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Inexpensive multigram-scale synthesis of cyclic enamines and 3-N spirocyclopropyl systems†

Pratik Kumar,[a] Omar Zainul[a] and S. T. Laughlin[a,b]

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Cyclic enamines are important synthons for many synthetic and pharmacological targets. Here, we report an inexpensive, catalyst-free, multigram-scale synthesis for cyclic enamines with exocyclic double bonds and four- to six-membered rings. This strategy is more conducive to scale up, permissive of functionalization around the cyclic system, and less sensitive to the nature of the N-protecting group than previously-described methods for cyclic enamine synthesis. Further, we explore application of these enamines to the synthesis of highly-strained spirocyclic 3N-cyclopropyl scaffolds.

Cyclic enamines are valuable building blocks for the preparation of synthetic, naturally-occurring, and pharmacologically active molecules[1–6]. For example, they are key components of synthetic azacyclic hexahydroindoles[7], the naturally-occurring alkaloid Plakoridine A[8], and a pharmaceutically relevant derivative of the sugar α-D-xylofuranose[9] (Fig. 1). Naturally, chemists have devoted considerable effort to developing strategies for the synthesis of cyclic enamines. Among the cyclic enamines, those containing an exocyclic double bond, like azetidine enamine **1** and pyrrolidine enamine **2** (Fig. 1), have garnered attention[7,10–15] for their wide use as precursors in the syntheses of biologically active molecules ranging from β-lactams[10,16] and macrolactams[11] to unnatural amino acids[14] and substituted 2-pyrrolidines[8]. Our interest in cyclic enamines **1** and **2** stems from their potential use as intermediates in the creation of 3-N spirocyclopropyl (*i.e.*, 4-azaspiro[2.n]alkane) and 3-N spirocyclopropenyl (*i.e.*, 4-azaspiro[2.n]alkene) systems, which have utility in diverse subfields of chemistry as synthons for cyclin-dependent kinase2[17] and tyrosine kinase inhibitors[18], monomers for both

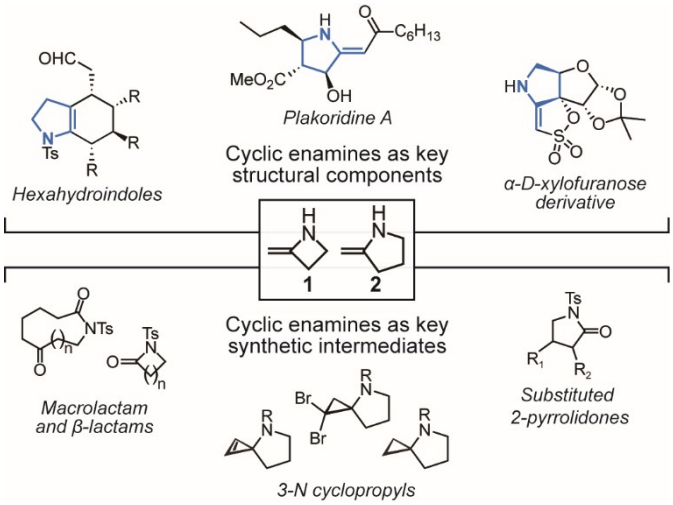

Fig 1. An array of synthetic, naturally-occurring, and pharmaceutical molecules utilizes cyclic enamines as key motifs. Additionally, cyclic enamines containing an exocyclic double bond can provide access to 3-N spirocyclic systems.

ROM polymerization[19,20] and poly-cyclopropane-based materials[21], and reagents in the bioorthogonal tetrazine ligation[22–24].

Traditionally, cyclic enamines like compounds **1** and **2** have been synthesized in modest yields by cyclization of the respective halo-imine precursors with strong bases[25–27]. Unfortunately, these strategies are limited in their substrate scope by their use of strong base and requirement for a quaternary carbon adjacent to the amine to prevent elimination of the halogen.

