

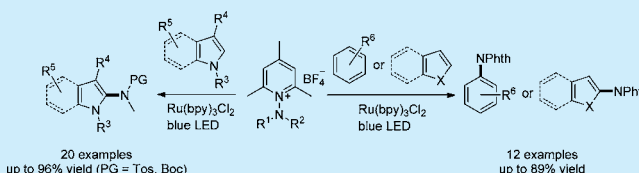
N-Aminopyridinium Salts as Precursors for N-Centered Radicals – Direct Amidation of Arenes and Heteroarenes

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S Supporting Information

ABSTRACT: Readily prepared *N*-aminopyridinium salts are valuable precursors for the generation of N-centered radicals. Reduction of these salts by single electron transfer allows for clean generation of amidyl radicals. It is shown that direct radical C–H amination of heteroarenes and arenes can be achieved with *N*-aminopyridinium salts under mild conditions by using photoredox catalysis.



In contrast to C-centered radicals, N-centered radicals have not received that much attention in synthesis.¹ This is likely due to their higher reactivity and to the fact that there are fewer methods for their clean generation. Mostly, N-centered radicals are formed via cleavage of a reactive N–X bond, where X can be a halogen atom, a N-substituent, an O-group, or a S-substituent.¹ Due to the rather strong C–N bond, cleavage of N–C bonds for generation of the corresponding N-centered radicals is not efficient.² There are a few examples of oxidation of N–H bonds in amides to directly generate amidyl radicals.³ Since most reactive N-radical precursors of the type R¹R²N–X are generally not stable¹ⁱ and have to be prepared *in situ*, development of novel, stable, readily prepared, cheap, and efficient N-radical precursors is of importance. We report herein that *N*-aminopyridinium salts readily prepared in large scale are highly efficient N-radical precursors and document their potential for direct radical C–H amidation of arenes and heteroarenes.

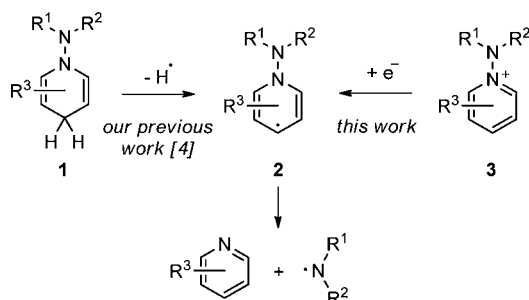
Previously, we reported radical hydroamination of alkenes by using aminated dihydropyridines **1** as N-radical precursors (Scheme 1).⁴ It was shown that reagents **1** are good H-donors for reduction of reactive C- and S-radicals to give stabilized proaromatic radicals of type **2**. These readily fragment to amidyl radicals and the corresponding pyridines. The driving force for the release of N-radicals from **2** is the gain in entropy

and pyridine resonance energy.⁵ Encouraged by these results we assumed that intermediates **2** can also be generated from pyridinium salts **3** upon single electron reduction. Whereas N-radical generation from **1** occurs via a H-transfer and subsequent fragmentation, reagents **3** will offer a complementary approach to N-radicals via an initial electron transfer process. Compounds **1** are radical hydroamination reagents where chains are reductively sustained and **3** should be good amination reagents which can be used in redox processes, therefore offering as compared to **1** a broader application range (chains can be sustained by oxidation of arene amidyl radical adducts).

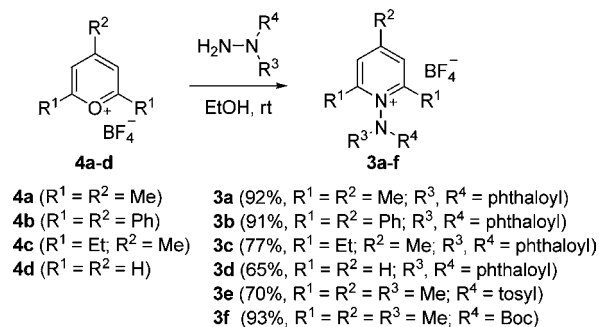
Reagents of type **3** are readily accessed in one step according to a literature procedure⁶ by reacting commercially available⁷ pyrylium salts **4** with a hydrazine derivative to give the *N*-aminopyridinium salts **3a–f** in good to excellent yields (Scheme 2). All salts **3a–f** can be stored for months, and phthaloyl derivatives **3a,b** and **d**^{8d} were previously described.⁸

