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Iron(II)-Catalyzed Oxidation of sp^3 C−H Bonds Adjacent to a Nitrogen Atom of Unprotected Arylureas with *tert*-Butyl Hydroperoxide in Water

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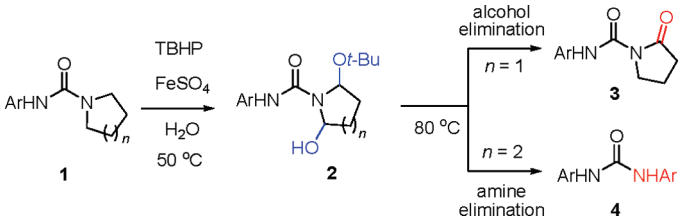
ABSTRACT



With a $FeSO_4$/TBHP system in water, direct oxidation of sp^3 C−H bonds adjacent to nitrogen of arylureas to give both unprecedented *tert*-butoxylated and hydroxylated products 2 was revealed. Under elevated temperatures, either 2-oxo-*N*-arylpyrrolidine-1-carboxamides 3 or 1,3-diarylureas 4 were attained, depending on the aliphatic ring size of the arylurea substrates.

Direct formation of a C−X (X = C, N, O, etc.) bond from unactivated C−H bonds is one of the most challenging projects in organic synthesis.[1] In this context, C−X bond formation via C−H bond functionalization adjacent to a nitrogen atom has received considerable attention.[2] In our ongoing research, we aimed to explore the sp^2 and/or sp^3 C−H bond functionalizations adjacent to nitrogen atoms toward various C−X bond formations with newly developed arylureas[3] in our laboratory.[4] Herein, we wish to present the reaction of unprotected arylureas with nontoxic, and cheap *tert*-butyl hydroperoxide (TBHP) as the oxidant and iron salts as the catalyst.[5] The result demonstrated that the reactions performed at 50 °C gave unprecedented oxidative products, 2-*tert*-butoxy-5-hydroxy-*N*-arylpyrrolidine(piperidine)-1-carboxamides **2**, by direct oxidation of sp^3 C−H bonds adjacent to the nitrogen of arylureas.[6] Under elevated temperatures of 80 °C, urea derivatives, either 2-oxo-*N*-arylpyrrolidine-1-carboxamides **3** or 1,3-diarylureas **4**, were attained respectively, depending on the aliphatic ring size of the arylurea substrates.

(1) For recent reviews on C−H activation and functionalization, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.—Eur. J.* **2002**, *8*, 2423. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (f) Jia, C. G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (i) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 6245.

(2) For direct sp^3 C−H bond activation adjacent to nitrogen in heterocycles, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3351. (d) Murahashi, S.-I. *Angew. Chem., Int. Ed.* **1995**, *34*, 2443.

(3) Substituted ureas have a wide range of applications in agriculture, petrochemicals, medicine, and biology and as important intermediates and bifunctional organocatalysts in organic synthesis. For reviews on substituted ureas, see: (a) Gallou, I. *Org. Prep. Proced. Int.* **2007**, *4*, 355. (b) Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140. (c) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Ed.)* **1985**, *54*, 249.

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(6) Selected papers on selective C−H bond oxidation: (a) Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2008**, *10*, 1863. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (c) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861. (d) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387. (e) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464.

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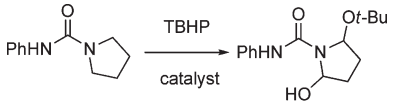
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

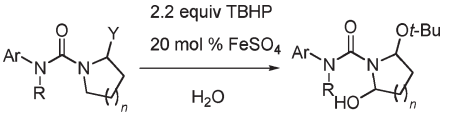
entry	catalyst (mol %)	TBHP (equiv)	solvent	T (°C)	time (h)	yield (%)[b]
1		1.1	MeCN	80	8	nr
2	$FeCl_3$ (10)	1.1	MeCN	80	7	32
3	$FeCl_3$ (10)	1.1	DCE	80	7	48
4	$FeSO_4$ (10)	1.1	DCE	80	7	55
5	$FeSO_4$ (10)	2.2	DCE	80	7	62
6	$FeSO_4$ (20)	2.2	DCE	50	5	70
7	$FeSO_4$ (20)	2.2	H_2O	50	4.5	75
8	CuBr (20)	2.2	H_2O	50	4.5	51

[a] Conditions: **1a** (0.5 mmol) and TBHP (5−6 M in decane or 70% in water) under open air. [b] Isolated yields. DCE = dichloroethane.

