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# Nucleophilic Functionalizations of Aniline Derivatives: Aromatic Pummerer Reaction for Umpolung Halogenation and Hydroxylation on Benzene Ring

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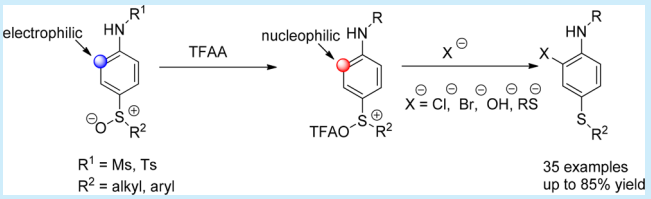
Supporting Information

**ABSTRACT:** In this paper, a metal-free protocol of nucleophilic *ortho*-halogenation and hydroxylation of anilines via an aromatic Pummerer process is reported.




Anilines are arguably the most ubiquitous electron-rich benzenoid compounds, correspondingly, the *ortho*-functionalizations of aniline derivatives generally belong to electrophilic substitution. Halogenations using electrophilic halogenating agents, albeit with disadvantages of functional group tolerance and overhalogenations,[1] are common tools for electrophilic functionalization; however, nucleophilic substitutions of halide ions on the benzene ring, i.e., nucleophilic halogenations, are not well documented. On the other hand, the direct hydroxylations of anilines are even rarer.[2]

The Pummerer reaction, first reported by Pummerer in 1909,[3] has been widely applied in organic synthesis,[4,5] which typically involves a thionium ion generated by the treatment of sulfoxide with acid anhydride. Based on our understanding of organosulfur chemistry,[6] we wish to report a realization of umpolung via a thionium ion to make the electrophilic *ortho*-position of anilines nucleophilic, which may allow facile halogenation and hydroxylation under Pummerer conditions (Scheme 1).

As a first attempt, we chose sulfinyl aniline (**1a**) as the starting material, which could be readily prepared via a sulfonylation and oxidation of 4-phenylthioaniline. We initiated our study by treatment of **1a** with acetic anhydride and tetrabutylammonium bromide (TBAB) in THF at room temperature and isolated bromide (**2a**) in 5% yield (Table 1, entry 1). When acetic anhydride was replaced with trifluoroacetic anhydride (TFAA), the yield of **2a** was raised to 30% (Table 1, entry 2). Decreasing the temperature to 0 °C offered a 43% yield (Table 1, entry 3), and the solvent screening showed that DCM gave an acceptable yield of 70% (Table 1,

**Scheme 1. Proposal of Nucleophilic Halogenation and Hydroxylation of Aniline**

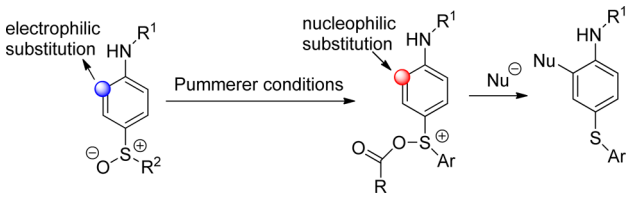
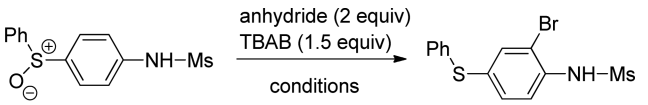



**Table 1. Optimization of Reaction Conditions**[a]




**1a** **2a**

| entry | anhydride | solvent | base | *T* (°C) | **2a** (%) |
|---|---|---|---|---|---|
| 1 | $Ac_2O$ | THF | | rt | 5 |
| 2 | TFAA | THF | | rt | 30 |
| 3 | TFAA | THF | | 0 | 43 |
| 4 | $Tf_2O$ | THF | | 0 | 0 |
| 5 | TFAA | MeCN | | 0 | 39 |
| 6 | TFAA | acetone | | 0 | 10 |
| 7 | TFAA | DCM | | rt | 47 |
| 8 | TFAA | DCM | | 0 | 70 |
| 9 | TFAA | DCE | | 0 | 40 |
| 10 | TFAA | DCE | | 50 | 12 |
| 11 | TFAA | DCM | TEA | 0 | 0 |
| 12 | TFAA | DCM | pyridine | 0 | 12 |
| 13 | TFAA | DCM | DMAP | 0 | 5 |
| 14 | TFAA | DCM | | 0 | 18[b] |

