Published in final edited form as:
Org Lett. 2010 November 19; 12(22): 5174–5177. doi:10.1021/ol102193x.

Intramolecular Hydroamination of Dithioketene Acetals: An Easy Route To Cyclic Amino Acid Derivatives

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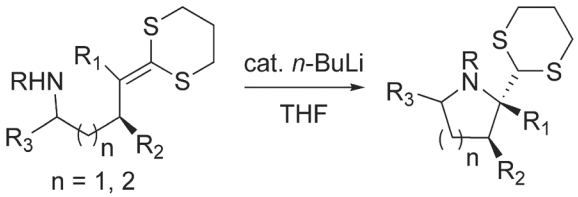
Abstract



Catalytic intramolecular hydroamination of dithioketene acetals was developed for the synthesis of cyclic amino acid derivatives. Triggered by the addition of a catalytical amount of *n*-BuLi, the reaction proceeds to give proline and pipecolic acid derivatives in excellent yields and diastereoselectivity.

Recently, we reported that the anodic coupling[1] of a dithioketene acetal and an amine provided an efficient route to cyclic amino acid derivatives[2–6] containing a tetrasubstituted α carbon atom (Scheme 1).[7,8] The reactions are intriguing because they utilize the cyclization to lower the oxidation potential of the substrate to a point lower than that of the product.[9] This avoids overoxidation of the product and allows for the use of the unprotected amine nucleophile. The reactions are compatible with the synthesis of both proline and pipecolic acid derivatives.

While these reactions are excellent for building amino acid derivatives with tetrasubstituted α carbon atoms, they fail when the tetrasubstituted α carbon is not required. For example, while the oxidation of substrate **1a** led to an 84% isolated yield of the corresponding proline derivative, oxidation of substrate **1b** led to none of the cyclized product (Scheme 2).[7]

Cyclic voltammetry data suggest both that cyclizations are very fast and that the difference between these two reactions does not result from the cyclization step.[7] The oxidation potential for the dithioketene acetal in **1a** is $E_{p/2}$ = +1.06 V vs Ag/AgCl.[10] Substrate **1a** has a potential of $E_{p/2}$ = +0.60 V vs Ag/AgCl, a 460 mV drop in potential from the isolated dithioketene acetal indicating a rapid cyclization. For comparison, the potential for substrate **1b** was measured to be $E_{p/2}$ = +0.54 V vs Ag/AgCl, again a large drop in potential that is indicative of a fast cyclization (the dithioketene acetal in **1b** has an $E_{p/2}$ = +1.10 V vs Ag/AgCl).

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Supporting Information Available: Full experimental and characterization data, copies of proton and carbon NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

A possible explanation for the failure of the reaction originating from **1b** is that it leads to an intermediate like **4** (Scheme 3) that suffers from the elimination of a proton to give a very electron-rich N-substituted dithioketene acetal (**5**). Once formed, **5** would undergo immediate oxidation leading to undesired products. Efforts to avoid this elimination during the electrolysis met with failure.

With this in mind, we looked for an alternative strategy for cyclizing substrates like **1b** and making amino acid derivatives that did not contain tetrasubstituted α carbons. To this end, an anionic hydroamination looked very attractive (Scheme 4).[11]

Deprotonation of the amine would lead to an anion (**6**) that can add across the double bond to lead to a dithiane-stabilized intermediate (**7**). In this case, the cyclized intermediate has the opposite polarity relative to intermediate **4** in the oxidative pathway. No elimination to reform a dithioketene acetal is possible. Reprotonation would then lead to the product. While the reaction leads to an aldehyde equivalent at the C-terminus of the amino acid derivative and would therefore require a subsequent oxidation reaction, it would allow for utilization of the same substrates used in the electrolysis reaction thereby taking advantage of the synthetic strategies already developed for their preparation.

