A formal (3+2) cycloaddition strategy toward 2-azanorbornanes

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Abstract
Reported herein is the development of a photochemical method which allows for the construction of 2-azanorbornane scaffolds from cyclopropylsulfonamide derivatives. Access to the amine radical cation of these species is promoted by a Lewis acid additive which enables the ring opening of the cyclopropylamine moiety to initiate a cascade radical cyclization sequence. Notably, the method allows access to substituted 2-azanorbornane derivatives at all possible carbon centers and 1,3 stereocontrol is observed for C3 substituted derivatives. Preliminary mechanistic investigations suggest an integral role for the Lewis acid additive in facilitating single-electron transfer and avoiding deleterious dealkylation of the starting material. Thus, this method constitutes a modular, mild, and operationally simple approach to privileged saturated aza-heterocycles.

Introduction
The design and synthesis of highly saturated structures as drug candidates is an emerging trend within medicinal chemistry. The presence of 3-dimensional, sp³-rich structures correlates with increased success in drug development. This has been attributed to the increased solubility, lipophilicity, and metabolic stability of these compounds relative to traditional planar, sp²-rich drug scaffolds.¹ Both aromatic and saturated aza-heterocycles constitute some of the most common motifs in biologically active molecules and FDA approved drugs.² However, access to saturated aza-heterocycles – especially bridged bicyclic aza-heterocycles – is a synthetic challenge, yet demand for these scaffolds has increased due to their conformational rigidity, unique active site binding capabilities, and chirality.³ Ref These myriad benefits from combining saturation with a rigidified bicyclic core make such aza-heterocycles desirable candidates as biologically active molecules. To this end, our lab has recently reported on several photochemically enabled aminocyclopropane ring-opening methods to yield a variety of saturated nitrogen containing scaffolds including 1-aminonorbornanes, 1-aminocyclopentanes, and 1-amino-[3.1.1]bicycloheptanes.³,⁴ Within this same chemical space of highly saturated amines, we were interested to apply a ring-opening strategy towards the synthesis of aza-heterocycles, i.e. one where the nitrogen functionality is incorporated into a saturated ring.
As a target for a new ring-opening strategy, 2-azanorbornanes presented themselves as particularly attractive for their preliminary use in a variety of drug candidates. This scaffold has been demonstrated as a proline peptidomimetic with the rigidity of the scaffold ensuring maximum contact with the enzyme. Additionally, Ledipasvir is an anti-viral clinical drug candidate containing a 2-azanorbornane. It was originally developed from its piperidine analog, but incorporation of the 2-azanorbornane in place of the piperidine was found to be a key factor in the pharmacokinetics of the drug. 2-azanorbornanes were also used to mimic the bioactivity of epibatidine, which exhibits analgesic activity in the nervous system. The application of epibatidine has been hindered by its extreme toxicity, but 2-azanorbornane analogs preserve the backbone while minimizing toxicity. Despite these initial studies and their appealing properties for medicinal chemists, 2-azanorbornanes remain underutilized largely due to the paucity of synthetic methods reported for these systems.

Currently, following studies from Grieco, aza-Diels-Alder (aza-DA) reactions dominate the literature to access the carbon skeleton of these privileged heterocycles. This strategy, however, typically necessitates high reaction temperatures and the in situ formation of an imine reaction partner which limits both the functional group tolerance and modularity of the approach. The synthesis of substituted cyclopentadiene reaction partners in a regio- and stereochemically controlled manner also increases difficulty in accessing the many different substitution patterns available for this highly saturated aza-heterocycle. Finally, the aza-DA reaction furnishes the 2-aza-norbornene core, necessitating a hydrogenation step to the fully saturated 2-azanorbornane core. Other methods to arrive at 2-azanorbornanes rely on circuitous, multi-step procedures from highly functionalized pyrrolidines, but these methods suffer from a lack of generality and modularity. Given the promising biological activity of 2-azanorbornane containing molecules, a complementary approach relying on photochemistry at reduced temperatures and with greater
substitutional flexibility would enable the increased study and adoption of the core in biological applications.\textsuperscript{14-17} We envisioned that the ring-opening of a protected $N$-cyclopropyl amine with an intramolecular alkene tether could initiate a cascade radical cyclization sequence to furnish a 2-azanorbornane in analogy to our previously reported methods.\textsuperscript{20}

