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Unstabilized azomethine ylides for the stereoselective synthesis of substituted piperidines, tropanes and azabicyclo[3.1.0] systems

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Abstract

Acid treatment of densely substituted 2-silyl-1,2-dihydropyridines provides a new and convenient entry to reactive azomethine ylides that can (1) be protonated and reduced with high stereoselectivity to give piperidines, (2) participate in [3+2] dipolar cycloaddition to give tropanes, and (3) undergo a Nazarov-like 6- π electrocyclization that upon reduction give 2-azabicyclo[3.1.0] systems.

Nonaromatic nitrogen heterocycles such as piperidines, tropanes and pyrrolidines are valuable, ubiquitous structural motifs in biologically active alkaloids as well as drugs that have had a major impact on disease.¹ While C-H bond functionalization strategies have been extensively applied to the synthesis and elaboration of aromatic nitrogen heterocycles,² few applications to nonaromatic frameworks have been reported.³ Recently, we disclosed a highly diastereoselective process that enables the formation of densely substituted tetrahydropyridines^{4,5} from α,β -unsaturated imines and alkynes using Rh(I) catalyzed C-H activation⁶ (Scheme 1). A current limitation of this process is the requirement that internal alkynes be used, which necessarily introduces substitution at the 6-position. Terminal alkynes would be attractive coupling partners but are not viable due to competitive homocoupling leading to complex mixtures of products.⁷ Herein, we report a strategy for using TMS acetylenes as terminal alkyne surrogates for the convergent assembly of diverse tetrahydropyridines with high stereo- and regiocontrol. This class of alkynes provides access to piperidines with a substitution pattern commonly found in drugs and natural products.⁸ Moreover, mechanistic inquiry reveals that the intermediate silyldihydropyridine can function as a new and convenient azomethine ylide precursor enabling rapid entry into highly substituted tropanes, and through an unprecedented rearrangement, 2-azabicyclo[3.1.0] systems.

Treatment of imine **1** (eq 1) with 1.5 equiv of 1-phenyl-2-trimethylsilylacetylene, 2.5 mol % of [RhCl(coe)₂]₂ and 5 mol % of 4-Me₂N-C₆H₄-PEt₂ in toluene (1 M) at 100 °C for 1 h resulted in alkenylation to give azatriene **2** that undergoes a 6- π electrocyclization *in situ* leading to the clean formation of silyldihydropyridine **3** as a single detectable regioisomer,

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ASSOCIATED CONTENT

Supporting Information. Full experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

as assessed by ^1H NMR. When the reduction sequence was carried out according to previously optimized conditions (HOAc and $\text{NaBH}(\text{OAc})_3$ in $\text{MeOH}/\text{PhCH}_3$ from 0°C to rt),⁴ desired product ($\pm$)-**4** was formed in modest yield and with a considerable amount of olefin isomerization (7:1 mixture of inseparable isomers).

Investigation of different acids and hydride sources established that direct addition of $\text{Me}_4\text{NBH}(\text{OAc})_3$ in CH_2Cl_2 followed by $(\text{PhO})_2\text{PO}_2\text{H}$ to the Rh(I)-catalyzed reaction mixture provided clean formation of ($\pm$)-**4** in excellent overall yield as a single observable diastereomer and regioisomer (eq 1). The relative configuration of ($\pm$)-**4** was determined by single crystal X-ray analysis of the hydrochloride salt.⁴ This stereoselective protonation/reduction sequence proceeds with concomitant cleavage of the trimethylsilyl moiety to formally introduce a terminal acetylene unit with complete regiocontrol in one pot from the TMS acetylene and imine starting materials. This strategy consequently addresses a major synthetic limitation to our previously published reports.

