Synthesis of Highly Functionalized Diarylamines through an N-, C-Cascade Reaction via Ammonium Salts

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ABSTRACT: The diarylation and skeletal diversification of unstrained cyclic amines was exploited to expand and modify the favorable properties of this important substrate class with pivotal roles in drug discovery. Cyclic amines were employed in the synthesis of a novel class of amino-substituted diaryliodonium salts, which were converted to highly functionalized diarylamines through an atom-efficient one-pot N-arylation/ring opening reaction with external nucleophiles. The reaction proceeds through the in situ formation of a diarylammonium intermediate that undergoes a nucleophilic ring opening by cleavage of the strong C-N bond. A wide variety of diarylamines was obtained through introduction of two different aryl groups of varied electronics, and the retained iodo-substituent enables downfield diversifications of the products. More than 20 nucleophiles, including amines, phenols, carboxylic acids, thiols and halides, were alkylated with high functional group tolerance, and the strategy could be utilized in late-stage functionalization of natural products and pharmaceuticals.

INTRODUCTION
Arylated amines are valuable motifs in organic synthesis due to their prevalence in natural products, pharmaceuticals and functional materials.1 N-aryl amines are commonly prepared through transition-metal catalyzed cross-couplings2 or by the increasingly popular C-H aminations.3 These methods are undeniably efficient and well established, however, their overall sustainability is compromised by the requirement of scarce metals and often expensive / time-consuming multi-step synthesis to attain more complex products with different N-aryl groups. Cyclic aliphatic amines constitute essential cornerstones in drug discovery, and methods for functionalization to modify their biological properties is of high value. Skeletal diversification trough ring opening by selective breakage of the strong C-N σ-bond4 is a powerful strategy to change the overall shape of the molecule and achieve increased structural complexity.5 Such modifications have in the past been attained through reductive6 or oxidative7 pathways using transition metals or by von Braun type degradation via ammonium intermediates.8 However, there are limited examples of C-N bond cleavage that occur with simultaneous introduction of versatile functionalities at both the N- and C-terminal to afford complex value-added products, especially for unstrained cyclic amines.8,9
Diaryliodonium salts (Ar2IX) are acknowledged as excellent electrophilic arylating agents with desirable properties such as high reactivity, stability and synthetic accessibility.10 They have found extensive application in arylations of both carbon and heteroatom nucleophiles,10 and are recognized as attractive multi-purpose reagents also in material chemistry.11 Their main drawback is the generation of stoichiometric ArI waste in the majority of their arylation pathways.12 To overcome this atom-economy limitation, our group recently developed a sustainable strategy for incorporation of both aryl groups and the iodine of diaryliodonium salts I onto N-, O- and S-nucleophiles through a metal-free cascade reaction (Scheme 1A).13 Mechanistic studies suggested this atom-efficient diarylation to proceed through a novel pathway, with initial nucleophilic aromatic substitution (SNAr) followed by intramolecular arylation, as supported by isolation of SNAr intermediates A with O- and S-nucleophiles.13

We envisioned that utilization of secondary amines in our diarylation strategy could lead to potent cascade reactions to yield a wide scope of functionalized diarylamines. Novel ortho-
amino-functionalized diaryliodonium salts 3 could be synthesized through SsAr on 1, followed by a one-pot sequential arylation and ring-opening pathway via ammonium intermediates 4 (Scheme 1B). Upon C-N cleavage of 4 by external nucleophiles, highly functionalized diarylamines 5, 6 would be obtained with excellent atom- and step economy. Moreover, diaryliodonium salts 3 with unprotected aliphatic amine substituents, could have interesting applications in organic synthesis and materials chemistry. They are, to the best of our knowledge, unknown in literature, which is likely due to the incompatibility of such functionalities with the oxidizing and acidic conditions required for the synthesis of diaryliodonium salts.

RESULTS AND DISCUSSION

Piperidine derivatives are particularly interesting compounds due to their versatile medicinal properties, e.g. as anticancer, antipsychotic and anti-Alzheimer agents. The introduction of such nucleophiles to iodonium salts 1 could hence be of special interest, and piperidine (2a) was chosen as the model substrate in reactions with 1a. To our delight, the desired product 3a was obtained in excellent yield under the conditions used in the previous isolation of SsAr intermediate A with water (EtOAc, 40 °C, 2 h). A small optimization study revealed that toluene was the superior solvent for most substrates (see SI, Table S1). The substrate scope of salts 3 was first evaluated by varying aryl group Ar1, and both electron rich and electron deficient substituents in ortho-, para- and meta-position were tolerated, giving the corresponding products 3b-j in high to excellent yields (Scheme 2). Carbonyl containing aryl groups could be incorporated, as demonstrated by products 3i-j, and sterically congested Ar1 were well tolerated (3k-3l).

