New Trialkylsilyl Enol Ether Chemistry: Intramolecular [2 + 2] Cyclizations of β-Amido Triisopropylsilyl Enol Ethers

Philip Magnus,* Pascal Rigollier, Jérôme Lacour, and Hans Tobler

Department of Chemistry and Biochemistry
University of Texas at Austin
Austin, Texas 78712

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The β-azido functionalization reaction allows ready access to β-amino triisopropylsilyl (TIPS) enol ethers by reduction of the azido group in **2** with lithium aluminum hydride to give **3**, Scheme I.[1] Compound **3** is relatively stable and can be stored as its hydrochloride salt without noticeable decomposition to cyclohexenone.[2]

It was decided to examine the intramolecular conjugate addition reaction depicted in Scheme I.[3] The cyclization of the acrylamide **4**, to give the octahydroquinoline **5**, is a favored process (6-*endo*-*trig*),[4] but requires the higher energy *cis*-amide conformer **4a** in order to arrive at **5**.[5]

The amine **3** was converted into the α,β-unsaturated amide derivatives **4**, **8–10**, **15**, and **18** either by direct acylation with an acid chloride in the presence of triethylamine or by mixed anhydride methodology. In all of the examples the yields are high (77–96%), and the amides are stable crystalline compounds that show no tendency to decompose by β-elimination to cyclohexenone and the corresponding primary amide.

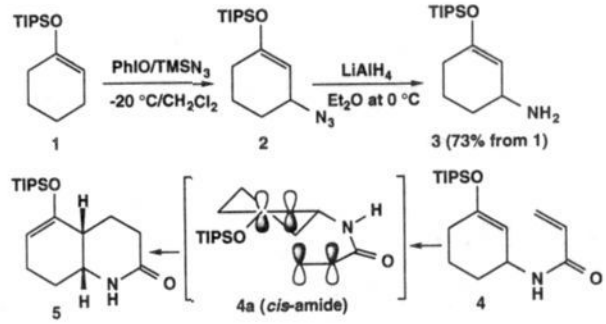
Treatment of the amide **4** with Me_3Al (3 equiv of 2.0 M solution *in toluene*) *in 1,2-dichloroethane (DCE, at 80 °C) for 42 h* produced compound **5** (9%) as a minor component. To our surprise the major product has the structure **7** (43%, structure by X-ray crystallography), Scheme II.[6]

In an effort to improve the yield of **5**, a series of experiments were run at different temperatures. It was found that treatment of **4** with Me_3Al (2.5 equiv) in 1,2-dichlorobenzene (DCB, at 180 °C) gave the lactam **5** (10%). The major product was shown to have the structure **6** (42%, structure by X-ray crystallography). No reaction occurred if **4** was heated in the absence of Me_3Al. Treatment of **8** with Me_3Al (2.5 equiv)/180 °C/DCB for 22 h gave only one cyclization product, **11** (73%). When **9** was treated with Me_3Al (1.1 equiv in DCB) at 120 °C for 22 h, the lactam **12** (structure by X-ray crystallography) was obtained as a single product in 74% yield. At lower temperatures (83 °C/DCE reflux), the γ-lactam **12** (46%) was formed along with the cyclobutane adduct **14** (9%). Adduct **14** was not converted into **12** under the above reaction conditions. The amide **10** did not yield any cyclization product **13**. Irradiation of **9** gave an equilibrium mixture of (*E*)-**9**/(*Z*)-**9** (1.6:1) with no indication of any cyclization. Treatment of (*Z*)-**9** with Me_3Al/DCE at reflux gave **12** as the major product along with small amounts of (*E*)-**9** and **14**. Treatment of the *E*-isomer **15** with Me_3Al (2.0 equiv/DCE reflux, 3 h) gave a mixture of **16** (51%) and **17** (24%).

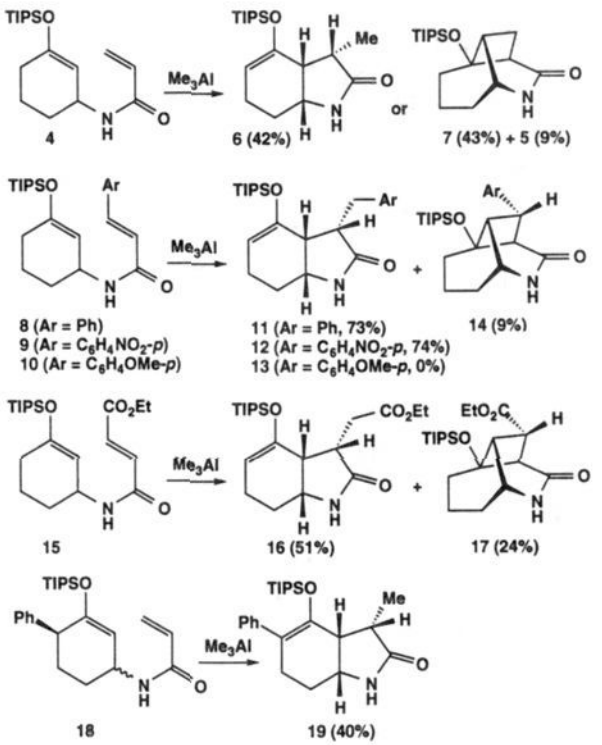
A mixture of the *cis*- and *trans*-acrylamides **18** (*trans* structure by X-ray crystallography) was treated with Me_3Al/DCB/180 °C for 5 h, and the cyclized adduct **19** was isolated in 40% yield.

