Organic LETTERS

Letter

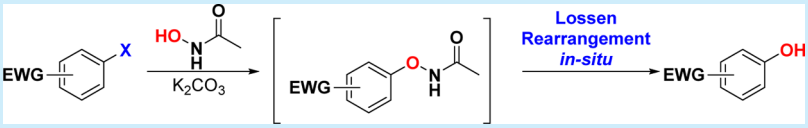
pubs.acs.org/OrgLett

Direct Conversion of Haloarenes to Phenols under Mild, Transition-Metal-Free Conditions

Patrick S. Fier* and Kevin M. Maloney*

Department of Process & Analytical Chemistry, Merck Research Laboratories, 126 East Lincoln Avenue, Rahway, New Jersey 07065, United States

Supporting Information

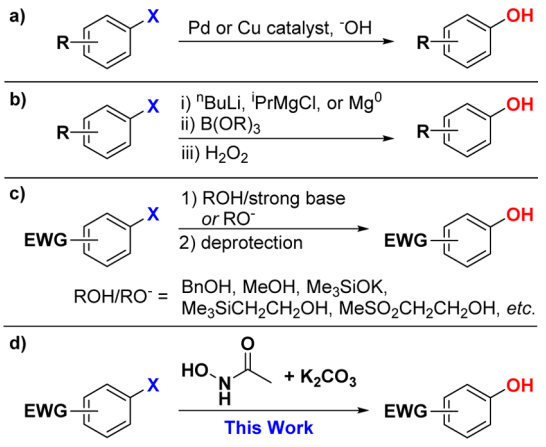


ABSTRACT: A high-yielding and practical method for the synthesis of phenols from electron-deficient haloarenes and heteroarenes has been developed. The products are formed from acetohydroxamic acid as the hydroxide source via a novel S_NAr reaction/Lossen rearrangement sequence. Notably, these reactions employ inexpensive and air-stable reagents, require no special handling, occur under mildly basic conditions, and form products in high yields in the presence of electrophilic and protic functionality. The utility of this methodology is demonstrated by the high-yielding hydroxylation of two base-sensitive complex substrates.

Phenols and their derivatives are ubiquitous in natural products and medicinally important molecules.[1] Furthermore, phenols and their protected analogs are important synthetic intermediates for electrophilic arene functionalization, directed *ortho*-metalation, quinone synthesis, the preparation of aryl ethers and esters, and cross-coupling. Due to their utility and practicality in organic synthesis, several methods have been developed for their preparation.

Three of the most common routes to synthesize phenols from aryl halides are shown in Scheme 1. In recent years, significant progress has been made to directly couple hydroxide salts with aryl halides in the presence of a Pd or Cu catalyst (Scheme 1a).[2,3] However, these reactions require high temperatures, strongly basic conditions, are sensitive to oxygen, and often require the use of expensive specialized ligands. The combination of hydroxide salts and high temperatures limits the generality of these methods to substrates lacking esters or epimerizable stereocenters.

Scheme 1. Common Methods for the Synthesis of Phenols from Aryl Halides



An alternative approach is the three-step conversion of aryl halides to phenols through (i) metalation, (ii) quenching of the aryl-metal species with a borate ester, and (iii) oxidation of the intermediate aryl boronate ester to the corresponding phenol (Scheme 1b). However, in the case of halogen-metal exchange (Li or Mg) the intermediacy of reactive aryl metal species is not amenable to the hydroxylation of substrates bearing protic or electrophilic functionality. More recently, transition metal catalyzed C−X[4] and C−H[5] borylation reactions have been applied to the synthesis of phenols[6] via arylboronate esters, avoiding aryllithium or arylmagnesium intermediates. While the borylation reactions can occur under mild conditions, the conversion of the arylboron species to phenols is limited to substrates that are not sensitive toward the oxidation conditions.[7]

Finally, the direct nucleophilic aromatic substitution (S_NAr) of electron-deficient haloarenes with hydroxide can allow for a straightforward synthesis of phenols without the need for transition metals or highly reactive intermediates. However, due to the low nucleophilicity and high basicity of hydroxide salts, such a direct S_NAr reaction is limited to simple and highly activated aryl electrophiles.[8] To overcome the low nucleophilicity of hydroxide ions, several hydroxide surrogates have been used (Scheme 1c).[9] Yet, these reactions still operate under strongly basic conditions and require the need for a subsequent deprotection step. Herein we report the development of a simple, high-yielding, one-step synthesis of phenols from electron-deficient haloarenes and heteroarenes under mild

