Organic LETTERS
Letter
pubs.acs.org/OrgLett

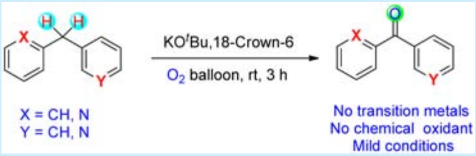
KO^tBu-Promoted Oxidation of (Hetero)benzylic C_{sp^3}–H to Ketones with Molecular Oxygen

Huiqiao Wang,*[†] Zhong Wang,[§] Hongchun Huang,[†] Jiajing Tan,*[‡] and Kun Xu*[†]

[†]College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, Henan 473061, China
[‡]Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China
[§]Catalyst Plant of PetroChina, Fushun Petrochemical Company, Fushun, Liaoning 113000, China

S Supporting Information

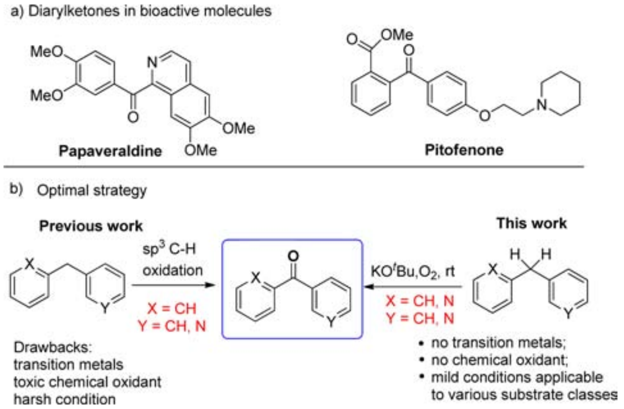
ABSTRACT: An efficient and practical (hetero)benzylic sp^3 C–H oxidation method has been developed. Notably, this user-friendly protocol employs inexpensive potassium *tert*-butoxide (KO^tBu) as a promoter and proceeds under mild conditions using oxygen as the oxidant. A large variety of oxidation products were prepared in good to excellent yields. The utility of this "green" methodology was further demonstrated by the scale-up preparation of a biologically valued molecule.



Oxidation reactions are among the most important classes of reactions in organic synthesis, and their synthetic scope and utility have advanced significantly over the past few decades.[1] Oxidation reactions have also been widely utilized in industry.[2] More recently, there have been steadily growing demands for novel environmentally benign and cost-effective oxidation methods, particularly within the pharmaceutical industry.[3] When considering industrial applications, direct C–H oxidations are often recognized as one of the most essential and promising classes of reactions among other oxidation methods, given their vantage point within molecular economy and reaction "greenness". In view of this, numerous C–H oxidation methods have been developed to date.[4]

(Hetero)aryl ketones and their derivatives are widely employed as versatile synthetic intermediates for complicated molecule syntheses, and they also serve as common scaffolds in many natural products and biologically active molecules (Scheme 1a).[5] Because of their utility in organic synthesis, several methods have been developed for the preparation of (hetero)aryl ketones. Traditionally, aryl ketones have been synthesized by Friedel–Crafts acylation or by oxidation of the corresponding alcohols into ketones.[6] However, some of these protocols suffer from poor selectivities and require expensive catalysts or the use of stoichiometric quantities of less sustainable oxidants such as peroxides and metal oxides. Thus, new convenient and sustainable synthetic strategies are highly desirable.

Scheme 1. Diaryl Ketones and Their Synthesis Strategy



The direct oxidation of (hetero)benzylic sp^3 C–H bonds, as we propose, would be a powerful strategy to make (hetero)aryl ketones in a "greener" and more cost-effective fashion (Scheme 1b). Nevertheless, key challenges still needed to be addressed for this strategy to be practical enough for widespread utilization, as most of available methods require either transition metal catalysts[7] or excessive use of chemical oxidants such as PhIO,[8] *tert*-butyl hydroperoxide (TBHP),[9] and oxone.[10] To make benzylic C–H oxidation more sustainable, Kawabata and Hayashi[11] realized this C–H oxidation with molecular oxygen in the presence of activated carbon. SanMartin, Domínguez, and co-workers developed an outstanding catalytic system employing only 10^{-5} mol % nickel catalyst.[12] Pandey[13] and Lei[14] independently identified photoredox C–H oxidation approaches to synthesize aryl ketones. Li, Wang, and co-workers also achieved benzylic C–H oxidation using a recyclable TEMPO catalyst.[15] However, in comparison with the well-established benzylic C–H oxidations, there are only a few examples of direct oxidation of heterobenzylic C–H bonds to construct heteroaryl ketones. Recently, the groups of Maes,[16] Miura,[17] and Lei[18] independently developed transition-metal-catalyzed oxidations of heteroaryl methylenes to provide various heteroaryl ketones. Gao and co-workers also disclosed a similar oxidation protocol employing an synergistic H_4NI–HOAc catalyst.[19] Although much progress has been made in