Moreover, all the reactions could proceed efficiently in water, which represents a facile and convenient oxidation of unprotected arylureas in a "green" fashion.[7] Although much effort has been devoted to the metal-catalyzed C−H bond functionalization at the α-position of amines, examples of C−H bond activation of amides and ureas are scarce.[8] To the best of our knowledge, no report has been found in the literature on the aliphatic C−H bond activation of ureas.

Initially, optimization of the reaction conditions was conducted (Table 1). The model reaction of *N*-phenylpyrrolidine-1-carboxamide **1a** and TBHP (1.1 equiv) in CH_3CN at 80 °C could not occur in the absence of metal catalyst (entry 1). When 10 mol % of $FeCl_3$ was introduced to the reaction system, 2-*tert*-butoxy-5-hydroxy-*N*-phenylpyrrolidine-1-carboxamide (**2a**) was obtained in 32% yield (entry 2). Dichloroethane proved to be a more suitable solvent than CH_3CN (entry 3). It was found that when a low oxidation state iron salt, such as $FeSO_4$, was used as the catalyst, the reaction of **1a** with TBHP in DCE exhibited higher efficiency with a yield of 55% (entry 4). When the feed ratio of $FeSO_4$/TBHP was increased, i.e., 20 mol % of $FeSO_4$ and 2.2 equiv of TBHP, the reaction temperature was lowered and the yields were enhanced along with shortened reaction time (entries 5 and 6). Water, as an easily available, cheap, safe, and environmentally benign solvent, was also tested. To our delight, the reaction gave the best results and the desired product **2a** was obtained in 75% yield at 50 °C within 4.5 h (entry 7). Comparatively, copper catalyst CuBr was less efficient for the explored reaction (entry 8).

Table 2. Iron-Catalyzed Oxidation of Unprotected Arylureas with TBHP in Water[a]



1 2

entry	1	Ar	n	R	Y	2	time (h)	yield (%)[b]
1	**1a**	C_6H_5	1	H	H	**2a**	4	75
2	**1b**	4-$OMeC_6H_4$	1	H	H	**2b**	4	72
3	**1c**	4-MeC_6H_4	1	H	H	**2c**	4	65
4	**1d**	2,4-$Me_2C_6H_3$	1	H	H	**2d**	5	70
5	**1e**	4-ClC_6H_4	1	H	H	**2e**	3	78
6	**1f**	5-Cl-2-$OMeC_6H_3$	1	H	H	**2f**	5	76
7	**1g**	2-Py	1	H	H	**2g**	4	50
8	**1h**	C_6H_5	1	Me	H	**2h**	11	32
9	**1i**	C_6H_5	2	H	H	**2i**	6	54[c]
10	**1j**	C_6H_5	2	H	Me	**2j**	10	n.r.

[a] Conditions: **1** (0.5 mmol) and TBHP (0.15 mL, 70% in water) under open air. [b] Isolated yields. [c] Along with the formation of diphenylurea **4a** (18% yield).

Under the optimized conditions (Table 1, entry 7), a range of reactions were performed with various substrates **1** (Table 2). It was observed that various *N*-arylpyrrolidine-1-carboxamides **1a**−**f** afforded the corresponding 2-*tert*-butoxy-5-hydroxy-*N*-arylpyrrolidine-1-carboxamides **2a**−**f** in good yields (entries 1−6). *N*-Heteroaryl counterparts such as *N*-(2-pyridyl)urea **1g** also gave both the desired hydroxylated and *tert*-butoxylated product **2g** in 50% yield (entry 7). Comparatively, when *N*-methyl-protected arylurea **1h** was used, the reaction gave the oxidative product **2h** with a yield of merely 32% (entry 8).[9] For *N*-phenylpiperidine-1-carboxamide **1i**, 2-*tert*-butoxy-6-hydroxy-*N*-phenylpiperidine-1-carboxamide **2i** was obtained in 54% yield (entry 9). The reaction with 2-methyl-*N*-phenylpiperidine-1-carboxamide **1j** did not occur, presumably due to the steric effect of the methyl group on the piperidine ring (entry 10). The results shown above demonstrated the efficiency and synthetic interest of the C−O bond formation reaction via C−H bond functionalization with respect to arylureas **1** bearing various substituents. Indeed, there are no generally effective methods for simultanious dioxygenation of both α-positions to the nitrogen atom.