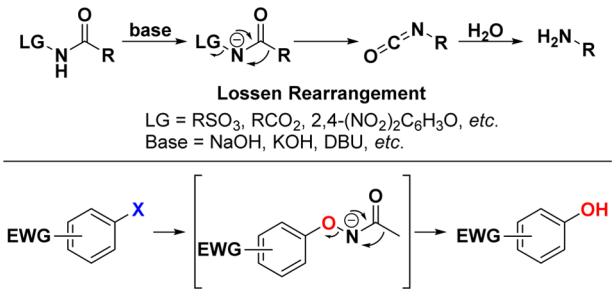
Received: March 25, 2016

DOI: 10.1021/acs.orglett.6b00876
Org. Lett. XXXX, XXX, XXX−XXX

reaction conditions with acetohydroxamic acid as a novel nucleophilic surrogate for hydroxide.

To develop a mild and direct S_NAr reaction for the synthesis of phenols, we sought to identify a hydroxide surrogate that is (i) more nucleophilic than hydroxide salts, (ii) reacts under mildly basic conditions, (iii) is tolerant of electrophilic and protic functional groups, and (iv) forms an intermediate that reveals the phenol under the reaction conditions without a separate deprotection step. We hypothesized that a hydroxamic acid as the nucleophile would satisfy all of these criteria. In this proposal, the phenol would be formed via an intermediate *O*-aryl hydroxamate ester that subsequently undergoes a Lossen-type rearrangement. The Lossen rearrangement has been used for the preparation of amines through the formation of an isocyanate (Scheme 2).[10] Most commonly, reactions are

Scheme 2. Lossen Rearrangement and Proposed Application toward the Synthesis of Phenols

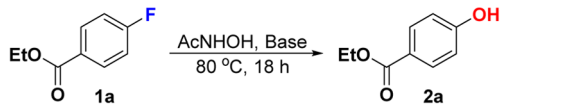


performed with a highly activated leaving group on nitrogen in the presence of a strong base. Since the only examples with a phenoxide leaving group have been with 2,4-dinitrophenoxide, it was unclear if this rearrangement reaction could be applied to the synthesis of phenols where the conjugate base is a worse leaving group.

In order to develop a tandem S_NAr/Lossen rearrangement reaction, we investigated reactions with ethyl 4-fluorobenzoate. The choice of this electrophile would allow for the identification of conditions that were mild enough to tolerate esters and conditions which promote the Lossen rearrangement with a weakly activated leaving group on nitrogen. We chose to focus on acetohydroxamic acid as the nucleophile, as it is inexpensive, available on large scale, and the most atom economical hydroxamic acid for the synthesis of phenols.

A series of polar aprotic solvents, weak bases, and stoichiometries were examined for the conversion of ethyl 4-fluorobenzoate to ethyl 4-hydroxybenzoate, and the results are summarized in Figure 1. The combination of 3 equiv of acetohydroxamic acid, 5 equiv of K_2CO_3, and DMSO at 80 °C formed the product in high yield and in a short reaction time. A control experiment was conducted with 3 equiv of water in place of acetohydroxamic acid. However, none of the phenol product was detected, ruling out adventitious water as a hydroxide source.

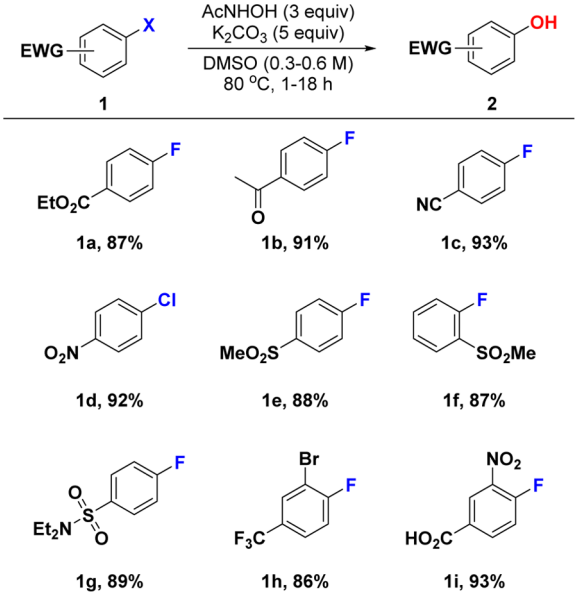
We explored the generality of this sequence for the synthesis of phenols from electron-deficient haloarenes and heteroarenes. As shown in Schemes 3 and 4, the reaction conditions formed phenols in the presence of esters, enolizable ketones, nitriles, nitro groups, sulfones, sulfonamides, aryl bromides, free carboxylic acids, and primary amides. Activated aryl and heteroaryl chlorides and bromide substrates also underwent the transformation in high yield (Scheme 4). *In all cases, the*