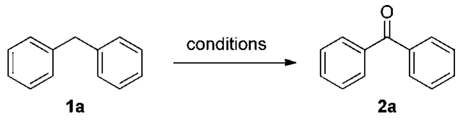
Received: September 27, 2016
Published: October 25, 2016

DOI: 10.1021/acs.orglett.6b02914
Org. Lett. 2016, 18, 5680–5683

this area, further research is still highly necessary. Herein we report our recent efforts to develop a simple and practical potassium *tert*-butoxide-promoted (hetero)benzylic sp^3 C−H oxidation reaction with molecular oxygen as the oxidant to make (hetero)aryl ketones. The in situ-generated radical intermediate is trapped by TEMPO and 1,1-diphenylmethene, providing a direct insight into the reaction mechanism.

Our investigation began with the oxidation of diphenylmethane (**1a**) under basic conditions using oxygen as the oxidant (Table 1). Initially, different inorganic bases were optimized (entries 1−4). The results showed that KO^{t}Bu could give the oxidation product **2a** in 58% yield (entry 1), while other commonly used bases gave lower yields (entries 2−4). Examination of a range of additives revealed that 18-crown-6 turned out to be optimal, producing **2a** in 89% yield (entries 5−7). Moreover, lowering the reaction temperature to room temperature increased the yield to 96% (entry 8). The solvent screening experiments suggested that DMF is the optimal solvent (entry 1 vs entries 9−12). The control experiment also showed that no product was obtained in the absence of potassium *tert*-butoxide (entry 13). When the reaction was placed under an air atmosphere instead, the yield decreased to 37% (entry 14). Reducing the amount of potassium *tert*-butoxide and 18-crown-6 led to a sharp decrease of the yield (entry 15). Finally, increasing the amount of potassium *tert*-butoxide to 200 mol % while decreasing the loading of 18-crown-6 to 30 mol % led to a slight decrease in the yield (entry 16).

Table 1. Optimization of the Reaction Conditions[a]