[a]Conditions: **1a** (0.5 mmol), base (1.0 mmol), and anhydrous solvent (5.0 mL). [b]A mixture of TBAB (0.1 mmol) and KBr (1 mmol) was used.

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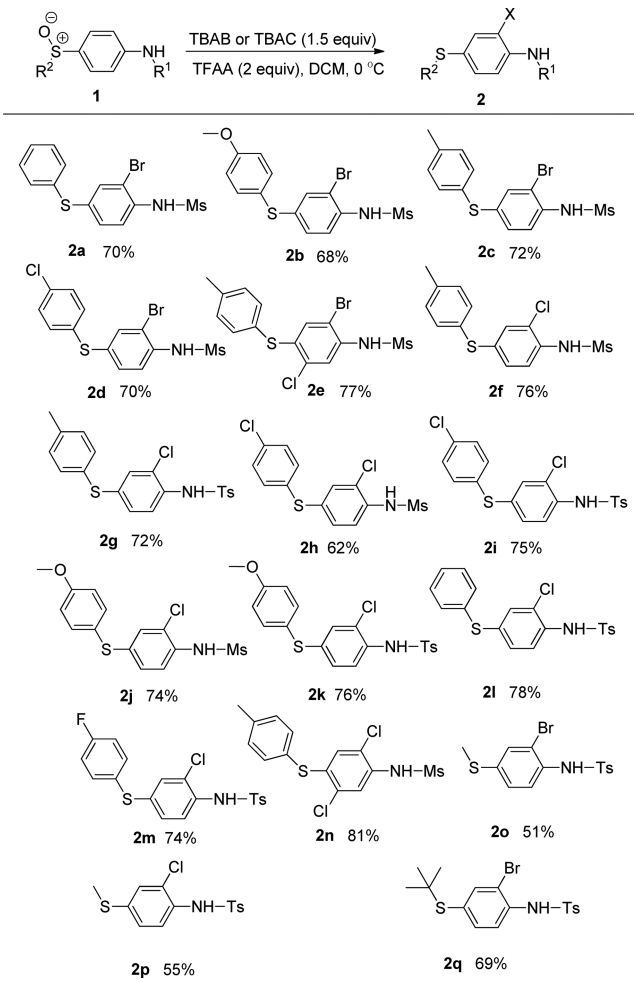
entries 5−9). Addition of trimethylamine (TEA), pyridine, or 4-dimethylaminopyridine (DMAP) did not improve the reaction but afforded sluggish results instead (Table 1, entries 11−13).

With this result in hand, the scope of the reaction was examined. As shown in Scheme 2. The reaction was successful

**Scheme 2. Nucleophilic Brominations and Chlorinations of Anilines**[a]

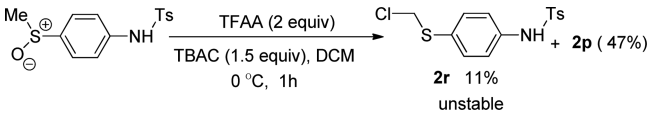



[a]The reaction was carried out using **1** (0.5 mmol), TFAA (1.0 mmol), and TBAB or TBAC (0.75 mmol) in DCM at 0 °C.

for TBAB as the bromide source (Scheme 2, **2a−e**) and also for TBAC as the chloride source (Scheme 2, **2f−n**). The $R^1$ group could be a methanesulfonyl (Ms) or *p*-tolylsulfonyl (Ts); and the $R^2$ group could be an aryl group or alkyl group. Substituents on the benzene ring of aniline even improved the yields slightly (Scheme 2, **2e** and **2n**). Notably, using TBAI gave elementary iodine instead of the corresponding iodide, showing that the reaction system under the Pummerer conditions is comparatively oxidative.

