Rapid Construction of Tetrahydropyridine Scaffolds via Formal Imino Diels-Alder Reactions of Schiff Bases and Nazarov Reagents

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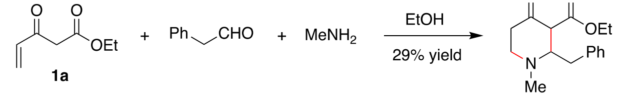
Described is a one-flask, two-step method for the synthesis of highly functionalized piperidines. The process involves formal [4+2] cycloadditions of Schiff bases and Nazarov reagents, followed by facile elaborations of the initial cycloadducts. Notably, these aza-annulations are facilitated by protic solvents and proceed smoothly under ambient conditions, without other additives. The synthetic utility of this annulation protocol is further showcased through a concise, convergent synthesis of (±)-tetrabenazine.

Introduction

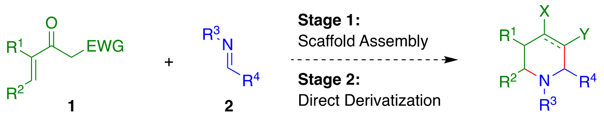
The search for small organic molecules possessing useful pharmacological properties drives much of the research effort of organic and medicinal chemists.[1] Of primary importance in this pursuit is the availability of reliable synthetic methods—processes that are operationally simple and efficacious for a broad spectrum of substrates—for the synthesis of the types of bonds and fragments that are found in molecules of biomedical interest. A subunit that is frequently encountered in bioactive molecules is the heterocycle piperidine. Given its presence in several classes of privileged chemotypes,[2] considerable effort has been devoted to the development of general routes to this heterocycle, and an assortment of methods have emerged.[3] The importance of piperidines combined with our interest in the development of reactions that can be enabled by chiral hydrogen bond donors[4] motivated an exploration and refinement of the Hohenlohe-Oehringen reaction. This little-studied process conjoins a Nazarov reagent (e.g., **1a**) with an imine to afford the product of what is formally an imino Diels-Alder reaction.[5] We have carefully examined and greatly expanded the efficacy of this useful reaction and describe below an operationally simple, two-stage protocol for the synthesis of a variety of piperidine-based compounds, as well as the successful implementation of the method for the efficient synthesis of (±)-tetrabenazine.[6]

Representing activated forms of methyl vinyl ketone, Nazarov reagents have proven to be highly versatile reactants that have enabled the development of numerous carboannulation reactions.[7] Among the few applications of these reagents for heterocycle synthesis is the pioneering report by Hohenlohe-Oehringen, who described a single example that coupled Nazarov reagent **1a** with methylamine and phenyl acetaldehyde to directly furnish a substituted 4-piperidone, albeit in a modest isolated yield (Scheme 1).[8] In a later, specialized application, van der Gen and co-workers reported the reaction of the preformed Schiff base of salicylaldehyde and methyl amine with a Nazarov reagent to provide the piperidine nucleus, through what amounts to a formal imino Diels-Alder reaction.[9] A limited number of related annulation processes with selected substrates have also been described in seminal papers.[10] Although narrow in overall scope, these early applications augured well for the development of a general aza-annulation route to various piperidine derivatives, with the ultimate objective of developing an enantioselective method to such compounds. We summarize below our extensive studies on the breadth and capability of the Hohenlohe-Oehringen aza-annulation.

(a) Hohenlohe-Oehringen's aza-annulation



(b) Proposed two-stage, diversity-oriented strategy



Scheme 1 Formal Imino Diels-Alder Reaction with Nazarov Reagents.

Results and discussion

Our initial efforts were directed at developing an optimized, reliable protocol for carrying out the aza-annulation reaction. Using imine **2a** as a model substrate, we examined its reaction with Nazarov reagent **1a** under a variety of conditions,

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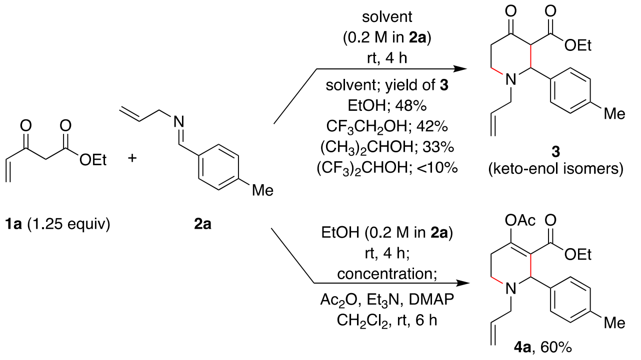
monitoring the reaction progress by ^{1}H NMR.[11] While the ring formation proceeded in both polar and nonpolar solvents, protic solvents gave a faster reaction with a cleaner product profile. Of the many common alcohol solvents that were examined (e.g., EtOH, *i*-PrOH, TFE, and HFIP), the best result was obtained with ethanol, which gave 4-piperidone **3**, as a mixture of *cis*/*trans*-keto isomers and enol tautomer, in 48% isolated yield (Scheme 2). This simple method unifies two readily available fragments under remarkably mild conditions (at ambient temperature and with no additives). In order to circumvent complications associated with purifying the isomeric products, the volatiles were removed and the crude product was subjected directly to acetylation, which afforded acetate **4a** in 60% isolated yield.



