Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 6557

Received 19th May 2014,
Accepted 8th July 2014

DOI: 10.1039/c4ob01025f

www.rsc.org/obc

Metal-free oxidative olefination of primary amines with benzylic C–H bonds through direct deamination and C–H bond activation†

Liang Gong,‡ Li-Juan Xing,‡ Tong Xu, Xue-Ping Zhu, Wen Zhou, Ning Kang and Bin Wang*

An oxidative olefination reaction between aliphatic primary amines and benzylic sp^3 C–H bonds has been achieved using *N*-bromosuccinimide as catalyst and *tert*-butyl hydroperoxide as oxidant. The olefination proceeds under mild metal-free conditions through direct deamination and benzylic C–H bond activation, and provides easy access to biologically active 2-styrylquinolines with (*E*)-configuration.

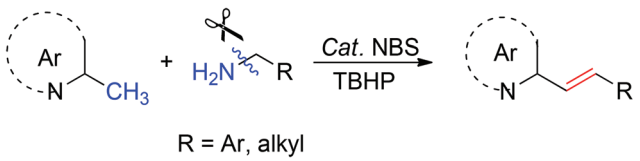
Introduction

The deamination of aliphatic primary amines to achieve α-carbon functionalization is an important transformation in organic synthesis. Traditionally the deamination has been achieved by the aggressive oxidation of aliphatic amines using oxidants such as nitrous acids,[1] permanganates,[2] dichromates,[3] quinonoid species[4] and other oxidants,[5] but these suffer from low selectivity and a tendency to overoxidation. The deamination of primary amines under mild conditions has remained a challenge.

Very recently a novel type of iodide-catalyzed oxidative cross-dehydrogenative coupling reactions has received considerable attention due to its use of mild metal-free conditions and environmentally friendly oxidants such as hydrogen peroxide, oxygen or *tert*-butyl hydroperoxide (TBHP).[6] In contrast, the catalytic use of bromine, a similarly important halogen in organic synthesis and occupying the same column as iodine in the periodic table, has been ignored in these oxidative coupling reactions. A number of recent studies have revealed that the replacement of iodides with bromides may significantly improve catalytic efficiency and perhaps lead to unexpected transformations.[7] The exploration of bromide-catalyzed oxidative coupling reactions is therefore highly desirable.

2-Styrylquinolines have been recognized as potent HIV-1 integrase inhibitors that are able to block HIV-1 replication in cell-based assays.[8] Structure–activity relationship study clearly indicates that the (*E*)-configuration is required in these structures for biological activity.[8b,9] The conventional approach to the preparation of 2-styrylquinolines is an aldol-type condensation of 2-methylquinolines with aldehydes using acetic anhydride at high temperature.[8a,10] Recent advances include the use of alternatives to aldehydes, such as *N*-aryl imines,[11] *N*-sulfonyl imines[12] or *in situ* generated *N*-aryl imines,[13] which enable successful olefination with 2-methylquinolines. To our knowledge, however, the olefination of aliphatic primary amines with sp^3 C–H bonds through direct deamination and C–H activation is unknown (Scheme 1). As part of our ongoing efforts toward the development of halide-mediated cross-dehydrogenative coupling (HCDC) reactions,[14] we are now able to describe a *N*-bromosuccinimide (NBS)-catalyzed method for the construction of olefins by direct deamination of aliphatic primary amines and the benzylic C–H bond activation of 2-methylquinolines. This method employs TBHP as a green oxidant and enables direct deamination and benzylic C–H bond olefination to take place under mild and metal-free conditions, furnishing the alkenes with (*E*)-configuration.

We initiated our investigation using 2-methylquinoline (**1a**) and benzylamine (**2a**) as model substrates to identify the optimum reaction conditions (Table 1). Iodine-based catalysts were initially investigated in olefination reactions. When **1a** was treated with **2a** (2 equiv.) in the presence of tetra-*n*-butylammonium iodide (40 mol%) and TBHP (2 equiv.) at 80 °C for



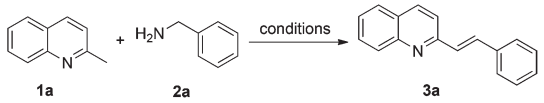
Scheme 1 The olefination of a primary amine.