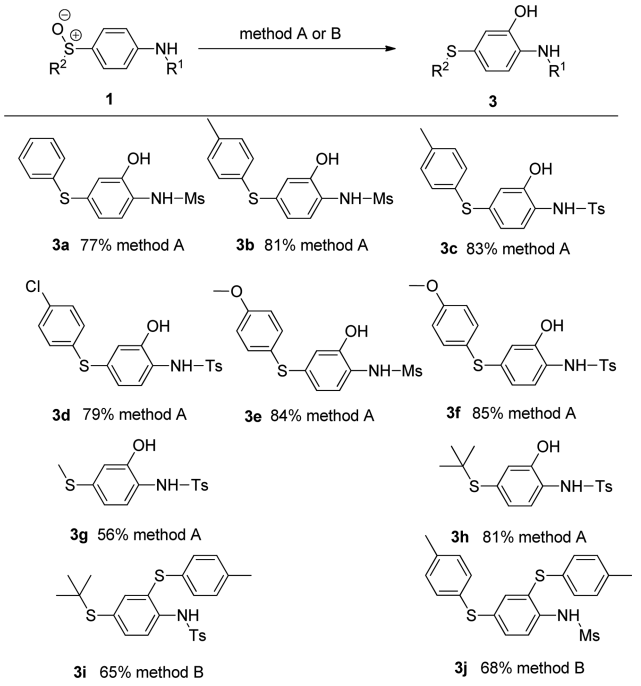
We noticed that the yields decreased obviously in the cases of methylsulfinyl substrates (Scheme 2, **2o** and **2p**). We quenched the reaction over 1 h and isolated a highly unstable (chloromethyl)thio byproduct (**2r**) in 11% yield, demonstrating that the loss of $\alpha$-proton may occur as a classic Pummerer process (Scheme 3).

**Scheme 3. Loss of $\alpha$-Proton**




Our attention was diverted to hydroxylation, probably because when base-sensitive TFAA was used as a promotor as shown in Scheme 2 tetrabutylammonium hydroxide failed to yield the expected hydroxyl aniline. We changed the reaction solvent to THF and charged saturated aqueous $NaHCO_3$ after the addition of TFAA. The hydroxylation of anilines was achieved in good yields (Scheme 4, **3a−h**). Softer nucleophile thiophenol also worked well to afford sulfides in good yields (Scheme 4, **31** and **3j**).

**Scheme 4. Hydroxylation of Anilines**[a]




[a]Method A: To **1** (0.5 mmol) and TFAA (1.0 mmol) in THF (5 mL) was added saturated aqueous $NaHCO_3$ (1 mL) at 0 °C. Method B: **1** (0.5 mmol), TFAA (1.0 mmol), *p*-methylthiophenol (0.75 mmol) in THF at 60 °C

Although the exact mechanism of this reaction is unclear at this stage, we believe that the formation of aza-quinone thionium intermediate would be involved in the pathway.[7] First, an aromatic Pummerer reaction gives aza-quinone thionium intermediate **A**, which is attacked by the nucleophile to afford **B**. Intermediate **B** undergoes aromatizatian to offer product **2** or **3** (Scheme 5).

