Organic LETTERS

Letter

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Transition-Metal-Free Amine Oxidation: A Chemoselective Strategy for the Late-Stage Formation of Lactams

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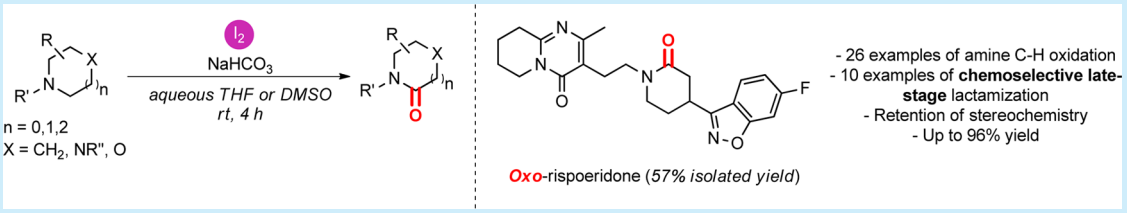
Supporting Information



ABSTRACT: A metal-free strategy for the formation of lactams via selective oxidation of cyclic secondary and tertiary amines is described. Molecular iodine facilitates both chemoselective and regioselective oxidation of C−H bonds directly adjacent to a cyclic amine. The mild conditions, functional group tolerance, and substrate scope are demonstrated using a suite of diverse small molecule cyclic amines, including clinically approved drug scaffolds.

Late-stage C−H oxidation is a step- and atom-efficient strategy to tune the efficacy and physicochemical properties of biologically active small-molecule scaffolds.[1] The underlying driver of this powerful approach is the facile and chemoselective oxidation of C−H bonds in complex molecular architectures by exploiting the subtle differences in C−H bond reactivity. This in turn enables the formation or diversification of molecular frameworks that would otherwise require the development of a dedicated synthetic route at an early stage in the process. Of the myriad of privileged heterocycles found in clinically approved medicinal agents and natural products,[2] the lactam motif is ubiquitous.[3] From a medicinal chemistry perspective, lactams reduce the hydrophilicity of secondary and tertiary ammonium species and provide additional hydrogen bond acceptor sites that could enhance drug efficacy and potentially reduce toxicity. Current preparative methods of lactams typically involve condensation of amines with a tethered carboxylic acid,[4] Beckmann rearrangement,[5] or dehydrogenative coupling of amines with alcohols.[6] Each of these strategies involve lactam formation early in the synthetic sequence, which in turn limits the downstream diversification of complex molecular scaffolds.

A comparative process that involves the formation of the lactam moiety by chemoselective oxidation of cyclic amines is less well refined and typically requires the use of expensive and toxic transition-metal catalysts such as osmium[7a] or mercury[7b] complexes and harsh oxidative conditions such as organic peroxides[7c−e] or ruthenium oxides.[7f−h] Recent work by Milstein et al. shows that catalytic oxidation of cyclic amines to the corresponding lactam is indeed possible, although the efficiency of this process is limited by the need to heat an air-sensitive ruthenium catalyst **1** to 150 °C for more than 2 days to effect this transformation (Figure 1, eq 1).[8]

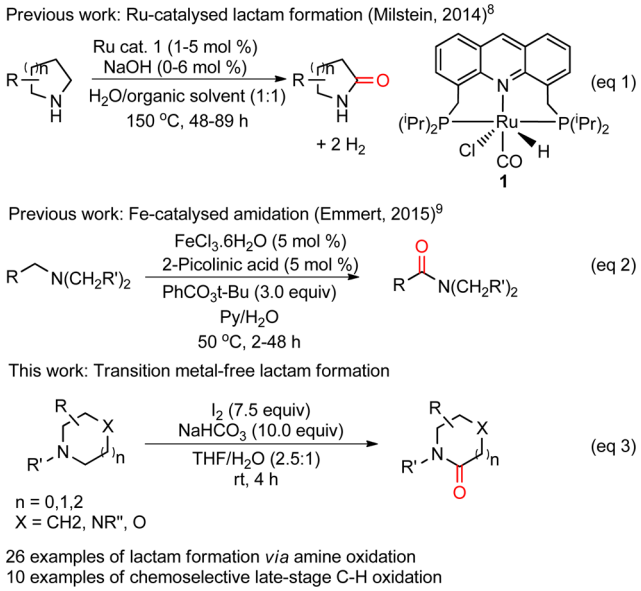


Figure 1. Lactam formation via C−H oxidation of cyclic amines: (a) ruthenium-catalyzed lactam formation;[8] (b) iron(III)-catalyzed oxidation of acyclic amines;[9] (c) late-stage lactam formation mediated by iodine oxidation of cyclic amines.

