Introducing N-X Anomeric Amides: Powerful Electrophilic Halogenation Reagents

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**ABSTRACT:** Electrophilic halogenation is a widely-used tool employed by medicinal chemists to either pre-functionalize molecules for further diversity or incorporate a halogen atom in drugs or drug-like compounds to solve metabolic problems or modulate off-target effects. Current methods to increase the power of halogenation rely either on the invention of new reagents or activating commercially available reagents with various additives such as Lewis/Bronsted acids, Lewis bases and hydrogen bonding activators. There is a high demand for new reagents that can halogenate otherwise unreactive compounds under mild conditions. Herein we report the invention of a new class of powerful halogenating reagents based on anomeric amides, taking advantage of the energy stored in the pyramidalized nitrogen of N-X anomeric amides as a driving force. These robust halogenating methods are compatible with a variety of functional groups and heterocycles, as exemplified on over 50 compounds (including 13 gram-scale examples and 1 flow chemistry scale-up). Their high halogenating prowess is also demonstrated in other reactivity contexts. A DFT computational study supports the defining role of the anomeric amide motif.

Generally speaking, chlorine and bromine atoms are amongst the only functional groups that can be viewed as both facile precursors (gateways) to other functionality (through cross-coupling\(^1\)) and potentially useful for their inclusion in a final drug substance\(^2\)-\(^3\). Indeed, numerous FDA approved drugs contain these halogen atoms, and their introduction can often have a documented "magical" effect on desired properties\(^4\). For instance (Figure 1A), the potency of lead structures\(^5\)-\(^6\) could be improved by several orders of magnitude by the simple installation of chlorine and bromine atoms, respectively. Electrophilic aromatic halogenation\(^7\) is arguably the earliest example of industrial practitioners embracing the now wildly popular strategies of “late-stage functionalization”\(^8\)-\(^11\) and C–H functionalization\(^12\)-\(^13\). In fact, recent reviews point to electrophilic halogenation as being one of the reaction classes most prized by medicinal chemists\(^14\)-\(^15\). Numerous elegant approaches relying on C–H activation\(^16\)-\(^17\) or indirect halogenation\(^18\)-\(^21\) via intermediate species have emerged to provide alternative tactics to access halogenated arenes. That said, there are numerous contexts for which the available reaction and reagent toolkit are insufficient to satisfy demand such as the halogenation of the simple triazole found in vericonazole (3, Figure 1A). Historical approaches to increase the power of electrophilic halogenation are summarized in Figure 1B and generally rely either on the invention of new reagents\(^22\)-\(^23\) or by activating known reagents with additives\(^24\)-\(^30\). The majority of electrophilic halogenation reagents are based on stable N-X bonds wherein the flanking substituents on nitrogen include various electron withdrawing groups. Anomeric amides (Figure 1C), first introduced by Glover\(^31\) and widely studied in the 1980’s have historically been utilized as nitrenium ion precursors via nucleophilic attack at nitrogen\(^32\)-\(^33\). In contrast, there have been no investigations we are aware of wherein these unusual species have been harnessed to activate a halogen atom. The premise of this study was that enhanced reactivity might result from the use of reagents based on an anomeric amide by virtue of a spring-loaded driving force to rehybridize following halogenation from a sp\(^\dagger\) to sp\(^\dagger\) nitrogen center. In this disclosure (Figure 1D), a new class of powerful electrophilic reagents based on anomeric amides is presented. Through extensive benchmarking with state-of-the-art protocols, it is shown that such reagents are extremely useful for achieving scalable (in batch and flow settings) and efficient arenes chlorination and bromination at both an early and late stage. Their halogenating power is not limited to arenes as advantages are observed with other reaction manifolds; a computational study supports the defining role of the anomeric amide motif.

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Very little precedent exists for the synthesis of anomic amide halogenating agents such as 6 and 7 (Figure 1D). Studies commenced from the known compound 5, constructed using a modified procedure 14 that avoids chromatographic purification on decagram scale (see SI). In order to access chlorinating reagent 6, BuOCl was employed as it proceeded in quantitative yield and simpliﬁed subsequent puriﬁcation (ﬁltration). Related systems had been chlorinated before using TCCA 15 which was deliberately avoided for practical reasons. In the case of brominating reagent 7, a AgOAc-mediated procedure using Bu3SnCl was employed 16 followed by recrystallization. Although reagents 6 and 7 are bench-stable solids prepared through scalable and practical procedures, they were stored below 0°C to minimize gradual decomposition.