entry	base	equiv of base	equiv of AcNHOH	solvent (0.6 M)	conversion to 2a (%)[a]
1	K_3PO_4	3.0	2.0	DMSO	82
2	Na_2CO_3	3.0	2.0	DMSO	15
3	DBU	3.0	2.0	DMSO	65
4	K_2CO_3	3.0	2.0	DMSO	84
5	K_2CO_3	5.0	3.0	DMSO	99
6	K_2CO_3	5.0	3.0	DMF	61
7	K_2CO_3	5.0	3.0	THF	1
8[b]	K_2CO_3	5.0	H_2O, 3.0	DMSO	0

Figure 1. Conditions screened for the hydroxylation of ethyl 4-fluorobenzoate with acetohydroxamic acid. [a] Conversion based on HPLC area percent, uncorrected. [b] Water (3.0 equiv) used in place of AcNHOH.

Scheme 3. Scope for the Hydroxylation of Electron-Deficient Haloarenes with AcNHOH[a]



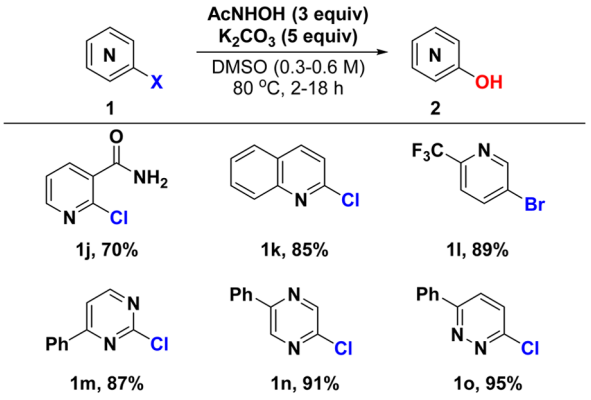
[a]Isolated yields for reactions performed on 2.0−5.0 mmol scale. All reactions proceeded in >95% yield by HPLC, uncorrected.

phenol or hydroxylated heteroarene products were formed in >95% yield by HPLC analysis; lower isolated yields were the result of losses during the purification process. In some cases, the products precipitated directly from the reaction mixture upon the addition of water and a pH adjustment with dilute HCl.

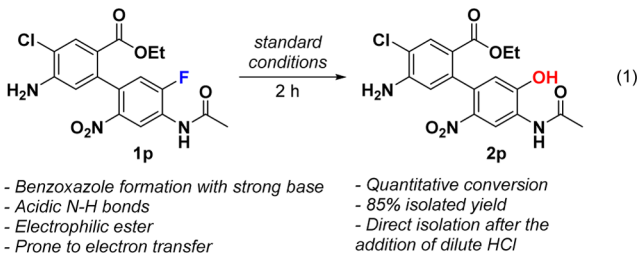
The mild reaction conditions allow for the hydroxylation reaction to be applied to more complex molecules containing sensitive functionality. To demonstrate the application of this methodology, we applied our new reaction conditions to the hydroxylation of a densely functionalized pharmaceutical intermediate bearing an ester, primary aniline, aryl chloride, and *ortho*-acetamide group (eq 1). Notably, under strongly basic conditions an intramolecular S_NAr reaction of the acetamide group occurred to generate the corresponding benzoxazole. Using the conditions described here, only the phenol was formed and the product was isolated directly upon the addition of water and dilute HCl.

DOI: 10.1021/acs.orglett.6b00876
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Scope for the Hydroxylation of Halogenated Heterocycles with AcNHOH[a]

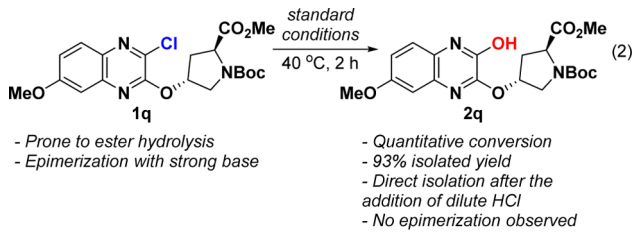


[a]Isolated yields for reactions performed on 2.0−5.0 mmol scale. All reactions proceeded in >95% yield by HPLC, uncorrected.