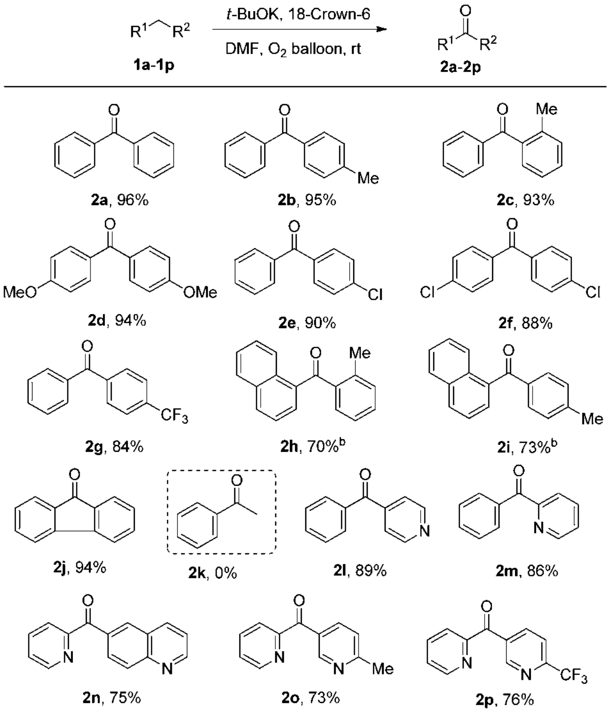


entry	base	additive	solvent	yield/%
1[b]	KO^{t}Bu		DMF	58
2[b]	KOH		DMF	44
3[b]	NaOH		DMF	41
4[b]	K$_2$CO$_3$		DMF	0
5[b]	KO^{t}Bu	TMEDA	DMF	38
6[b]	KO^{t}Bu	PEG-300	DMF	8
7[b]	KO^{t}Bu	18-crown-6	DMF	89
8	KO^{t}Bu	18-crown-6	DMF	96
9	KO^{t}Bu	18-crown-6	THF	65
10	KO^{t}Bu	18-crown-6	Tol	34
11	KO^{t}Bu	18-crown-6	DMSO	91
12	KO^{t}Bu	18-crown-6	CH$_3$CN	22
13		18-crown-6	DMF	0
14[c]	KO^{t}Bu	18-crown-6	DMF	37
15[d]	KO^{t}Bu	18-crown-6	DMF	40
16[e]	KO^{t}Bu	18-crown-6	DMF	94

[a] Reaction conditions: **1a** (0.5 mmol), base (0.5 mmol), additive (0.5 mmol), solvent (1 mL), O$_2$ balloon, rt, 3 h; yields were determined by GC with mesitylene as an internal standard. [b] The reaction temperature was 100 °C. [c] Under air. [d] KO^{t}Bu (0.25 mmol) and 18-crown-6 (0.25 mmol) were used. [e] KO^{t}Bu (1.0 mmol) and 18-crown-6 (0.15 mmol) were used.

With the optimized reaction conditions established, we then started investigating the scope of this oxidative transformation. As revealed in Scheme 2, this reaction protocol smoothly converted diarylmethanes to the desired diaryl ketones in excellent yields (**2a**−**g**, 84−96%). In general, electron-donating groups had little effect on the reaction outcomes (**2a**−**d**), while electron-deficient groups decreased the chemical yields of the oxidation products slightly (**2e**−**g**). In addition, we discovered that this reaction is sensitive to *ortho* steric hindrance. 1-Naphthyl-substituted substrates were less reactive under the optimized reaction conditions, giving the desired ketones **2h** and **2i** in only 70−73% yield with a longer reaction time. Furthermore, fluorene could also be employed to give the corresponding fluorenone **2j** in 94% yield. Unfortunately, acetophenone was not compatible with this transformation, and the starting material was recovered completely after 10 h (**2k**).

Scheme 2. Substrate Scope of the Oxidative Reaction[a]



[a] Reaction conditions: substrate (0.5 mmol), KO^{t}Bu (0.5 mmol), 18-crown-6 (0.5 mmol), and DMF (1 mL) were stirred at rt for 3 h with an O$_2$ balloon; isolated yields are shown. [b] Ten h.

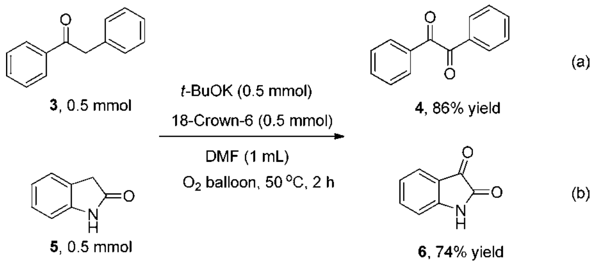
More importantly, using the optimal conditions identified in Table 1, we were also delighted to find that this C−H oxidation reaction is quite general in scope with respect to the *N*-heteroaryl methylene. For instance, the reactions also proceeded smoothly to afford the biologically valued diheteroaryl ketones (**2n**−**p**) in good yields (73−76%).

To expand the utility of this oxidative protocol, we then tested other typical benzylic sp^3 C−H compounds as substrates for this reaction. With a minor modification of the standard reaction conditions, 1,2-diphenylethan-1-one (**3**) and indolin-2-one (**5**) underwent the oxidation smoothly to give the desired 1,2-dicarbonyl compounds in 86% and 74% yield, respectively (Scheme 3).

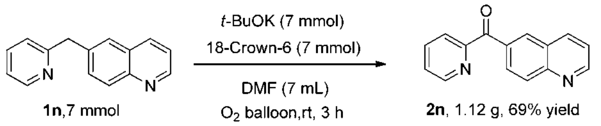
The gram-scale preparation of ketone **2n** also highlighted the utility and operational simplicity of this procedure. When the reaction was scaled up to 7 mmol, the product **2n** was still obtained in a comparable 69% yield (Scheme 4).

