

Tetronamides as Latent Acyclic Vinylogous Amides in Formal Aza-[3 + 3] Cycloaddition Reactions with α , β -Unsaturated Iminium Salts. An Unexpected Rearrangement and an Approach to Synthesis of Substituted Piperidines

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Received May 26, 2004

A detailed account regarding formal *aza*-[3 + 3] cycloaddition reactions of tetronamides with α , β unsaturated iminium salts is described here. This investigation uncovers regioisomeric cycloadducts that were not found in previous studies involving this formal cycloaddition and an unexpected rearrangement that led to pyridines and dihydropyridines. Both stereochemical and regiochemical issues raised in this study provide further mechanistic insights into this cycloaddition. With careful control of reaction temperatures, the desired formal cycloadducts are obtained. Ensuing transformation of these cycloadducts into functionalized piperidines establishes the concept of employing tetronamides as latent acyclic vinylogous amides for the formal *aza*-[3 + 3] cycloaddition.

Introduction

Annulations of vinylogous amides with α,β -unsaturated iminium salts provide a convergent and practical approach for synthesis of alkaloids.^{1,2} The formation of six-membered nitrogen heterocycles **3** [Figure 1] constitutes a formal *aza*-[3 + 3] cycloaddition³⁻⁵ because two of the five carbons along with the nitrogen atom originate from vinylogous amides **1** with the remaining three carbons from the α,β -unsaturated iminium salts.⁶ Specifically in our studies, α,β -unsaturated iminium salts **2** have been employed to afford exclusively 1,2-dihydropyridines **3** in a highly regioselective manner [Figure 1].⁷⁻¹⁰ The regiochemistry of our reactions is opposite from that



FIGURE 1. Overview of the formal [3 + 3].

of Hickmott–Stille's *aza*-annulation using acid anhydrides or chlorides.^{11–13} Mechanistically, we demonstrated that they proceed through a 6π -electron electrocyclic ring-closure of 1-azatrienes **4**^{7a,b,14,15} [derived from a Knoevenagel condensation], a process that can be rendered highly diastereoselective.^{7a,15a,16}

However, one severe limitation has remained in our formal aza-[3 + 3] cycloaddition. We have been unable

10.1021/jo049108d CCC: \$27.50 © 2004 American Chemical Society Published on Web 09/08/2004

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to carry out the transformation using acyclic vinylogous amides to construct dihydropyridines 5 as a single-ring system. We have attributed this limitation to the fact that the corresponding 1-azatrienes 4 are less constrained geometrically for the desired ring-closure, and given their reactive nature, they could competitively proceed through other reaction pathways.¹⁷ Given the significance of piperidinyl alkaloids,^{18,19} we have been developing a latent acyclic vinylogous amide to render our formal aza-[3+3] cycloaddition method amenable and practical for syntheses of piperidines. In this article, we disclose full details regarding the use of tetronamides as latent acyclic vinylogous amides, an unexpected rearrangement, and the feasibility of constructing piperidinyl derivatives.

Results and Discussions

1. Synthetic Feasibility, Scope, and Stereoselectivity. Although reactions of tetronic acid itself did not proceed well with α,β -unsaturated iminium salts **2** to

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TABLE 1.	Generality	of Aza-[3	+ 3]	Cycloadditions
Using Tetro	onamides			-



^a All reactions were carried out in EtOAc/toluene [2:3] at 120-150 °C in a sealed tube for 36-72 h unless otherwise noted. ^b Iminium salt was generated by addition of 2.0 equiv of piperidine to the enal at $-10\ \mbox{°C}$ in EtOAc. After stirring for 5 min, 2.0 equiv of Ac₂O was added and the mixture was heated at 80 °C for 1 h in a sealed tube before being transferred to the respective tetronamide. ^c Isolated yields only. ^d NA: not applicable. Ratios were determined by ¹H NMR. ^e An additional 10-38% of the regioisomer was also isolated. See Section 2. ^f In entries 7-16, the R* group denotes the corresponding chiral auxiliaries present in 17-20. ^g Heated at 180 °C. ^h Heated at 200 °C for 7 days. ⁱ Reaction took 96 h. ^j Heated at 170 °C for 96 h.

construct pyrans 6 en route to highly substituted dihydropyrans 7 [W = O in Scheme 1], we prepared a series of achiral [8A] and chiral [8B-E] tetronamides by condensing the corresponding amines with tetronic acid in refluxing toluene [Scheme 1]. The feasibility, scope, and stereoselectivity for reactions of tetronamides with α,β unsaturated iminium salts are summarized in Table 1.

