Heterocyclic Group Transfer Reactions with I(III) N-HVI Reagents: Access to N-Alkyl (Heteroaryl)onium Salts via Olefin Aminolactonization

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Abstract

Pyridinium and related N-alkyl (heteroaryl)onium salts are versatile synthetic intermediates in organic chemistry, with applications ranging from ring functionalizations to provide diverse piperidine scaffolds to their recent emergence as radical precursors in deaminative cross couplings. Despite their ever-expanding applications, methods for their synthesis have seen little innovation, continuing to rely on a limited set of decades old transforms. Herein, we leverage (bis)cationic nitrogen-ligated I(III) hypervalent iodine reagents, or N-HVIs, as “heterocyclic group transfer reagents” to provide access to a broad scope of (heteroaryl)onium salts via the aminolactonization of alkenoic acids. The reactions proceed in excellent yields, under mild conditions, and are capable of incorporating a broad scope of sterically and electronically diverse aromatic heterocycles. The N-HVI reagents can be generated in situ, the products isolated via simple trituration, and subsequent derivatizations demonstrate the power of this platform for diversity-oriented synthesis of 6-membered nitrogen heterocycles.

Introduction

Pyridinium and related (heteroaryl)onium salts (1) possessing N-alkyl substituents are versatile functional handles that have applications across Nature1, materials science2,3, and medicinal and synthetic chemistry (Figure 1a,b)4. In organic chemistry, they serve as ionic liquids5 (2) and phase transfer catalysts6, exhibit a diverse range of biological activities (3, 4) (Figure 1a), and have a long history as synthetic intermediates, an area that has seen a recent surge of new advancements. Representative of their versatile reactivity, pyridinium and related salts can undergo full or partial reductions7-9, cycloadditions10,11, photochemical isomerizations12, cross couplings13, addition of one- or two-electron
heteroatom or carbon nucleophiles\textsuperscript{8,14}, and facile C–H metalations\textsuperscript{15}, and many of these include asymmetric variants\textsuperscript{16-18} (Figure 1b). The breadth of available transformations make pyridinium salts valuable templates for accessing functionalized 6-membered aza-heterocyclic scaffolds, which are prevalent in agrochemicals, alkaloid natural products, and are the most commonly encountered heterocyclic motif in FDA approved small molecule drugs\textsuperscript{19}. In addition to manipulations of the heterocyclic ring, pyridinium salts can undergo ring openings to produce Zincke aldehydes, which have shown utility as synthetic building blocks\textsuperscript{20}, and 2,4,6-triphenylpyridinium salts have emerged as a new and powerful class of radical precursors for deaminative metal-catalyzed cross couplings (Figure 1b)\textsuperscript{21,22}.

A current limitation to the rapidly expanding applications of (heteroaryl)onium salts is the lack of practical methods for their synthesis that accommodate diversity at both the nitrogen heterocycle and the coupling partner. At present, pyridinium salts are most commonly accessed either by reaction of a primary amine with an oxopyrylium (5) or Zincke salt (6), or via nucleophilic substitutions of activated electrophiles, none of which offer a truly general solution (Figure 1c)\textsuperscript{4,15}. Both Zincke reactions and oxopyrylium condensations are restricted to coupling with an amine nucleophile, and the latter is not applicable when the goal is structural diversity at the heterocycle. Typical nucleophilic substitutions require the use of primary or activated electrophiles, often necessitating prolonged reaction times and harsh conditions, and are limited by both the steric and electronics of the heterocycle nucleophile. The development of a general and mild strategy for the synthesis of (heteroaryl)onium salts that allows for diversity at both the heterocycle and the coupling substrate would be highly enabling for the further application and development of these powerful intermediates in catalysis, total synthesis, and medicinal chemistry.