The initial substrates (**1a**–**1h**) used in this study were either the same as the ones reported earlier[7] or synthesized from previously utilized alcohols (Scheme 5).[12]

The first substrates studied were **1a** and **1b**. The results were exactly opposite to those obtained with the oxidative cyclizations (Table 1, entries 1 and 2). The cyclization challenged with the formation of a tetrasubstituted carbon failed to afford any cyclic product, while the cyclization not challenged in this manner led to a 92% isolated yield of the desired product. In this way, the hydroamination reaction strategy is complementary to the earlier oxidative approach.

A hint as to why the hydroamination reaction originating from **1a** failed was obtained when 1,3-dithiane was isolated from the reaction. A likely source of the 1,3-dithiane is deprotonation of the secondary amine in the product **2a** followed by an elimination of the 1,3-dithiane group. The elimination reaction would relieve the congestion surrounding the tetrasubstituted carbon and generate a more stable dithiane anion. If this was the case, then protecting the amine and removing the NH proton in the cyclized product would stop this side reaction. For this reason, **1c** was synthesized and exposed to the hydroamination conditions (Table 1, entry 3). The reaction led to a 98% yield of the cyclic product. The presence of the benzyl protecting group also improved the hydroamination originating from **1b**. As shown in entry 4, hydroamination of **1d** led to a 97% isolated yield of the product **2d**. The cyclization originating from **1d** was faster than the one originating from **1b**, proceeding in 10 min relative to the 30 min required for the cyclization of **1b**.

When a methyl group was placed on the allylic carbon of the dithioketene acetal (entry 5), the hydroamination led to a 98% yield of cyclic product **2e** as a single diastereomer. The stereochemistry of the product was assigned using a NOESY experiment as having the dithioacetal *trans* to the methyl group in position R_2 (Figure 1). When the methyl group was placed on the carbon bearing the amine (entry 6), a 95% yield of **2f** was obtained as a 10:1 ratio of diastereomers. Since the methyl group in this case is remote from the forming tetrasubstituted carbon, the stereoselectivity observed in this reaction must result from the conformation of the coiling chain. The major product was assigned as having the two methyl groups *trans* to each other using a NOESY experiment (Figure 1). A related cyclization using a PMB protecting group proceeded in a nearly identical fashion leading to the product in a high yield with excellent diastereoselectivity (entry 7).

The first attempt to synthesize pipecolic acid derivatives using the hydroamination reaction met with failure (Table 1, entry 8). Treatment of substrate **1h** with *n*-BuLi led to none of the desired product. The reaction led to recovery of the starting material suggesting that the twin challenges of six-membered ring and tetrasubstituted carbon formation stopped the cyclization. Evidence for this suggestion was gathered using substrates **1i** and **1j** (Table 1, enties 9 and 10). Substrates **1i** and **1j** were synthesized as outlined in Scheme 6.[12]

Hydroamination of **1i** led to a 95% yield of product indicating that six-membered ring formation proceeded nicely when not challenged with the formation of a tetrasubstituted carbon (Table 1, entry 9). The product was formed as a single diastereomer, and the *trans* stereochemistry was assigned in analogy to the five-membered ring cyclization (entry 5) and early observations.[7,8] The cyclization was also compatible with the use of a benzyl-protected amine (Table 1, entry 10).

Further evidence that steric interactions can interfere with the hydroamination reaction was obtained when a chiral auxiliary was used as the amine protecting group (Scheme 7). With the more bulky group on the nitrogen, the reaction led to none of the desired cyclic product, even though the reaction would have led to the formation of a five-membered ring.

In summary, base-catalyzed intramolecular hydroamination of dithioketene acetals has been developed for the synthesis of cyclic proline and pipecolic acid derivatives. The reactions complement earlier oxidative cyclizations that require the formation of cyclic amino acids having tetrasubstituted α carbon atoms. The hydroamination reactions do not have this restriction. They can also be used to synthesize proline derivatives with tetrasubstituted α carbon atoms but in these cases require protection of the amine. The nature of a desired amino acid derivative will dictate whether the hydroamination or oxidative cyclization method is most useful. For amino acid derivatives having a tetrasubstituted α carbon, the anodic cyclizations are preferred because they do not require protection of the amine and directly afford a product having the correct oxidation state for the amino acid. For amino acid derivatives either not having a substituted α carbon or requiring an aldehyde at the C-terminus, use of the hydroamination reaction is preferred.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Science Foundation (CHE-0809142) for their generos support of our work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

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(10). All potentials were measured by cyclic voltammetry using a BAS 100B Electrochemical Analyzer, a carbon working electrode and a Pt wire auxiliary electrode, a Ag/AgCl reference electrode, a 0.1 M Et_4NOTs in acetonitrile electrolyte solution, a substrate concentration of 0.025 M, and a sweep rate of 25 mV/s.