Scheme 2 Protic Solvent-Mediated aza-Annulation Reaction and Facile Derivatization to Enol Acetate.

The two-part protocol allowed facile access to a collection of tetrahydropyridines decorated with diverse functionalities, as summarized in Figure 1. Reactions of Nazarov reagent **1a** and Schiff bases with distinct steric and electronic properties revealed some general trends in reactivity. For imines of aromatic aldehydes (R^5 = Ar), the results (**4a**-**f**) showed that electron-withdrawing groups on the aryl moiety are advantageous; however, substituents at the *ortho* position slightly decreased the overall efficiency of the process. As expected, steric bulkiness around the imine nitrogen negatively impacted the outcome of the reaction. Reactions with imine substrates bearing benzyl, 4-methoxybenzyl, and long-chain alkyl groups (**4g**-**i**) progressed more slowly and required additional equivalents of Nazarov reagents to achieve full conversion compared to those with an ally group (**4a**-**f**). Unsurprisingly, *N*-methyl and *N*-propargyl Schiff bases (products **4j** and **4k**, respectively) reacted similarly to those possessing an allyl group, and gave products in good yields. The reaction sequence also enabled the synthesis of α-heteroaryl-substituted piperidines (**4l**-**n**). Only one imine of an α,β-unsaturated aldehyde was examined. The reaction of **1a** with the allyl-imine of cinnamaldehyde gave piperidine **4o** in 27% yield, accompanied by intractable byproducts. Incorporation of a cyclopropyl group, as seen in azacyclic compound **4p,** proved uneventful and afforded piperidine **4p** in good yield.

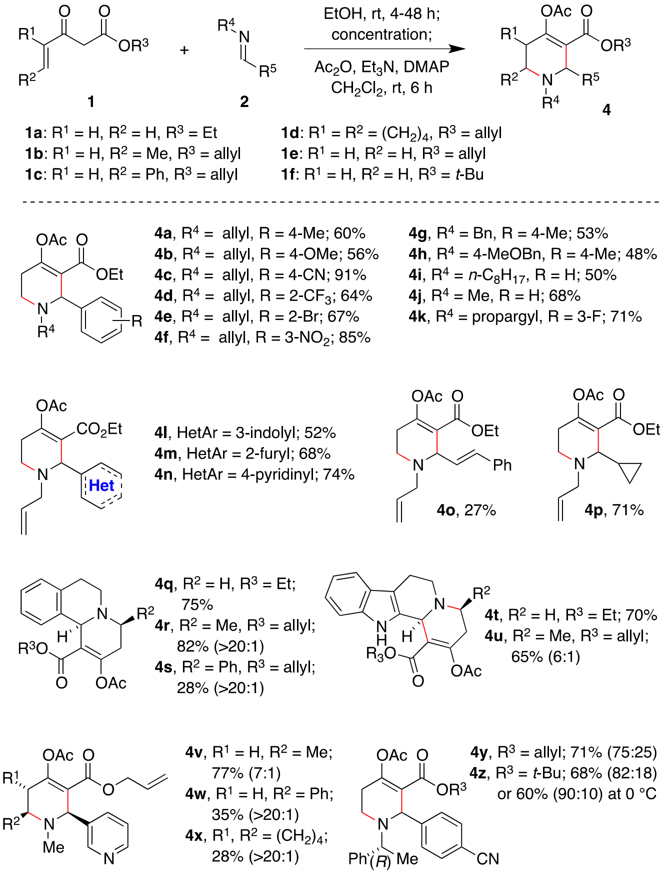
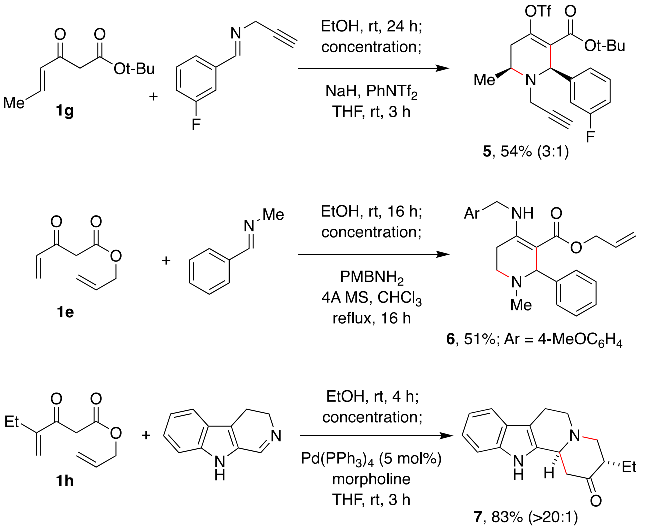


Figure 1. Scope of Two-Step Synthesis of Highly Functionalized Tetrahydropyridines.