Both *o*-halo anilines and *o*-hydroxyl anilines are useful building blocks,[8] and we chose **2a** and **2c** for further functionalization. The classical Suzuki coupling (Scheme 6, a), cyanation (Scheme 6, b), and intramolecular Heck reaction (Scheme 6, c) proceeded smoothly. In addition, the phenylthio group, which triggered the halogenation and hydroxylation, could be used in transformations such as reduction,[9] oxidation to sulfoxide or sulfone,[10] and hydrogenation.[11]



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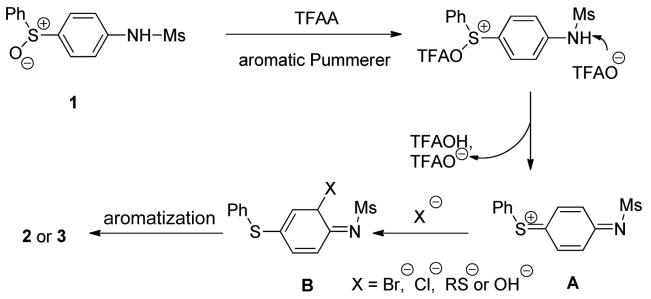
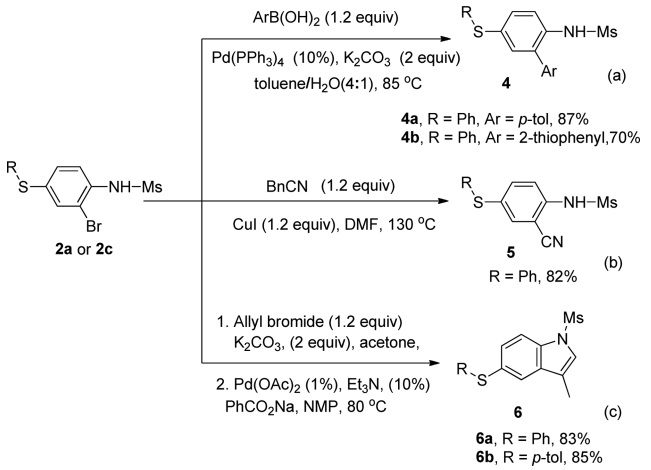
**Scheme 5. Plausible Pathway**




**Scheme 6. Further Transformations of 2a and 2c**




In summary, we have reported nucleophilic halogenation and hydroxylation of anilines via aromatic Pummerer process. As a result of this metal-free protocol with readily accessible starting materials and convenient operation, the method presented here should have potential utility in organic synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02720.

General experimental procedures and characterization data for new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) Przybylek, M.; Gaca, J. *Chem. Pap.* **2012**, *66*, 699. (b) Gowda, B. T.; Rao, P. J. M.; Jyothi, K. *Oxid. Commun.* **2000**, *23*, 255. (c) Ding, X.; Liu, G. *Synth. Commun.* **1989**, *19*, 1261. (d) Onaka, M.; Izumi, Y. *Chem. Lett.* **1984**, *13*, 2007. (e) Paul, D. F.; Haberfield, P. *J. Org. Chem.* **1976**, *41*, 3170.

(2) (a) Boyland, E.; Sims, P. *J. Chem. Soc.* **1954**, 980. (b) Boyland, E.; Manson, D.; Sims, P. *J. Chem. Soc.* **1953**, 3623.

(3) (a) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282. (b) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401.

(4) For recent reviews, see: (a) Yorimitsu, H. *Chem. Rec.* **2017**, *17*, 1. (b) Pulis, A. P.; Procter, D. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9842. (c) Yorimitsu, H. *Yuki Gosei Kagaku Kyokaishi* **2013**, *71*, 341. (d) Hugenberg, V.; Haufe, G. *J. Fluorine Chem.* **2012**, *143*, 238. (e) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. (f) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35. (g) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. (h) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