With abundant quantities of 6 and 7 in hand, their halogenating potential was explored on the antifungal agent voriconazole (3), a substrate identiﬁed as being particularly difﬁcult to halogenate under a variety of conditions (Table 1A). Indeed, 23 different chlorinating and brominating reagents/conditions were explored. A small selection of the most potent of these combinations are depicted with the highest yields ranging from 27–36%. In these optimal known conditions, the yields were determined by NMR; many of these reactions produced a number of other impurities aside from recovered starting material. In contrast, reagents 6 and 7 cleanly provided the desired chlorinated (3–Cl, 52% isolated) and brominated (3–Br, 79% isolated) products respectively, along with re-bonding activation modes. C. Well-precedented usage of anomic amide as nitrenium ion precursors and our design of it as powerful halogenating reagents; D. This work: practical synthesis of anomic amide halogenating reagent 6 and 7 and their applications in (hetero)arenes chlorination and bromination.
Table 1. Demonstration of the electrophilic halogenation reactivity of anomic amides (6 – 12). A. Comparison of 6 and 7 with known halogenating reagents/conditions; B. Investigation of substituent effect on halogenation reactivity arrived on optimal reagent 6.

A. A survey of precedented halogenation methods/reagents on 3

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>3</th>
<th>VIA</th>
<th>3</th>
<th>X</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BuOCl: 21%</td>
<td>F</td>
<td>Cl</td>
<td>F</td>
<td>3</td>
<td>NC</td>
</tr>
<tr>
<td>NCS, AcOH: 7%</td>
<td>O</td>
<td>NC</td>
<td>O</td>
<td>4</td>
<td>N</td>
</tr>
<tr>
<td>DCCMH, AcOH: 5%</td>
<td>OAc</td>
<td>Br</td>
<td>OAc</td>
<td>5</td>
<td>Br</td>
</tr>
<tr>
<td>TCCA, TiOH, HFIP: 27%</td>
<td>X = Cl</td>
<td>(6)</td>
<td>X = Br</td>
<td>[x-ray]</td>
<td></td>
</tr>
<tr>
<td>6, MeCN (0.15 M): 52%</td>
<td></td>
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</table>

B. Investigation of substituent effect on halogenation reactivity

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>3</th>
<th>6</th>
<th>7</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td>NO2</td>
<td>AcBrO</td>
<td>116b</td>
<td>52%</td>
<td>52%</td>
<td>53%</td>
<td>52%</td>
</tr>
<tr>
<td>NC</td>
<td>Br</td>
<td>115b</td>
<td>32%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>OMe</td>
<td>Cl</td>
<td>116b</td>
<td>29%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>OAc</td>
<td>Cl</td>
<td>116b</td>
<td>29%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>OPh</td>
<td>Cl</td>
<td>116b</td>
<td>29%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
</tbody>
</table>

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<th>3</th>
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</tr>
<tr>
<td>NC</td>
<td>Br</td>
<td>115b</td>
<td>32%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>OMe</td>
<td>Cl</td>
<td>116b</td>
<td>29%</td>
<td>17%</td>
<td>27%</td>
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</tr>
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<td>Cl</td>
<td>116b</td>
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</tr>
<tr>
<td>OPh</td>
<td>Cl</td>
<td>116b</td>
<td>29%</td>
<td>17%</td>
<td>27%</td>
<td>18%</td>
</tr>
</tbody>
</table>

110 °C instead of 60 °C; 2 room temperature; 3 using 3 as the model substrate.

Generally, the position-selectivity for halogenation was in accord with what one would normally predict, although 13 out of the 41 examples favored different sites (see SI for predicted halogenation sites). In some cases, such as 20, 44, and 46, the halogenation regioselectivity using 6/7 can be dramatically improved relative to known protocols. Anonomic amide halogenating reagents also exhibit exquisite chemoselectivity relative to the state-of-the-art. For instance, attempted chlorination of celecoxib (26) using Palau’chlor furnished only sulfonamide N-chlorination rather than the desired chloropyrazole product which was exclusively observed using reagent 6 (93% yield on gram-scale). When the simple indazole building block 17 was exposed to Palau’chlor (1.2 equiv, rt, 24 h), ca. 50% conversion to the NCl adduct was observed. Subsequent heating at 70 °C for 20 h delivered 47% of 17-Cl, 24% recovered 17, and 27% of dichlorinated 17 (NMRI yield). In contrast, using reagent 6 (1.2 equiv, rt, 24 h), a 91% isolated yield of the desired product 17-Cl was observed. In the case of pesticide reagent 7 delivered 42-Br in 47% isolated yield whereas treatment with NBS/AcOH led to 6% desired product (NMRI yield) along with a variety of unidentified products. Similarly, the tertiary-alcohol containing antifungal agent 33 could be brominated in 58% isolated yield. In contrast, exposure to NBS (in DMF or AcOH) led to 10-14% of 33-Br (NMRI yield) along with extensive decomposition (20-65% of 33 could be recovered). When thiazole 18 was exposed to excess Palau’chlor (5.0 equiv, 70 °C, 7 days), 14% 18-Cl along with 70% 18 was observed, while using reagent 6 (1.6 equiv, 50 °C, 40 h) delivered 44% 18-Cl as well as 50% recovered starting material 18.