More recently, catalysts based on copper[11,12] and palladium[13,15,28] have significantly improved the reaction yields for the formation of cyclic enamines and have provided access to new cyclic enamine scaffolds; however, they require multistep syntheses of the precursors required for the catalytic step. Additionally, the scalability of these reactions has not been determined, and the combined cost of the catalyst and multiple step synthesis of the precursor molecules can be prohibitive

[a] *Department of Chemistry, Stony Brook University, Stony Brook, New York, 11794, United States.*
[b] *Institute for Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, New York, 11794, United States*
Email: Scott.Laughlin@StonyBrook.edu
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when multigram quantities of cyclic enamines like **1** and **2** are required.

Thus, in our initial foray into the synthesis of enamines **1** and **2**, we explored the scalability of a metal-catalysed Ullman-type coupling, recently described by Li and co-workers[11], to produce protected enamine **6a** in six steps from commercially available 3-Butyn-1-ol (Fig. 2). Our initial attempt to synthesize the enamine **6a** was successful on the 100–150 mg scale, with yields of 90–92% for the final step, consistent with those reported by Li and co-workers, and an overall yield of 34–39% over six steps. However, five separate attempts to scale up the preparation of enamine **6a** to 500 mg scale quantities resulted in significant loss of material in the final copper-mediated coupling step, with yields of 45–53%. Our attempts to improve the yield for the copper catalysed coupling by optimizing the reaction duration, temperature, or amount of catalyst did not improve the yield. An extensive survey of the literature for alternative, gram-scale syntheses of molecules like cyclic enamines **1** and **2** did not yield useful synthetic precedents, so we devised the strategy described in this report for the large-scale synthesis of molecules similar to protected enamine **6a**.

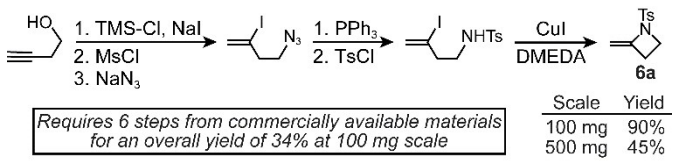
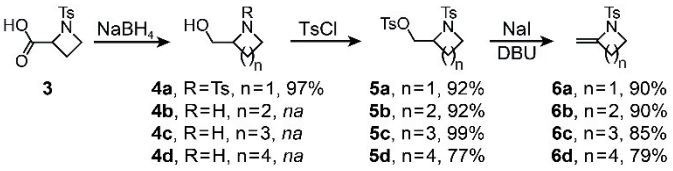


Fig 2. Initial attempts to synthesize the protected enamine **6a** in six steps were high yielding only at 100–150 mg scale. The reaction yields were significantly reduced upon scale up.

In our search for suitable starting materials for these transformations, we were intrigued by the possibility of leveraging economical, alcohol-based substrates for alkene production via a straightforward elimination reaction. Surveying the literature for N-heterocyclic rings with a methylene alcohol on the α-position, we identified prolinol, a commercially available inexpensive alcohol analogue of the amino acid proline, as an ideal substrate for our initial attempts to incorporate the alkene functionalization to form protected enamine **6b** (Scheme 1). Importantly, formation of an alkene adjacent to a nitrogen atom can lead to an imine rearrangement product, which can be suppressed by protecting the nitrogen with an electron withdrawing protecting group. Thus, we chose to begin with the electron withdrawing tosyl group for nitrogen protection prior to establishing the applicability of the approach to more conventional, and less electron withdrawing, nitrogen protecting groups.

Exploration of this synthetic route began with the synthesis of the N,O-bistosylated prolinol **5b** (Scheme 1) in one step from prolinol using TsCl in 94.4% yield (1.0 g scale with respect to prolinol). As expected for this reaction, the yield was consistent upon scaling up to the multigram scale (13.0 g scale with respect to prolinol, 91.7% yield). Next, we performed the elimination to obtain N-tosyl protected enamine **6b** using *in situ* activation with NaI in presence of the bulky base DBU under refluxing conditions, a method previously developed by Maier and co-workers for olefin syntehsis[29]. Our initial attempt afforded the 5-membered enamine **6b** in 92% yield (1.0 g scale). Importantly, we observed consistent reaction yields upon scaling up this reaction (37.0 g scale, 89.6% yield). Repeating this reaction three more times with different batches of **5b** on different days provided similar yields for **6b** (88–93% yield).

