

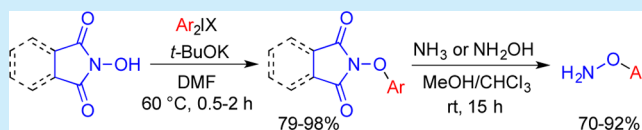
Metal-Free Synthesis of *N*-Aryloxyimides and Aryloxyamines

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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.

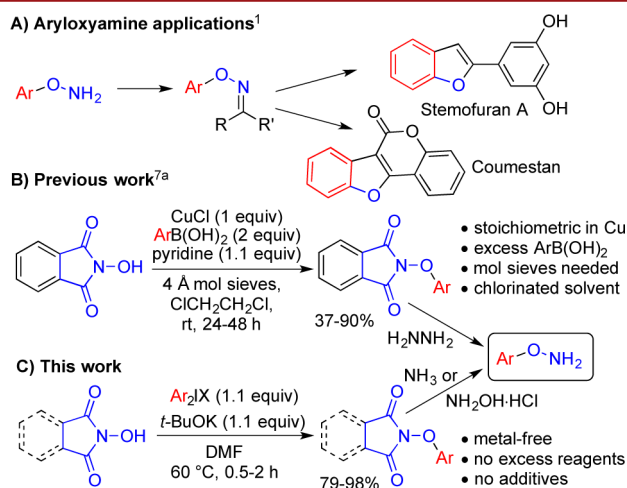


Figure 1. Synthesis and applications of aryloxyamines.

Classical $\text{S}_\text{N}\text{Ar}$ 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 a narrow scope.⁴ A more general, palladium-catalyzed arylation of ethyl acetohydroximate with aryl halides in the presence of air-sensitive alkyl-arylphosphine 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 a stoichiometric amount of copper salt and 2 equiv of 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}

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).

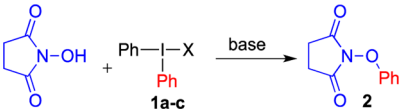
The arylation of NHS with diphenyliodonium triflate (**1a**) was initially screened in DMF with microwave heating to 100 °C. High yields of phenylated product **2** were obtained with several bases, of which potassium *tert*-butoxide was deemed most suitable for further optimization (Table 1, entries 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 a 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 the need for anion exchanges.¹⁰

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 parentheses were reported with the Cu-mediated methodology (Figure 1A)^{7a} and are shown for comparison. Arylations of NHS delivered *N*-aryloxysuccinimides **2a** and **2b** in good yields within 2 h. Nitro-substituted product **2c** was formed with complete chemoselectivity using the unsymmetric salt **1d** (*vide infra*).

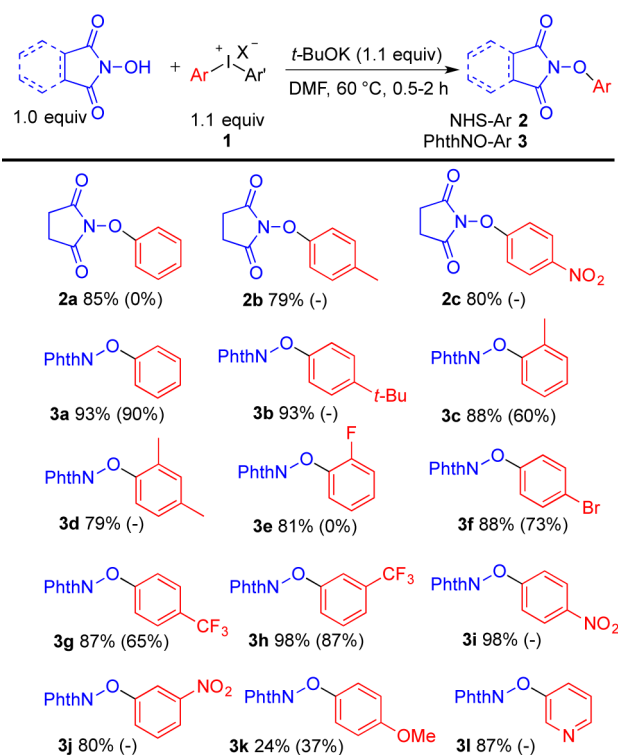
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Table 1. Optimization with NHS^a


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

^aReaction conditions: NHS (0.25 mmol) and base (1.1 equiv) were mixed in 1 mL of solvent at rt; salt 1 (1.1 equiv) was added after 10 min. ^bNMR yield with 4-anisaldehyde as internal standard. ^cMW heating.