N-Aminopyridinium salts have been shown to react with nucleophiles at the pyridinium moiety,⁹ with dipolarophiles in [3 + 2] cycloadditions¹⁰ and as electrophilic amination

Scheme 1. N-Radical Precursors **1** and **3**



Scheme 2. Preparation of *N*-Aminopyridinium Salts **3a–f**



Received: November 18, 2014

Published: December 26, 2014

reagents.¹¹ Moreover, photolysis leads to reactive nitrenium ions¹² and also the electrochemistry of some aminopyridinium salts was investigated.¹³ However, these salts have not been used as precursors for N-centered radicals in organic synthesis to date. For compound **3b** we obtained an X-ray structure revealing that the pyridinium plane and the amide plane are perpendicular to each other (Figure 1).

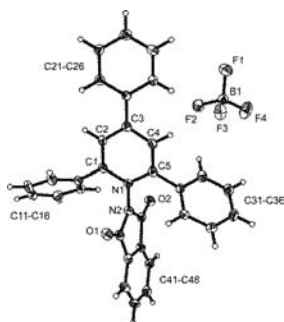


Figure 1. X-ray structure of **3b** (thermal ellipsoids are shown with 50% probability).

Cyclovoltammetry for **3a** and **3e** (see Supporting Information) showed irreversible reduction at -0.75 V and -0.70 V vs Ag/Ag⁺, respectively (Figure 2).

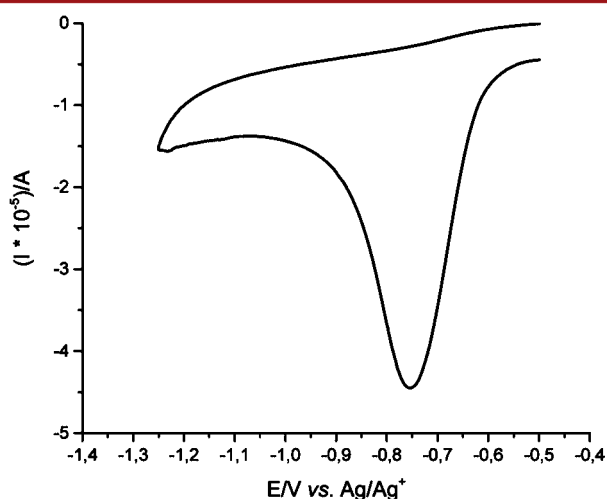


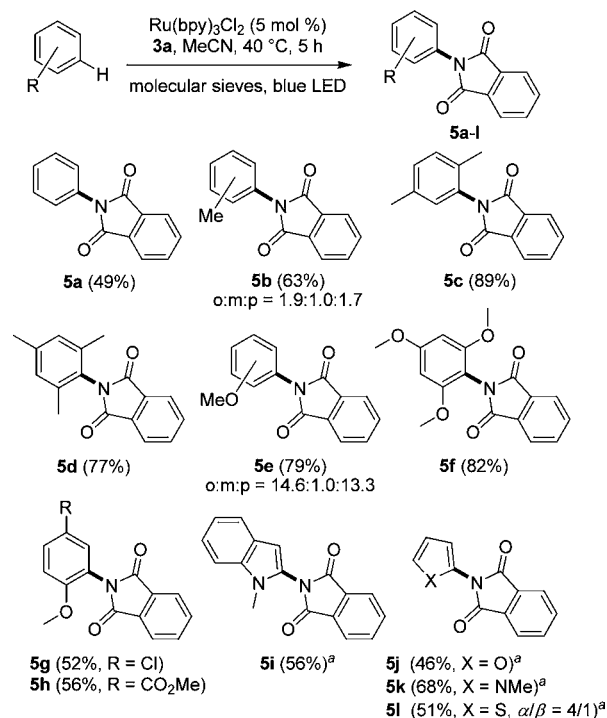
Figure 2. CV of **3a**.

We also recorded UV/vis spectra of the *N*-aminopyridinium salts. As expected, there is no significant absorption above 400 nm for these compounds (see Supporting Information). Considering the physical data of compounds **3** with the goal of amidyl radical generation, we were searching for an SET reducing reagent with a reduction potential of < -0.75 V vs Ag/Ag⁺. Moreover, if photochemistry is used to induce the SET process, irradiation has to occur above 400 nm in order to suppress excitation of **3** which will lead to unwanted nitrenium ion formation. Therefore, we decided to use photoredox catalysis applying blue light and Ru(bpy)₃Cl₂ as a catalyst.^{14,15} As a test reaction, direct amidation¹⁶ of benzene^{15a,b} was investigated first. Reactions were conducted in MeCN at 40 °C with *N*-aminopyridinium salts **3a–f** by using an excess of benzene (10 equiv) for 5 h. Note that a base is not necessary in

these reactions, since the released pyridine derivative will buffer the system.