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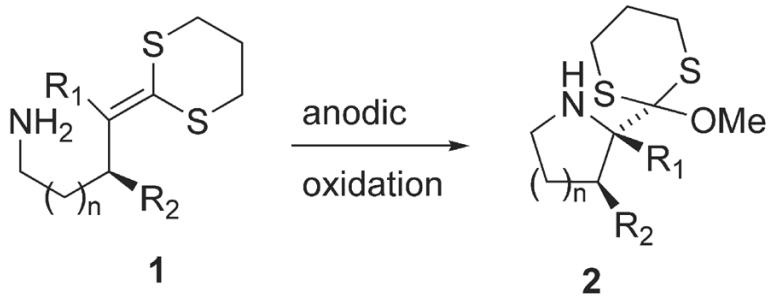
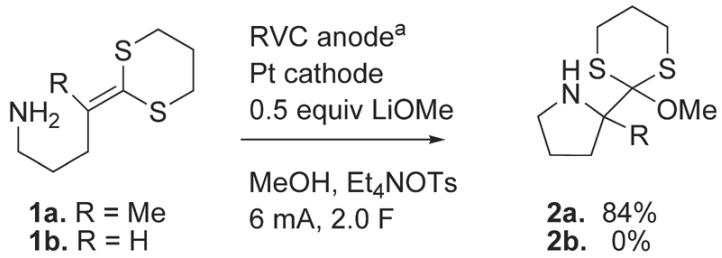
(12). For details please see the Supporting Information.



