Metal-Free Synthesis of *N*-Aryloxyimides and Aryloxyamines

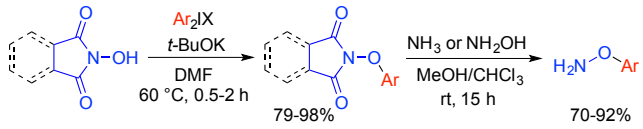
Raju Ghosh and Berit Olofsson*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

berit@organ.su.se

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



***N*-hydroxyphthalimide and *N*-hydroxysuccinimide have been arylated with diaryliodonium salts to provide *N*-aryloxyimides in excellent yields in short reaction times. A novel hydrolysis under mild and hydrazine-free conditions yielded aryloxyamines, which are valuable building blocks in the synthesis of oxime ethers and benzofurans.**

Aryloxyamines (*O*-arylhydroxylamines) are frequently employed in the synthesis of oxime ethers and benzofurans,[1] which are privileged pharmaceutical targets (Figure 1A).[2] Aryloxyamines can be synthesized by amine exchange with phenoxides,[3] or by arylation of various R_2NOH compounds followed by hydrolysis.

Classical S_NAr arylations with *tert*-butyl *N*-hydroxycarbamate or ethyl acetohydroximate and electron-deficient aryl fluorides followed by acid-promoted hydrolysis to aryloxyamines proceed in moderate-to-good yields but with narrow scope.[4] A more general, palladium-catalyzed arylation of ethyl acetohydroximate with aryl halides in the presence of air-sensitive alkylarylphosphine ligands was recently accomplished.[5]

N-Hydroxyphthalimide is another precursor of aryloxyamines. While it was phenylated with diphenyliodonium bromide in 1977,[6] the generally applied arylation conditions use stoichiometric amount of copper salt and 2 equiv arylboronic acid, as demonstrated by Sharpless and Kelly in 2001 (Figure 1B).[7] Subsequent cleavage of the phthalimide moiety to yield the aryloxyamines is usually performed with hydrazine.[6-7]

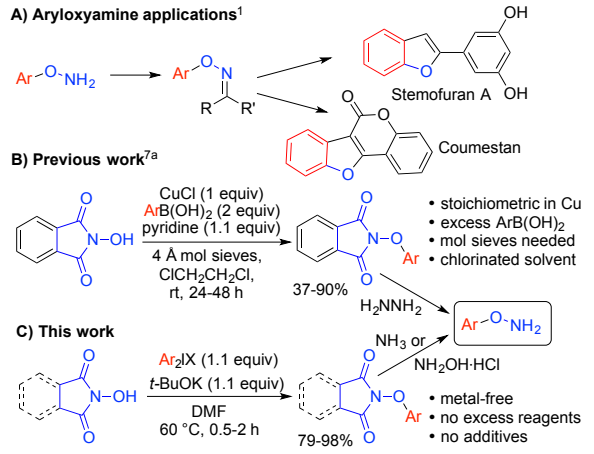


Figure 1. Synthesis and applications of aryloxyamines

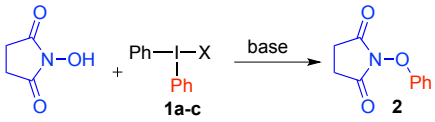
To the best of our knowledge, the arylation of *N*-hydroxysuccinimide (NHS) has never been reported.

Considering that the imide moiety is removed to produce the target aryloxyamine, the use of NHS instead of *N*-hydroxyphthalimide would increase the atom efficiency of the process. We envisioned that a general, metal-free arylation of *N*-hydroxyimides with diaryliodonium salts,[8] combined with a hydrazine-free hydrolysis, would be an attractive alternative to present routes to aryloxyamines. Herein, we report both a novel arylation and an efficient hydrolysis to yield aryloxyamines (Figure 1C).

The arylation of NHS with diphenyliodonium triflate (**1a**) was initially screened in DMF with microwave heating to 100 °C. High yields of phenylated product **2** were obtained with several bases, of which potassium *tert*-butoxide was deemed most suitable for further optimization (Table 1, entries 1-5). Lower temperatures were subsequently investigated, and 60 °C was sufficient when the reaction time was increased to 1 h (entry 6).[9]

Oil bath heating proved equivalent to microwave heating, and was more practical with longer reaction times. A solvent screen revealed that DMF was indeed most suitable (entries 6-9). Further decreases in temperature resulted in lower yields also with longer reaction time (entries 10-11). Importantly, arylations with diphenyliodonium tetrafluoroborate **1b** and tosylate **1c** were as efficient as **1a** (entries 12-13), thereby enabling arylations with a wide range of diaryliodonium salts without need for anion exchanges.[10]