State Key Laboratory of Medicinal Chemical Biology and College of Pharmacy, Nankai University, Tianjin, 300071, China. E-mail: wangbin@nankai.edu.cn; Fax: (+86)-22-23507760

†Electronic supplementary information (ESI) available. CCDC 942456. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01025f

‡Liang Gong and Li-Juan Xing contributed equally to this work.

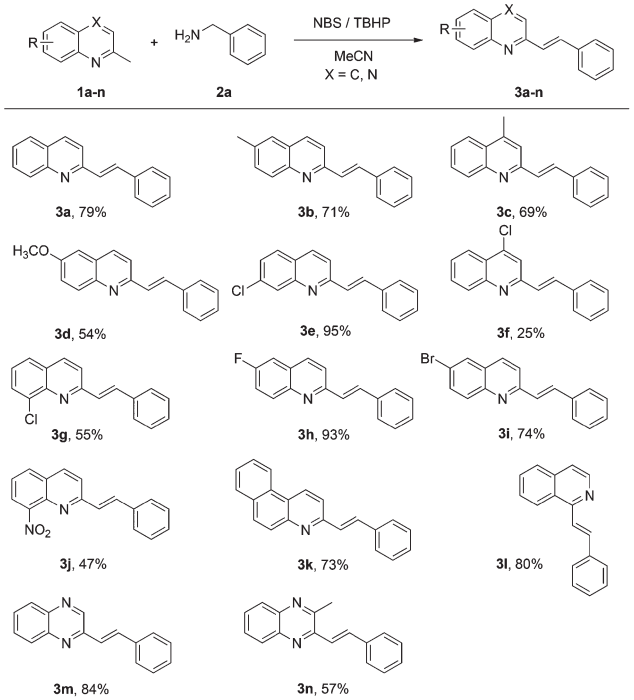
Table 1 Optimization of the reaction conditions[a]



Entry	**2a** (mmol)	Catalyst (mol%)	Oxidant (mmol)	Yield (%)
1	1.0	Bu_4NI (40)	TBHP (2.0)	Trace
2	1.0	I_2 (40)	TBHP (2.0)	0
3	1.0	KI (40)	TBHP (2.0)	34
4	1.0	Bu_4NBr (40)	TBHP (2.0)	37
5	1.0	PhBr (40)	TBHP (2.0)	25
6	1.0	NBS (40)	TBHP (2.0)	66
7	0.6	NBS (20)	TBHP (1.0)	67
8	0.6	NBS (20)	TBPB (1.0)	37
9	0.6	NBS (20)	H_2O_2 (1.0)	48
10	0.6	NBS (20)	$K_2S_2O_8$ (1.0)	0
11[b]	0.6	NBS (20)	TBHP (1.0)	28
12[c]	0.6	NBS (20)	TBHP (1.0)	70
13[d]	0.6	NBS (20)	TBHP (1.0)	79

[a] Reaction conditions: **1a** (0.5 mmol) and **2a** in 1 mL of CH_3CN under air, 80 °C, 24 h, isolated yield. [b] Under nitrogen. [c] 100 °C. [d] In the dark, 100 °C, 48 h.

Table 2 Substrate scope of various quinolines[a]



[a] Reactions were carried out in the dark with quinolines (0.5 mmol), benzylamine (0.6 mmol), NBS (0.1 mmol) and TBHP (1.0 mmol) in MeCN (1 mL) at 100 °C for 48 h; yield as indicated.