In the following work, the reactions described above were carried out at elevated temperatures. As a result, 2-oxo-*N*-arylpyrrolidine-1-carboxamides **3** were cleanly

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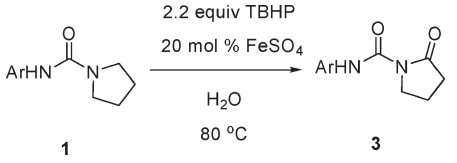
(8) For selected papers on C−H activation based on amides, see: (a) Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708. (b) Li, B.; Tian, S.-L.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (c) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (d) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (e) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. For aryl C−H bond activation of ureas, see:(f) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (g) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (h) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.

(9) It appears that the efficiency of *N*-protected arylurea is lower than that of unprotected arylurea, which is consistent with the possible mechanism proposed later.

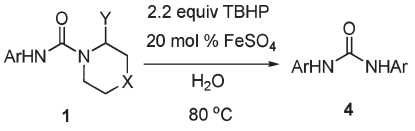
Table 3. Iron-Catalyzed Reaction of *N*-Arylpyrrolidine-1-carboxamides with TBHP in Water[a]



entry	1	Ar	3	time (h)	yield (%)[b]
1	**1a**	C_6H_5	**3a**	5	83
2	**1b**	4-$OMeC_6H_4$	**3b**	4	85
3	**1c**	4-MeC_6H_4	**3c**	5	80
4	**1d**	2,4-$Me_2C_6H_3$	**3d**	6	82
5	**1e**	4-ClC_6H_4	**3e**	5	87
6	**1g**	2-Py	**3g**	12	86

[a] Conditions: **1** (0.5 mmol) and TBHP (0.15 mL, 70% in water) under open air. [b] Isolated yields.

Table 4. Iron-Catalyzed Reaction of *N*-Arylpiperidine-1-carboxamides with TBHP in Water[a]



entry	1	Ar	X	Y	4	yield (%)[b]
1	**1i**	C_6H_5	CH_2	H	**4a**	82
2	**1k**	4-$OMeC_6H_4$	CH_2	H	**4b**	91
3	**1l**	4-ClC_6H_4	CH_2	H	**4c**	50[c]
4	**1m**	C_6H_5	O	H	**4a**	87
5	**1j**	C_6H_5	CH_2	Me	**4d**	n.r.
6[d]	**1k**	4-$OMeC_6H_4$	CH_2	H	**4e**	62[e]

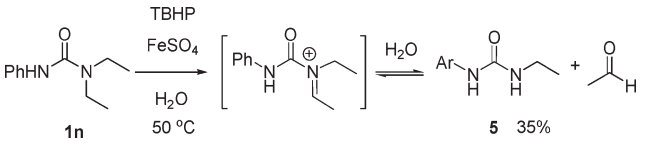
[a] Conditions: **1** (0.5 mmol) and TBHP (0.15 mL, 70% in water) under open air. [b] Isolated yields. [c] With 25 mol % of CuBr as the catalyst. [d] Methyl 4-methoxyphenylcarbamate was obtained. [e] With methanol as the solvent.

obtained from the five-membered pyrrolidine substrates (Table 3).[10] In particular, treating the substrates **1a**−**e** and **1g** with 2.2 equiv of TBHP in the presence of 20 mol % of $FeSO_4$ in water (0.5 mL) at 80 °C gave products **3a**−**e** and **3g** in high yields of 80−87% (entries 1−6). Surprisingly, when the corresponding six-membered piperidine substrates were subjected to identical conditions, no oxidative products **3** were observed. Instead, diarylureas **4** such as 1,3-diphenylurea **4a**, 1,3-bis(4-chlorophenyl)urea **4b**, and 1,3-bis(4-methoxyphenyl)urea **4c** were achieved in high efficiency from *N*-arylpiperidine-1-carboxamides **1i** and **1k**,***l*** (Table 4, entries 1−3). It was found that the reaction of *N*-phenylmorpholine-4-carboxamide substrate **1m** under identical conditions proceeded more efficiently, giving **4a** in 87% yield (entry 4). Similarly to that in Table 2, entry 10, the reaction of 2-methyl-*N*-phenylpiperidine-1-carboxamide **1j** did not occur even at 80 °C (entry 5). Furthermore, when the reaction of **1k** with $FeSO_4$/TBHP was carried out in methanol instead of water, methyl 4-methoxyphenylcarbamate (**4e**) was obtained in 62% yield (entry 6).