(1)

Next, we applied the S_NAr/Lossen rearrangement conditions to the hydroxylation of a chloroquinoxaline containing an epimerizable *N*-Boc amino ester. This compound is an intermediate in the synthesis of Grazoprevir (MK-5172), a selective NS3/4a protease inhibitor for the treatment of HCV (eq 2).[11] When subjected to AcNHOH and K_2CO_3 at 40 °C,

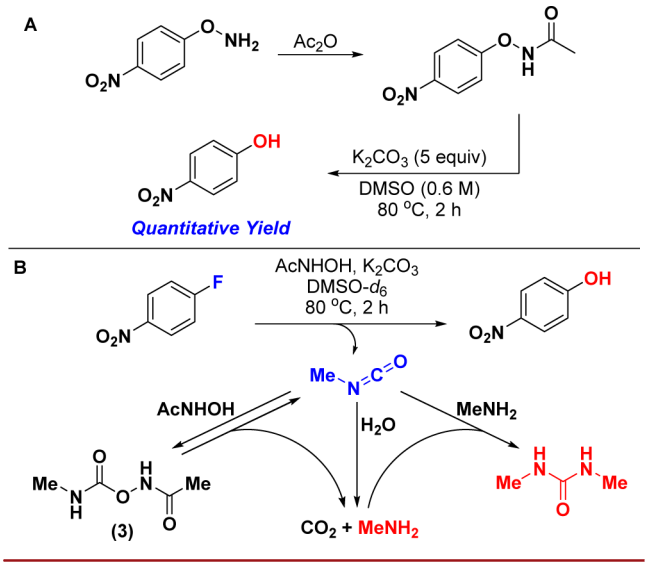


(2)

the hydroxyquinoxaline product was formed in high yield after 2 h. Again the product could be directly isolated after the addition of water and dilute HCl as a single diastereomer, with no trace of epimerization.

Throughout the course of the reactions, the *O*-aryl acetohydroxamate intermediates were observed by HPLC and LC/MS. To confirm the identity and reactivity of the proposed intermediates, an authentic *O*-(4-nitrophenyl) acetohydroxamate standard was prepared from *O*-(4-nitrophenyl)hydroxylamine and AcCl (Scheme 5A).[12] This species matched the observed intermediate in the reaction of 1-chloro-4-nitrobenzene with AcNHOH by HPLC and LC/MS analysis. The isolated hydroxamate ester reacted with K_2CO_3 in DMSO at 80 °C over 40 min to form 4-nitrophenol in quantitative yield. The rate of the rearrangement is consistent with the 2 h reaction time for the S_NAr/Lossen rearrangement of 1-chloro-4-nitrobenzene to 4-nitrophenol (Scheme 3, **1d**). These observations, along with the observation that water is not a

Scheme 5. (A) Synthesis and Rearrangement of Hydroxamate Ester Intermediate; (B) Fate of Methyl Isocyanate



competent nucleophile (Figure 1, entry 8), support our originally proposed hypothesis of an S_NAr/Lossen rearrangement mechanism.

During the Lossen rearrangement, MeNCO is formed in stoichiometric amounts. Because MeNCO is volatile and toxic, we studied the fate and persistence of this species in the reaction mixture. Performing the reaction in DMSO-d_6 allowed us to monitor the fate of MeNCO by ^{1}H NMR spectroscopy. At the end of the reaction, it was found that $MeNH_2$ and *N*,*N*′-dimethylurea were the major byproducts, and MeNCO was undetected. $MeNH_2$ results from quenching of the MeNCO with adventitious water or excess AcNHOH (Scheme 5B). The initial adduct (**3**) from reaction of MeNCO with AcNHOH can undergo further reactions to give *N*,*N*′-dimethylurea with the formation of $MeNH_2$, CO_2, and MeNCO.[13] The $MeNH_2$ that is formed during these reactions can also react with MeNCO to give *N*,*N*′-dimethylurea.

Having demonstrated that MeNCO is not present at the end of the reaction, we performed *in situ* gas phase IR spectroscopy to determine if MeNCO persists during the reaction. Due to the low boiling point (38 °C) of MeNCO, if it is present in solution, it will be detectable in the gas phase. In the reaction of 1-fluoro-4-nitrobenzene under the standard reaction conditions, MeNCO was not observed at ppm levels of detection. The results from these spectroscopic experiments suggest that the highly reactive MeNCO is quenched as soon as it is formed in solution.