24 h, only a trace amount of the product **3a** was observed (Table 1, entry 1). Further research demonstrated that iodine was ineffective for this transformation (Table 1, entry 2), and KI gave a low yield (34%) (Table 1, entry 3). We next investigated bromine-based catalysts, including Bu_4NBr, PhBr and NBS. With the addition of 40 mol% of Bu_4NBr or PhBr, it was found that the reaction provided the olefination product **3a** in 37% and 25% yield, respectively (Table 1, entries 4 and 5). On the other hand, when NBS was used as catalyst a 66% yield of **3a** was obtained (Table 1, entry 6). There was no decrease in yield when the quantities of **2a**, NBS and TBHP were reduced at the same time (Table 1, entry 7). We then continued optimizing the reaction conditions based on entry 7. Among the oxidants tested, such as 70% TBHP in water, *tert*-butyl peroxybenzoate (TBPB), 30% hydrogen peroxide (H_2O_2) in water, or potassium persulfate ($K_2S_2O_8$) (Table 1, entries 7–10), aqueous TBHP provided the best result, producing **3a** in 67% yield (Table 1, entry 7). The olefination products were isolated in lower yield in the presence of TBPB or H_2O_2 (Table 1, entries 8 and 9), while the use of $K_2S_2O_8$ gave no olefination product (Table 1, entry 10). The yield of **3a** was decreased when the reaction proceeded under a nitrogen atmosphere (Table 1, entry 11). Among the reaction temperatures examined, it turned out that reaction at 100 °C gave **3a** in 70% yield (Table 1, entry 12). Interestingly, the highest yield of **3a** was obtained when conducting this reaction in the dark over a prolonged reaction time (Table 1, entry 13). Thus, a combination of 20 mol% of NBS as catalyst and 2 equiv. of aqueous TBHP as oxidant at 100 °C for 48 h in the dark was found to be the optimal conditions for this transformation.

With the optimized reaction conditions established, the scope of the reaction substrates was investigated (Table 2). 2-Methylquinolines with functional groups such as fluoro, chloro, bromo, methoxy, methyl or nitro were compatible with the reaction conditions and gave the corresponding products in moderate to good yield (Table 2, **3a–3n**). 2,6- and 2,4-dimethyl-substituted quinolines provided the desired products in 71% and 69% yield, respectively (Table 2, **3b** and **3c**). Interestingly, the active C-4 methyl group of 2,4-dimethyl quinoline remained unaffected under these conditions. The reactions of various chloroquinolines gave the corresponding products in yields ranging from 25% to 95% (Table 2, **3e–3g**). The olefination of 7-chloro-2-methylquinoline successfully produced 7-chloro-2-styrylquinoline in 95% yield (Table 2, **3e**), while 4-chloro-2-methylquinoline only gave the desired product **3f** in 25% yield (Table 2, **3f**). When 8-chloro-2-methylquinoline was used, a moderate yield of **3g** was obtained. 2-Methylquinolines containing other electron-withdrawing groups (fluoro, bromo, nitro) were olefinated in moderate to good yield (Table 2, **3h–3j**). 3-Methylbenzo[*f*]quinoline (**1k**), with a large aromatic ring, also exhibited excellent reactivity (Table 2, **3k**). The olefination of 1-methyl-isoquinoline with benzylamine gave a good yield of product **3l**.

We also tested 2-methylquinoxaline and 2,3-dimethyl quinoxaline, which underwent the olefination reaction in moderate or high yield, respectively (Table 2, **3m** and **3n**). In addition, 2,3-dimethyl quinoxaline reacted with benzylamine **2a** to give the olefination product **3n** exclusively at the 2-methyl position, without any 3-methyl olefination. The structure of compound **3a** was further confirmed by single-crystal

