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A Facile BPO-Mediated *ortho*-Hydroxylation and Benzoylation of *N*-Alkyl Anilines for Synthesis of 2-Benzamidophenols

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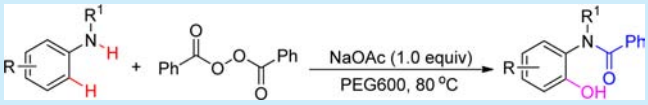
Supporting Information

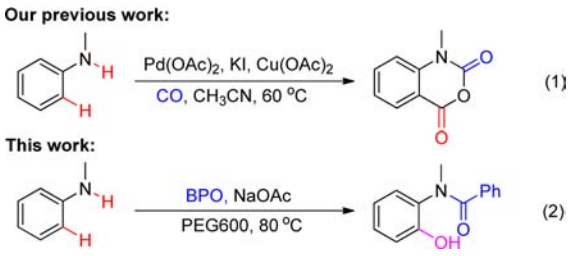
ABSTRACT: A facile benzoyl peroxide (BPO) mediated *ortho*-hydroxylation and benzoylation of *N*-alkyl anilines for the synthesis of 2-benzamidophenols has been developed. The reaction tolerates a wide range of functional groups and is a good method for the straightforward synthesis of valuable 2-benzamidophenols in good yields under mild conditions.



2-Aminophenol and their derivatives are valuable chemicals and have been widely applied in organic synthesis to synthesize various pharmaceutical heterocyclic compounds and dyes.[1] Conventionally, 2-aminophenols were synthesized by nitration of phenols sequential with reduction of the nitro group.[2] However, the nitration step involves poor regioselectivity to form 2- or 4-nitro phenol isomers under harsh conditions. Although an enzyme catalyzed method was also available for the synthesis of 2-aminophenols, it was limited in substrate scope.[3] Therefore, a novel, practical and mild protocol for the straightforward synthesis of 2-aminophenols remains highly desirable.

Recently, transition metal catalyzed chelation assisted C−H bond functionalization has become a very active area of research. Pd- or Ru-catalyzed *ortho*-acyloxylation or *ortho*-hydroxylation of a variety of aromatic substrates for the synthesis of substituted phenols has been developed by several groups.[4−6] Ru-catalyzed *ortho*-hydroxylation and *ortho*-benzoxylation of anilides has also been developed for the synthesis of 2-aminophenol derivatives.[7] In 2012, we developed a Pd-catalyzed carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides.[8] The nitrogen atom of *N*-alkyl anilines was first discovered to be a directing group in Pd-catalyzed *ortho* C−H carbonylation (Scheme 1, eq 1). Inspired by this work, we hypothesized that Pd-catalyzed *ortho* C−H bond hydroxylation of the *N*-alkyl anilines might provide an alternative route to synthesize 2-aminophenols. However, after extensive research, a transition-metal-free *ortho*-hydroxylation of the *N*-alkyl anilines by benzoyl peroxide (BPO) was found to synthesize 2-benzamidophenols straightforwardly (Scheme 1, eq 2).

Scheme 1. Transformations of *N*-Methyl Aniline



Transition-metal-free oxidative *ortho* hydroxylation of anilines was actually investigated in the 1950s.[9] However, the narrow substrate scope and low yield make the reaction less applicable in organic synthesis. In this paper, we have improved the synthetic method and developed an efficient BPO-mediated *ortho*-hydroxylation and benzoylation of *N*-alkyl anilines for the synthesis of 2-benzamidophenols. The reaction tolerates a wide range of functional groups and gives the corresponding 2-benzamidophenols in good yields under mild conditions.