The ability to cleanly halogenate at the end of a synthetic route could have benefits in a medicinal chemistry program. For example, structures 27, 30, and 34 have only been previously prepared through early-stage chloride introduction. Anonomic amide reagents can give those in a drug discovery program optionality enabling chlorination of end-stage products. In the specific case of rivoxaban (34), reagent 6 is uniquely successful for this late-stage chlorination relative to Palau’chlor.

Halogenation using 6/7 can be easily performed on gram-scale in batch, with 13 such examples shown in Table 2. Sulfonamides, amides, amines, tertiary alcohols, α-CF<sub>3</sub>-alcohols, 1,2-aminoalcohols, acetals, and cyclopropanes are all compatible functional groups. The current limitations of this method are not surprising with alkene, alkyne and sulfoxide-containing substrates being incompatible. Arenes which are too electron-deficient are recalcitrant to halogenation (see SI for examples of this).

Preliminary explorations also point to the enhanced reactivity of anomic amide reagents in settings other than electrophilic aromatic substitution (Figure 2A). For instance, in the α-bromination of (hetero)aromatic methyl ketones (47–49), superior selectivity for mono-bromination is observed across the board. Similarly, the acidic methylene group of cyclic N-sulfonylamine 50 could be efficiently brominated with a superior yield (83%) compared with known procedure (24%) using PyHBr<sub>2</sub>. An improved yield was also observed in allylic bromination of (R)-carvone (51) relative to standard conditions<sup>16–17</sup>. Finally, enol acetate 52 (prasugrel) could be chlorinated in nearly quantitative yield.

The most glaring concern a practitioner would have in considering the use of anomic amides such as 6 and 7 is safety on scale. This potential issue was studied extensively (see SI for experimental data). Since differential scanning calorimetry (DSC) showed both compounds 6 and 7 had decomposition energies above the Yoshida correlation for predicting shock sensitivity and explosive propagation, internal explosivity testing was carried out using modified accelerating rate calorimetry type equipment equipped with a fast rate data card and pressure transducer. The tests recorded pressure rise rates below the instrument’s calibrated threshold, hence were thought to be negative for potential explosivity<sup>18</sup>. UN Dangerous Goods Test 3a (ii) BAM Fall Hammer impact testing of 6 and 7 at 60 J resulted in decomposition, producing a change in both materials’ color and an odor without flame or explosion. The decomposition observed may be due to the impact test generating enough heat to reach each material’s low thermal onset at 79 °C and 84 °C, respectively, to catalyze their exothermic decomposition. During the many gram-scale batch runs using 6 and 7 (vide supra) no hazardous events were observed. However, in order to preemptively address potential concerns on scale, reagent 6 was tested on even larger scale using a flow setup (Figure 2B). Thus, chlorination of celecoxib analogue (53) was pursued in flow at 20 gram-scale. A separate substrate specific optimization was pursued in order to increase the reaction rate and subsequent potential throughput of the reaction. The reaction rate was sensitive to both temperature and solvent composition where the conditions shown in Figure 2B were found to provide >95% conversion in 25 minutes. From these optimized conditions a flow experiment was designed wherein 20 grams of 53 was converted to the desired product over 130 minutes in flow with 82% isolated yield. Observations from the lab-scale demonstration in flow determined that the reaction could be further scaled with minimal consideration.