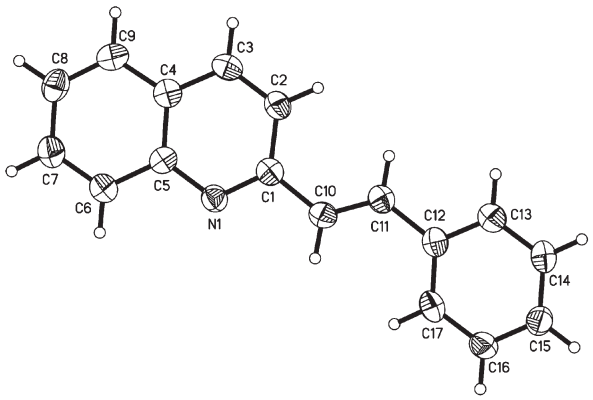
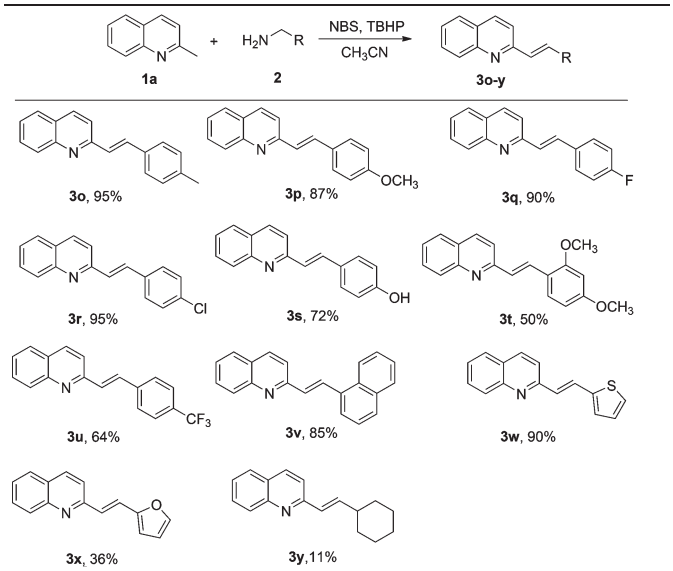


Fig. 1 The crystal structure of compound **3a**.

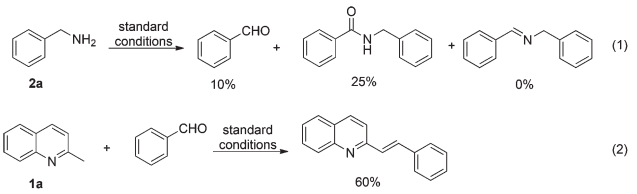
Table 3 Substrate scope of various amines[a]



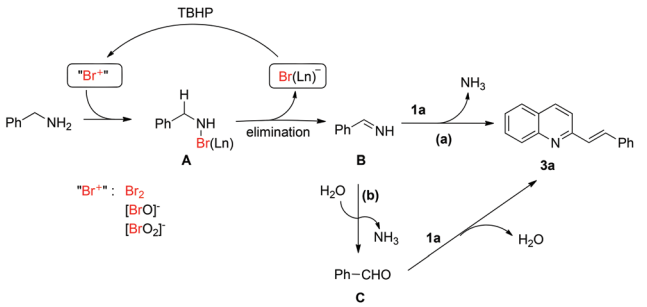
[a] Reactions were carried out in the dark with 2-methylquinoline (0.5 mmol), amines (0.6 mmol), NBS (0.1 mmol) and TBHP (1.0 mmol) in MeCN (1 mL) at 100 °C for 48 h; yield as indicated.

X-ray crystallographic analysis (Fig. 1).[15] The X-ray crystallography and ^{1}H NMR spectrum firmly established the absolute (*E*)-configuration of the product of olefination.

The present olefination was successfully extended to include various amines (Table 3). Benzylamines bearing electron-donating (Table 3, **3o**, **3p**, **3s**, **3t** and **3v**) or electron-withdrawing (Table 3, **3q**, **3r** and **3u**) groups reacted with 2-methylquinoline smoothly, giving the corresponding products in 50–95% yield. It was found that heterocyclic methanamines, such as 2-thiophen-methanamine and 2-furanmethanamine, could be transformed into their corresponding olefination products in good yield (Table 3, **3w**, **3x**). The deamination of aliphatic amine also proceeded to give the product **3y**, albeit in low yield.



Scheme 2 Control experiments to study reaction mechanism.



Scheme 3 Possible mechanism for the olefination reaction.

To obtain an insight into the mechanism of the olefination a number of control experiments were carried out. When benzylamine **2a** alone was subjected to the standard conditions, benzaldehyde and *N*-benzylbenzamide were obtained in 10% and 25% yield, respectively. The self-condensation product, benzylimine was not detected under oxidative conditions (Scheme 2, Reaction 1). 2-Methylquinoline **1a** was then treated with benzaldehyde under standard conditions, providing **3a** in 60% yield (Scheme 2, Reaction 2). The results indicate that benzaldehyde may be involved as a key intermediate in the olefination.