Recently, our laboratory and others have been exploring the synthetic applications of (bis)cationic nitrogen-ligated hypervalent iodine (III) reagents, or \(N\)-HVIs (8, Figure 1d)\textsuperscript{23,24}. \(N\)-HVIs possess two datively bound heterocyclic nitrogen ligands on the central iodine, resulting in altered and often novel reactivity relative to their common \(Ar\text{I}X_2\) counterparts. \(N\)-HVIs can be isolated as bench stable white solids upon treatment of commercially available \(Ph\text{I}(O\text{Ac})_2\) (7) with a silyl triflate activator and the \(N\) heterocycle of choice, making modular incorporation of diverse heterocyclic motifs very straightforward. To date, \(N\)-HVIs have been applied to umpolung heteroatom activations\textsuperscript{25,26}, oxidative couplings and
fragmentations\textsuperscript{27-30}, and access to high valent transition metal complexes\textsuperscript{24,31}, however the role of the heterocyclic ligands has been limited to modulating reagent reactivity. In recognizing the growing need for improved approaches to (heteroaryl)onium salts, we wondered if \( N \)-HVI\textsubscript{s} could serve as “heterocyclic group transfer” reagents to access diverse \( N \)-alkyl (heteroaryl)onium salts through incorporation of the heterocyclic ligand into a substrate of interest. Analogous to the versatile group transfer reactions available to traditional PhIX\textsubscript{2} species\textsuperscript{32}, such a platform for (heteroaryl)onium salt synthesis has the potential to accommodate significant complexity and variation in both the coupling partner and heteroarene. This flexibility would markedly advance the ability of chemists to leverage these salts as versatile precursors to saturated heterocycles and as advanced synthetic intermediates, as well as enable further development and expansion of the emerging field of pyridinium radical cross couplings.

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\begin{align*}
\text{coupling partners:} & \quad \text{primary amines, } \text{I} \text{ and/or activated electrophiles} \\
\text{heterocycles:} & \quad \text{oxopyrylium derived or nucleophilicity limited}
\end{align*}
\]
Figure 1. Pyridinium salts: Synthesis, applications, and synthetic utility. a,b, Pyridinium salts have diverse applications as the active component in materials and bioactive molecules and as versatile synthetic intermediates. c, Current methods for the synthesis of pyridinium salts remain limited in their ability to access broad structural diversity at the heterocycle and for incorporation into complex molecules. d, I(III) N-HVIs are bench stable, white solids that are readily accessed from commercially available PhI(OAc)₂ via a modular route that allows facile diversification at the heterocyclic ligands. e, This report. The metal-free aminolactonization of alkenoic acids via “heterocyclic group transfer” reactions of N-HVIs. The resulting pyridinium lactones can be further functionalized to a wide array of N-heterocyclic scaffolds.

Herein, we report the first example of the heterocyclic group transfer reactivity of I(III) N-HVIs, demonstrated in the aminolactonization of alkenoic acids (Figure 1e)³³, the products of which represent core scaffolds in a wide array of bioactive natural products³⁴. To the best of our knowledge this is only the second example of an aminolactonization facilitated by an I(III) reagent, the prior report requiring use of an unstable iminoiodane species³⁵, and therefore represents a significant advancement in I(III)-mediated olefin functionalizations. The reactions proceed in excellent yields, under mild conditions, and are capable of incorporating a broad scope of sterically and electronically diverse aromatic heterocycles. The N-HVI reagents can be generated in situ, the products isolated via simple trituration, and subsequent derivatizations demonstrate the power of this platform for diversity-oriented synthesis of 6-membered nitrogen heterocycles. Mechanistic studies indicate the reaction proceeds via initial olefin activation followed by lactonization and subsequent intermolecular nucleophilic displacement of an (alkyl)(aryl)iodonium salt hypernucleofuge.