### Results and Discussion

**Figure 2.** Selected results from the optimization of our method.

Beginning our optimization of the above proposed methodology, we screened several variables including photocatalyst, Lewis acid identity and loading, $N$-protecting group, reaction time, and concentration. An initial reaction using title substrate 1\textsuperscript{a} with conditions like those utilized in our former 1-aminonorbornane methodology in entry 1 provided minimal conversion and yield of the desired 2-azanorbornane 2\textsuperscript{a} (11% conv, 2% yield). Switching to a more oxidizing Ir photocatalyst (Ir-2) (+1.68 V vs. +0.89 V for the Ir(III)$^*$ $\rightarrow$ Ir(II) redox couple) provided slightly further conversion and yield (21% conv., 8% yield) (entry 2). Notably, exclusion of ZnCl\textsubscript{2} as a Lewis acid additive shut down reactivity in both cases, giving only returned starting material (entries 3 and 4). Switching the protecting group from an aryl sulfonyl group to benzyl under the same conditions provided very high conversion and increased yield (entry 5, 80% conv. 20% yield). However, it was ascertained that in addition to conversion to the desired 2-azanorbornane, deleterious $N$-dealkylation of our starting material was occurring via in situ NMR reaction monitoring (see supporting information). Complex reaction mixtures resulting from this dealkylative degradation of the starting material made isolation of the product difficult. Efforts to exclude H\textsubscript{2}O (necessary for the hydrolysis which occurs during dealkylation; see **Figure 4.**) by setting up the reaction in a glovebox did not yield different results than setting the reaction up on the benchtop with a freeze-
pump-thaw sequence. Other efforts to suppress dealkylation by exclusion of α-amino protons by switching to an N-benzoyl protected starting material led to no conversion of the starting material (entry 6). While N-phenyl protected substrates had moderate percent conversion (entry 7), deprenylation along with undesired side reactivity with the protecting group aryl ring competed with the desired cyclization sequence. As we could not avoid the inclusion of α-amino allylic protons due to our substrate design, we returned to the original arylsulfonyl protecting group as this group. Continuing to increase the photocatalyst oxidation potential with an acridinium organophotocatalyst gave encouraging conversion, but still low yields of the desired product (entry 8, 56% conv., 17% yield). Finally, reintroduction of ZnCl₂ at 1.6 equivalents completely consumed the starting material in only 6 hours and furnished the desired 2a in 66% yield (entry 9). A less oxidizing 4CzIPN photocatalyst gave only returned starting material (entry 10). Interestingly, increasing the intensity of the blue LED lamp resulted in an increase in N-dealkylation (see Supporting Information). As a last attempt to avoid deprenylation, utilizing anthracene as a redox mediator in the reaction gave comparable results to the optimized conditions, however, it necessitated longer reaction times (20 h vs. 6 h for full conversion, see Supplementary Information for details). A survey of Lewis acids including Cu(OTf)₂, Ti(OPr)₄, TiCl₄, and LiBF₄ did not result in an increase in yield of the desired product, while aqueous HCl completely suppressed reactivity (see Supplementary Information). Of note, dried Zn(OTf)₂ performed comparably to ZnCl₂ and had the benefit of being handled outside of the glovebox. The storage of ZnCl₂ solutions inside the glovebox was implemented to avoid degradation of the stock solution over time, particularly when the solutions were used in diethyl ether. Suspected decay or concentration variability of ZnCl₂ solutions in diethyl ether stored in a desiccator was evidenced by reproducibility errors over extended periods of time of using the solution. This necessitated the delivery of the ZnCl₂ as a solution in higher-boiling 2-methyl-THF with storage of the solution in a glovebox.

Other polar solvents such as nitromethane, methanol, and THF did not lead to an increase in the desired product (see supporting information). In benzene, the reaction was slower (55% conv., 40% yield in 6 h) than in acetonitrile.