It was quickly evident that reactions of various tetronamides **8A**–**E** with α , β -unsaturated iminium salts generated from aldehydes 9-12 were feasible. There were three features that captured our attention. First, yields

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are mostly poor to modest with the exception of aldehydes **9b** [entry 2], **9c** [entry 3], **10** [entry 4], and **12** [entries 6 and 16], which provided the desired cycloadducts in good yields. Yields are noticeably poor when using chiral tetronamides **8B**-**E** [entries 7–16] or aldehydes **9a** and **11** [entries 1 and 5].

Second, none of the chiral tetronamides **8B**–**E** [entries 7–16] were useful in providing reasonable diastereoselectivity, the best dr being 65:35 with **8C** and **8D** but again in poor yields [entries 10–15]. Chiral tetronamide **8B**, containing the auxiliary that was very useful in highly diastereoselective *aza*-[3 + 3] cycloadditions as reported previously,^{7a} provided cycloadducts in a stereorandom manner [entries 7–9].

Third, we found noticeable byproducts from reactions of **8A** with **9a**-**c** and **11** [entries 1–3 and 5]. Although these byproducts resembled the desired formal [3 + 3] cycloadducts [**13a**-**c** and **15**] with similar chemical shift patterns in ¹H NMR and fragmentation patterns in the mass spectrum, they are not the same. In addition, reactions of chiral tetronamide **8E** with **9a**-**c** [not shown in Table 1] provided no desired formal cycloadducts but unknowns that puzzled us for quite some time.

2. Regiochemical Issues. The aforementioned peculiarities led us to further examine the formal *aza*-[3 + 3] cycloaddition reaction of tetronamides more carefully. As shown in Scheme 2, in addition to desired cycloadducts **13a**-**c** [head-to-head: See the lower left box for definitions], formal cycloaddition reactions of tetronamide **8A** with iminium salts **21a**-**c**, generated from the corresponding aldehydes **9a**-**c**, provided the respective head-to-tail regioisomers **22a**-**c** as byproducts.

Regiochemistry was unambiguously assigned via positive and negative NOE experiments using both **13a** and **22a**.²⁰ While **13a**–**c** were likely derived from respective ring-closure of 1-azatrienes **23**, isolation of these regioisomers was surprising since we have not seen head-totail products in any of our previous formal *aza*-[3 + 3] cycloaddition studies. A closer examination revealed that this is a temperature-dependent phenomenon. When the SCHEME 3. Competing Experiment



reaction temperature was less than 130 °C, very little [<5%] regioisomers 22a-c were observed from their respective reactions, but when the temperature was greater than 130 °C, as much as 10-38% of 22a-c could be seen.

Retrospectively, if we had pursued this investigation first, we might have abandoned the entire methodology, since it would be no different from Hickmott–Stille's *aza*annulation, which provides exclusively head-to-tail regioselectivity. Consequently, we revisited our previous work by allowing vinylogous amide **24** to react with **9b** at a temperature greater than 150 °C [Scheme 3]. Only if we were very careful could we see the head-to-tail regioisomer **26** in the crude ¹H NMR and isolate it in 4.5% yield. This result reaffirms that reaction temperature is a critical factor and that when this reaction was first carried out in the range of 100 to <150 °C, we observed no significant amounts of any other regioisomers.⁷ We are not certain at this point why the reaction temperature is impacting the two reaction pathways.

Furthermore, when a mixed experiment was carried out using both **24** and **8A**, we found that at temperatures greater than 150 °C, the head-to-tail regioisomer **22b**, derived from reacting **8A** with **9b**, was consistently isolated in higher yields than **26**, deriving from vinylogous amide **24**. This suggests that for reasons unknown at this point, tetronamides such as **8A** are more prone than vinylogous amides such as **24** to annulate with α,β unsaturated iminium salts in a head-to-tail manner.