Scheme 1. Synthesis of *N*-Aryloxyimides^a

^aPhthNH = Phthalimide. Isolated yields; (yields) refer to the Cu-mediated methodology.^{7a}

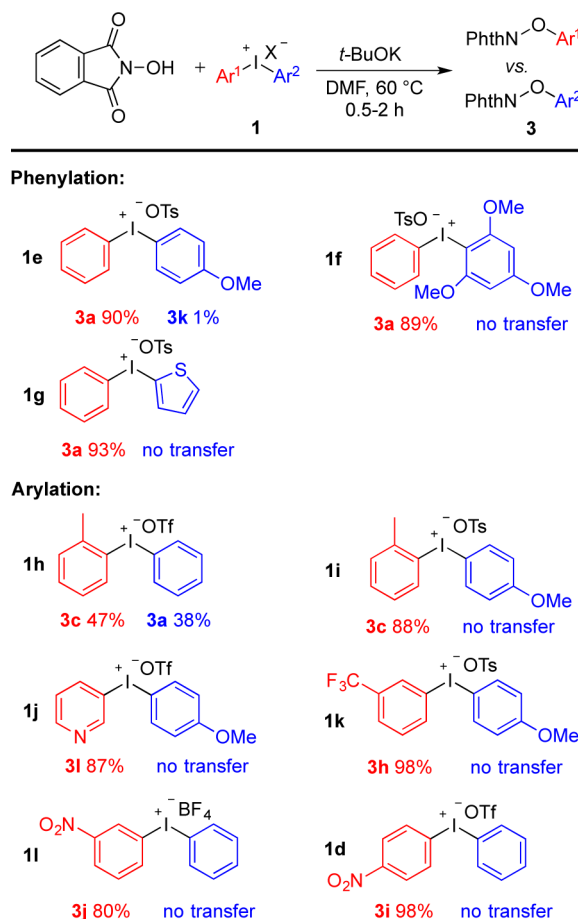
The arylation conditions proved ideal also for reactions with *N*-hydroxyphthalimide, and high-to-excellent yields of *N*-aryloxyphthalimides 3 were obtained with a variety of iodonium salts. Alkyl-substituted aryl groups were conveniently transferred (3b–3d), and also sterically congested, *ortho*-substituted products 3c–3e were obtained in good yields. Also halide substituted and electron-withdrawing aryl groups were easily

introduced (3e–3j). The 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 unsuccessful.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 those with the previous Cu-mediated methodology, which failed to arylate NHS and lacks scope with heteroaryl groups and *ortho*-electron withdrawing groups.⁷

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-Ar¹ vs PhthNO-Ar². The most electron-deficient aryl group, i.e. the phenyl group, was transferred with high or complete selectivity in salts 1e–1g, and both

Scheme 2. Chemoselectivity Trends^a

^aYields of PhthNO-Ar¹ vs PhthNO-Ar²; no transfer means that no product was formed with the blue aryl group.

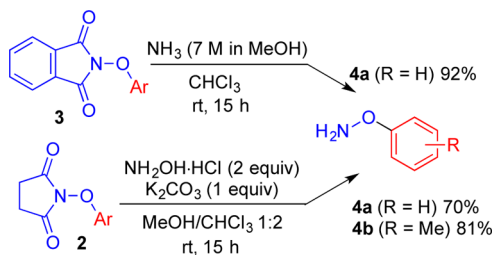
trimethoxyphenyl and thienyl groups were ideal as non-transferable “dummy” groups.

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 the *ortho*-effect and electronic properties favoring formation of **3c**. Selective transfer of pyridyl or CF₃-substituted groups required a *p*-methoxy dummy (**1j**, **1k**), whereas nitrophenyl groups were transferred with complete selectivity using a phenyl dummy group (**1l**, **1d**).

The atom efficiency in arylations with diaryliodonium salts is improved by recovering and reusing the resulting iodoarenes for the 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 a 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).

Scheme 3. Hydrolysis to Aryloxyamines



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 to be 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 a source of 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 a straightforward access to Stemofuran A^{1a} and other biologically important benzofurans under metal-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

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>.

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Notes

The authors declare no competing financial interest.

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