Results and Discussion

Reaction Development To begin our studies, 2,2-diphenyl-pentenoic acid (12) was used as a model substrate along with pyridine-ligated N-HVI (Py-HVI, 9) and complete conversion to desired pyridinium lactone 13 was observed after only 20 minutes in MeCN at room temperature (Figure 2a). The product (13) could then be isolated via trituration with Et₂O, yielding pure 13 in 96% yield. Control reactions indicated that the N-HVI was required for high yields of

![Figure 2. Initial reaction development and in situ N-HVI protocol.](image-url)

a. Conversion of 2,2-diphenyl-pentenoic acid (12) to pyridinium lactone 13 with N-HVI. Pure 13 can be obtained by simple trituration with Et₂O. Control reactions indicated the necessity of the N-HVI as activator. b. Development of operationally simplified variants including in situ generation of N-HVIs and “precaution-free” which does not rigorously exclude air or moisture.
13, as typical halo-lactonization or oxy-lactonization conditions using NIS, NBS, or Phl(OAc)$_2$ in the presence of pyridine gave no conversion to the desired pyridinium lactone (see Supporting Information for full details). Attention then turned to maximizing the efficiency and operational simplicity of the transformation by developing an in situ protocol for the generation of N-HVIs, thereby eliminating the additional step of reagent isolation. It was found that a one-pot protocol involving sequential addition of Phl(OAc)$_2$, TMSOTf, and pyridine in MeCN, leading to formation of 9, followed by addition of 12, gave 13 in nearly equivalent yield of 94\% (Figure 2b). Furthermore, the reaction could be run “precaution free”, where stringent drying of glassware and use of inert atmosphere was omitted, with minimal effect on the reaction yield (Figure 2b).

With efficient procedures in hand, the scope of the heterocycle was examined and found to be extremely general (Figure 3a). Substitution at the 2-position was well tolerated, with 2-Me-pyridine, 2-OMe-pyridine, and 2-OEt-pyridine all incorporated in excellent yield to give (14–16); somewhat unsurprisingly, use of sterically encumbered 2,6-lutidine led to only 21\% yield of lactone 17. Turning to the 4-position of the pyridine, both electron-donating (18–23) and electron-withdrawing groups (25–28) were well tolerated and gave the corresponding pyridinium lactones in high yields, with the exception of 24, possessing a free carboxylic acid, wherein we postulate the low yield could be due to the formation of zwitterionic protonated pyridinium salts. Pyridines possessing substitution at the 3- and 5-position were of particular interest as access to these substitution patterns on the corresponding piperidines can be extremely challenging due to a lack of inherent activation or directing ability and in turn have extremely limited commercial availability. 3-Acyl, 3-bromo, and 3-fluoro-pyridine, as well as 3,5-disubstituted derivatives were all found to give the pyridinium salts (29–31) in high yields. An oxidatively sensitive boronic ester was compatible with the mild conditions, yielding the versatile 3-Bpin (34) or 4-Bpin (35) pyridinium salts. Finally, we examined other aromatic azaheterocycles; benzfused derivatives including quinolines and isoquinoline could be efficiently incorporated (36–39), as well as both pi-deficient and pi-excessive diazines, including pyrazines to give 40 and 41, and N-Me-imidazole to give lactone 42.

During the course of the above scope studies, it was found that amino acid derived pyridines 43 and 44 were unsuccessful under the standard conditions, giving no conversion to desired product (Figure
3b). This was hypothesized to be due to the amino acid functionality being incompatible with formation of the N-HVI. To circumvent this issue, we envisioned an activation strategy wherein an N-HVI possessing relatively non-nucleophilic “dummy ligands” would be used for olefin activation followed by incorporation of the heterocycle of interest (Figure 3b). Not only would such a “dummy ligand” protocol allow for the incorporation of heterocycles possessing sensitive functionality, but it would also require only one equivalent of the heterocycle of interest, which is advantageous when considering use of either expensive heterocycles or those that require multi-step sequences to produce. To this end, we looked to 2,6-lut-HVI (10) as the activator due to the low nucleophilicity of 2,6-lutidine which had already translated to a low yield in pyridinium salt formation (17, Figure 3a). Gratifyingly, it was found that treatment of alkenoic acid 12 with 2,6-lut-HVI 10 in the presence of just one equivalent of either Boc-3-(pyridyl)-L-alanine methyl ester (43) or Fmoc-3-(pyridyl)-L-alanine methyl ester (44) under otherwise standard conditions now produced the desired pyridinium lactones (45, 46) in 71% and 41% yield respectively.
OH

OH

ON

PhI(OAc)$_2$ (1.1 equiv.), TMSOTf (2.2 equiv.)