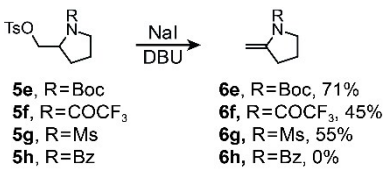


Scheme 1: Synthesis of N-tosyl protected enamines **6a–d** in multigram-scale quantities using inexpensive and commercially available reagents.

Buoyed by the initial success of this strategy to prepare gram-scale quantities of enamine **6b** in high-yields, we tested its generality in the preparation of cyclic enamines containing varying ring sizes (Scheme 1, compounds **6a–d**). We synthesized N,O-bistosylated compounds **5a** and **5c** starting from the relatively inexpensive and commercially available 2-azetidinecarboxylic acid or piperidine-2-methanol. For **5a**, we prepared the N-tosyl protected **3** in 95.2% yield (Scheme 1, ESI†). Subsequent reduction of the carboxylic acid group using $NaBH_4$ afforded the alcohol **4a** in 97% yield. Compound **4a** was then N,O-bistosylated using TsCl to obtain **5a** in 92% yield**.** N,O-bistosylated **5c** was obtained in one step using TsCl in 99.6% yield. Subsequent elimination of the tosylate under the above-mentioned conditions afforded the enamines **6a** and **6c** in 90% (30 g scale) and 85% (18.0 g scale) yields respectively. Further, we also tested this strategy for the seven-membered ring **4d**. N,O-bis-tosylation afforded **5d** in 77% yield, which, upon subsequent elimination, afforded enamine **6d** in 79% yield.

With an inexpensive two to four-step synthesis for enamines **6a–d** in hand, we challenged the scope of this strategy by testing the effect of alternative N-protecting groups on the stability and yields of these N-protected enamines. Importantly, the strength of the electron withdrawing nature of the N-protecting group has been shown to greatly affect the synthetic yields of enamines in previously-described methods[10]. For example, when the enamine **6a** was synthesized by Li and co-workers using their Ullman-type coupling strategy (Fig. 2) the yield for enamine formation reduced by half when Boc was used for N-protection instead of tosyl[10]. Additionally, most of the reported procedures for cyclic enamine syntheses have used only tosyl-protection of the amine[7,10–13,28], so the stability and yields for the formation of N-protected enamines with other strategies are unknown.

Scheme 2: Use of alternative N-protecting groups for synthesis of enamines **6e–h** in multigram-scale quantities.



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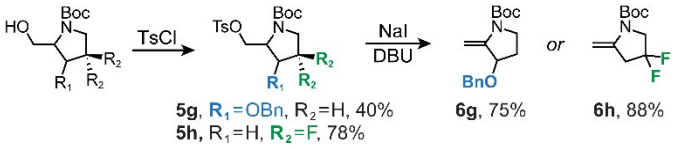
Using the same reaction conditions employed for the N-tosyl protected compound **5a–d**, we attempted eliminations of activated alcohol analogues of N-boc, N-trifluoroacetamide, N-mesyl, and N-benzoyl prolinols **5e–h** (Scheme 2). N-boc, N-trifluoroacetamide, and N-mesyl tosylated prolinols (Scheme 2, ESI†) afforded the Boc protected enamine **6e** and the volatile enamines **6f** and **6g** in 71 % (15 g scale), 45% (5 g scale), and 55% (2.5 g) yields respectively, whereas the Bz-protected activated alcohol **5h** was not stable to the elimination conditions and produced no observable enamine product **6h**. Further, tosylation of trityl protected prolinol to obtain N-trityl enamine was unsuccessful, possibly due to the steric hindrance provided by the bulky trityl group. Importantly, the reaction's compatibility with deprotection conditions for removal of protecting groups that are gentler than Ts provides a significant advantage over strategies that require Ts protection, especially when using these enamines as precursors for sensitive or complex targets.