(1)

An important feature of this approach is the vast number of readily available TMS acetylene and α,β -unsaturated ketone inputs that enable the rapid assembly of a range of piperidine analogs. To this end, a number of TMS acetylenes and α,β -unsaturated imines have been surveyed to establish broad reaction scope (Table 1). Alkyne components containing electron-rich and -deficient aromatic as well as heteroaromatic groups are tolerated and result in the desired tetrahydropyridines in excellent yield and diastereoselectivity (**9a–d**). Alkynes bearing aliphatic groups also react efficiently under the reaction conditions (**9e,f**). Furthermore, functional groups such as Boc-protected primary amines (**9h**), phthalimides (**9g**), and silyl ethers (**9i**) that are sensitive to either strongly acidic or reducing conditions are viable coupling partners for this process and provide a platform for further diversification.

The substitution pattern of the α,β -unsaturated imine was also explored. Imines bearing no substitution in the β -position (**9j**) and differential substitution patterns (**9k**) react efficiently enabling the site-specific functionalization of the piperidine core. Furthermore, a piperidine bearing different substitution at each position of the ring (**9l**) could be constructed by appropriate choice of imine and acetylene inputs. Bicyclic tetrahydropyridines can be accessed from a cyclic α,β -unsaturated imine precursor (**9m–p**). Moreover, consistent with our previous work,⁴ this process is not restricted to benzyl imines as *N*-cyclopropylmethyl (**9o**) and *N*-cyclohexyl (**9p**) imines are also suitable directing groups.

While this method works exceedingly well for ketimine precursors, aldimine substrates underwent incomplete desilylation under the standard reaction conditions. We reasoned that the aldiminium intermediate is sufficiently reactive that hydride delivery to **8** ($\text{R}_3 = \text{H}$) competes with desilylation (vide infra). For these substrates, we found it beneficial to conduct the reaction in THF using pyridinium fluoride as the acid source to give the desired tetrahydropyridines **9q,r** with complete desilylation.

We envisioned that upon protonation of the dihydropyridine **7**, desilylation could occur through two possible reaction pathways (Scheme 2). In scenario A, iminium **8** would be reduced to **10** followed by protonation/desilylation to give the observed product **9**. Alternatively, **8** could undergo desilylation resulting in the intermediacy of unstabilized azomethine ylide **11**. Subsequent protonation followed by reduction of **11** would also account for the formation of the desired product. In support of pathway B, Padwa has leveraged species **12** to access unstabilized azomethine ylides under acidic conditions for [3+2]-dipolar cycloadditions.¹⁰ This class of dipoles has been widely utilized for the synthesis of substituted pyrrolidines including those found in natural products and drugs.^{11,12} However, approaches for generating more highly substituted azomethine ylides typically require the presence of a stabilizing electron withdrawing group.

To distinguish between the two proposed mechanisms, we first resubmitted a silyl-substituted tetrahydropyridine, isolated as a byproduct during early optimization experiments, to the (PhO)₂PO₂H and TMABH(OAc)₃ reaction conditions (eq 2). Cleavage of the silyl group was not observed ruling out pathway A.

(2)

We therefore set out to intercept the transient azomethine ylide in pathway B with a dipolarophile. In support of its intermediacy, direct addition of the [Rh]-reaction mixture containing crude DHP **3** to a solution of 1.2 equiv of (PhO)₂PO₂H and 2 equiv of dimethylacetylene dicarboxylate (DMAD) at 0 °C resulted in the clean formation of tropane **13a** (Table 2), which was characterized by 2D NMR spectroscopy and single crystal X-ray diffraction. While [3+2]-dipolar cycloadditions of azomethine ylides have been widely employed in pyrrolidine synthesis, relatively few examples that provide access to tropanes have been disclosed.¹³ Furthermore, dipole generation, which proceeds through protonation of the enamine followed by desilylation, represents a new entry into unstabilized azomethine ylides.

A number of substituted tropanes were then constructed using this new transformation, showing broad scope in both the imine and trimethylsilyl alkyne inputs (Table 2, **13a–e**). Utilization of the unsymmetrical alkyne methyl propiolate also resulted in moderate to good regioselectivity for the dipolar cycloaddition (**13f** and **g**), with the regioisomers readily separated by silica gel chromatography. This process represents a new strategy for rapid entry into structurally dense tropanes that would otherwise be challenging to prepare.