Mechanistically, regioisomers 22a-c could be derived from an initial *N*-1,2-addition of **8A** to give aminal **28** [Scheme 4]. A subsequent loss of an amino group would give the 3-azatriene **29**, and an ensuing pericyclic ring closure followed by an appropriate tautomerization would give the desired regioisomers **22a**-c. It could also be derived from an initial *C*-1,4-addition followed by an *aza*-[3,3] sigmatropic rearrangement to yield the same aminal

⁽²⁰⁾ The head-to-head regiochemistry resulting from formal *aza*-[3 + 3] cycloadditions of these tetronamides was also unambiguously assigned using the X-ray structure of the hydrogenated cycloadduct **16**. Please see Supporting Information for the X-ray information.







SCHEME 5. Formation of Pyridines



28. An alternative pathway from **28** would involve an intramolecular $S_N 2'$ addition followed by an appropriate tautomerization. These assessments are in accord with those described in Hickmott–Stille's *aza*-annulation.^{11–13}

3. An Unexpected Rearrangement. In addition to isolating the respective regioisomers **22b** and **22c** in reactions of tetronamide **8A** with aldehydes **9b** and **9c**, we found that when the reaction temperature was raised to 240 °C, the respective pyridines **30b** and **30c** accounted for the major mass balance [Scheme 5]. Pyridines **30b** and **30c** were initially assigned using NMR and mass spectroscopy but later unambiguously assigned on the basis of the X-ray structure of a related example.

These pyridines are likely derived from some kind of rearrangement of the desired formal *aza*-[3 + 3] cycloadducts because pericyclic ring closures of 1-azatrienes are completely reversible at temperatures as high as 240 °C.^{7a,21} We heated a sample of **13b** at 220–240 °C for 64 h and found exclusively **30b** in 55% yield. This experiment was actually designed originally to explore whether **13b** was equilibrating with **22b**. However, there was no such equilibration between these two regioisomers. Instead, we isolated only the pyridine product **30b**. This experiment thoroughly supports the notion that the pyridines were derived from the desired cycloadducts that were formed initially.

On the basis of these results, one can suggest that pyridine products **30b** and **30c** were mechanistically derived via an imine isomerization going from 1-azatriene



FIGURE 2. X-ray structure of 35c.

SCHEME 6. Mechanistic Model for the Pyridine Formation



SCHEME 7. Formation of Dihydropyridines



31 to 2-azatriene **32** [Scheme 6]. Subsequent pericyclic ring-closure of 2-azatriene **32** would lead to 2,3-dihydropyridine **33**, and upon aromatization at high temperatures, pyridines **30b** and **30c** could be obtained.

With an understanding of this rearrangement, we reexamined the unknowns isolated from the reactions of chiral tetronamide **8E** with **9a**-**c** [those that are not displayed in Table 1]. These unknowns turned out to be 1,2dihydropyridines **35a**-**c** derived from **9a**-**c**, respectively [Scheme 7]. An X-ray structure of compound **35c** was obtained to unambiguously identify these rearranged products [Figure 2]. The formation of **35b**-**c** could be rationalized in the same manner as described for **30b** and **30c** with the exception that the aromatization is arrested for **35b**-**c** leaving behind a quaternary carbon adjacent to the nitrogen atom.

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FIGURE 3. Stereochemical model.

Although we did not vigorously reexamine the other reactions involving chiral tetronamides **8B**–**D** at lower temperatures, it is reasonable to suggest that the generally observed poor yield is likely due to the formation of related dihydropyridine byproducts and/or regioisomers. This could be reasonable especially considering that most of these reactions had to be carried out at temperatures much higher than 130 °C. Ultimately, our work suggests that temperature is critical to controlling various reaction pathways and maximizing the formal *aza*-[3 + 3] cycloadditions to afford the desired cycloadduct as the major product.

4. Stereochemical Issues. The lack of diastereoselectivity using chiral tetronamides **8B**–**E** prompted us to revisit the stereochemical model proposed in our previous studies.^{7a,b} As shown in Figure 3, although the ring-closure is reversible at high temperature, and although the observed diastereoselectivity ultimately can be attributed to thermodynamic control, it is evident that a selective rotation of the C5–6 vinyl strand in 1-azatriene **39** also contributes significantly to the observed diastereoselectivity. Rotational preferences leading to stereoselective constructions of sp²- and sp³-hybridized stereocenters have excellent precedents in various pericyclic processes, and such stereoselectivity has been appropriately termed torquoselectivity.^{16,22}