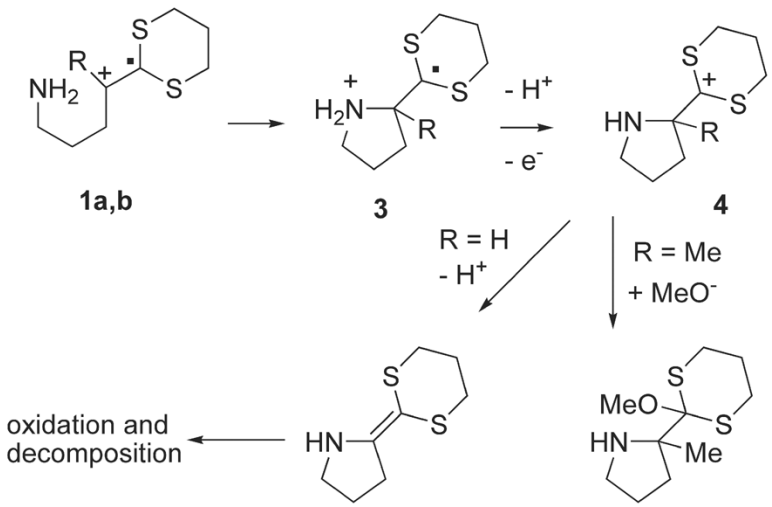
1 2

Scheme 1.
Anodic Cyclizations to Form Cyclic Amino Acid Derivatives

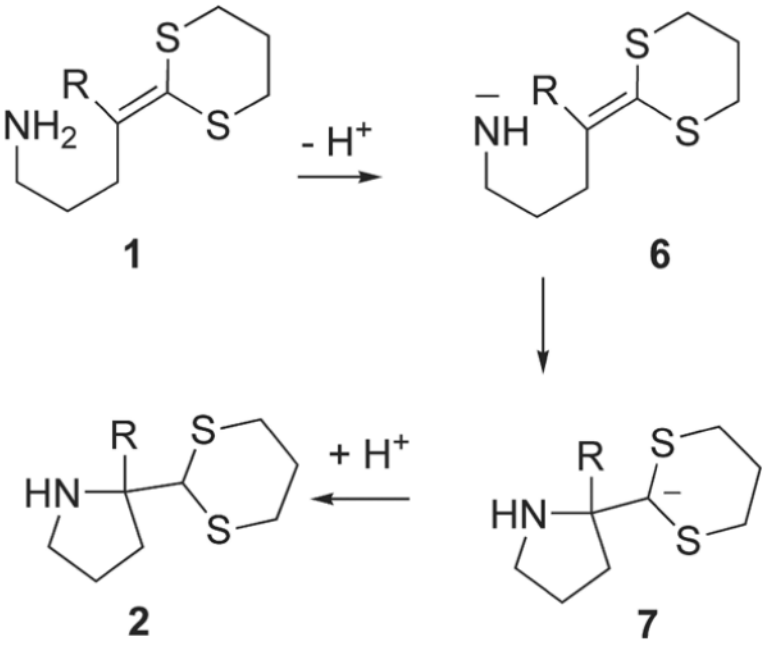


[a] RVC = Reticulated vitreous carbon.

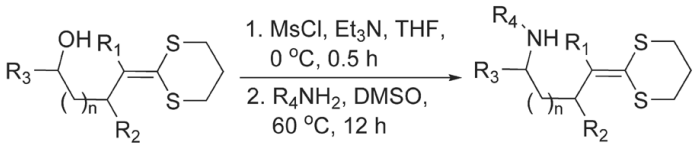
Scheme 2.
Limitations to the Anodic Cyclizations[a]



Scheme 3.
Mechanism for Elimination



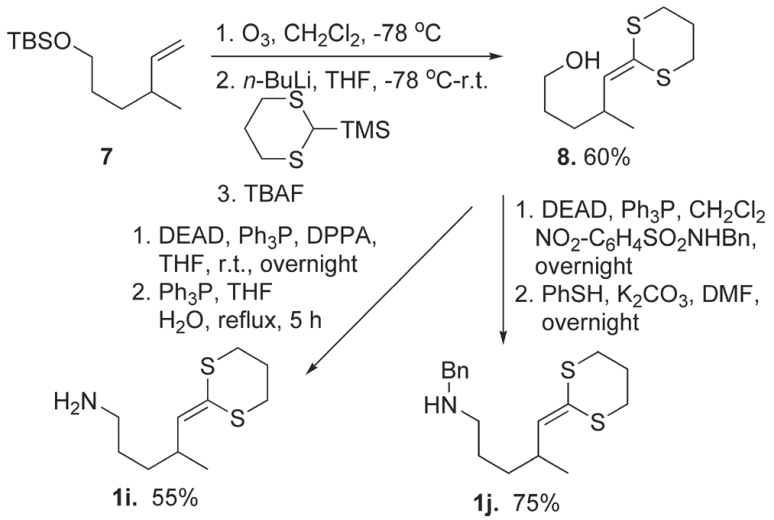
Scheme 4.
Proposed Hydroamination



6a. n = 1
6b. n = 1
6c. n = 1
6d. n = 1
6d. n = 1
6h. n = 2
6a. n = 1

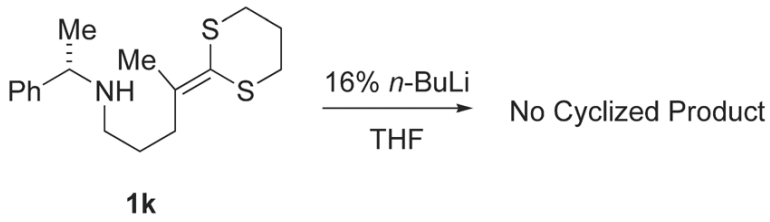
1c. R_1 = Me, R_2 = R_3 = H, R_4 = Bn; 65%
1d. R_1 = R_2 = R_3 = H, R_4 = Bn; 27%
1e. R_1 = R_2 = Me, R_3 = H, R_4 = Bn; 70%
1f. R_1 = R_3 = Me, R_2 = H, R_4 = Bn; 62%
1g. R_1 = R_3 = Me, R_2 = H, R_4 = PMB; 57%
1h. R_1 = R_3 = Me, R_2 = H; R_4 = Bn; 72%
1k. R_1 = Me, R_2 = R_3 = H, R_4 = 1-Phenylethyl; 45%

Scheme 5.
Synthesis of Substrates **1c**–**h** and **1k**



[a] DEAD = diethyl azodicarboxylate; DPPA = diphenylphosphoryl azide.