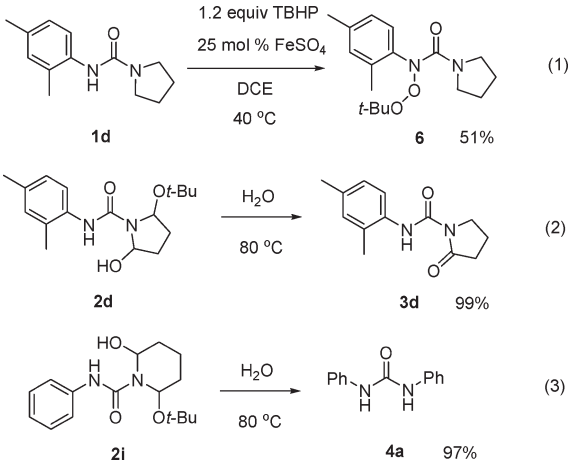
Acyclic arylurea such as 1,1-diethyl-3-phenylurea underwent an oxidative *N*-dealkylation reaction in the presence of $FeSO_4$/TBHP in water at 50 °C, giving 1-ethyl-3-phenylurea **5** in 35% yield (Scheme 1).[10b] The low yield was most probably attributed to the existence of an equilibrium between **1n**, **5**, and acetaldehyde.

To elucidate a possible mechanism, we performed the following control experiments (Scheme 2). In the reaction of substrate **1d** in the presence of 20 mol % of $FeSO_4$ and 1.1 equiv of TBHP in DCE at 40 °C, *N*-(*tert*-butylperoxy)-*N*-(2,4-dimethylphenyl)pyrrolidine-1-carboxamide **6**, although unstable, was separated and identified by ^1H NMR spectroscopy and HRMS (eq 1).[11] Additionally,

Scheme 1. Reaction of Acyclic Arylurea with $FeSO_4$/TBHP in Water



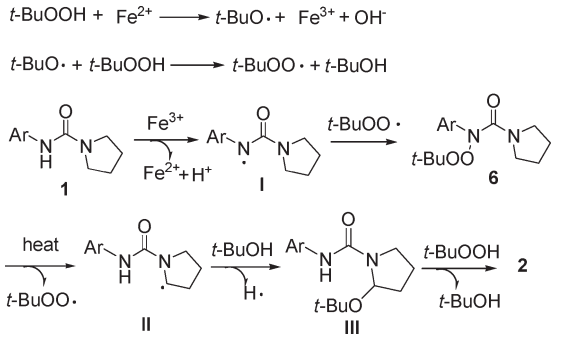
Scheme 2. Control Experiments



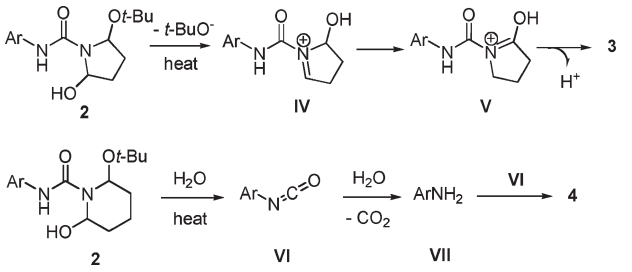
(10) For the preparation of *N*-acylureas, see: (a) Liptrot, D.; Alcaraz, L.; Roberts, B. *Adv. Synth. Catal.* **2010**, *352*, 2183. (b) Constantino, L.; Iley, J. *Org. Biomol. Chem.* **2004**, *2*, 1894.