(5) (a) Kawashima, H.; Yanagi, T.; Wu, C. C.; Nogi, K.; Yorimitsu, H. *Org. Lett.* **2017**, *19*, 4552. (b) Shang, L.; Chang, Y. H.; Luo, F.; He, J. N.; Huang, X.; Zhang, L.; Kong, L. C.; Li, K. X.; Peng, B. *J. Am. Chem. Soc.* **2017**, *139*, 4211. (c) Shrives, H. J.; Fernandez-Salas, J. A.; Hedtke, C.; Pulis, A. P.; Procter, D. J. *Nat. Commun.* **2017**, *8*, 14801. (d) Yanagi, T.; Otsuka, S.; Kasuga, Y.; Fujimoto, K.; Murakami, K.; Nogi, K.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2016**, *138*, 14582. (e) Fernandez-Salas, J. A.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 790. (f) Eberhart, A. J.; Shrives, H.; Zhang, Y. T.; Carrer, A.; Parry, A. V. S.; Tate, D. J.; Turner, M. L.; Procter, D. J. *Chem. Sci.* **2016**, *7*, 1281. (g) Eberhart, A. J.; Shrives, H. J.; Alvarez, E.; Carrer, A.; Zhang, Y. T.; Procter, D. J. *Chem. - Eur. J.* **2015**, *21*, 7428.

(6) (a) Chen, D.; Zhang, L.; Yao, J.; Zhou, H. *J. Org. Chem.* **2017**, *82*, 6202. (b) Chen, D.; Xing, G.; Yao, J.; Zhou, H. *Org. Chem. Front.* **2017**, *4*, 1042. (c) Chen, D.; Xing, G.; Zhou, H. *Org. Chem. Front.* **2015**, *2*, 947. (d) Zhou, H.; Xing, Y.; Yao, J.; Lu, Y. *J. Org. Chem.* **2011**, *76*, 4582. (e) Zhou, H.; Xing, Y.; Liu, L.; Hong, J. *Adv. Synth. Catal.* **2011**, *353*, 3146. (f) Zhou, H.; Xie, Y.; Ren, L.; Su, R. *Org. Lett.* **2010**, *12*, 356. (g) Zhou, H.; Zhu, D.; Xie, Y.; Huang, H.; Wang, K. *J. Org. Chem.* **2010**, *75*, 2706. (h) Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674.

(7) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279.

(8) (a) Panyam, P. K. R.; Gandhi, T. *Adv. Synth. Catal.* **2017**, *359*, 1144. (b) Poon, J.; Yan, J.; Singh, V. P.; Gates, P. J.; Engman, L. *Chem. - Eur. J.* **2016**, *22*, 12891. (c) Desrosiers, J. N.; Hie, L.; Biswas, S.; Zatolochnaya, O. V.; Rodriguez, S.; Lee, H.; Grinberg, N.; Haddad, N.; Yee, N. K.; Garg, N. K.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 11921. (d) Liu, Z. T.; Wang, Y. H.; Zhu, F. L.; Hu, X. P. *Org. Lett.* **2016**, *18*, 1190. (e) Feng, W.; Teo, X. Y.; Novera, W.; Ramanujulu, P. M.; Liang, D.; Huang, D.; Moore, P. K.; Deng, L. W.; Dymock, B. W. *J. Med. Chem.* **2015**, *58*, 6456. (f) Matralis, A. N.; Kourounakis, A. P. *J. Med. Chem.* **2014**, *57*, 2568.

(9) (a) Yu, Z.; Verkade, J. G. *Tetrahedron Lett.* **1998**, *39*, 2671. (b) Gutierrez, C. G.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206.

(10) (a) Fareghi-Alamdari, R.; Zekri, N.; Moghadam, A. J.; Farsani, M. R. *Catal. Commun.* **2017**, *98*, 71. (b) Wagh, R. B.; Nagarkar, J. M. *Catal. Lett.* **2017**, *147*, 181. (c) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340.

(11) (a) Van Buren, R. L.; Baltisberger, R. J.; Woolsey, N. F.; Stenberg, V. I. *J. Org. Chem.* **1982**, *47*, 4107. (b) Truce, W. E.; Tate, D. P.; Burdge, D. N. *J. Am. Chem. Soc.* **1960**, *82*, 2872. (c) Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1943**, *65*, 1013.




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