N-heterocycle (2.2 equiv.);
then alkenoic acid (1.0 equiv.)

CH$_3$CN, rt; 20 min–6 h

PF: Precaution-free, no care taken to exclude air or moisture

preF: Pre-formed, isolated N-HVI instead of in situ procedure

13, 94% (PF: 91%)$^{ab}$

14, 89% (preF: 74%)$^{ac}$

15, R = Me (84%)

16, R = Et (61%)

17, 21%

18, 95%

19, 88%

20, 73%$^{d}$

21, 70%$^a$

22, 41%$^a$

23, 64%$^a$

24, R = H (21%)

25, R = Me (67%)

26, 43%

27, 81%

28, 91% (PF: 53%)$^b$

29, 66%

30, 83%

31, 71%

32, 71%

33, 65%

34, 3-Bpin (68%)

35, 4-Bpin (72%)

36, 40%

37, 70%

38, 35%

39, 83%

40, 59%$^a$

41, 60%

42, 83%$^a$

43, CO$_2$Me

44, FmocHN

45, CO$_2$Me

46, FmocHN

standard procedure: 0%

"dummy ligand" strategy: 71%

standard procedure: 0%

"dummy ligand" strategy: 41%
Figure 3. Variation of \(N\)-heterocycle and use of dummy ligand strategy in \(N\)-HVI aminolactonization. a. Heterocycle scope using 2,2-diphenyl-pentenoic acid as coupling partner. b. In cases where heterocycle contains sensitive functionality, 2,6-lut-HVI can be used as a non-nucleophilic dummy activator in the presence of 1 equiv. of desired heterocycle. In the examples shown, none of the desired lactones were obtained under standard conditions. \(^a\) Reaction was heated to 50 °C. \(^b\) Reaction performed under “precaution free” conditions, without exclusion of air or moisture. \(^c\) Reaction performed with pre-formed, isolated \(N\)-HVI, as shown in Figure 2a. \(^d\) Reaction time was 4 days.

Having established a broad scope with respect to the nitrogen heterocycle, diversity at the alkenoic acid was examined and again found to be quite general (Figure 4). Beginning with substitution at the \(\alpha\)-position, 2,2-dimethyl, 2-Me, 2-Bn, and \(\alpha\)-methylene lactones (47–50) could all be produced in high yields, indicating the Thorpe Ingold effect is not required for efficient cyclization. Lactone ring size was not limited to butyrolactones, with a larger 6-membered lactone (51) produced in good yield. Finally, benzoic acid derivatives were examined and found to give benzofused pyridinium lactones 52–54 in good yields.

Figure 4. Variation of alkenoic acid in \(N\)-HVI aminolactonization. All reactions were performed under general conditions shown unless otherwise indicated. \(^a\) Reaction was heated to 45 °C. \(^b\) Reaction time was 14 h.