We next explored the enamine formation's compatibility with substitutions around the pyrrolidine ring (Scheme 3). Towards this, we synthesized the tosylated alcohol analogues of N-boc benzylether pyrrolidine **5i** and N-boc difluoropyrrolidine **5j** from the corresponding alcohols in 40% and 78.3% yields respectively. Subsequent elimination produced the enamines **6i–j** in 75% and 87.5 % yields. Compatibility of this NaI/DBU-mediated elimination with heteroatom substitutions at different ring position should be straightforward to extend to other ring sizes and substitutions for generating a diverse array of enamines.

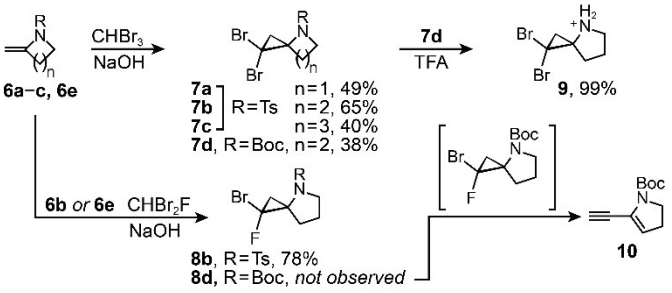


Scheme 3: Tolerance towards ring substitutions on the synthesis of cyclic enamines **6i–j**.

With access to multigram-scale quantities of desired enamines, we were interested in exploring the conversion of cyclic enamines to 3-N spirocyclopropanes (*i.e.*, 4-azaspiro[2.n]alkanes) via dibromocarbene addition, and then, potentially, to 3-N spirocyclopropenes (*i.e.*, 4-azaspiro[2.n]alkenes). As described above, 4-azaspiro[2.n]alkyl systems have utility as enzyme inhibitors[17,18], interesting monomers for poly-cyclopropane-based materials[19–21], and reagents in the biorthogonal cyclopropene-tetrazine[22–24] ligation. To the best of our knowledge, there are only a handful of reports describing the synthesis of 4-azaspiro[2.n]alkanes. Most of these strategies utilized carbenoid insertion on lactams or cyanoesters using a combination of Grignard reagents and titanium catalysts[30–33]. Others utilized the cyclization reaction between an amine and nitrile present on a cyclopropane ring using a strong base[17], carbenoid insertion on enamines flanked by aromatic rings using zinc catalyst[34], or palladium-catalysed alkene and isocyanate reaction[35].

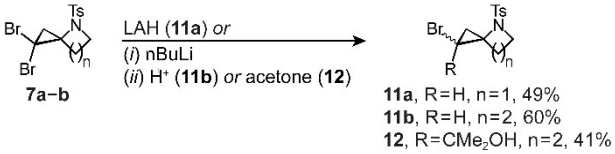
We employed the cyclic enamines in the preparation of 4-azaspiro[2.n]alkanes by insertion of a dibromocarbene generated using bromoform and NaOH (Scheme 4). Both the N-tosylated enamines **6a–c** and N-boc enamine **6e** produced the corresponding dibromo-4-azaspiro[2.n]alkanes **7a–d** in 49%, 65.2%, 40% and 37.6% yields respectively, and boc deprotection of **7d** proceeded in excellent yield (99%) to the free amine cyclopropane **9**. To the best of our knowledge, this is the first report of dibromo-4-azaspiro[2.n]alkanes . Furthermore, **7a** adds another entry to the short list of 4-azaspiro[2.n]alkanes with a spiro[2.3]hexane spirocyclic system.