Ferric chloride offers a cheap alternative to ruthenium catalysts (Figure 1, eq 2); however, substrate scope is currently limited by the requirement of a strong peroxide oxidant.[9] Gold nanoparticles supported on alumina do offer a mild and chemo-

Received: January 4, 2017

DOI: 10.1021/acs.orglett.7b00021
Org. Lett. XXXX, XXX, XXX−XXX

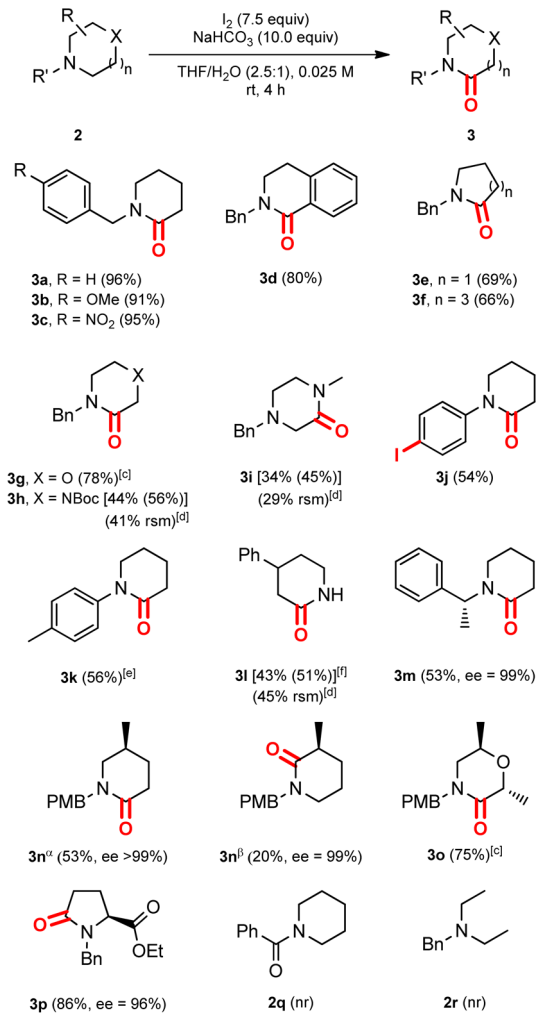
selective route to amide and lactam formation. However, large amounts of this expensive catalyst are required, which is further complicated by the multistep process to prepare the colloid.[10] In contrast to the use of transition-metal catalysts, molecular iodine is a mild, cheap, and metal-free oxidant[11] that has been used to chemoselectively oxidize a piperidine ring found in natural products to the corresponding lactam in the presence of aldehyde, alkene, alcohol, and heteroaromatic functionalities.[12] Although there are a number of reports that describe the use of electrophilic halogen sources to carry out α-oxidation of cyclic amines,[13] these procedures to date have limited functional group tolerance[13a] and require harsh reaction conditions.[13b−e] Herein, we report a general strategy for the chemoselective oxidation of a range of secondary and tertiary saturated N-heterocycles to form γ-, δ- and ε-lactams (Figure 1, eq 3). To explore the selectivity of our approach, a reaction screen was undertaken using the model substrate **2a**. The parameters of solvent, concentration, stoichiometry of iodine and iodine source were surveyed (see Table S1). Aqueous THF and aqueous DMSO were both found to be optimal solvents, resulting in 91% and 90% conversion of **2a** into **3a**, respectively. The stoichiometry of iodine and concentration of the substrate proved critical for high conversion to **3a**, with 7.5 equiv of iodine and substrate concentration at 0.025 M required to produce 96% of **3a**.