Table 1. Optimization with NHS[a]



entry	solvent	base	1	X	temp (°C)	time (min)	yield (%)[b]
1	DMF	*t*-BuOLi	**1a**	OTf	100[c]	15	98
2	DMF	*t*-BuOK	**1a**	OTf	100[c]	15	97
3	DMF	*t*-BuONa	**1a**	OTf	100[c]	15	83
4	DMF	NaOH	**1a**	OTf	100[c]	15	78
5	DMF	K_2CO_3	**1a**	OTf	100[c]	15	88
6	DMF	*t*-BuOK	**1a**	OTf	60	60	94
7	MeCN	*t*-BuOK	**1a**	OTf	60	60	55
8	THF	*t*-BuOK	**1a**	OTf	60	60	52
9	PhMe	*t*-BuOK	**1a**	OTf	60	60	8
10	DMF	*t*-BuOK	**1a**	OTf	40	60	83
11	DMF	*t*-BuOK	**1a**	OTf	rt	14 h	80
12	DMF	*t*-BuOK	**1b**	BF_4	60	60	94
13	DMF	*t*-BuOK	**1c**	OTs	60	60	94

[a] Reaction conditions: NHS (0.25 mmol) and base (1.1 equiv) were mixed in 1 mL solvent at rt; salt **1** (1.1 equiv) was added after 10 min. [b] NMR yield with 4-anisaldehyde as internal standard. [c] MW heating.

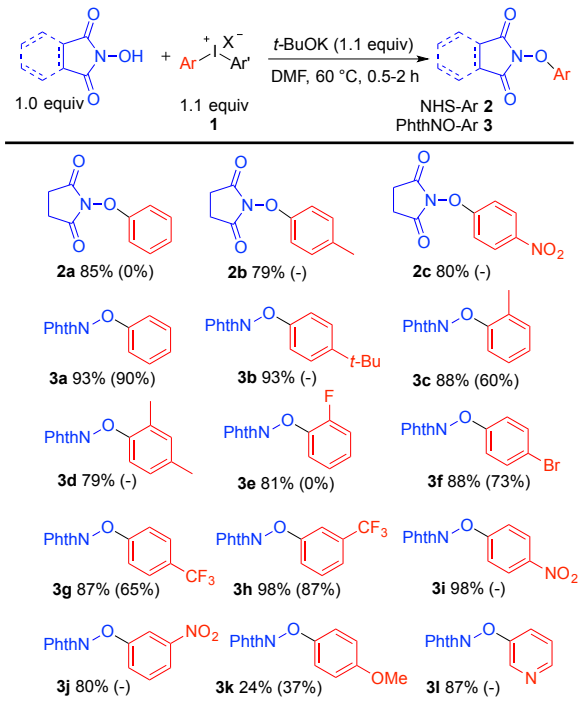
The arylation of *N*-hydroxysuccinimide and *N*-hydroxyphthalimide with a range of symmetric and unsymmetric diaryliodonium salts **1**[11] was subsequently explored (Scheme 1). Yields in parenthesis were reported with the Cu-mediated methodology (Figure 1A),[7a] and are shown as comparison. Arylations of NHS delivered *N*-aryloxysuccinimides **2a** and **2b** in good yields within 2 hours. Nitro-substituted product **2c** was formed with complete chemoselectivity using the unsymmetric salt **1d** (*vide infra*).

The arylation conditions proved ideal also for reactions with *N*-hydroxyphthalimide, and high-to-excellent yields of *N*-aryloxyphthalimides **3** were obtained with a variety of iodonium salts. Alkyl-substituted aryl groups were conveniently transferred (**3b**-**3d**) and also sterically congested, *ortho*-substituted products **3c**-**3e** were obtained in good yields. Also halide substituted and electron-withdrawing aryl groups were easily introduced (**3e**-**3j**). Transfer of a *p*-methoxyphenyl group to give product **3k** was achieved in modest yield due to byproduct formation.[12]

Arylations of *N*-hydroxyphthalimide with heteroaryl groups have previously proved unsuccesful.[7] Since *N*-heteroaryliodonium salts recently have become easily available,[11a] the transfer of a heteroaryl group seemed viable with the present methodology. Indeed, the pyridyl product **3l** was obtained in 87% yield within 90 min.