With our optimized conditions in hand, we began to explore the tolerance of this approach with special concern in accessing derivatives at the many different carbon centers of the 2-azanorbornane core. Varying the cyclopropylamine moiety of the starting materials would allow for derivatives substituted at C1, C5, and C6. Beginning at the C1 bridgehead, we were delighted to synthesize both alkyl (e.g., 2b) and aryl (e.g., 2c) substituted derivatives in modest yields. Notably, a free alcohol derivative 2e was synthesized in 34% yield. An aryl bromide moiety tolerated the reaction conditions giving 2d in 16% yield, providing a valuable cross-coupling handle for use in post-reaction functionalization. A 59:41 mixture of C5 and C6 isomers were observed for the methyl-substituted derivative in a combined 27% yield. The dimethyl substituted 1i did not yield a desired 2-azanorbornane 2i under the standard conditions, however extending the reaction time (16 h) and elevating the reaction temperature (60 °C) gave a 70:30 mixture of C5:C6 regioisomers in 57% yield. The increased heat likely promotes the 6-exo-trig cyclization of the tertiary radical resulting from ring opening of 1i, which otherwise is too sterically encumbered to cyclize at room temperature.
More derivatives were readily synthesized by varying the tethered allylic moiety of the substrate cyclopropylsulfonamides. These variations allowed for novel 2-azanorbornanes with C3, C4, and C7 substitution. At C3, A,1,3 stereocontrol during the initial 6-exo-trig cyclization of the radical cascade gave exclusive endo stereoisomers (e.g., 2j). Similar stereocontrol was observed in our previous radical cascading 1-aminonorbornanes. This contrasts with the typically high C3-exo selectivity observed in aza-Diels-Alder methods for 2-aza-norbor dane synthesis, thus offering a complementary synthetic strategy for C3 stereocontrol. The simple methyl substituted 2j was synthesized in 58% yield. At the C4 bridgehead, reduced yields (12%) for 2k may be attributed to the increased steric hindrance of the alkene radical acceptor. The decreased rate of cyclization allows for competitive dealkylation of the sulfonamide starting material.

Finally, disubstitution (e.g., 2a and 2n) at C7 gave the highest yields of the corresponding 2-azanorbornanes due to the stability of the radical intermediate prior to the 5-exo-trig cyclization in the cascade. Monosubstitution at C7 was also tolerated with a methyl group but led to a 53:47 mixture of C7 diastereomers in 34% yield. However, the ester-substituted 2m was synthesized as a single diastereomer in 39% and gave a functional handle for further C7 functionalization. However, substrates lacking substitution at C7 were not competent in the radical cascade, likely due to the instability of the primary radical intermediate formed upon the first 6-exo-trig cyclization. Ring opening of an N-cyclobutyl sulfonamide cyclized to give the desired 2-aza-bicyclo[3.2.1]octane, albeit in low yield (10%) likely due to the slower ring opening of cyclobutane permitting significant N-dealkylation.
Figure 4. Proposed mechanism for the synthesis of 2-azanorbornanes from N-cyclopropylsulfonamide derivatives. This mechanism also accounts for the competitive dealkylation observed in our studies.

The proposed mechanism of the rearrangement begins with the single-electron oxidation of the sulfonamide starting material I to its radical cation II by the excited state of the acridinium photocatalyst. This process is promoted by ZnCl₂ and other Lewis acids in a manner that is not fully understood at this moment. This N-centered radical cation can undergo strain-driven homolysis to a distonic sulfoniminium radical cation III. Alternatively, deprotonation of the allylic methylene of the alkene tether in the sulfonamide followed by hydrolysis of the resultant sulfoniminium leads to a net dealkylation to a cyclopropylsulfonamide VII and carbonyl compound VIII. This degradation pathway is mitigated by the addition of a Lewis acid such as ZnCl₂. Returning to the productive reaction pathway, the distonic radical cation can undergo a 6-exo-trig cyclization in the radical cascade to arrive at intermediate IV. Then, a serial 5-exo-trig cyclization onto the electrophilic sulfoniminium cation delivers the 2-azanorbornane scaffold in the form of the penultimate N-centered radical cation intermediate V. Single electron reduction of V by the reduced acridinium photocatalyst completes the photoredox catalytic cycle and furnishes the 2-azanorbornane product VI.

Conclusion

Our work in the reactivity of N-cyclopropyl radical cations detailed above has allowed the synthesis of a variety of novel 2-azanorbornane building blocks under mild conditions. The modularity of our approach is notable in that the starting materials of the reaction are derived from a cyclopropylamine, sulfonyl chloride, and allylic electrophiles. Furthermore, the reaction allows for access to substituted 2-azanorbornanes at all possible sites of substitution. We envision that
these scaffolds should find greater utility in medicinal chemistry as part of the recent trend to implement highly saturated cores into drug development programs.

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