Intramolecular, Visible Light-Mediated Aza Paternò-Büchi Reactions of Unactivated Alkenes

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Supporting Information Placeholder

ABSTRACT: Azetidines are of particular interest in medicinal chemistry for their favorable properties, including increased resistance to oxidative metabolism and lower lipophilicity. The recent development of [2+2] reactions has significantly benefited the previously limited methods for azetidine synthesis, but access to more complex architectures still requires further development. Herein we report a visible-light enabled intramolecular [2+2] cycloaddition to access tricyclic azetidines with 3D complex structures and high levels of saturation.

Incorporation of highly substituted, three-dimensional scaffolds into target structures is an essential strategy in medicinal chemistry to facilitate the development of future pharmaceuticals. Current discovery efforts are shifting towards the inclusion of more saturated, complex scaffolds to increase the likelihood of identifying promising lead structures. Benefits from higher saturation and higher complexity range from increased solubility to greater specificity, and lower toxicity, desirable qualities for a drug. Azetidines are 4-membered nitrogen-containing heterocycles that recently garnered a lot of attention as medicinally desirable scaffolds in the quest for new lead compounds in drug design and development. Specifically, azetidines exhibit favorable pharmacokinetic properties and biological activities including decreased lipophilicity, high polarity, and rigidity, in addition to facilitating the rapid build-up of molecular complexity. Implementation of azetidines as alternatives for 5- and 6-membered nitrogen-containing heterocycles in current potential therapeutic candidates is known to improve their metabolic stability by enhancing their overall structural rigidity, resulting in enhanced resistance to oxidative metabolism. Furthermore, these compounds often exhibit lower lipophilicity and higher polarity, which represent additional important contributions to enhance the efficacy of a compound. For example, 5-HT₂C agonists, 1 and 2 identified by Pfizer, differ only in the ring size of the N-heterocycle, yet the azetidine results in a more potent compound with an EC₅₀ of 12 nM compared to 273 nM (Fig. 1A).

However, despite these desirable characteristics, the incorporation of azetidines in current pharmaceutical lead compounds remains limited. Importantly, less than 1% of all nitrogen-heterocycles included in current FDA-approved pharmaceuticals are functionalized azetidines. This divide is due to a dearth in efficient synthetic methods to access these desirable 4-membered ring nitrogen-containing heterocycles. Among the synthetic strategies most often

Figure 1. A. Azetidines as important scaffolds for current drug design and development. B. Currently available synthetic strategies to access functionalized azetidines.
applied are nucleophilic substitutions (3), strain release of azabicyclobutanes (4), and the reduction of lactams (5, Fig. 1B). However, all of these approaches require the synthesis of specific precursors and are prone to limitations in scope. Arguably, the most efficient and direct strategy towards functionalized azetidines relies on [2+2]-cycloaddition reactions between imines and alkenes, or an aza Patañó-Büchi reaction (6). Select efficient procedures for these aza Patañó-Büchi reactions have recently been developed, relying on visible light-mediated energy transfer (Fig. 2). These methods harness the triplet energy excited states of either alkenes or oximes, generated upon energy transfer from the triplet excited states of suitable photocatalysts. Following this approach, intramolecular aza Patañó-Büchi reactions proceed upon accessing the triplet excited states of activated alkenes (7) to undergo the desired [2+2]-cycloaddition with pendant oximes in up to 99% yield to form azetidines (8) (Fig. 2A). An intermolecular variant of this transformation was subsequently developed that relies on unactivated alkenes 9 and the triplet excited states of cyclic oximes 10 to promote the formation of azetidines 11 in up to 99% yield (Fig. 2B). Herein we report the development of an intramolecular aza Patañó-Büchi reaction of unactivated alkenes by relying on the design principle of oxime excitation to access complex azetidine scaffolds. Specifically, cyclic oximes react with the unactivated alkene moieties in 12 to result in the formation of tricyclic azetidines 13 to access substrates with opposite substitution patterns in comparison to the previous intramolecular approach. Notably, both metal-based and organic photocatalysts are shown to promote the desired transformation in yields up to 87% and 41% respectively.