With optimized conditions in hand, the substrate scope of this reaction was explored using a range of cyclic amines **2a−r** (Scheme 1). Our optimized conditions tolerated both electron-rich and electron-poor benzyl-protected piperidines (**2b**,**c**) and tetrahydroisoquinoline **2d**, with no oxidation of the exocyclic benzylic methylenes observed in **3a−d**. Chemoselective oxidation of the cyclic α-C−H bond was observed in both five-membered and seven-membered cyclic amines **2e−f**, morpholine **2g**, and piperazines **2h**,**i**. Interestingly, stalling of the reaction was seen for substrate **2g**, which was alleviated by using a DMSO/H_2O solvent system instead.[14] In contrast to benzylic substrates **3a−i**, concomitant lactamization and para-iodination resulted in the formation of **3j** from **2j**. Blocking the para position of the phenyl ring with a methyl group produced lactam **3k** exclusively. Formation of the secondary lactam **3l** and sterically hindered **3m** was also tolerated. Oxidation of the asymmetric piperidine **2n** formed **3n*α*** and **3n*β***, isolated in a ratio of 2.7:1, demonstrating bias toward the sterically less hindered product. Notably, no racemization of the stereogenic centers in **3m** and **3n** was observed. Retention of stereochemistry at positions β to the nitrogen in morpholine **2o** was also observed, with the trans orientation of the methyl groups conserved. The stereogenic center in the proline-derived substrate **2p** was also conserved, which could potentially enable access to non-natural proline derivatives and proline-tagging experiments. However, no reaction was observed with benzoyl-protected **2q** or acyclic substrate **2r**. This suggests the availability of the amine lone pair and the conformationally restricted ring structure is essential for chemoselective oxidation.

With the substrate scope and robustness of this methodology established, the chemoselectivity profile was further explored on a suite of drug molecules (Figure 2). Lactams **5a−e** were isolated in moderate to excellent yields (15−92%), demonstrating chemoselective oxidation in the presence of alkenes, electron-rich aromatic rings, pyridines, carboxylic acids, and sulfonamides.

Products **5d** and **5e** were recovered in low isolated yields (15% and 26%, respectively) and were formed in moderate conversions (56% and 57%, respectively). This is attributed to formation of other oxidative byproducts that were detected by mass

Scheme 1. Substrate Scope of Iodine-Mediated Oxidation of Cyclic Amines[a]



[a]Conditions: **2** (1.0 equiv), $NaHCO_3$ (10.0 equiv), I_2 (7.5 equiv) in THF/H_2O (2.5:1, 0.025 M), rt, 4 h. [b]Isolated yields shown; values in parentheses show conversion to product determined by ^1H NMR analysis of the crude material against an internal standard. [c]Reaction run in 2.5:1 DMSO/H_2O solvent system. [d]% rsm = percentage of remaining starting material observed by crude ^1H NMR. [e]Iodine was added in three portions of 2.5 equiv each hour. [f]Reaction stirred for 20 h.

spectrometry, in addition to their challenging purification, which required the use of HPLC (see the SI), all of which resulted in low recovery of product. The morpholino lactam **5f** was also produced in 55% yield with retention of the cis orientation of the ring-methyl groups. Of particular note was the regioselective oxidation of the asymmetrical azepane ring in **4g**, forming lactams **5g*α*** and **5g*β*** in a ratio of 4.3:1. These results demonstrate the general chemoselectivity of this methodology for oxidation of cyclic amines in complex small molecules.

When compared to other conditions reported for oxidation of amines directly to amides/lactams[7h,8,9,13c] (Figure 3), the conditions developed here offer substantially better chemoselective oxidation when applied to drugs **4h** and **4i** (conditions A) with **5h** isolated in high yield (83%) and **5i** formed in high conversion (81%). Product **5i** could only be isolated in low yield (30%) because further purification was required due to coelution with an iodinated byproduct during the first purification (see the