We began our study by investigating the Pd-catalyzed *ortho*-hydroxylation of *N*-methyl aniline **1a**. Initially, a variety of common oxidants were screened in the reaction, but no reaction occurred. Delightedly, when BPO was used as the oxidant, an unexpected but valuable 2-benzamidophenol **2a** was observed in 26% yield (Table 1, entry 1). The structure of **2a** was confirmed by X-ray diffraction analysis. However, further investigation indicated that the $Pd(OAc)_2$ catalyst plays no role in the reaction (Table 1, entries 2−3). It was a simple BPO-mediated *ortho*-hydroxylation and benzoylation of *N*-methyl aniline (Table 1, entries 4−5). This interesting result prompted us to optimize the reaction conditions in order to develop a synthetically useful process for the direct synthesis of substituted 2-benzamidophenols from simple *N*-alkyl anilines.

Therefore, various solvents such as CH_3CN, toluene, DMSO, MeOH, *t*-BuOH, glycol, and poly(ethylene glycol) (PEG) were screened to examine if they improved the reaction efficiency (Table 1, entries 6−12). PEG600 was found to be the most effective solvent in the reaction, affording the 2-benzamidophenol **2a** in 47% yield. To further improve the reaction efficiency, bases which may neutralize the benzoic acid byproduct in the reaction were screened (Table 1, entries 13−19). NaOAc gives the best result to afford **2a** in 62% yield.[10] Other bases are less effective than NaOAc.

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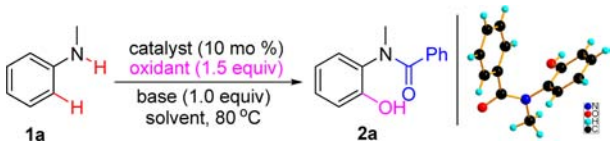
Table 1. Optimization of the Reaction Conditions[a]



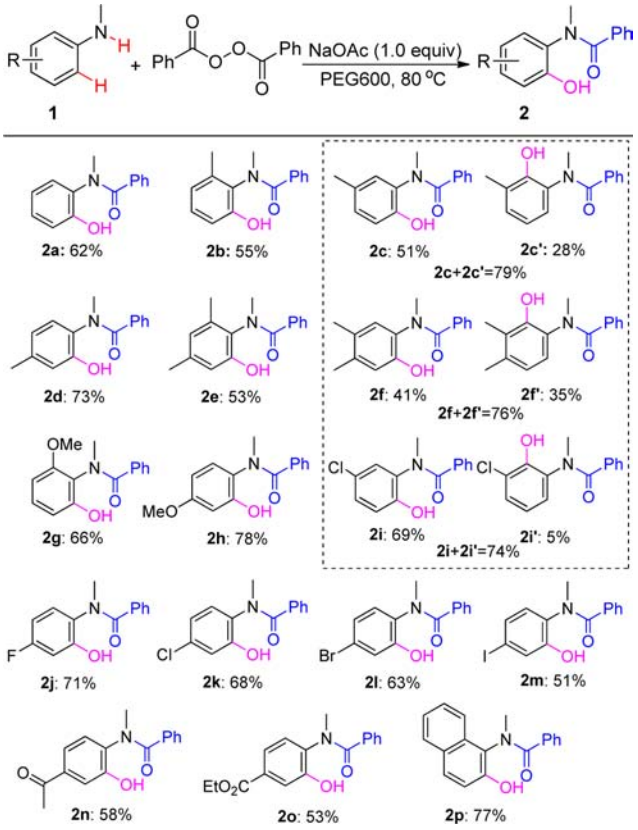
entry	catalyst	oxidant	base	solvent	yield (%)
1	$Pd(OAc)_2$	BPO		THF	26
2	$Pd(OAc)_2$			THF	0
3		BPO		THF	33
4		TBHP		THF	0
5		DTBP		THF	0
6		BPO		CH_3CN	24
7		BPO		toluene	22
8		BPO		DMSO	29
9		BPO		MeOH	23
10		BPO		*t*-BuOH	39
11		BPO		glycol	35
12		BPO		PEG600	47
13		BPO	K_2CO_3	PEG600	48
14		BPO	Na_2CO_3	PEG600	46
15		BPO	KOAc	PEG600	56
16		**BPO**	**NaOAc**	**PEG600**	**62**
17		BPO	LiOAc	PEG600	37
18		BPO	CsOAc	PEG600	51
19		BPO	NaOH	PEG600	29

[a]Reaction conditions: *N*-methylaniline **1a** (0.2 mmol), oxidant (1.5 equiv), base (1.0 equiv) in solvent (2 mL) at 80 °C, 20 h. Isolated yields. BPO = benzoyl peroxide, DTBP = di-*tert*-butyl-peroxide, PEG600 = The average molecular mass of poly(ethylene glycol) is 600.