Variations on aryl group Ar1 are more restricted, to retain the required SsAr reactivity of this moiety. Thus, we were pleased to see that the electron-withdrawing group (EWG) could be varied from nitro to other activating groups e.g. SO2CF3 and CN (3m, 3n), and allow for introduction of additional substituents such as CF3 (3o). Other cyclic amines, such as morpholine and thiomorpholine, were also productive in the reaction with salt 1a (3p, 3q). Additional functionality could be introduced by decorating amines 2 with a variety of functional groups (3r-3v), including a free hydroxyl group (3u). Also 5- and 7-membered cyclic amines 2 could be utilized, giving products 3w and 3x in 87% and 88% yield, respectively. Limitations of the scope were encountered with acyclic aliphatic amines, which underwent a competing reductive pathway (see SI, section 3.1). Since the synthesis of salts 3 was performed without excess reagents, the pure products were generally isolated after a simple filtration to remove the base residues.

Next, the envisioned arylation/ ring-opening sequence was investigated using salt 3a and piperidine as the external nucleophile for the ring-opening of 4a, with the aim to install this valuable moiety at the end of the carbon chain of 5a (Table 1). The synthesis of organic ammonium salts is generally difficult, and only a few examples are known in literature. Our key intermediate, ammonium salt 4, could be particularly challenging due to the high steric congestion from the two aryl moieties as well as the large ortho-iodo substituent. To our delight, the reaction proved to be possible using a mild base and no excess reagents, by heating salt 3a in MeCN at 100 °C for 4 h followed by reaction with K2CO3 and piperidine at rt for 2 h, to provide 5a as the only product in 47% yield (entry 1). Extension of the reaction time of step 1 to 16 h, to allow full formation of 4a prior to the piperidine addition, provided 5a in 93% yield (entry 2). Lowering the temperature had a negative impact on the yield (entry 3), as did using the other explored solvents and bases (entries 4-6).
While the full synthesis sequence from salt 1a to product 5a could be performed in one pot without isolation of 3a, the yields of 5a were considerably decreased (entry 10, see SI section 2.2.1 for further details). The substrate scope was first evaluated by variation of iodonium salt 3, using piperidine as the external nucleophile (Scheme 3). Purification of 5a did not require column chromatography; an aqueous wash to remove inorganic impurities was sufficient to isolate 5a in 90% yield. The reaction was also possible using the 7-membered substrate 3x to provide 5b in a moderate yield, whereas the 5-membered substrate 3w decomposed upon heating. To the contrary, substrates 3r-v, containing decorated amine cores, reacted efficiently and delivered the corresponding products 5c-g in high to excellent yields. Even hydroxy-substituted substrate 3u, comprising of a competing nucleophilic site, reacted with complete selectivity in the desired pathway to afford amino alcohol 5f.

The generality of the N-arylation was then evaluated with substrates 3b-o, carrying a variety of aryl groups. Satisfyingly, transfer of Ar\(^2\) with varied electronic properties proceeded smoothly, delivering a range of electron deficient and electron rich products 5h-n in 61-92% yields. Even functional groups susceptible to nucleophilic additions, such as esters and amides, remained unaltered in the products 5o and 5p. The sterically congested ortho-Me product 5n could also be synthesized, whereas mesityl substrate 3k proved unreactive under the current conditions. The pyridinyl salt 3i-OTS was also unproductive, as the reaction with piperidine led to complex reaction mixtures. Substrates 3 with alterations on Ar\(^1\) efficiently underwent the desired transformation, yielding products 5q-s in 78-86% yield.

Next, our focus was directed towards prospective nucleophiles for the ring opening of 4 (Scheme 3). To make this step efficient for less potent nucleophiles than piperidine, two methods were developed. For aliphatic and aromatic amines, the reactions were performed for 2-6 h at 50-60 °C (method A), to give products 6a-o in good to excellent yields. Cyclic and acyclic secondary amines were proficient nucleophiles (6a-c), including the proline methyl ester, forming 6c in 95% yield. A common issue with N-alkylation strategies is the challenge to avoid over-alkylation. Thus, we were pleased to achieve selective monoalkylation of primary amine nucleophiles, with no detectable trace of dialkylated products. The methodology was compatible with a range of functionalities e.g. olefins, alkenyls, furanyl and thionyl groups (6d-h). Even the ambident nucleophile 2-aminoenol reacted with complete selectivity for the C-N bond formation, giving 6i in 81% yield. Anilines could also be employed in the ring-opening, despite being weaker nucleophiles, and could be used for incorporation of an indolyl functionality and for derivatization of the commercial pharmaceutical cytden, affording 6j-l in 61-84% yield. While an ortho-blocked phenol was efficient in the ring opening of 4a to provide 6m, unhindered phenols underwent a competing S\(_0\)Ar pathway with the ammonium moiety as the leaving group (see SI section 3.4). Halogenations were easily achieved with CsCl and KBr, providing products 6n and 6o in 80% and 88% yield, respectively.

Some nucleophiles proved incompatible with the conditions of method A, either due to competing pathways (ArOH, CsF, KCN) or by causing decomposition of 4a (S-nucleophiles). Method B was designed to overcome this limitation through the use of substrates 3-OTs (Scheme 4). Upon formation of ammonium salts 4-OTs, direct ring-opening by the tosylate takes place, giving products 7 in quantitative yield with 100% atom economy (see SI section 3.3). Compounds 7 then undergo an in situ S\(_{2}\)2 reaction with the external nucleophile to yield the target products 6. A short optimization revealed that the second S\(_{2}\)2 reaction was more efficient in DMF at 70 °C for 4 h (see SI Table S3).