We had proposed that 1-azatriene **39** assumes a conformation similar to that observed in an X-ray structure of the final product **40**-*major*,^{7a,b} and that prior to the ring-closure, the C2'-Ph ring is π -stacked underneath with the C5–6 vinyl strand. This results in two possible rotations for the C5–C6 vinyl strand in **39** during the ring-closure. Rotation **a** should be favored, leading to **40**-*major* [the minor isomer not drawn], while rotation **b** is less favored, for it leads to severe steric interaction between the R and the C2'-Ph groups.^{7a,b}

SCHEME 8. Attempts to Improve the Stereochemistry



However, in comparison with **40**, there is a loss in the selectivity for cycloadduct **42** derived from vinylogous amides containing a five-membered ring. To rationalize this loss, we had suggested that the steric interaction between the C2'-H and the C-10 methylene in 1-azatriene **39** [boxed] could be critical.⁷ To alleviate such steric interaction in **39** to give **40**-*major*, the C2'-Ph would need to be pushed further toward the C5–6 vinyl strand, leading to a greater biasing of the rotational preference in favor of direction **a**.

In the case of cycloadduct **42**, the corresponding interaction between the C2'-H and the methylene unit [boxed] in 1-azatriene **41** is diminished on the basis of molecular modeling, thereby leading to a diminished interaction between the C2'-Ph and C5–6 vinyl strand and the rotational bias. For reactions of **8B**, a similar rationale could be invoked using 1-azatriene **43**, but given the structural similarity between 1-azatriene **41** and **43**, we did not expect that the dr for **17a** would be as low as 55:45.

Nevertheless, this presents an opportunity to further examine our original mechanistic model. If we bulk up the methylene unit shown in the box of **43** to enhance its interaction with the C2'-H, the C2'-Ph group could again be closer to the C5–6 vinyl strand to enhance the rotational bias in favor of direction **a** to enhance the diastereoselectivity.

As shown in Scheme 8, chiral tetronamide 44 could be prepared in three steps [40% overall yield] from methyl α -hydroxy- α -methyl propanoic ester,²³ but its reaction with the iminium salt 21a [generated from 9a] provided the regioisomeric cycloadducts 45a and 45b in 25% yield with a ratio of 52:48. While the diastereomeric ratio is not all that surprising, the regioselectivity prompted us to speculate that the desired cycloadduct would have been much too congested. However, using chiral tetronamide 46 and iminium salt 21a also gave the undesired regioisomeric cycloadducts 47a and 47b in only 8% yield with a ratio of 52:48. These experiments unfortunately at this time do not provide conclusive support for the aforementioned mechanistic analysis. Identifying new insights to ultimately achieve highly stereoselective formal aza-[3 + 3] cycloaddition reactions using chiral tetronamides will remain as a future endeavor.

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5. Syntheses of Substituted Piperidines. To construct substituted piperidines, primary tasks are (1) to hydrogenate the C2-3 tetrasubstituted olefin and (2) to open the γ -lactone ring. These exercises were carried out using the aza-[3 + 3] formal cycloadduct **13b** [only one enantiomer is shown in Scheme 9 for clarity of the relative stereochemistry in later substrates].

As shown in Scheme 9, the C4-5 olefin in cycloadduct 13b was readily hydrogenated under standard conditions to give the unsaturated lactone 48 in 93% yield. We then ran into problems with the C2-3 olefin. We were able to initially hydrogenate the C2-3 tetrasubstituted olefin employing 60-80 psi H₂ to give lactone **49** as a single diastereomer with the best yield of 60%.²⁴ However, we soon found that the usage of Pd-C or $Pd(OH)_2$ was erratic, for the rate of the reaction varied greatly even when the pressure was elevated to 1500 psi, and the yield of 49 was quite unpredictable. When we switched to using PtO₂ as the catalyst,²⁵ the hydrogenation behaved more consistently and afforded 50 in 50% yield using only at 1 atm of H₂, but instead of a concomitant debenzylation, the phenyl ring was hydrogenated. The isomeric ratio of **50** was 9:1 in favor of an anti relative stereochemistry at C2 and C6 as shown with NOE experiments.