With regards to the mechanism, we wished to probe both substrate activation and the key C–N bond forming event (Figure 5). Our initial hypothesis involved olefin activation followed by 5-exo-trig lactonization to form an intermediate (alkyl)(aryl)iodonium salt (56), and C–N bond formation would then occur via \(S_n2\) displacement with the nitrogen heterocycle (Path A–IPh). Beginning with the substrate activation step, we also considered an alternative pathway involving ligand exchange at iodine by the carboxylic acid to give 57, promoting attack of the olefin on the umpoled oxygen (Path B), more akin to
our previous findings on oxygen activation with N-HVIs\textsuperscript{25,26}. To test this, the reaction was run with methyl ester 60, which would not participate in ligand exchange; this gave near identical yield and reaction rate as the alkenoic acid, lending support to olefin activation being operative (Figure 5b). Regarding the proposed lactone (alkyl)(aryl)iodonium intermediate 56, unfortunately, all attempts at direct characterization via \textsuperscript{1}H-NMR or x-ray crystallography were unsuccessful; however prior literature lends strong support to formation of such a species via a kinetically favored 5-exo-trig lactonization on a 3-membered iodonium\textsuperscript{32}. This left us to consider the final C–N bond formation event, where we envisioned three plausible pathways: 1) via SN\textsubscript{2} displacement, either of the iodonium hypernucleofuge (56, Path A-IPh)\textsuperscript{36}, 2) a subsequently formed triflate intermediate (58, Path A-OTf), or 3) via an intramolecular ligand coupling event from 59 (Path A-LC)\textsuperscript{37}. To first probe the intermediacy of triflate lactone 58, 58 was generated \textit{in situ} via treatment with PhI(OAc)\textsubscript{2}/TMSOTf, followed by addition of 4-CN-pyridine (Figure 5c). While using our standard conditions gave 90\% conversion to the desired salt 28 after 40 minutes by \textsuperscript{1}H-NMR, conversion from 58 gave just 20\% conversion after 14 hours; therefore, while triflate lactone 58 is a viable substrate for heterocycle displacement, it does not appear to be the major operative intermediate. Finally, Path A-LC vs. Path A-IPh was examined via a cross over experiment in which 2-OMe-Py-HVI was used as an activator in the presence of free 2-OEt-pyridine. Selective formation of 2-OMe-pyridine lactone 15 would support Path A-LC, and a mixture of 15 and 16 would indicate the intermolecular attack by free heterocycle in solution of Path A-IPh. This experiment yielded a 1.2:1.0 mixture of lactones 15 and 16, supportive of Path A-IPh with C–N bond formation via an intermolecular SN\textsubscript{2} displacement of iodonium 56.
b Path B, N-HVI O-activation

Path B

\[
\begin{align*}
&\text{Path B, N-HVI O-activation} \\
&\text{Py-HVI (1.1 equiv.)} \\
&\text{CH}_{2}CN, \text{rt, 15 min} \\
&\text{from } 12, R = H: 94\% \\
&\text{from } 60, R = \text{Me}: 95\% \\
\end{align*}
\]

60

12

Path A-LC

intramolecular ligand coupling

Path A-OTf

intermolecular S_{2}2

Path A-IPh

heterocycle attack

b Path B, N-HVI O-activation

Forcing Path A-OTf

\[
\begin{align*}
&\text{Forcing Path A-OTf} \\
&\text{PhI(OTf)_{2}, rt, 30 min; then 4-CN pyridine} \\
&\text{CH}_{2}CN, \text{rt, 14 h} \\
&\text{4 : 1 } (\text{H-NMR ratio}) \\
\end{align*}
\]

Standard Conditions

4-CN-Py-HVI, CH\textsubscript{2}CN, rt, 40 min

1 : 9 (\text{H-NMR ratio})

d Path A-IPh vs. Path A-LC: Crossover experiment

Path A-IPh

Path A-LC

supports Path A-IPh
**Figure 5. Mechanistic investigation of aminolactonization.**

**a.** Mechanistic pathways considered for aminolactonization. Our initial hypothesis followed Path A-IPh, and alternatives including umpolung O-activation (Path B), intramolecular ligand coupling (Path A-LC), and the intermediacy of a triflate lactone (Path A-OTf) were probed. **b.** Path B: Umpolung O-activation. Prior studies with N-HVIs in our laboratory indicated this pathway could be operative. **c.** Path A-OTf: Intermolecular –OTf displacement. It was hypothesized that 56 could undergo initial exchange with free –OTf, followed by S$_2$ displacement. **d.** Path A-IPh vs Path A-LC: Both an inter- vs. intramolecular C–N bonding forming event was considered based on literature precedent of operative reductive ligand coupling pathways in hypervalent iodine mediated reactions.