Fluorine incorporation into organic molecules has spurred a large research interest due to the favorable medicinal properties and the importance of \(^{19}\)F radiolabeled pharmaceuticals.\(^{6b, 18}\)

### Table 1. Selected optimization data in synthesis of 5a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>T(^1) (°C)</th>
<th>T(^2) (°C)</th>
<th>Yield (%)(\text{a})</th>
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<tr>
<td>1</td>
<td>K(_2)CO(_3)</td>
<td>MeCN</td>
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<td>100</td>
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<td>47</td>
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<tr>
<td>2</td>
<td>K(_2)CO(_3)</td>
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<td>16</td>
<td>100</td>
<td>rt</td>
<td>93</td>
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<tr>
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<td>90</td>
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</tr>
<tr>
<td>6</td>
<td>K(_2)CO(_3)</td>
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<td>100</td>
<td>28</td>
</tr>
<tr>
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<td>100</td>
<td>rt</td>
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<td>MeCN</td>
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<td>Na(_2)CO(_3)</td>
<td>PhMe</td>
<td>4</td>
<td>110</td>
<td>-</td>
<td>31</td>
</tr>
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\(\text{a}\) Ar\(^2\) = 2-iodo-4-nitrophenyl. \(\text{b}\) NMR yields with 1,3,5-trimethoxybenzene as internal standard. \(\text{c}\) Reaction performed without isolation of 3a.

![Scheme 3. Scope of products 5 from variation of substrates 3.](image-url)
Scheme 4. Scope of products 5 from variation of NuH. *80 °C, 16 h. † Reaction performed under dark conditions. ‡ Ring-opening step at 100 °C, 2 h.

Using method B, efficient fluorination was achieved in quantitative yield, allowing straightforward isolation of the pure product 6p by filtration. Furthermore, a range of C-, S- and O-nucleophiles with varying nucleophilicity could be employed, such as cyanide, aromatic/aliphatic thiols, thioamides, phenols and carboxylic acids, to afford products 6q-w in good to excellent yields. Notably, the competing S

Ar pathway observed for phenols with method A was circumvented, and even complex substrates such as the steroid estrone could be derivatized into 6u in 77% yield. Moreover, the unprotected natural product cholic acid, with three competing nucleophilic hydroxy groups, underwent selective alkylation of the carboxylate moiety, to give product 6w in 88% yield.

Some nucleophiles reacted in unexpected ways with 4a. For instance, the addition of water resulted in amide product 8 in 55% yield (see SI section 3.3), rather than the intended ring opening by hydroxide. The formation of 8 can be rationalized through a Ritter-type reaction in the presence of the MeCN solvent. † Surprisingly, also DMF could be used as a productive nucleophile for the ring opening of 4a. When 3a was heated in DMF instead of MeCN, followed by addition of piperidine at room temperature, the formate product 9 was obtained in 88% yield. Furthermore, when the reaction was performed without addition of an external nucleophile, the primary alcohol product 10 was obtained in quantitative yield after aqueous workup. We anticipate that products 9 and 10 stem from an iminium intermediate formed through the ring opening of 4a by DMF in similarity with the Vilsmeier-Haack intermediate3⁰ (see SI section 3.3).

Ammonium salt 4 are potentially interesting compounds since organic ammonium salts find various industrial applications1⁶ owing to their antimicrobial,2¹ antistatic2² and surfactant2³ properties. To demonstrate the efficient preparation of 4, a small set of these products were synthesized by heating of 3, and isolated in good to excellent yields by simple evaporation of the solvent (Scheme 5).
CONCLUSIONS

We herein present a method for preparation of previously synthetically inaccessible amino-functionalized diaryliodonium salts through an S$_2$Ar reaction with fluorinated diaryliodonium salts. After incorporation of a range of cyclic amines, these salts were efficiently utilized in a sequential arylation/ring opening pathway, allowing for skeletal diversification of this valuable substrate class. The reaction takes place via an intramolecular arylation, forming an ammonium salt, which upon ring opening by external nucleophiles affords C- and N-functionalized diaryl amines. The reaction displays excellent functional group tolerance and transfer of aryl groups with varied electronic properties was demonstrated. The ring-opening allows for incorporation of common N-, O-, S-, C-, and halogen nucleophiles and derivatization of various natural products, giving a versatile set of amine products in a metal-free manner with high atom- and step-economy. The majority of the products contain a range of reactive sites/unprotected polar functionalities that increase their versatality and likeliness to attain medicinal applicability.  

ASSOCIATED CONTENT

 Supporting Information

Additional optimization, mechanistic suggestions, full experimental details, and analytical data (PDF).

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E. L. and B. O. designed the study; E. L. performed all experimental and analytical work; E. L. and B. O. wrote the manuscript; E. L. wrote the SI.

Notes

The authors declare no competing financial interest.

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REFERENCES