In all cases but **3k**, the yields of compounds **3** were higher than with the previous Cu-mediated methodology, which failed to arylate NHS and lacks scope with heteroaryl groups and *ortho*-electron withdrawing groups.[7]

Scheme 1. Synthesis of *N*-aryloxyimides[a]



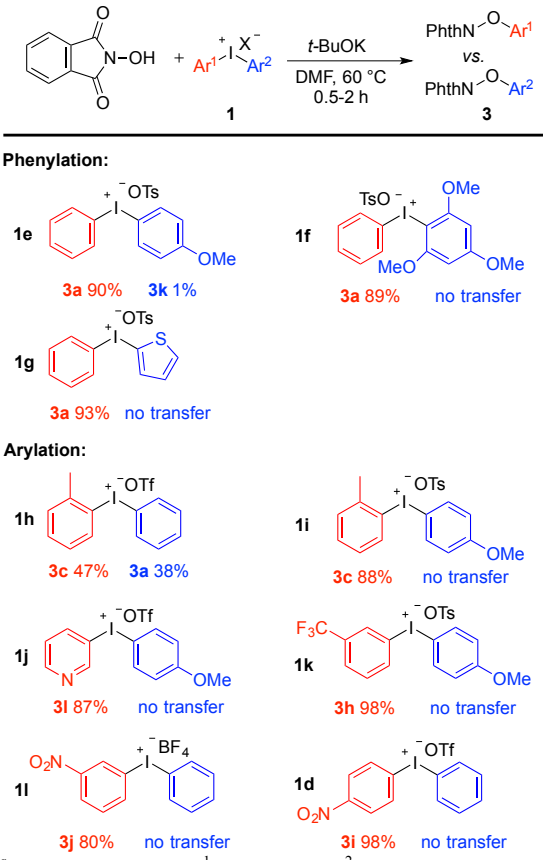
[a] PhthNH = Phthalimide. Isolated yields; (yields) refer to the Cu-mediated methodology.[7a]

Unsymmetric diaryliodonium salts are often preferable in arylations, as they tend to be cheaper and easier to synthesize.[8] Still, their use requires highly chemoselective

arylations, as even minor amounts of byproducts can be difficult to separate from the desired product. We have previously investigated chemoselectivities with unsymmetric iodonium salts and various nucleophiles,[13] and the trends for this reaction proved similar to previous *O*-arylations. Several of the products in Scheme 1 were synthesized with unsymmetric salts, and the obtained chemoselectivities are highlighted in Scheme 2, which lists the yields of PhthNO-Ar^1 *vs* PhthNO-Ar^2. The most electron–deficient aryl group, *i.e*. the phenyl group, was transferred with high or complete selectivity in salts **1e-1g**, and both trimethoxyphenyl and thienyl groups were ideal as non-transferable "dummy" groups.

An *ortho*-effect was seen with salt **1h**, yielding **3c** as the major product despite this aryl group being more electron-rich than the phenyl. Complete chemoselectivity was obtained with salt **1i**, with both *ortho*-effect and electronic properties favoring formation of **3c**. Selective transfer of pyridyl or CF_3-substituted groups required a *p*-methoxy dummy (**1j**, **1k**), whereas nitrophenyl groups were transferred with complete selectively using a phenyl dummy group (**1l**, **1d**).

Scheme 2. Chemoselectivity trends[a]



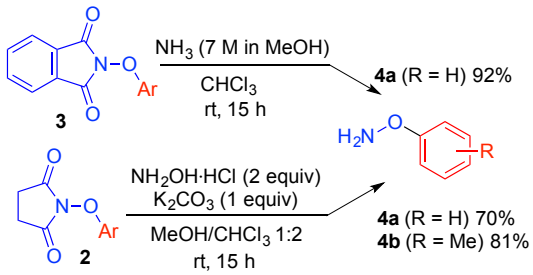
[a] Yields of PhthNO-Ar^1 *vs* PhthNO-Ar^2, no transfer means that no product was formed with the blue aryl group.

The atom efficiency in arylations with diaryliodonium salts is improved by recovering and reusing the resulting iodoarenes for synthesis of salts **1**. While iodobenzene is somewhat volatile, heavier dummy groups are easily recovered, as exemplified by the isolation of trimethoxyiodobenzene in quantitative yield in arylations with salt **1f**.[9]

The phthalimide moiety in **3** is usually cleaved with hydrazine,[6-7] which is a highly toxic compound. Hydrolysis with ammonia in methanol has been reported without experimental details,[14] while treatment with aminomethylated polystyrene resin required 48 h reaction time.[7b] Hydrazine-free hydrolytic conditions were thus investigated to further improve the green and user-friendly synthesis of aryloxyamines. After some experimentation, the hydrolysis of *N*-phenoxyphthalimide (**3a**) with ammonia provided **4a** in high yield (Scheme 3).