With **3a** the amidation product **5a** was isolated in 49% yield (Scheme 3), and a similar result was obtained with **3c** (39%).

Scheme 3. Amidation of Arenes and Heteroarenes with **3a**



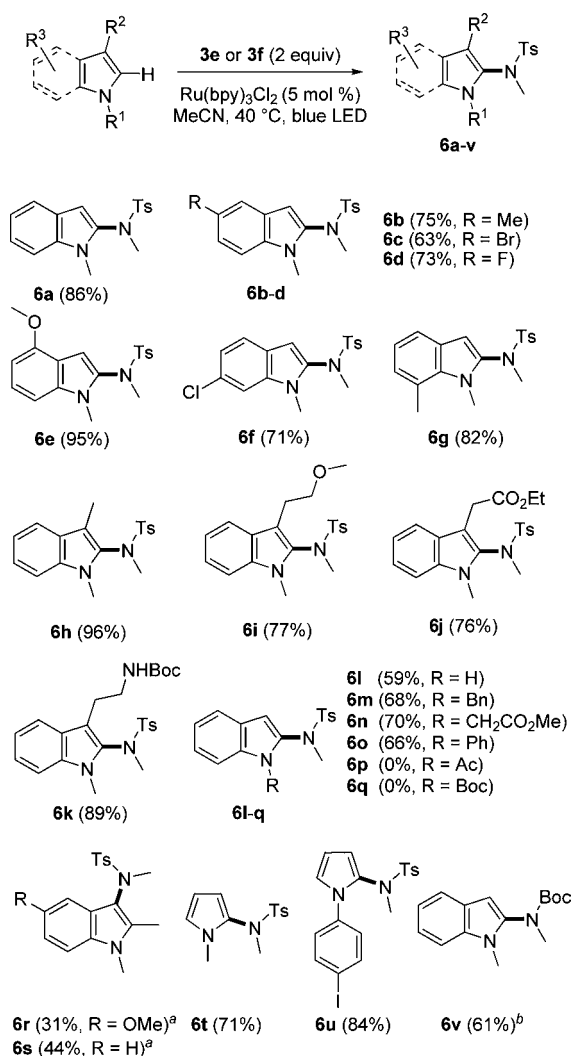
^aConducted with the corresponding heteroarene.

For **3b**, we observed significant amounts of amidation of the phenyl groups of the released 2,4,6-triphenylpyridine (**5a**: 40%, see Supporting Information). No amidation product was identified by using **3d**, **3e**, and **3f** (see Supporting Information). The following experiments were therefore conducted with **3a**. Due to the electrophilicity of the phthalamidyl radical, direct amidation worked more efficiently for electron-rich arenes and yields between 63% and 89% were obtained for **5b–f**. As expected, for monosubstituted arenes a mixture of regioisomers was formed (see **5b** and **5e**). *para*-Disubstituted arenes bearing an electron-donating and -withdrawing group reacted regioselectively *ortho* to the electron-donating substituent with complete regiocontrol (**5g,h**). Heteroarenes were investigated, and the α -amidation products **5i–k** were regioselectively formed for the indole, furan, and pyrrole substrates (46–68%). However, thiophene provided **5l** as a mixture of regioisomers.

We found that amidation of *N*-methylindole^{15c} works even better with reagent **3e** where the highest yield was achieved by using a 2-fold excess of **3e** to give regioselectively α -amidation product **6a** (86%, Scheme 4). Therefore, other experiments with heteroarenes were mainly conducted with **3e**.

To test scope and limitations, various indole derivatives were reacted under optimized conditions. Substituents at the 5-position of the indole core showed small electronic effects. The electron poorer Br-, F-derivatives and also the electron richer Me-substituted indole delivered good yields (see **6b–d**, 63–75%). The congener with the MeO-substituent at the 4-position also provided an excellent yield (**6e**, 95%).