On the basis of earlier studies[6b,13b,16] and the above results, we propose the reaction mechanism shown in Scheme 3 as plausible, taking for simplicity 2-methylquinoline and benzylamine as substrates. Firstly, oxidation of the bromine source with TBHP produces a highly active electrophilic bromine species (Br_2, $[BrO]^-$, $[BrO_2]^-$), which then adds to benzylamine to give *N*-bromoamine **A**, followed by an elimination to generate imine **B**. Two alternative pathways for imine **B** are proposed to provide the target compound. In pathway (a), imine **B**, which bears an electrophilic carbon atom, is attacked directly by 2-methylquinoline and loses a molecule of ammonia to generate product **3a**. In the alternative pathway (b), the imine **B** is partly hydrolyzed to benzaldehyde **C** in the presence of water, which further reacts with 2-methylquinoline *via* aldol-type condensation to give the olefination product **3a**.

Conclusions

We have developed a non-aggressive metal-free olefination reaction between primary amines and benzylic C–H bonds. Through direct deamination and benzylic C–H bond acti-

vation, this oxidative olefination provides biologically active 2-styrylquinolines with (*E*)-configuration. Further work on the synthetic application of the catalysts is in hand.

Acknowledgements

We are grateful to the National Science Foundation of China (no. 21172120) and National University Student Innovation Programs BX111359 and 20130055020, for financial support for this research.