A subsequent investigation of the effect of acid strength on reaction yield uncovered an unanticipated reaction product (Scheme 3). Treatment of DHP-**3** with PhSO₃H in dichloromethane at room temperature resulted in an intractable mixture of products as determined by ¹H NMR. However, by adding PhSO₃H and Me₄NBH(OAc)₃ at –78 °C with slow warming to room temperature, a new product was formed in good yield. On the basis of extensive NMR spectroscopy, we assigned the structure as the 2-azabicyclo[3.1.0] system (±)-**15a**, which was unambiguously confirmed through single crystal X-ray diffraction of the hydrochloride salt. Use of an alkyl rather than an aryl substituted TMS acetylene input also provided the related bridged pyrrolidine **15b**, in a one pot process. This core structural motif

has significant relevance to drug discovery. For example, it was specifically introduced into the approved drug Saxagliptin to enhance metabolic stability.¹⁴

Variable temperature NMR was performed to gain insight into the formation of **15a** from **3**. The presence of 1.05 equiv of PhSO₃H resulted in the rapid and persistent generation of the *N*-protonated dihydropyridine **16** between –78 °C and –20 °C. This was converted to a complex mixture of products upon gradual warming between –20 °C and +23 °C. In the presence of Me₄NBH(OAc)₃, we observed the formation of iminium **17** starting at –20 °C. Upon warming to +5 °C, we observed the gradual formation of **15a**.

On the basis of these studies, we conclude that this reaction proceeds through *N*-protonation of the dihydropyridine followed by proton transfer to generate *C*-protonated ketiminium **17**. Assisted desilylation, either by the sulfate counteranion or hydride, induces a torquoselective disrotatory Nazarov-like¹⁵ 6- π electrocyclization to form enamine **18**,¹⁶ which could undergo subsequent stereoselective protonation and reduction resulting in the desired product **15a**. This serendipitous finding provides a new avenue for the preparation of highly substituted derivatives of this azabicyclic framework.

In summary, densely substituted 2-silyl 1,2-dihydropyridines are readily prepared from α,β -unsaturated imines and TMS acetylenes by a C-H bond functionalization and electrocyclization sequence. Without any purification or isolation, treatment with acid generates unstabilized azomethine ylides as versatile intermediates that lead to valuable nitrogen heterocycles. In situ protonation and reduction provides tetrahydropyridines with a substitution pattern matching that expected for terminal alkyne incorporation. Alternatively, azomethine generation in the presence of a dipolarophile provides highly substituted tropanes. Finally, by selectively tuning the acid in the protonation step, an unprecedented rearrangement was observed that can be used to produce 2-azabicyclo[3.1.0] systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. To the best of our knowledge, no other literature examples have been reported for intramolecular allylsilane additions to imines or carbonyls to give cyclopropyl amines or alcohols, respectively.

Previous work

This Work

Scheme 1.
Rapid entry into substituted piperidine, tropane and 2-azabicyclo[3.1.0] frameworks

Padwa's azomethine synthesis

Scheme 2.
 Proposed mechanistic pathways

Scheme 3.
 Nazarov-like electrocyclization

Table 1

Convergent assembly of piperidines with terminal acetylene equivalent.^a

^aYields correspond to isolated product after silica gel chromatography and represent overall yields from the imine precursor **6**. Diastereoselectivity was determined by ¹H NMR of the crude reaction mixture.

^bConducted using HF-pyridine in THF at 0 °C.

Table 2

Tropane synthesis via azomethine

^aYields correspond to isolated product after silica gel chromatography and represent overall yields from the imine precursor 6. Diastereoselectivity was determined by 1H NMR of the crude reaction mixture.

^bConducted at -78 °C in toluene.