To complete the hydrogenation of the C2-3 olefin, the unsaturated lactone 48 was cleanly debenzylated using 60-80 psi H₂ to provide **51** in 83% yield [Scheme 10]. An ensuing hydrogenation of 51 employing PtO₂ as the catalyst and 1 atm of H_2^{25} led to 49 in 69% yield with a diastereomeric ratio of \geq 15:1. The relative stereochemistry of 49 was assigned using NOE experiments with the C2-C6 relative stereochemistry being syn. Reductive ring-opening of the lactone in 49 using LAH gave piperidine 52 in 83% yield as a single stereoisomer.

On the other hand, Dibal-H reduction of 48 followed by hydrogenation of the C2-3 olefin using 60-80 psi H₂ and Pd-C did give diol 53 in 67% yield with an isomeric ratio of \geq 15:1. The relative stereochemistry of **53** was assigned using NOE with C2-C6 being anti, and subsequent debenzylation afforded diol 54 with the complementary C2-C6 anti stereochemistry. These collective



FIGURE 4. Mechanistic model for stereoselective hydrogenations.

55d: conformer D



55c: conformer C



studies illustrate the concept of transforming these formal aza-[3 + 3] cycloadducts into piperidinyl derivatives and the concept of tetronamides serving as useful latent acyclic vinylogous amides. However, the relative stereochemistry observed deserves some comments as shown in Figure 4.

From our own previous work^{7a} and those reported in the literature,²⁶ when the **R** substituent on the nitrogen atom is not hydrogen, the conformer B [55b in Figure 4] can be favored, in which the *N*-**R** and C6-*n*-Pr group are anti or diaxial to alleviate the pseudo A^{1,2} strain [or the gauche interaction] between these two respective groups.²⁶ With the top face blocked by the pseudoaxial **R** group, which is more proximal than the pseudoaxial C6-n-Pr group, hydrogenation from the bottom face should give lactone 49 with C2 and C6 being anti. A similar analysis can be invoked using 56b to rationalize the observation of the anti relative stereochemistry at C2 and C6 in 53 [see inside the box].

49

⁽²⁴⁾ Debenzylated product 51 was also occasionally isolated in 16% yield.

^{(25) (}a) Akhrem, A. A.; Lakhvich, F. A.; Lis, L. G.; Pshenichnyi, V. N.; Arsen'ev, A. S. *Zh. Org. Khim.* **1980**, *16*, 1290. (b) Akhrem, A. A.; Lakhvich, F. A.; Lis, L. G.; Kuz'mitskii, B. B.; Mizulo, N. A.; Gorbacheva, I. A. Zh. Org. Khim. 1985, 21, 1348.

⁽²⁶⁾ Kolocouris, A.; Outeirino, J. G.; Anderson, J. E.; Fytas, G.; Foscolos, G. B.; Kolocouris N. J. Org. Chem. 2001, 66, 4989.

On the other hand, when $\mathbf{R} = H$, conformers A, C, and D [**55a**, **55c**, and **55d**, respectively] can dominate, with all three providing the top face as the relatively more open one.^{7a} Hydrogenation should then lead to lactone **49** with the complementary C2–C6 syn stereochemistry. Such a stereodivergence should be useful for natural product synthesis.

Conclusion

We have described here a detailed investigation of formal *aza*-[3 + 3] cycloaddition reactions of tetronamides with α , β -unsaturated iminium salts. In the process of this investigation, we uncovered interesting regioisomeric cycloadducts, which were not found in previous studies involving related formal *aza*-[3 + 3] cycloadditions, and unexpected rearrangements that led to pyridine and 1,2-dihydropyridine products. Both regiochemical and stereochemical issues raised in this study provide further

mechanistic insights into this formal *aza*-[3 + 3] cycloaddition. More importantly, it allowed us to recognize that when the reaction temperature is carefully controlled, the desired formal cycloadduct could be obtained in synthetically useful yields using tetronamides. Ensuing transformations of these formal cycloadducts into functionalized piperidinyl derivatives illustrate the concept of utilizing tetronamides as latent acyclic vinylogous amides for the formal *aza*-[3 + 3] cycloaddition.

Acknowledgment. R.P.H. thanks NIH [N.S.38049] for funding. We are grateful to Dr. L. G. Lis for the key suggestion of using PtO_2 as the hydrogenation catalyst.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, ¹H NMR spectra, NOE data, and X-ray information. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049108D