With the optimized conditions in hand, the scope of the reaction was investigated (Scheme 2). This BPO-mediated *ortho*-hydroxylation and benzoylation reaction displayed high functional-group tolerance and proved to be a facile and general protocol for the synthesis of substituted 2-benzamidophenols. *N*-Methyl anilines substituted with electron-donating groups, such as methyl and methoxyl, or electron-withdrawing groups, such as fluoro, chloro, bromo, iodo, acetyl, and ethoxycarbonyl, all gave the corresponding 2-benzamidophenols **2b**−**2o** in good to high yields, thus implying that the electronic nature of the substrates has little influence on the reaction. A single isomer was obtained when 2- or 4-substituted *N*-methyl anilines were used as the substrates. 3-Substituted *N*-methyl anilines produced two isomers of the 2-benzamidophenols, such as the examples listed in the gridline in Scheme 2. It should be noted that the steric hindrance of the substrates plays a role in the reaction. A less sterically hindered isomer, such as **2c**, **2f**, and **2i**, was formed as the major product in the reaction. Similarly, the slightly lower yields of **2b**, **2e**, and **2g** may be assumed to be due to the steric hindrance of *ortho*-methyl or *ortho*-methoxyl on the *N*-methyl anilines. Additionally, when *N*-methylnaphthalen-1-amine was used as the substrate, 1-benzamidonaphthalen-2-ol **2p** was also obtained in 77% yield.

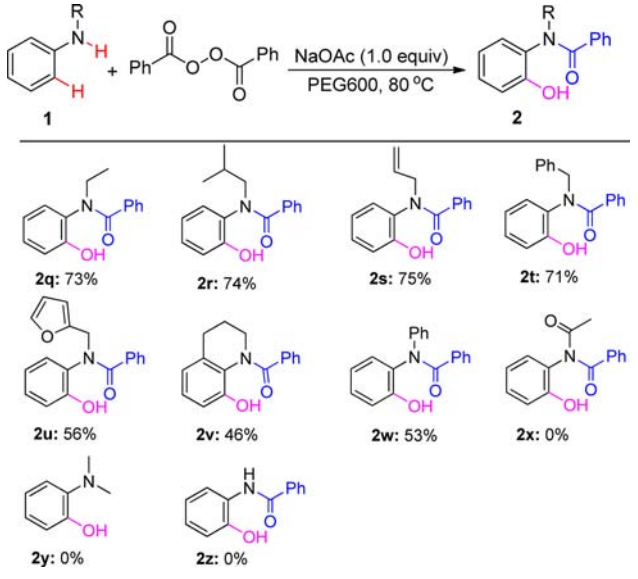
Furthermore, anilines with a different substituent on the nitrogen atom were investigated to extend the reaction scope (Scheme 3). It was found that anilines with ethyl, isobutyl, allyl, benzyl, or furfuryl on the nitrogen atom were all tolerated in the reaction to give the corresponding 2-benzamidophenols **2q**−**2u** in high yields. Cyclic substrates, such as tetrahydroquinoline, were also tolerated to afford the desired (8-hydroxy-

Scheme 2. BPO-Mediated *ortho*-Hydroxylation and Benzoylation of *N*-Methyl Anilines for Synthesis of 2-Benzamidophenols[a]



[a]Reaction conditions: **1** (0.2 mmol), BPO (1.5 equiv), NaOAc (1.0 equiv) in PEG600 (2 mL) at 80 °C, 20 h. Isolated yields.