(11) For *N*-*tert*-butylperoxylated intermediates, see: (a) Förster, S.; Rieker, A. *J. Org. Chem.* **1996**, *61*, 3320. For C-*tert*-butylperoxylated intermediates, see:(b) Xie, J.; Huang, Z.-Z. *Angew Chem., Int. Ed.* **2010**, *49*, 10181. (c) An, G.; Zhou, W.; Zhang, G.; Sun, H.; Han, J.; Pan, Y. *Org. Lett.* **2010**, *12*, 4482. (d) Terent'ev, A. O.; Borisov, D. A.; Yaremenko, I. A.; Chernyshev, V. V.; Nikishin, G. I. *J. Org. Chem.* **2010**, *75*, 5065. (e) Russoa, A.; Lattanzia, A. *Adv. Synth. Catal.* **2008**, *350*, 1991. (f) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.

Scheme 3. Possible Mechanism for the Formation of **2**



Scheme 4. Possible Mechanism for the Formation of **3** and **4**



nearly quantitative formation of *N*-(2,4-dimethylphenyl)-2-oxopyrrolidine-1-carboxamide (**3d**) and 1,3-diphenylurea (**4a**) from dioxygenated **2d** and **2i**, respectively, were observed in the control reactions performed in water at 80 °C in the absence of the combination of $FeSO_4$ and TBHP (eqs 2 and 3).

On the basis of all the results mentioned above, a possible mechanism for the highly efficient transformation into 2-*tert*-butoxy-5-hydroxy-*N*-arylpyrrolidine(piperidine)-1-carboxamides **2** was proposed, as depicted in Scheme 3. TBHP decomposes into a *tert*-butoxyl radical in the presence of the ferrous catalyst, which further gives a *tert*-butylperoxy radical. The resulting peroxyl radical can react with aminyl radical **I** derived from the oxidation of the arylurea **1** to form the unstable *N*-(*tert*-butylperoxyl) urea **6**.[11] The elimination of the *tert*-butylperoxy radical generates a new carbon radical **II** via 1,4-hydrogen radical transfer,[12] which is trapped by *tert*-butanol to give a α-*tert*-butoxylated urea **III** and regenerates TBHP.[13a] Finally, a hydroxyl group is introduced to the other α-position of **III** via hydrogen abstraction by TBHP (regenerates *tert*-butanol) and product **2** is formed.

A possible mechanism for further formation of products **3** and **4** from **2** is given in Scheme 4. For *N*-arylpyrrolidine-1-carboxamides **2**, an imimium ion **IV** is generated via elimination of a *tert*-butoxyl anion upon heating.[13,14] Followed by hydride transfer and removal of the proton, 2-oxo-*N*-arylpyrrolidine-1-carboxamides **3** is produced. As for six-membered counterparts **2**, isocyanate **VI** may be produced in water via amine elimination.[15,16] The hydrolysis and subsequent decarboxylation of intermediate **VI** leads to the formation of amine **VII**, which undergoes nucleophilic addition to the isocyanate to give the final products **4**. Obviously, ring size of the cyclic arylurea determines the formation of different products (**3** or **4**).[17]

In conclusion, we have reported an unprecedented iron-(II)-catalyzed oxidation of sp^3 C−H bonds adjacent to a nitrogen atom of unprotected arylureas with TBHP in water. At 50 °C, the hydroxylated and *tert*-butoxylated products were obtained efficiently. At 80 °C, the oxidative products undergo either alcohol elimination or amine elimination to give 2-oxo-*N*-arylpyrrolidine-1-carboxamides and 1,3-diarylureas, respectively, depending on the aliphatic ring size of the arylurea substrates. Moreover, we anticipate that the intact N−H on the unprotected arylurea may be applicable to a wide variety of valuble transformations.[18] Further work to explore the sp^2 and/or sp^3 C−H bond functionalization adjacent to nitrogen atoms of arylureas is ongoing in our laboratory.

Acknowledgment. Financial support from NSFC (209-72027), the Department of Science and Technology of Jilin Province (20100535), and NENU-STC08013 is gratefully acknowledged.

Supporting Information Available. Detailed synthetic procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For examples of 1,5-hydrogen transfer, see: (a) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (b) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (c) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 9483. For examples of 1,4-hydrogen transfer, see:(d) Gulea, M.; López-Romero, J. M.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591.

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(15) For relative reactivity of five- versus six-membered ring *N*-acyliminium ions, see: D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854.

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(17) For the possible mechanism of oxidation/dealkylation of acyclic arylurea, see the Supporting Information.

(18) For an example, see: Wasa, M.; Engle, K. M.; Yu, J-.Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.