To gain insight into this oxidative reaction, radical scavengers such as TEMPO and 1,1-diphenylethene were employed. As shown in Scheme 5a,b, the yield dropped to 51% and 37%

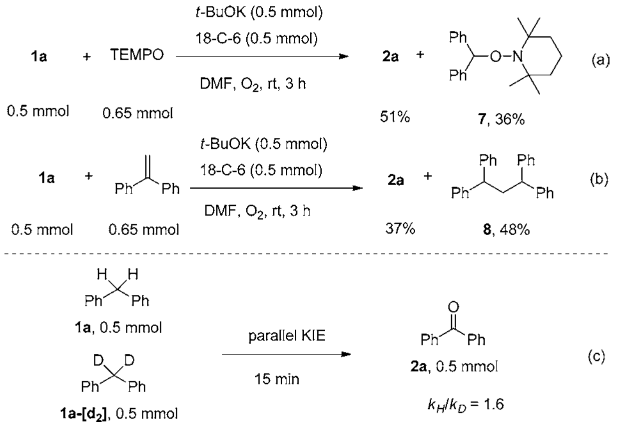
Scheme 3. Oxidative Reactions of 1,2-Diphenylethane-1-one and Indolin-2-one



Scheme 4. Gram-Scale Synthesis



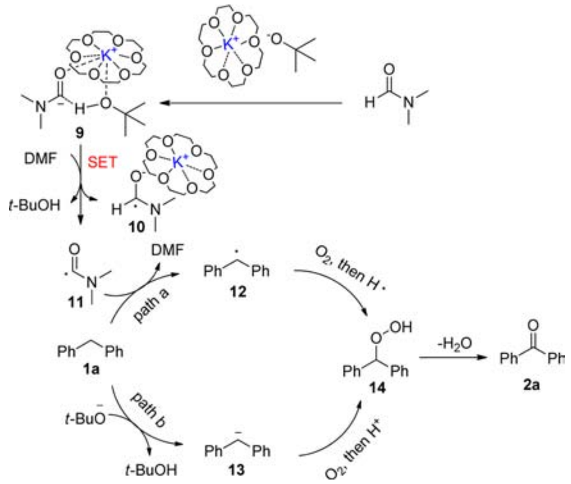
Scheme 5. Radical Trapping Experiments and Parallel KIE Experiments



respectively. Meanwhile, the radical adducts **7** and **8** were obtained in 36% and 48% yield, respectively. These results indicated that this transformation involves radical intermediates, although an anion pathway could not be ruled out. Additional parallel kinetic isotope effect (KIE) experiments showed that C−H/D bond cleavage should not be included in the rate-determining step (Scheme 5c; see the Supporting Information for details).

On the basis of the aforementioned observations and previous reports,[20,21] a plausible reaction mechanism involving two different pathways is proposed in Scheme 6. For path a, the *tert*-butoxide anion first abstracts a proton from DMF to give carbamoyl anion **9**.[20] The interaction between the complex of KO^{t}Bu with 18-crown-6 and DMF was demonstrated by NMR experiments (see the Supporting Information for details). Carbamoyl anion **9** then transfers an electron to DMF to generate carbamoyl radical **11**.[21] Intermediate **11** can abstract a hydrogen from **1a** to provide radical **12**, which then reacts with an O_2 to generate hydroperoxide intermediate **14**. For path b, the *tert*-butoxide anion first abstracts a proton from diphenylmethane (**1a**) to afford anion **13**, which then reacts with an O_2 followed by protonation to give hydroperoxide intermediate **14**. Finally, intermediate **14** eliminated one molecule of water to generate the desired ketone **2a**.

Scheme 6. Plausible Mechanism for This Reaction



In conclusion, we have developed a simple and efficient KO^{t}Bu-promoted (hetero)benzylic C−H oxidation reaction using oxygen as the oxidant. This user-friendly approach provides ready access to versatile (hetero)aromatic ketones as well as other 1,2-dicarbonyl compounds under mild conditions. Finally, we have demonstrated the utility of this strategy by the gram-scale synthesis of heteroaryl ketones. Further studies on expanding the reaction scope and understanding the reaction mechanism are currently underway in our groups.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02914.

> Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*wanghq@mail.ustc.edu.cn
*tanjj@mail.buct.edu.cn
*xukun@nynu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21602119 and U1504208), the He'nan Provincial Department of Science and Technology (152300410117), and the Fundamental Research Funds for the Central Universities at Beijing University of Chemical Technology.