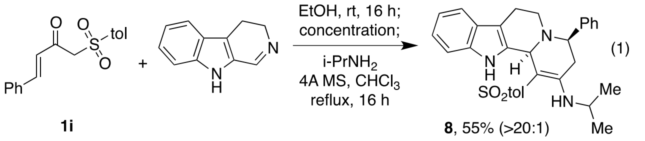
To further explore the capability of the cyclization sequence, we examined the reaction of bi- and tricyclic imines with different Nazarov reagents. Reagent **1a** reacted smoothly with 3,4-dihydroisoquinoline, to afford tricycle **4q** in good yield. Even better outcome was observed with the β-methyl-substituted Nazarov reagent **1b** (R^2 = Me, R^3 = allyl), which afforded product **4r** with nearly complete diastereoselectivity. On the other hand, reaction progress was diminished considerably by having an aryl substituent at the β position of the reagent (see **4s**). Gratifyingly, here too the product was formed with excellent diastereoselectivity. The established protocol could be translated easily to a dihydro-β-carboline system, thereby opening access to tetracyclic products.[12] The reactions of Nazarov reagents **1a** and **1b** with the unprotected 3,4-dihydro-β-carboline gave tetracycles **4t** and **4u**, respectively, in good yields, the latter being formed with good diastereocontrol. Applying the two-step sequence to the *N*-methylimine of 3-pyridinecarboxaldehyde and a series of Nazarov reagents delivered compounds possessing an anabasine ring skeleton in good to excellent diastereoselectivity (**4v-4x)**. As observed earlier, β-phenyl-substituted Nazarov reagent **1c** gave the cyclization product in low yield, but with nearly complete diastereoselectivity. The use of a Nazarov reagent wherein the alkene portion is constrained in a six-membered ring produced the highly functionalized, hydroquinoline product **4x** as a single diastereomer. The synthesis of **4x** constitutes a straightforward entry to a platform that fuses the hydroquinoline and anabasine features.[13] Next, we investigated asymmetric variants of this protocol based on a chiral auxiliary approach. With a chiral Schiff base derived from (*R*)-(+)-methylbenzylamine, the annulation reaction proceeded with higher diastereoselectivity when the Nazarov reagent contained a *t*-butyl ester (**4y**) rather than an allyl ester (**4z**); the diastereocontrol for the formal [4+2] reaction was even more pronounced at 0 °C, though necessitating a longer reaction time.

The formal aza-cycloaddition reaction can be coupled with useful functional group manipulations to provide expedient access to various building blocks for synthesizing piperidine derivatives. Scheme 3 summarizes selected strategic transformations that can be carried out in a one-flask operation on the β-keto-ester intermediate. Thus, subjection of the β-keto-ester intermediate to triflation conditions, afforded compound **5**, a versatile compound for an assortment of transition metal-catalyzed coupling reactions. Vinylogous carbamate **6**, obtained on condensation of keto-ester intermediate with an amine, can be a competent reaction partner in divergent heterocycle synthesis.[14] Deallylative-decarboxylation of the aza-annulation product can provide 4-piperidones, as demonstrated by the formation of **7**, which has been employed as a general intermediate in the total synthesis of Calabash curare alkaloids.[15]

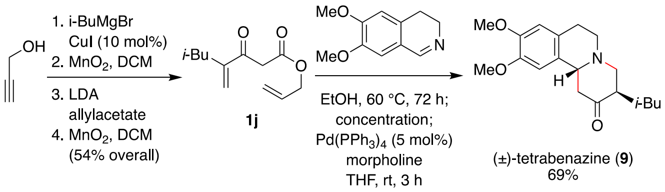


Scheme 3 Sequencing the Formal Imino Diels-Alder Reaction with Selected Synthetic Transformations.

A modified Nazarov reagent **1i** can also be utilized in the two-step sequence, delivering vinylogous sulfonamide **8** in moderate yield and excellent diastereoselectivity (Eq. 1). To our knowledge such Nazarov reagents have not previously been used in the Hohenlohe-Oehringen reaction.