DOI: 10.1021/acs.orglett.7b00021
Org. Lett. XXXX, XXX, XXX−XXX

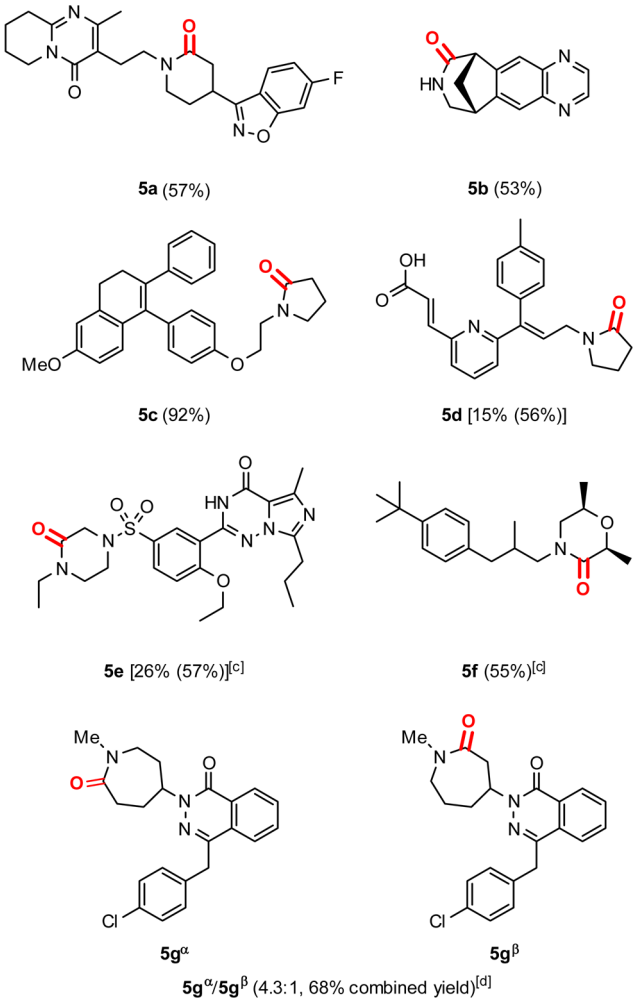


Figure 2. Substrate scope of late-stage C−H oxidation of industrially relevant drug scaffolds. (a) Conditions: **4** (1.0 equiv), $NaHCO_3$ (10.0 equiv), I_2 (7.5 equiv) in THF/H_2O (2.5:1, 0.025 M), rt, 4 h. (b) Isolated yields shown; values in parentheses show conversion to product determined by ^{1}H NMR analysis of the crude material against an internal standard. (c) Reaction run in 2.5:1 DMSO/H_2O solvent system. (d) Ratio of products determined by NMR analysis.

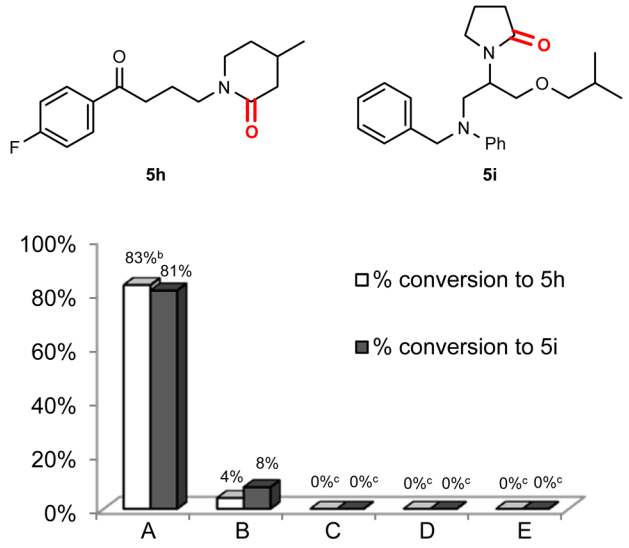
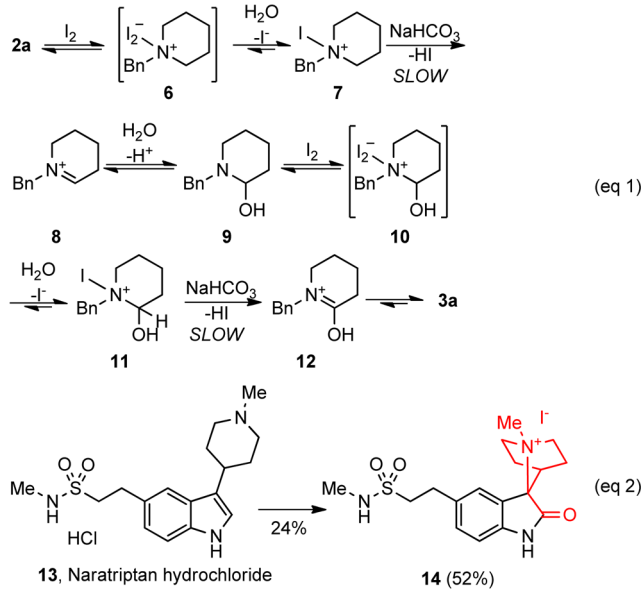