■ REFERENCES

(1) For selected recent reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.

(2) For a review, see: Cavani, F.; Teles, J. H. *ChemSusChem* **2009**, *2*, 508.
(3) Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. *J. Am. Chem. Soc.* **2013**, *135*, 12346.
(4) For selected recent reviews, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (c) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (d) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.
(5) (a) Hodkova, J.; Vesely, Z.; Koblicova, Z.; Holubek, J.; Trojanek, J. *Lloydia* **1972**, *35*, 61. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Georg Thieme: Stuttgart, Germany, 2001.
(6) For selected recent reports, see: (a) Dai, W.; Lv, Y.; Wang, L.; Shang, S.; Chen, B.; Li, G.; Gao, S. *Chem. Commun.* **2015**, *51*, 11268. (b) Kamijo, S.; Tao, K.; Takao, G.; Tonoda, H.; Murafuji, T. *Org. Lett.* **2015**, *17*, 3326. (c) Shen, D.; Miao, C.; Xu, D.; Xia, C.; Sun, W. *Org. Lett.* **2015**, *17*, 54. (d) Chebolu, R.; Bahuguna, A.; Sharma, R.; Mishra, V. K.; Ravikumar, P. C. *Chem. Commun.* **2015**, *51*, 15438. (e) Song, H.; Kang, B.; Hong, S. H. *ACS Catal.* **2014**, *4*, 2889.
(7) (a) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. *Org. Lett.* **2005**, *7*, 4549. (b) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861. (c) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. *Adv. Synth. Catal.* **2011**, *353*, 401. (d) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M. *Chem. Sci.* **2011**, *2*, 2187. (e) Hruszkewycz, D. P.; Miles, K. C.; Thiel, O. R.; Stahl, S. S. *Chem. Sci.* **2016**, DOI: 10.1039/C6SC03831J, and references cited therein.
(8) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2008**, *73*, 7365.
(9) (a) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167. (b) Zhang, J.; Wang, Z.; Wang, Y.; Wan, C.; Zheng, X.; Wang, Z. *Green Chem.* **2009**, *11*, 1973. (c) Peng, H.; Lin, A.; Zhang, Y.; Jiang, H.; Zhou, J.; Cheng, Y.; Zhu, C.; Hu, H. *ACS Catal.* **2012**, *2*, 163. (d) Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* **2014**, *16*, 1108.
(10) Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* **2012**, *14*, 2414.
(11) Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2004**, *45*, 5457.
(12) Urgoitia, G.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Chem. Commun.* **2015**, *51*, 4799.
(13) Pandey, G.; Pal, S.; Laha, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 5146.
(14) Yi, H.; Bian, C.; Hu, X.; Niu, L.; Lei, A. *Chem. Commun.* **2015**, *51*, 14046.
(15) Zhang, Z.; Gao, Y.; Liu, Y.; Li, J.; Xie, H.; Li, H.; Wang, W. *Org. Lett.* **2015**, *17*, 5492.
(16) De Houwer, J.; Tehrani, K. A.; Maes, B. U. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 2745.
(17) Itoh, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2050.
(18) Liu, J.; Zhang, X.; Yi, H.; Liu, C.; Liu, R.; Zhang, H.; Zhuo, K.; Lei, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1261.
(19) Ren, L.; Wang, L.; Lv, Y.; Li, G.; Gao, S. *Org. Lett.* **2015**, *17*, 2078.
(20) Drapeau, M. P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10587.
(21) (a) Chen, Y. Y.; Zhang, X. J.; Yuan, H. M.; Wei, W. T.; Yan, M. *Chem. Commun.* **2013**, *49*, 10974. (b) Wei, W. T.; Dong, X. J.; Nie, S. Z.; Chen, Y. Y.; Zhang, X. J.; Yan, M. *Org. Lett.* **2013**, *15*, 6018. (c) Wang, W.-J.; Zhao, X.; Tong, L.; Chen, J.-H.; Zhang, X.-J.; Yan, M. *J. Org. Chem.* **2014**, *79*, 8557. (d) Wei, W.-T.; Cheng, Y.-J.; Hu, Y.; Chen, Y.-Y.; Zhang, X.-J.; Zou, Y.; Yan, M. *Adv. Synth. Catal.* **2015**, *357*, 3474. (e) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, *138*, 7402.