Figure 2. A. Intramolecular methodology using excited alkenes and unactivated alkenes. B. Intermolecular methodology using excited oximes and unactivated alkenes. C. Novel intramolecular methodology using excited oximes and unactivated alkenes.

To identify optimal conditions for intramolecular azapatañó-Buchi reactions of unactivated alkenes, we evaluated a range of photocatalysts varying in triplet energies upon irradiation of oxime 14 with blue LED lights (Table 1). Specifically, conversion of oxime 14 with Ir2 gave rise to azetidine 15 with increased yields of 90% (entry 3, Table 1). Using a catalyst with a lower triplet energy of 58.6 kcal mol\(^{-1}\), fac-[Ir(fppy)\(_2\)] resulted in a decreased yield of 61% for 15 (entry 4, Table 1). Catalysts with triplet energies below 57 kcal mol\(^{-1}\) including [Ir(dFppy)(dtbbpy)]PF\(_6\), fac-[Ir(fppy)\(_2\)], and fac-[Ir(4'-CF\(_3\)-

Table 1. Evaluation of photocatalysts in intramolecular, visible light-mediated azapatañó-Buchi reactions.

| entry | photocatalyst | \(E_T\) (kcal·mol\(^{-1}\)) | \(\lambda\) (nm) | yield (%) |
|-------|--------------|-----------------|-------|--------|
| 1     | [Ir(dF(Me)ppy)\(_2\)](dtbbpy)]PF\(_6\) | 60.2 | 427   | 73     |
| 2     | Ir1·PF\(_6\) | 60.1 | 427   | 78     |
| 3     | Ir2          | 60.1 | 427   | 90     |
| 4     | fac-[Ir(Fppy)\(_3\)] | 58.6 | 427   | 61     |
| 5     | [Ir(dFppy)(dtbbpy)]PF\(_6\) | 56.4 | 427   | 29     |
| 6     | fac-[Ir(fppy)\(_2\)] | 55.4 | 427   | 3      |
| 7     | fac-[Ir(4'-CF\(_3\)-fppy)] | 55.2 | 427   | 7      |
| 8     | Thioxanthone | 65.5 | 427   | 0      |
| 9     | 2-MeOTx      | 57.8 | 427   | 41     |
| 10    | 2CzPN        | 60.6 | 427   | 41     |
| 11    | 4CzPN        | 58.3 | 427   | 0      |
| 12    | Thioxanthone \* | 65.5 | 427   | 6      |
| 13    | 2-MeOTx\*    | 57.8 | 427   | 28     |
| 14    | 2CzPN\*      | 60.6 | 427   | 38     |
| 15    | 4CzPN\*      | 58.3 | 427   | 19     |
| 16    | Ir2 (0.2 M)  | 60.1 | 427   | 76     |
| 17    | Ir2 (0.1 M)  | 60.1 | 427   | 84     |
| 18    | Ir2 (0.05 M) | 60.1 | 427   | 85     |
| 19    | Ir2 (0.01 M) | 60.1 | 427   | 85     |
| 20    | no catalyst  | -    | -     | 0      |

Conditions: 0.1 mmol 22 and photocatalyst are dissolved in acetonitrile (0.1 M) and the solution was sparged for 10 min. The sample was irradiated with blue LED lamps 16 hours. Percent yield was determined by NMR with mesitylene as internal standard. \*Ran in toluene for increased solubility of some organic catalysts.
ppry)] resulted in diminished formation of azetidine 15 in yields of less than 29% (entries 5-6, Table 1). Organic photocatalysts were also considered under similar conditions, varying the triplet energy of the catalyst used. In particular, utilizing thioxanthone with a higher triplet energy than the optimal iridium catalyst, Ir2, no product was observed (entry 8, Table 1).