Scheme 3. BPO-Mediated *ortho*-Hydroxylation and Benzoylation of *N*-Alkyl Anilines for Synthesis of 2-Benzamidophenols[a]



[a]Reaction conditions: **1** (0.2 mmol), BPO (1.5 equiv), NaOAc (1.0 equiv) in PEG600 (2 mL) at 80 °C, 20 h. Isolated yields.

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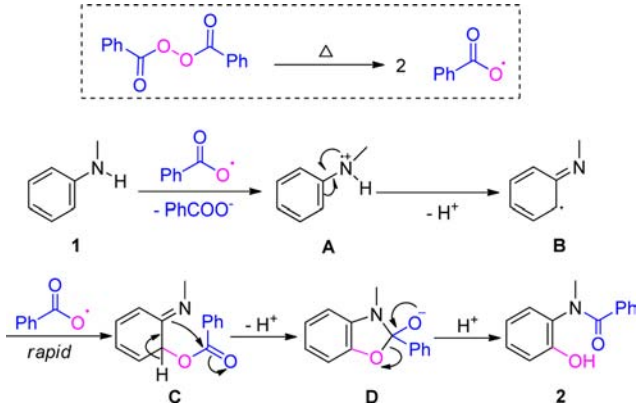
3,4-dihydroquinolin-1(2*H*)-yl)(phenyl)methanone **2v** in 46% yield. In addition, diphenylamine was also tolerated in the reaction to give the desired *N*-(2-hydroxyphenyl)-*N*-phenylbenzamide **2w** in 53% yield. However, no reaction occurred when *N*-acetyl aniline, *N*,*N*-dimethylaniline, or simple aniline was employed as the substrate.[9a−d]

On the basis of the above results, a tentative mechanism for the reaction is proposed in Scheme 4. First, single-electron

Scheme 4. Tentative Mechanism of the Reaction



oxidation of *N*-methyl aniline **1** by BPO produces a radical cation **A**. Deprotonation and radical migration of **A** generates a radical intermediate **B**.[9b] Rapid coupling of radical intermediate **B** with a free radical forms an intermediate **C**. Rearomatization of intermediate **C** sequential with a 1,4-benzoyl shift through a 5-exo-trig cycle intermediate **D** gives 2-benzamidophenol **2**.

In summary, a facile and efficient BPO-mediated *ortho*-hydroxylation and benzoylation of *N*-alkyl anilines for the synthesis of 2-benzamidophenols was developed. The reaction employs readily available *N*-alkyl anilines as the starting materials and tolerates a wide range of functional groups. The reaction provides a practical protocol for the straightforward synthesis of a variety of valuable 2-benzamidophenols in good yields under mild conditions. Further studies of the reaction scope and mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all products, and X-ray data of **2a** and **2c′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hernandez-Olmos, V.; Abdelrahman, A.; El-Tayeb, A.; Freudendahl, D.; Weinhausen, S.; Müller, C. E. *J. Med. Chem.* **2012**, *55*, 9576. (b) Matralis, A. N.; Katselou, M. G.; Nikitakis, A.; Kourounakis, A. P. *J. Med. Chem.* **2011**, *54*, 5583. (c) Beltrán-Heredia, J.; Sánchez-Martín, J.; Martín-Sánchez, C. *Ind. Eng. Chem. Res.* **2011**, *50*, 686. (d) Rosenhauer, R.; Fischer, T.; Stumpe, J.; Giménez, R.; Piñol, M.; Serrano, J. L.; Viñuales, A.; Broer, D. *Macromolecules* **2005**, *38*, 2213. (e) Mitchell, S. C.; Waring, R. H. Aminophenols. In *Derivatives of 2-Aminophenol*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; pp 8−12.

