + t\text{-BuOH} \qquad (2)$$

In summary, we have developed a direct acetoxylation of quinoline *N*-oxides catalyzed by a cheap copper(I) salt. This novel protocol provided a simple pathway to synthesize pharmaceutically active quinoline-containing esters. The method features direct dual C–H bond activation as a key step and uses a minimally toxic and relatively cheap copper salt as a catalyst. The scope, applications and mechanism of this reaction are under investigation.

This work was supported by NSF of China (21102133, 21172200) and the NSF of Henan (082300423201).

Notes and references

1 J. Otera and J. Nishikido, *Esterification: methods, reactions, and applications*, Wiley-VCH, 2010.
2 R. C. Larock, *Comprehensive organic transformations: a guide to functional group preparations*, Wiley-VCH, New York, 1999.
3 (*a*) K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302; (*b*) W.-J. Yoo and C.-J. Li, *Tetrahedron Lett.*, 2007, **48**, 1033; (*c*) X.-F. Wu and C. Darcel, *Eur. J. Org. Chem.*, 2009, 1144; (*d*) B. Xu, X. Liu, J. Haubrich and C. M. Friend, *Nat. Chem.*, 2009, **2**, 61; (*e*) C. Qin, H. Wu, J. Chen, M. Liu, J. Cheng, W. Su and J. Ding, *Org. Lett.*, 2008, **10**, 1537; (*f*) J. o. N. Rosa, R. S. Reddy, N. R. Candeias, P. M. S. D. Cal and P. M. P. Gois, *Org. Lett.*, 2010, **12**, 2686; (*g*) R. Gopinath and B. K. Patel, *Org. Lett.*, 2000, **2**, 577; (*h*) R. Gopinath, B. Barkakaty, B. Talukdar and B. K. Patel, *J. Org. Chem.*, 2003, **68**, 2944; (*i*) B. Maji, S. Vedachalan, X. Ge, S. Cai and X.-W. Liu, *J. Org. Chem.*, 2011, **76**, 3016; (*j*) B. R. Travis, M. Sivakumar, G. O. Hollist and B. Borhan, *Org. Lett.*, 2003, **5**, 1031; (*k*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331.
4 (*a*) J.-Q. Yu and Z. Shi, *C–H Activation*, Springer, 2010; (*b*) C.-J. Li, *Acc. Chem. Res.*, 2008, **42**, 335; (*c*) G. Deng, L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 6278; (*d*) Z. Li and C.-J. Li, *Eur. J. Org. Chem.*, 2005, 3173; (*e*) X. Guo and C.-J. Li, *Org. Lett.*, 2011, **13**, 4977; (*f*) C. A. Correia, L. Yang and C.-J. Li, *Org. Lett.*, 2011, **13**, 4581; (*g*) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu and X. Wan, *Chem.–Eur. J.*, 2011, **17**, 4085; (*h*) H. Jiang, A. Lin, C. Zhu and Y. Cheng, *Chem. Commun.*, 2013, **49**, 819; (*i*) H. Liu, L. Cao, J. Sun, J. S. Fossey and W.-P. Deng, *Chem. Commun.*, 2012, **48**, 2674; (*j*) S. Gowrisankar, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 5139; (*k*) C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2011, **50**, 5144; (*l*) Y.-M. Huang, F. J. Song, Z. Wang, P. H. Xi, N.-J. Wu, Z.-G. Wang, J.-B. Lan and J.-S. You, *Chem. Commun.*, 2012, **48**, 2864; (*m*) T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 11846.
5 (*a*) W.-J. Yoo and C.-J. Li, *J. Org. Chem.*, 2006, **71**, 6266; (*b*) C. Liu, S. Tang, L. Zheng, D. Liu, H. Zhang and A. Lei, *Angew. Chem., Int. Ed.*, 2012, **51**, 5662; (*c*) J. Feng, S. Liang, S.-Y. Chen, J. Zhang, S.-S. Fu and X.-Q. Yu, *Adv. Synth. Catal.*, 2012, **354**, 1287.
6 J. Huang, L.-T. Li, H.-Y. Li, E. Husan, P. Wang and B. Wang, *Chem. Commun.*, 2012, **48**, 10204.
7 S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee and B. K. Patel, *Org. Lett.*, 2012, **14**, 3982.
8 L. C. Blumberg, J. F. Remenar, O. Almarrson and T. A. Zeidan, *US. pat.* US2011/041830, 2011.
9 Y. Tagawa, J. I. Tanaka, K. Hama, Y. Goto and M. Hamana, *Tetrahedron Lett.*, 1996, **37**, 69.
10 G. Deng and C.-J. Li, *Org. Lett.*, 2009, **11**, 1171.
11 (*a*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (*b*) E. Boess, C. Schmitz and M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317; (*c*) F. Minisci, F. Fontana, S. Araneo, F. Recupero, S. Banfi and S. Quici, *J. Am. Chem. Soc.*, 1995, **117**, 226.