Using organic catalysts with lower triplet energies than thioxanthone, 2-MeOTx and 2CzPN, gave rise to azetidine 15 in 41% yield for both catalysts (entries 9-10, Table 1). However, conversion of oxime 14 relying on 4CzPN exhibiting a triplet energy between 2-MeOTx and 2CzPN failed to provide the desired azetidine 15 (entry 12, Table 1). Suspecting that the solubility of the organic photocatalyst may be influencing the yield, the solvent was switched to toluene. Under these modified reaction conditions, thioxanthone produced trace amounts of azetidine 15 in 6% yield (entry 12, Table 1). 2-MeOTx did not perform as well in toluene as it did in acetonitrile, resulting in a decreased yield of 26%, while 2CzPN performed similarly, producing 15 in 38% yield (entries 13-14, Table 1). 4CzPN in toluene produced an increased yield of 19% (entry 15, Table 1). The optimal organic catalyst conditions were identified as 2-MeOTx or 2CzPN in acetonitrile, which is the first instance of organic photocatalysts being used in a visible light-mediated [2+2] cycloaddition between alkenes and oximes to access azetidines products by exciting the oxime to its triplet state.

With an optimal photocatalyst identified, we subsequently focused on further improving the reaction conditions, with a particular emphasis on concentration (Table 2). Specifically, at 0.2 M a conversion of 98% was observed, however the desired product 15 was formed in diminished yields of only 76% (entry 16, Table 1). In comparison, decreasing the concentration to 0.1 M resulted in the formation of azetidine 15 with improved yields of 84% while complete consumption of oxime 14 was observed (entry 17, Table 1). Notably, decreasing the concentration further to 0.05 M or 0.01 M did not result in an improvement in yield (entries 18-19, Table 1). Notably, without photocatalyst no formation of azetidine 15 was observed when oximes 14 was irradiated with blue LED light (entry 20, Table 1).

Utilizing the optimized conditions, the substrate scope for intramolecularaza Paternò-Büchi reactions of oximes incorporating unactivated alkenes was explored. The optimal reaction conditions identified proved to be compatible with a variety of alkene substitution patterns, chain lengths, and oxime backbone substituents, providing access to azetidines in up to 87% yield. The trisubstituted alkene substrate resulted in the formation of tricyclic azetidine 15 in 87% yield, while disubstituted alkenes (19, 20, and 23) produced yields up to 68% yield. The optimal reaction conditions were found to tolerate terminal alkenes, which was surprising as the postulated reaction mechanism for this intramolecular aza Paternò-Büchi reaction relied on the formation of a primary radical. Employing substrates incorporating terminal alkenes allows access to azetidines with methylene groups adjacent to the nitrogen, which were previously only accessible using ethylene gas following the former intermolecular reaction protocol. Terminal alkene 16 resulted in a yield of 25%, however this was improved by decreasing the concentration of the reaction to 80%, Substitution adjacent to the ester moiety resulted in a higher yield of 69% for the dimethyl substrate 17 although a decrease in yield to 9% was observed for azetidine 18, bearing a monomethyl substituent. Conversely, the croyl ester resulted in a 68% yield of azetidine 19 with a 1:1 mixture of diastereomers. Increasing the size of the substituent to a n-propyl group did not improve the diastereoselectivity, however did produce 20 in 61% yield. Importantly, azetidines incorporating 6-membered ring lactones were similarly readily accessible, albeit in slightly diminished yields compared to their 5-membered ring analogs. The substrate utilizing a terminal alkene resulted in 21 being formed in 6% while the trisubstituted alkene resulted in 22 being formed in an in-

**Table 2. Evaluation of the scope of intramolecular, visible light-mediated aza Paternò-Büchi reactions.**

| R1 | R2 | R3 | R4 | R5 | R6 | Yields (%) |
|----|----|----|----|----|----|------------|
| 15 | (87%) | 16 | (25%), (90%) | 17 | (66%) | 18 | (5%) |
| 19 | (68%), (1 : 4) | 20 | (61%), (1 : 1, 1 : 1) | 21 | (6%), (25%) |
| 22 | (41%), (71%) | 23 | (47%) | 24 | (72%) | 25 | (22%), (31%) |
| 26 | (60%) | 27 | (R = Ph, 58%) | 28 | (R = OEt, 26%) | 29 | (67%) |

**Conditions:** 0.25 mmol isoxazoline and Ir2 (1 mol %) are dissolved in acetonitrile (0.1 M) and the solution is sparged for 10 min. The reaction is irradiated with blue LED lamps at 427 nm for 16-24 hours. *Reaction run at 0.01 M or 0.05 mmol scale yield by HNMR.
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