(2) (a) Smith, C.; Ali, A.; Chen, L.; Hammond, M.; Anderson, M.; Chen, Y.; Eveland, S.; Guo, Q.; Hyland, S.; Milot, D.; Sparrow, C.; Wright, S.; Sinclair, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 346. (b) Imoto, M.; Matsui, Y.; Takeda, M.; Tamaki, A.; Taniguchi, H.; Mizuno, K.; Ikeda, H. *J. Org. Chem.* **2011**, *76*, 6356. (c) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* **2010**, *46*, 4767.

(3) (a) Luckarift, H. R.; L. Nadeau, J.; Spain, J. C. *Chem. Commun.* **2005**, 383. (b) Kadiyala, V.; Nadeau, L. J.; Spain, J. C. *Appl. Environ. Microbiol.* **2003**, *69*, 6520. (c) Toussaint, O.; Lerch, K. *Biochemistry* **1987**, *26*, 8567.

(4) Recent Pd-catalyzed C−H bond acyloxylation or hydroxylation: (a) Zhang, H.-Y.; Yi, H.-M.; Wang, G.-W.; Yang, B.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 6186. (b) Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5827. (c) Choy, P. Y.; Kwong, F. Y. *Org. Lett.* **2013**, *15*, 270. (d) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (e) Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075. (f) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912. (g) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409. (h) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (i) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (j) Huang, C.; Ghavtadze, N.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 17630. (k) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270. (l) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236. (m) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (n) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (o) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504. (p) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476.

(5) Recent Ru-catalyzed C−H bond acyloxylation or hydroxylation: (a) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (b) Ackermann, L. *Acc. Chem. Res.* **2013**, *47*, 281. (c) Liu, W.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3484. (d) Yang, F.; Ackermann, L. *Org. Lett.* **2013**, *15*, 718. (e) Thirunavukkarasu, V. S.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6206. (f) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210. (g) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874. (h) Shan, G.; Han, X.; Lin, Y.; Yua, S.; Rao, Y. *Org. Biomol. Chem.* **2013**, *11*, 2318.

(6) Recent Cu-, Fe-, or Au-catalyzed C−H bond acyloxylation or hydroxylation: (a) Rout, S. K.; Guin, S.; Gogoi, A.; Majji, G.; Patel, B. K. *Org. Lett.* **2014**, *16*, 1614. (b) Pradal, A.; Toullec, P. Y.; Michelet, V. *Org. Lett.* **2011**, *13*, 6086. (c) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(7) (a) Yang, X.; Shan, G.; Rao, Y. *Org. Lett.* **2013**, *15*, 2334. (b) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 9651.

(8) (a) Guan, Z.-H.; Chen, M.; Ren, Z.-H. *J. Am. Chem. Soc.* **2012**, *134*, 17490. (b) Gao, S.; Chen, M.; Zhao, M.-N.; Du, W.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *J. Org. Chem.* **2014**, *79*, 4196. (c) Guan, Z.-H.; Lei, H.; Chen, M.; Ren, Z.-H.; Bai, Y.; Wang, Y.-Y. *Adv. Synth. Catal.* **2012**, *354*, 489. (d) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Angew. Chem. Int. Ed.* **2013**, *52*, 14196. (e) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Asian J.* **2014**, *9*, 577.

(9) (a) Gambarjan. *Ber.* **1909**, *42*, 4003. (b) Edward, J. T. *J. Chem. Soc.* **1954**, 1464. (c) Boyland, E.; Sims, P. *J. Chem. Soc.* **1958**, 4198. (d) Roy, R. B.; Swan, G. A. *J. Chem. Soc. C* **1968**, 80.

(e) Venkateswarlu, V.; Kumar, K. A. A.; Balgotra, S.; Reddy, G. L.; Srinivas, M.; Vishwakarma, R. A.; Sawant, S. D. *Chem.—Eur. J.* **2014**, *20*, 6641.

(10) The reaction conversion was very good. 2-Benzamidophenol **2a** was isolated as the main product, together with the *N*,*N*′-dimethylhydrazobenzene byproduct and a small amount of complex colored mixtures. A similar result was observed in Schemes 2 and 3. See: Edward, J. T. *J. Chem. Soc.* **1956**, 222.

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