Finally, the initial hypothesis that halogenating agents based upon an anomic amide backbone would exhibit superior reactivity was evaluated computationally (Figure 3). Although anonomic amide chlorinating reagent 6 and Palau’chlor have the same N-Cl bond length (both 1.73 Å, longer than 1.66 Å for TCCA<sup>19</sup> and 1.69 Å for NCS<sup>20</sup>), the conversion of 14 to 14-Cl is calculated to be more energetically favorable by a factor of 10.27 (ΔΔG = 3.75 kcal/mol) using 6 (Figure 3A), which is in accord with experimental findings. To gain deeper insight into this higher reactivity, DFT calculations of the N-Cl bond breaking energy (from the ground state to the corresponding anion and Cl<sup>−</sup>) for both reagents was performed. Calculations indicate that this bond breaking event is significantly uphill for both reagents, but reagent 6 requires 25 kcal/mol less energy for bond breaking than Palau’chlor, which means 6 has a more active N-Cl bond (Figure 3B). In the case of reagent 6, when
Table 2. Substrate scope of (hetero)arenes electrophilic halogenation.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Yield</th>
<th>NMR Yield</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palau'chlor: 28%</td>
<td>Cl (0.1 M)</td>
<td>72%</td>
<td>60% (4:1)</td>
<td>clopidogrel (1.23 g, 80%) ( \text{NBS: 20%} )</td>
</tr>
<tr>
<td>Palau'chlor: 0%</td>
<td>Br (0.1 M)</td>
<td>78%</td>
<td>78%</td>
<td>rivaroxaban (34)-Br ( X = \text{Cl}, 64% [x-ray]; \text{Palau'chlor: 3%} )</td>
</tr>
<tr>
<td>Ac-sulfadiazine (29)-Cl</td>
<td>Cl (0.1 M)</td>
<td>85%</td>
<td>85% ( 1.4 g, 90% )</td>
<td>piritrexim (30) ( X = \text{Br}, 94% [x-ray]; \text{Palau'chlor: 73%} )</td>
</tr>
<tr>
<td>clopidogrel (36) ( X = \text{Cl}, 74% )</td>
<td>Cl</td>
<td>156 g (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>triflumuron (38) ( X = \text{Cl}, 73% [x-ray] )</td>
<td>Cl</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole (41)-Br</td>
<td>Br</td>
<td>62%</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: for chlorination: reagent 6 or Palau’chlor (1.2 – 2.4 equiv), \( \text{CHCl}_3 \) \( 0.1 – 0.15 \text{ M} \), \( t = 60 \text{ °C}, 1 – 40 \text{ h} \); for bromination: reagent 7 (1.2 – 2.4 equiv), \( \text{CHCl}_3 \) \( 0.1 – 0.15 \text{ M} \), \( t = 60 \text{ °C}, 1 – 40 \text{ h} \); for reagents 6 and 7, yields refer to isolated yields; for Palau’chlor and NBS, yields refer to \( ^1\text{H} \) NMR yield using \( \text{CHBr}_3 \) as internal standard; note: for substrates with a poor solubility in \( \text{CHCl}_3 \), DMSO was used instead; \( \text{rt} \) for 24 h then 70 °C for 20 h \( 48\% \); \( \text{CH}_2\text{CN} / \text{DMF} (4:1, v/v) \) as solvent; \( \text{DMF} \) as solvent; \( \text{CHCl}_3 \) as solvent; \( 0.05 \text{ M} \); \( \text{CH}_2\text{NO}_2 \) as solvent; \( \text{AcOH} \) as solvent; \( \text{CH}_2\text{CN} / \text{DMF} (2:1, v/v) \) as solvent.
DFT Calculation Based Mechanistic Discussion

A. Higher reactivity of 6 is computationally validated

\[
\begin{align*}
\text{C–N bond shortening indicates the formation of C–N multiple bond} \\
\Delta G = 3.75 \text{ kcal/mol more downhill for chlorination with reagent 6.}
\end{align*}
\]

B. Energy difference in N–Cl heterolysis

\[
\begin{align*}
\Delta G &= 25 \text{ kcal/mol less uphill for 6 over Palau’chlor} \\
\Delta G &= 25 \text{ kcal/mol less uphill for 6 over Palau’chlor}
\end{align*}
\]

C. Estimation of driving force stored in pyramidalized nitrogen

\[
\begin{align*}
\Delta G_{\text{planar}} &= 3.5 \text{ kcal/mol} \\
\Delta G_{\text{pyramidalized}} &= 3.5 \text{ kcal/mol}
\end{align*}
\]

At least 3.5 kcal/mol of energy is stored by distorting planar amide structure.
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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no conflict of interest.

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