Scheme 4. Amidation of Indoles and Pyrroles with Reagent 3e or 3f

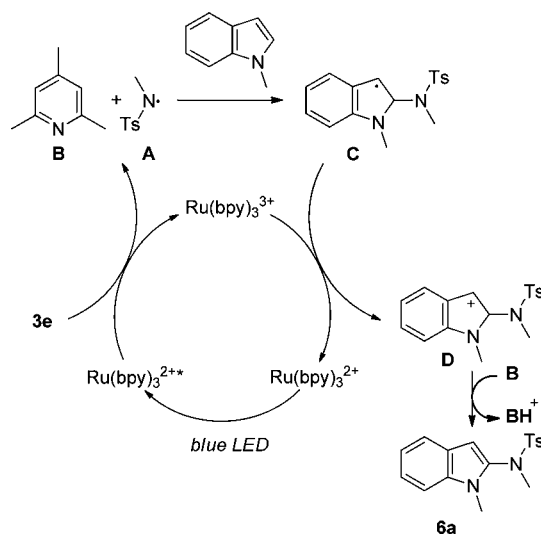


^aConducted with 2-methyl-*N*-methylindole. ^bConducted with 3f.

Substituents at the 6- and 7-position are tolerated as demonstrated by the successful preparation of **6f** (71%) and **6g** (82%). We also showed that 3-substituted *N*-methylindoles are readily α -amidated in good to excellent yields (**6h–k**, 76–96%). Varying the *N*-substituent revealed that the free *N*-H-indole and its alkyl and aryl derivatives delivered good yields (**6l–o**, 59–70%). However, electron poorer indoles bearing an acetyl- or a Boc-protecting group were not substrates for the direct α -amidation with the electrophilic sulfamidyl radical and the targeted products **6p** and **6q** were not formed. Substrates where the 2-position is blocked reacted slowly to provide the corresponding 3-amidated indoles (**6r** and **6s**). Pleasingly, regioselective radical α -amidation also works on *N*-substituted pyrroles as shown by the successful preparation of **6t** (71%) and **6u** (84%). Amidation of *N*-methylindole with the Boc-protected reagent **3f** afforded the α -product **6v** regioselectively in 61% yield.

The suggested mechanism for indole amidation with **3e** exemplified for preparation of **6a** is shown in Scheme 5 (amidation of (hetero)arenes with **3a** and pyrroles with **3e** work in analogy). In the first step excited Ru(bpy)₃^{2+*} is generated from Ru(bpy)₃²⁺ by absorption of blue light. This excited

Scheme 5. Suggested Mechanism



species reduces pyridinium salt **3e** by SET. Fragmentation of the thus generated radical leads to the sulfamidyl radical **A** and pyridine **B**. The amidyl radical **A** regioselectively adds to the α -position of *N*-methylindole to generate radical **C**. Oxidation of **C** by Ru(bpy)₃³⁺ affords the cationic species **D** thereby regenerating Ru(bpy)₃²⁺. Pyridine **B** formed in the fragmentation acts as a base to deprotonate **D** to eventually provide amidated indole **6a**.

In summary, we have successfully introduced pyridinium salts **3a**, **3e**, and **3f** as efficient *N*-radical precursors which are easily accessible from cheap starting materials. *N*-radicals are readily generated upon single electron reduction of these salts. It has been shown that these novel *N*-radical precursors can be used for regioselective radical amidation of heteroarenes and substituted arenes upon applying photoredox catalysis with Ru(bpy)₃Cl₂ as the catalyst. Reactions proceed in the absence of any additive by irradiating a mixture of the arene/heteroarene, *N*-aminopyridinium reagent and the photoredox catalyst. The reagent design allows for simple variation of the substituents at the amidyl radical. Therefore, the reactivity of a reagent can be readily adjusted to the radical acceptor. It has been shown that arene amidation works best with reagent **3a** and direct radical amidation of the more electron-rich heteroarenes is best conducted with *N*-aminopyridinium salt **3e**. Notably, in contrast to the recently reported photoredox catalyzed radical amidations which have to be conducted with expensive iridium-based photocatalysts,¹⁵ the reagents introduced herein allow reactions to be performed with the significantly cheaper Ru(bpy)₃Cl₂ catalyst.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for the products, supplementary crystallographic data (CCDC 1031875–CCDC 103187), CV, and UV/vis data. 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.

■ ACKNOWLEDGMENTS

This work was financially supported by the Deutsche Forschungsgemeinschaft (IRTG Münster/Nagoya).

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