Scheme 6.
Synthesis of Substrates **1i** and **1j**[a]



1k

Scheme 7.
Evidence of Steric Hindrance

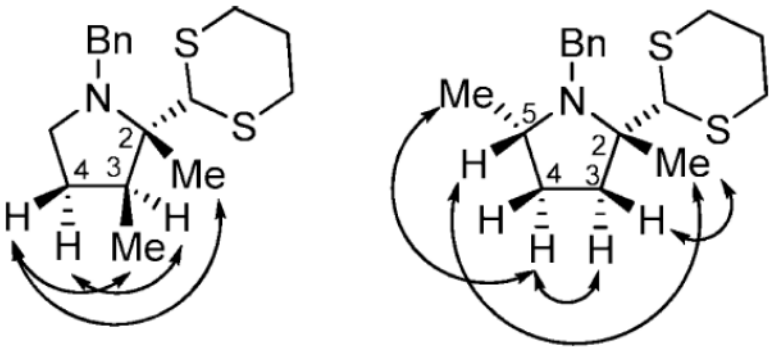
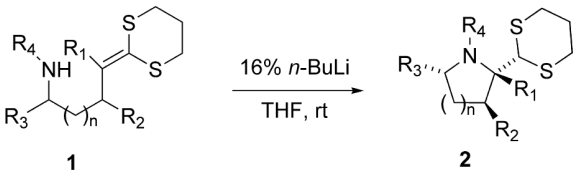


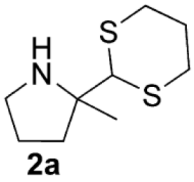
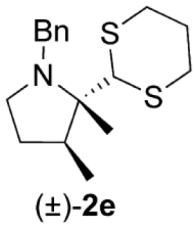
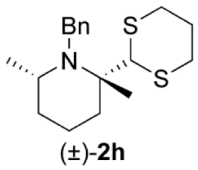
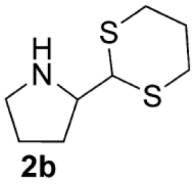
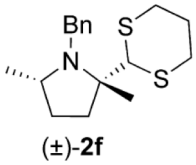
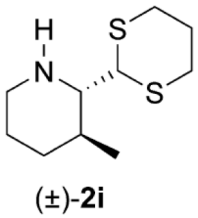
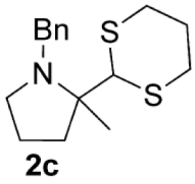
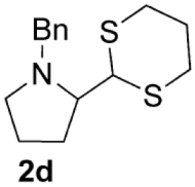
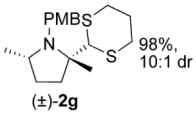
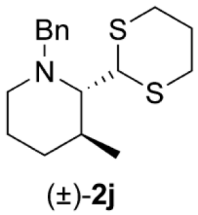
Figure 1.
Key NOE interactions in compounds **2e** and **2f**.

Table 1

Hydroamination Reactions[a]



1 2

entry	product	yield dr	entry	product	yield dr	entry	product	yield dr
1	 2a	0%	5	 (±)-2e	98%, >20:1dr	8	 (±)-2h	0%
2	 2b	92%	6	 (±)-2f	95%, 10:1 dr	9[c]	 (±)-2i	95%, >20:1 dr
3	 2c	98%						
4	 2d	97%	7[b]	 (±)-2g	98%, 10:1 dr	10	 (±)-2j	99%, >20:1 dr

[a] Results listed as isolated yield and diastereomeric ratio (dr) if appliable.

[b] PMB = *p*-methoxybenzyl.

[c] 30% *n*-BuLi was used.