References

1 T. A. Turney and G. A. Wright, *Chem. Rev.*, 1959, **59**, 497–513.
2 (*a*) S. S. Rawalay and H. Shechter, *J. Org. Chem.*, 1967, **32**, 3129–3131; (*b*) N. A. Noureldin and J. W. Bellegarde, *Synthesis*, 1999, 939–942; (*c*) D. C. Barman, P. Saikia, D. Prajapati and J. S. Sandhu, *Synth. Commun.*, 2002, **32**, 3407–3412.
3 S. Sobhani, S. Aryanejad and M. F. Maleki, *Helv. Chim. Acta*, 2012, **95**, 613–617.
4 (*a*) M. Largeron and M.-B. Fleury, *J. Org. Chem.*, 2000, **65**, 8874–8881; (*b*) K.-Q. Ling, J. Kim and L. M. Sayre, *J. Am. Chem. Soc.*, 2001, **123**, 9606–9611.
5 (*a*) J. K. Crandall and T. Reix, *J. Org. Chem.*, 1992, **57**, 6759–6764; (*b*) S. Chiampanichayakul, C. Kuhakarn, M. Pohmakotr, V. Reutrakul and T. Jaipetch, *Synthesis*, 2008, 2045–2048.
6 (*a*) M. Uyanik and K. Ishihara, *ChemCatChem*, 2012, **4**, 177–185; (*b*) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, 979–999.
7 (*a*) H. Rao, X. Ma, Q. Liu, Z. Li, S. Cao and C.-J. Li, *Adv. Synth. Catal.*, 2013, **355**, 2191–2196; (*b*) M. Ochiai, S. Yamane, M. M. Hoque, M. Saito and K. Miyamoto, *Chem. Commun.*, 2012, **48**, 5280–5282; (*c*) Z. Shi and F. Glorius, *Chem. Sci.*, 2013, **4**, 829–833.
8 (*a*) K. Mekouar, J.-F. Mouscadet, D. Desmaële, F. Subra, H. Leh, D. Savouré, C. Auclair and J. d'Angelo, *J. Med. Chem.*, 1998, **41**, 2846–2857; (*b*) J. Polanski, F. Zouhiri, L. Jeanson, D. Desmaële, J. d'Angelo, J.-F. Mouscadet, R. Gieleciak, J. Gasteiger and M. Le Bret, *J. Med. Chem.*, 2002, **45**, 4647–4654; (*c*) F. Zouhiri, J.-F. Mouscadet, K. Mekouar, D. Desmaële, D. Savouré, H. Leh, F. Subra, M. Le Bret, C. Auclair and J. d'Angelo, *J. Med. Chem.*, 2000, **43**, 1533–1540; (*d*) S. Bonnenfant, C. M. Thomas, C. Vita, F. Subra, E. Deprez, F. Zouhiri, D. Desmaële, J. d'Angelo, J. F. Mouscadet and H. Leh, *J. Virol.*, 2004, **78**, 5728–5736; (*e*) A. Mousnier, H. Leh, J.-F. Mouscadet and C. Dargemont, *Mol. Pharmacol.*, 2004, **66**, 783–788.
9 H. Yuan and A. L. Parrill, *Bioorg. Med. Chem.*, 2002, **10**, 4169–4183.
10 (*a*) C. Bénard, F. Zouhiri, M. Normand-Bayle, M. Danet, D. Desmaële, H. Leh, J.-F. Mouscadet, G. Mbemba, C.-M. Thomas, S. Bonnenfant, M. Le Bret and J. d'Angelo, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2473–2476; (*b*) M. Normand-Bayle, C. Bénard, F. Zouhiri, J.-F. Mouscadet, H. Leh, C.-M. Thomas, G. Mbemba, D. Desmaële and J. d'Angelo, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4019–4022; (*c*) F. S. Chang, W. Chen, C. Wang, C. C. Tzeng and Y. L. Chen, *Bioorg. Med. Chem.*, 2010, **18**, 124–133; (*d*) Y. Ogata, A. Kawasaki and H. Hirata, *J. Org. Chem.*, 1970, **35**, 2199–2203; (*e*) J. L. R. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, D. G. Borden and J. A. Ford, *J. Org. Chem.*, 1963, **28**, 387–390; (*f*) M. Staderini, N. Cabezas, M. L. Bolognesi and J. C. Menéndez, *Synlett*, 2011, 2577–2579; (*g*) C. Chaudhari, S. M. A. Hakim Siddiki and K.-i. Shimizu, *Tetrahedron Lett.*, 2013, **54**, 6490–6493; (*h*) M. Dabiri, P. Salehi, M. Baghbanzadeh and M. S. Nikcheh, *Tetrahedron Lett.*, 2008, **49**, 5366–5368.
11 (*a*) B. Bachowska and G. Matusiak, *Chem. Heterocycl. Compd.*, 2009, **45**, 80–84; (*b*) A. E. Siegrist, H. R. Meyer, P. Gassmann and S. Moss, *Helv. Chim. Acta*, 1980, **63**, 1311–1334; (*c*) T. Lifka, A. Oehlhof and H. Meier, *J. Heterocycl. Chem.*, 2008, **45**, 935–937.
12 (*a*) Y. Yan, K. Xu, Y. Fang and Z. Wang, *J. Org. Chem.*, 2011, **76**, 6849–6855; (*b*) B. Qian, P. Xie, Y. Xie and H. Huang, *Org. Lett.*, 2011, **13**, 2580–2583.
13 (*a*) Y. Li, F. Guo, Z. Zha and Z. Wang, *Chem. – Asian. J.*, 2013, **8**, 534–537; (*b*) Y.-G. Zhang, J.-K. Xu, X.-M. Li and S.-K. Tian, *Eur. J. Org. Chem.*, 2013, 3648–3652.
14 (*a*) J. Huang, L.-T. Li, H.-Y. Li, E. Husan, P. Wang and B. Wang, *Chem. Commun.*, 2012, **48**, 10204–10206; (*b*) L.-T. Li, J. Huang, H.-Y. Li, L.-J. Wen, P. Wang and B. Wang, *Chem. Commun.*, 2012, **48**, 5187–5189; (*c*) L.-T. Li, H.-Y. Li, L.-J. Xing, L.-J. Wen, P. Wang and B. Wang, *Org. Biomol. Chem.*, 2012, **10**, 9519–9522.
15 The information of crystal structure of **3a** (CCDC 942456) can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
16 (*a*) R. Dubey, S. Kothari and K. K. Banerji, *J. Phys. Org. Chem.*, 2002, **15**, 103–107; (*b*) W. E. Bachmann, M. P. Cava and A. S. Dreiding, *J. Am. Chem. Soc.*, 1954, **76**, 5554–5555.