Figure 3. Comparative analysis of amine oxidation conditions using drug compounds **5h** and **5i** as exemplars. (a) General conditions: A = I_2, $NaHCO_3$, rt, 4 h; B[8] = 1 (1 mol %), NaOH, 150 °C, 48 h; C[9] = $FeCl_3$ (5 mol %), picolinic acid (5.0 mol %), $PhCO_3t$-Bu (3.0 equiv), H_2O, 50 °C, 24 h; D[7h] = RuO_2 (10 mol %), $NaIO_4$ (6.3 equiv), rt, 64 h; E[13c] = $PhI(OAc)_2$ (2.2 equiv), H_2O, rt, 16 h. For detailed conditions, see the SI. (b) Isolated yield. (c) Complex mixture of oxidative byproducts observed.

Scheme 2. Proposed Reaction Mechanism (eq 1) and the Unexpected Cyclization of Naratriptan (eq 2)[a]



[a]Conditions: **13** (1.0 equiv), $NaHCO_3$ (10.0 equiv), I_2 (7.5 equiv) in THF/H_2O (2.5:1, 0.025 M), rt, 20 h. Isolated yield shown; value in parentheses shows conversion to product determined by ^{1}H NMR analysis of the reaction mixture run in deuterated solvents against an internal standard.

SI). ^{18}O-labeling studies were then undertaken using $Na^{18}OAc$ as the base and $H_2{}^{18}O$ (see the SI). Full ^{18}O-incorporation was observed in the conversion of **2a** into ^{18}O-**3a** when $H_2{}^{18}O$/$Na^{18}OAc$ was used. In contrast, only **3a** was formed when H_2O/$Na^{18}OAc$ was used. This confirmed that the source of the lactam oxygen in the product is derived from water and not from the base. Additionally, ^{1}H NMR experiments were carried out to further probe the mechanism of this reaction (see Table S2). These revealed the formation of an *N*-iodoammonium intermediate upon addition of iodine (7.5 equiv) to **2a**. Dilution of the reaction mixture to 0.025 M with d_8-THF and D_2O, followed by the stepwise addition of sodium bicarbonate resulted in full conversion after 2 h and 5.0 equiv of base.

Taken collectively, we propose that this reaction proceeds via the initial formation of the charge-transfer complex **6** (Scheme 2, eq 1).[15]

With moisture present, this would form **7**, followed by slow formation of iminium ion **8**. The observed endocyclic oxidation is most likely due to a more effective anti-periplanar E2-elimination of the N−I and C−H_α bonds relative to the conformationally flexible exocyclic site. The low basicity of sodium bicarbonate may also be responsible for the selectivity of deprotonation seen for **2p**, with the less sterically hindered hydrogen being deprotonated over the more acidic one. Nucleophilic attack by water at the iminium carbon in **8** and subsequent deprotonation forms **9**. A second iodination step to form **11** via **10** enables the formation of **12** via loss of hydrogen iodide, and tautomerization results in the formation of **3a**. The

DOI: 10.1021/acs.orglett.7b00021
Org. Lett. XXXX, XXX, XXX−XXX

unexpected formation of product **14** in 52% conversion from the indole **13** (Scheme 2, eq 2) further underpins the formation of the *N*-iodoammonium intermediate such as **7** on the piperidine ring, which can be sequestered by the proximal indole in this instance.

In summary, we have developed a mild, late-stage strategy for the chemoselective oxidation of cyclic amines to the corresponding lactams under mild conditions. We envisage that this approach could be generalized by medicinal chemists to create a diverse range of compounds from a small subset of molecular scaffolds, providing synthetic access to drug metabolites,[1e,16] potentially accelerating the hit-to-lead process of drug discovery compared to more traditional linear routes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00021.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by GSK via the GSK/University of Strathclyde Centre for Doctoral Training in Synthetic and Medicinal Chemistry. We also thank Stephen Richards and Sean Lynn (both GSK) for their assistance with NMR analysis.

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DOI: 10.1021/acs.orglett.7b00021
Org. Lett. XXXX, XXX, XXX−XXX