Finally, in order to demonstrate the versatility of the resulting (heteroaryl)onium lactones for heterocycle synthesis, we explored a variety of derivatizations to access functionalized and lower oxidation state derivatives (Figure 6). Fully saturated piperidines and piperazines could be readily accessed in excellent yields upon hydrogenation with Adam’s catalyst (Figure 6a, 62–66), providing a means of accessing piperidines with substitution patterns that are either expensive to purchase or challenging to install, such as 3-fluoro- or 3-acyl piperidines (65, 66). Partial hydride reductions led to 3,4-dehydropiperidines 67–70 with complete regioselectivity in all cases, providing vinyl halides or nitriles that serve as functional handles for further diversification (Figure 6b). Demethylation of 2-OMe pyridinium 51 with NaI gave the corresponding 2-pyridone 71 in 95% yield (Figure 6c). We then examined the addition of carbon nucleophiles and found addition of a trifluoromethyl group could be achieved with C2-selectivity on 13 to give 72 or that aryl Grignard (Conditions A) or cuprate additions (Conditions B) proceeded with C-2 or C-4 selectivity on 3-Ac- and 3-Bpin-pyridiniums, respectively, to give functionalized 1,2- and 1,4-dihydropyridines (73, 74) (Figure 6d). In all the above cases, completely selective reaction at the (heteroaryl)onium salt was observed with no competitive reactivity of the lactone moiety, leaving it available for further downstream manipulations.
a Hydrogenation with Adam's catalyst: saturated azaheterocycles

b Partial reductions: 3,4-dehydropiperidines or 1,4-dihydropyridines

c Aryl ether demethylation: 2-pyridones

d Addition of C-nucleophiles: 2-CF$_3$-1,2-dihydropyridines, arylated 1,2- and 1,4-dihydropyridines
Figure 6. Derivatizations of pyridinium lactones. a, Full reduction to functionalized piperidines could be achieved under catalytic hydrogenation with Adam’s catalyst. b, Partial reduction with either NaBH₄ or NaCNBH₃ could be achieved to selectively access 3,4-dehydropiperidines. See SI for full experimental details. c, Demethylation with NaI could be achieved to access 2-pyridones. d, Addition of C-nucleophiles could be achieved to selectively access both 1,2- and 1,4-dihydropyridines. *66 was produced as a ~1:1 mixture of diastereomers however lack of baseline resolution using several analytical methods prevented definitive determination of ratio. b NaBH₄ was used as reducing agent. c NaCNBH₃ was used as the reducing agent.

In conclusion, we report the first example of “heterocyclic group transfer” reactions of I(III) N-HVI reagents, providing a new platform for the synthesis of structurally diverse (heteroaryl)onium salts, demonstrated in the aminolactonization of alkenoic acids or esters. The reaction proceeds under remarkably mild conditions, tolerates a broad heterocycle and lactone scope, can be run without special considerations for air or moisture, and the N-HVIs can be generated in situ, making this strategy extremely general. For cases involving sensitive or precious heterocycles that are incompatible with N-HVI formation, an enabling “dummy ligand” activation strategy was also developed that allows for their efficient incorporation, further broadening the potential of the methodology. Mechanistic studies indicate that the reaction proceeds via initial olefin activation followed by lactonization and intermolecular S_N2 displacement of a (alkyl)(aryl)iodonium salt hypernucleofuge. Representative derivatizations of the resulting (heteroaryl)onium salts demonstrate the power of this platform for broadening the scope of available substitution patterns on the venerable piperidine scaffold for medicinal chemistry. Building on this seminal report, ongoing efforts in our laboratory are working to expand the upon the “heterocyclic group transfer” reactivity of I(III) N-HVIs with the goal of providing a general platform for the incorporation of (heteroaryl)onium salts into organic molecules, fueling the current renaissance of these moieties as functional handles across synthetic chemistry.

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**Author contributions**

A.F.T. and S.E.W conceived the work. A.F.T., J.C.W., A. V.-L., X.X., and S.E.W. designed experiments and analyzed data. A.F.T., J.C.W., A. V.-L., and X.X. performed the experiments. S.E.W wrote the manuscript with editing from J.C.W and A.F.T.

**Competing Interests**

The authors declare no competing interests.