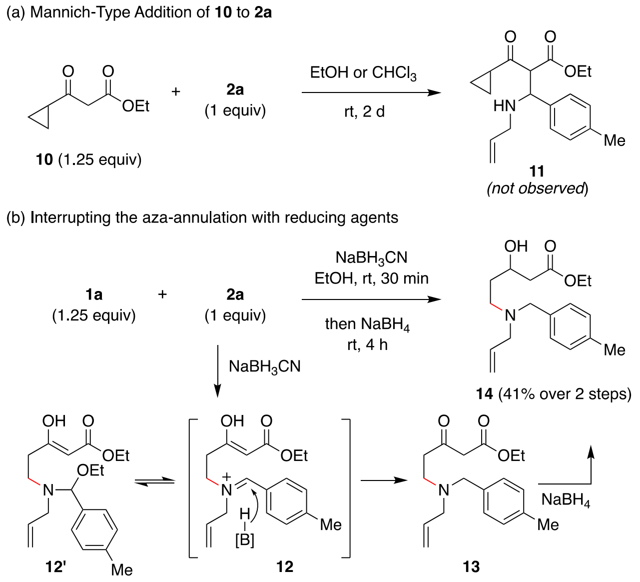


To further illustrate the synthetic utility of this methodology, we have carried out the synthesis of (±)-tetrabenazine (TBZ), which is used clinically for the treatment of chorea associated with Huntington's disease.[16, 17] The formal cycloaddition reaction of 6,7-dimethoxy-3,4-dihydro-quinonline and **1j**, readily prepared from propargyl alcohol in four steps, followed by Pd(0)-catalyzed deallylative-decarboxylation reaction, provided the desired target as a single diastereomer (Scheme 4). Unlike the reactions with simpler Nazarov reagents, the formal imino Diels-Alder reaction in this case required heating to 60 °C. The convergent route to TBZ illustrated herein provides new opportunities for the synthesis of novel analogs of this useful medicinal agent.



Scheme 4 Concise Synthesis of (±)-Tetrabenazine from Propargyl Alcohol.

The order of bond-forming events of the title reaction has been the subject of some speculation in the literature. Van der Gen has proposed that the reaction "likely proceeds via a Mannich reaction…with concomitant ring closure by conjugate addition," implying an imino-hetero-Diels-Alder reaction.[9] On the other hand Oehlschlager and Itoh have suggested that the reaction probably proceeds by an intermolecular aza-Michael addition followed by a Mannich-type cyclization.[10b,c] To gain insight into the reaction course, we examined the feasibility of a Mannich-type reaction of Schiff base **2a** and cyclopropyl ketoester **10**, whose steric and electronic properties are expected to be analogous to Nazarov reagent **1a**. Upon subjection of ketoester **10** and imine **2a** to the standard conditions, none of adduct **11** was observed by NMR, and the two reactants remained intact under the reaction conditions (Scheme 5). On the other hand, the putative iminium intermediate **12** derived from the intermolecular aza-Michael addition could be arrested by reducing agents to give the acyclic tertiary amine **13**, which was seen in the crude mixture.[18] As compound **13** was not suitable for column purification, it was further reduced to alcohol **14**, which was obtained in 41% yield over two steps. These observations indicate that protic solvents facilitate the aza-Michael addition of imine to the Nazarov reagent through a hydrogen-bonding network.[19]



Scheme 5 Preliminary Mechanistic Elucidation.

Conclusions

In conclusion, we have described here a series of operationally simple, modular synthetic sequences to piperidine derivatives from readily available Nazarov reagents and Schiff bases. The scope and utility of this aza-annulation reaction, rooted in the original report by Hohenlohe-Oehringen, were significantly broadened and a protocol was developed to transform the initial cyclization products to stable enol acetate derivatives. The utility of the formal imino Diels-Alder reaction was illustrated through a concise synthesis of (±)-tetrabenazine, which proceeded in 37% overall yield from inexpensive starting materials. Preliminary investigations on the order of the bond-forming events suggests an aza-Michael addition, facilitated by hydrogen bond activation, as the first elementary reaction step. This mechanistic foundation may help to guide the development of the asymmetric version of this reaction, potentially mediated by chiral hydrogen bond donor or Brønsted acid catalysts.

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Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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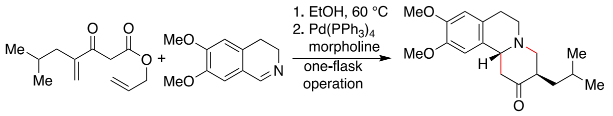

(±)-tetrabenazine; 69% yield, dr >20:1
30 other examples; yields up to 91%

A collection of piperidine derivatives including tetrabenazine was synthesized via aza-annulation of Nazarov reagents and Schiff bases in protic solvents.