In conclusion, we have developed a mild and general method for the hydroxylation of electron-deficient haloarenes and heteroarenes with acetohydroxamic acid as a novel hydroxide surrogate. These reactions occur under mildly basic conditions, are tolerant of several electrophilic and protic functional groups, and can be applied to the hydroxylation of complex, base-sensitive molecules. Mechanistic studies support a tandem S_NAr and Lossen rearrangement pathway for the reaction mechanism.

DOI: 10.1021/acs.orglett.6b00876
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00876.

(PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: patrick.fier@merck.com.
*E-mail: kevin_maloney@merck.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank L. C. Campeau, Kevin Campos, Zhijian Liu, and Wensheng Yu (all at Merck) for helpful suggestions. We thank Khateeta Emerson (Merck) for performing the gas phase IR spectroscopy experiments.

■ REFERENCES

(1) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: New York, 1996.

(2) For selected examples of Pd-catalyzed hydroxylation, see: (a) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912. (b) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (c) Chen, G.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2007**, *48*, 473. (d) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918. (e) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595. (f) Yu, C.-W.; Chen, G. S.; Huang, C.-W.; Chern, J.-W. *Org. Lett.* **2012**, *14*, 3688. (g) Lavery, C. B.; Rotta-Loria, N. L.; McDonald, R.; Stradiotto, M. *Adv. Synth. Catal.* **2013**, *355*, 981. (h) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 5351.

(3) For selected examples of Cu-catalyzed hydroxylation, see: (a) Tlili, A.; Xia, N.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725. (b) Yang, D.; Fu, H. *Chem. - Eur. J.* **2010**, *16*, 2366. (c) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8729. (d) Paul, R.; Ali, M. A.; Punniyamurthy, T. *Synthesis* **2010**, *2010*, 4268. (e) Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* **2010**, *2010*, 976. (f) Chan, C.-C.; Chen, Y.-W.; Su, C.-S.; Lin, H.-P.; Lee, C.-F. *Eur. J. Org. Chem.* **2011**, *2011*, 7288. (g) Thakur, K. G.; Sekar, G. *Chem. Commun.* **2011**, *47*, 6692. (h) Xu, H.-J.; Liang, Y.-F.; Cai, Z.-Y.; Qi, H.-X.; Yang, C.-Y.; Feng, Y. S. *J. Org. Chem.* **2011**, *76*, 2296. (i) Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 4340. (j) Songis, O.; Boulens, P.; Benson, C. G. M.; Cazin, C. S. J. *RSC Adv.* **2012**, *2*, 11675. (k) Xiao, Y.; Xu, Y.; Cheon, H.-S.; Chae, J. *J. Org. Chem.* **2013**, *78*, 5804. (l) Song, G.-L.; Zhang, Z.; Da, Y.-X.; Wang, X.-C. *Tetrahedron* **2015**, *71*, 8823.

(4) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271.

(5) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(6) (a) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792. (b) Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2092.

(7) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117.

(8) Feldman, D.; Segal-Lew, D.; Rabinovitz, M. *J. Org. Chem.* **1991**, *56*, 7350.

(9) (a) Preston, P. N.; Winwick, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1439. (b) Showalter, H. D. H.; Johnson, J. L.; Hoftiezer, J. M. *J. Heterocycl. Chem.* **1986**, *23*, 1491. (c) Krapcho, A. P.; Waterhouse, D. *Synth. Commun.* **1998**, *28*, 3415. (d) Levin, J. I.; Du, M. T. *Synth. Commun.* **2002**, *32*, 1401. (e) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585.

(10) (a) Lossen, W. *Liebigs Ann. Chem.* **1869**, *150*, 314. (b) Lossen, W. *Liebigs Ann. Chem.* **1875**, *175*, 271. (c) Lossen, W. *Liebigs Ann. Chem.* **1872**, *161*, 347. (d) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209. (e) Bauer, L.; Exner, O. *Angew. Chem.* **1974**, *86*, 419. (f) Dubé, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

(11) Harper, S.; et al. *ACS Med. Chem. Lett.* **2012**, *3*, 332.

(12) Shen, Y.; Liu, G.; Zhou, Z.; Lu, X. *Org. Lett.* **2013**, *15*, 3366.

(13) For similar reactions, see: (a) Pihuleac, J.; Bauer, L. *Synthesis* **1989**, *1989*, 61. (b) Jasikova, L.; Hanikyrova, E.; Skriba, A.; Jasik, J.; Roithova, J. *J. Org. Chem.* **2012**, *77*, 2829.

DOI: 10.1021/acs.orglett.6b00876
Org. Lett. XXXX, XXX, XXX−XXX