We also explored cyclic enamine conversion to a mixed bromo-fluoro-cyclopropane. As expected, the tosylated enamine **6b** formed the desired 1-bromo-1-fluoro-4-azaspiro[2.4]heptane **8b** in 78% yield. However, subjecting the weaker electron withdrawing N-boc-protected enamine **6e** to base-mediated bromofluorocarbene insertion resulted in a rearrangement-elimination to generate **10**. Ultimately, having access to the halogen-containing synthons (**7a–d**, **8b**, and **9**) opens the door for further functionalization with these N-heterocycles.



Scheme 4: Cyclic enamines **6a-d** provide access to 4-azaspiro[2.n]alkane synthons.

In addition to the dibromocyclopropanes **7a–d**, the corresponding monobromocyclopropanes present useful substrates for additional functionalization of the scaffold. Accordingly, we explored the conversion of dibromo precursors to the corresponding monobromo cyclopropanes. We evaluated several strategies for the reduction of dibromocyclopropane **7b** to **11b** (Table **S1**, ESI†). Importantly, this reaction required complete consumption of the dibromo starting material for purification of the monobromo product as they have the same retention factor on silica gel in all solvent systems tested. The best strategy employed lithium-halogen exchange using n-BuLi at -85 °C and subsequent quenching with a proton source like ammonium chloride to produce **11b** in 60% yield (Scheme 5). These conditions applied to compound **7a** produced the azetidine analogue bromo-4-azaspiro[2,3]hexane **11a** in 49% yield.



Scheme 5: Spirocyclic 3-N dibromocyclopropanes can be converted to corresponding monobromo versions with added functionalization.

Finally, we were interested in determining the ability of these monobromo spirocyclopropanes to produce the corresponding, highly-strained 4-azaspiro[2,n]alkene. We subjected **11b** to potassium tert-butoxide in an effort to achieve the elimination, but instead produced a complex mixture of products that could not be identified. Subjecting the spirocyclic dibromo-4-azaspiro[2,4]heptane **7b** to the similar elimination resulted in the alkyne rearrangement product, dihydropyrrole derivative **S2** (Scheme 9, ESI†). This ring opening rearrangement is thought to proceed via an electro deficient intermediate[36], so we attempted the elimination with electron withdrawing fluoro substitution on the cyclopropene ring **8b** only to produce the alkyne rearrangement product **S2** again. We further increased the electron withdrawing nature of the substitution by creating the difluoro substituted spirocyclopropane using enamine **6j** (Scheme 3). However, subjecting the enamine **6j** to carbene addition produced the fluoro-eliminated pyrrole **S1** (Scheme 5, ESI†) as the major product. Previous reports have observed that addition of alkyl groups can impart stability[37] to cyclopropenes in solution, so we attempted the elimination with a monobromocyclopropane bearing a bulky tertiary alcohol group **12**, which resulted in the formation of the allene rearrangement product, tetrahydropyrrole derivative **S3** (Scheme 9, ESI†). Finally, we explored elimination with N-trifluoroacetate **6f**, a substrate bearing more heavily electron withdrawing N-protecting group. In this case, the reaction produced a crude reaction mixture with a characteristic cyclopropene peak in the ^{1}H NMR spectrum at 6.4 ppm. However, attempts at purification via Flash chromatography resulted in isolation of only the alkyne rearrangement product. These results suggest that forming a 4-azaspiro[2.n]alkene system requires the addition of stronger electron withdrawing components to promote long-term stability, which may be accomplished by appending electron withdrawing groups to positions closer to the quaternary carbon that is expected to form the offending electron deficient intermediate.

Conclusions

We have devised an inexpensive, catalyst-free, multigram-scale and high yielding synthesis of protected cyclic enamines with varying ring sizes. Additionally, we described a route for the preparation of pharmacologically relevant 4-azaspiro[2.n]alkanes with an azetidine ring. This route produced novel dihalo and mono-halo 4-azaspiro[2.n]alkanes, which provide possibilities for further functionalization using established halide chemistry.

Conflicts of interest

There are no conflicts to declare.

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