Hydrolysis of the *N*-aryloxysuccinimides **2** proved more difficult, and only one amide bond was cleaved under a variety of conditions, while more forcing conditions delivered **4** contaminated with the corresponding phenol.[9] Finally, hydroxylamine in the presence of base was found efficient, and aryloxyamines **4** were obtained in good yields also from compounds **2**. These novel hydrolytic conditions make arylation of NHS a viable alternative to the less atom efficient *N*-hydroxyphthalimide as source of aryloxyamines.

Scheme 3. Hydrolysis to aryloxyamines



In conclusion, a metal-free and general arylation of *N*-hydroxyimides has been developed, yielding aryloxyamines after a subsequent hydrolysis under mild and hydrazine-free conditions. The methodology allows for straightforward access to Stemofuran A[1a] and other biologically important benzofurans under metal-free conditions.

Acknowledgment Wenner-Gren Foundations and Carl Trygger Foundation are gratefully acknowledged.

Supporting Information Available Experimental details, analytical data and NMR copies of novel compounds. This material is available free of charge via the Internet at http:// pubs.acs.org.

(1) (a) Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761-1763. (b) Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamedmohaideen, N. N.; Purkey, H. E.; Nichols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K. B.; Kelly, J. W. *J. Med. Chem.* **2005**, *48*, 1576-1587. (c) Liu, Y.; Qian, J.; Lou, S.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 6300-6303. (d) Contiero, F.; Jones, K. M.; Matts, E. A.; Porzelle, A.; Tomkinson, N. C. O. *Synlett* **2009**, *2009*, 3003-3006. (e) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 1491-1509.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930.

(3) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1348-1352.

(4) (a) Boyles, D. C.; Curran, T. T.; Parlett, R. V.; Davis, M.; Mauro, F. *Org. Process Res. Dev.* **2002**, *6*, 230-233. (b) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 594-600. (c) Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833-3843.

(5) Maimone, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 9990-9991.

(6) Cadogan, J. I. G.; Rowley, A. G. *Synth. Commun.* **1977**, *7*, 365-366 (1.4 equiv Ph_2ICl, DMSO 15 h, 60% yield, no scope).

(7) (a) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139-142. (b) Gaucher-Wieczorek, F. S.; Maillard, L. T.; Badet, B.; Durand, P. *J. Comb. Chem.* **2010**, *12*, 655-658.

(8) Diaryliodonium salts are stable hypervalent iodine compounds of low toxicity: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052-9070. (b) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, 370-409. Results from studies of the biological activities of several diaryliodonium salts are summarized in: (c) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123-1178. Diaryliodonium salts have even been found suitable to use in dental materials and oral mouthwash; see: (d) Gonçalves, L. S.; Moraes, R. R.; Ogliari, F. A.; Boaro, L.; Braga, R. R.; Consani, S. *Dental Materials* **2013**, *29*, 1251-1255. (e) Goldstein, E. J. C.; Citron, D. M.; Warren, Y.; Merriam, C. V.; Tyrrell, K.; Fernandez, H.; Radhakrishnan, U.; Stang, P. J.; Conrads, G. *Antimicrob. Agents Chemother.* **2004**, *48*, 2766-2770.

(9) See the Supporting Information for details.

(10) One-pot routes to diaryliodonium salts yield triflate, tosylate or tetrafluoroborate anions depending on electronic and steric properties of the salt, see ref 11 or the Supporting info for details.

(11) (a) Bielawski, M.; Malmgren, J.; Pardo, L. M.; Wikmark, Y.; Olofsson, B. *ChemistryOpen* **2014**, *3*, 19-22. (b) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592-596. (c) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602-4607. (d) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521-2523. (e) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610-2618.

(12) The byproducts are probably formed via an aryne mechanism, see Graskemper, J. W.; Wang, B.; Qin, L.; Neumann, K. D.; DiMagno, S. G. *Org. Lett.* **2011**, *13*, 3158-3161.

(13) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem. Eur. J.* **2013**, *19*, 10334-10342.

(14) Tang, D.; Gai, Y.; Polemeropoulos, A.; Chen, Z.; Wang, Z.; Or, Y. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5078-5082.