Disilylation of **7** with *n*-$Bu_4N^+F^-$ (1.2 equiv) in THF at 0 °C (5 min) caused cyclobutane opening to give the known hydroquinoline-2,5-diones **20** (7:1 *trans*/*cis*, 87%).[7] The *trans*-fused product resulted from epimerization of the *cis*-fused compound under the reaction conditions. Similarly, desilylation of **16** and **17** gave the adducts **21** and **22**, respectively. Desilylation of **11** gave the product **23** in 90% yield. When **11** was exposed to the β-azidonation reaction conditions (PhIO/$TMSN_3$), a single

Scheme I



Scheme II



(1) Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767. Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 3993. Magnus, P.; Evans, A.; Lacour, J. *Tetrahedron Lett.* **1992**, *33*, 2933.

(2) Other reducing agents can be used to convert **2** into **3** such as 4,4′-di-*tert*-butylbiphenyl/Li in THF or Na/NH_3.

(3) The closest analogy to the reaction depicted in Scheme II is the intramolecular Michael addition of a cyclic β-keto ester to a conjugated ketone. Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5451. Intermolecular Michael–Mukaiyama reactions of trimethylsilyl enol ethers have been examined. Narasaki, N.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779. Yamami, T.; Miyashita, M.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 607. Jung, M. E.; Pan, Y.-G. *Tetrahedron Lett.* **1980**, *21*, 3127. Heathcock, C. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017.

(4) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; pp 221–241.

(5) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337.

(6) Initial attempts to induce intramolecular 1,4-addition with Lewis acids such as $TiCl_4$, trimethylsilyl triflate, Me_2AlCl, or BF_3-OEt_2, all failed. The only product isolated, apart from the starting material, was 3-(propenoylamino)-cyclohexanone. However, desilylation of **4** was avoided by the use of Me_3Al.

(7) Momose, T.; Miyata, T.; Imanishi, T. *Heterocycles* **1978**, *9*, 17. Momose, T.; Uchida, S.; Miyata, T.; Ohshima, K.; Chiamchittrong, K.; Imanishi, T. *Heterocycles* **1979**, *12*, 393. Witiak, D.; Patch, R. J.; Enna, S. J.; Fung, Y. K. *J. Med. Chem.* **1986**, *29*, 2.

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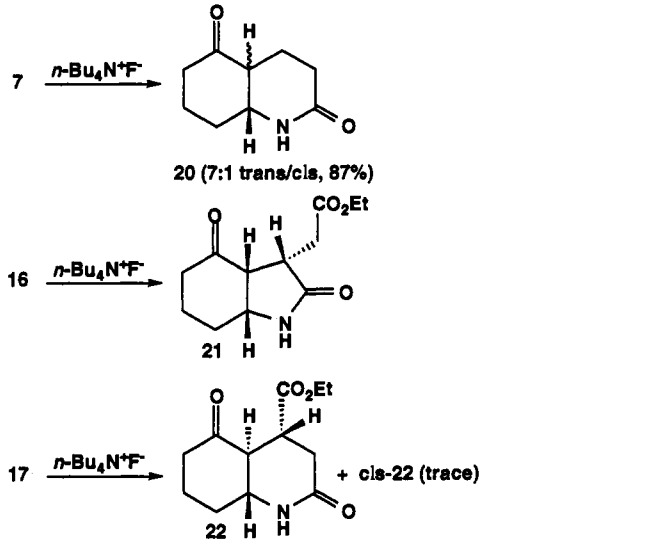
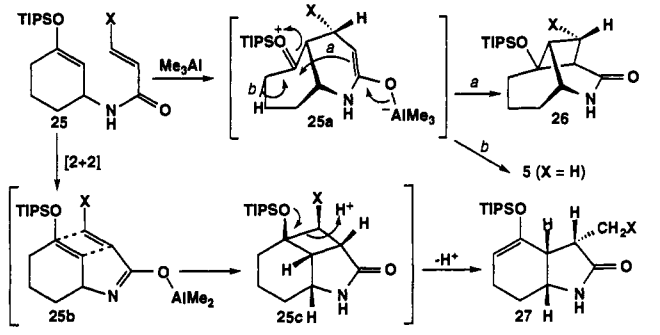
Scheme III



Scheme IV



epimer **24** was produced very cleanly as shown by the ^{1}H NMR of the crude reaction mixture, Scheme III.

The formation of the tricyclic amide **26** might involve the intermediate aluminate enolate **25a**, which can either react by pathway a leading to **26** or undergo proton loss (pathway b) resulting in the minor product **5**, Scheme IV. It is also possible that **26** arises from a direct [2 + 2] cycloaddition catalyzed by the Lewis acid.

The unusual formation of five-membered-ring lactam **26** can be explained by a Lewis acid mediated [2 + 2] cycloaddition of the imino aluminum ether **25b** to give **25c** (opposite regiochemistry from **25** into **26**), followed by opening of the cyclobutane ring and proton loss to give **27**.[8] This mechanism readily explains the otherwise curious *endo* stereochemistry of the newly generated secondary methyl group. The transformation of **25** into **27** appears to be stereospecific since we could not detect any other stereoisomers of **27**.

This new cyclization works best with electron-deficient acrylamides and provides a very short stereospecific route to annulated γ-lactams with contrathermodynamic stereochemistry α to the lactam carbonyl. The conversion of **1** into **11** in four steps, with the TIPS enol ether functionality still available for further transformations (e.g., **24**), is illustrative of this new methodology. We are currently examining the mechanism of the cyclization[9] and extensions to carbocyclic systems.

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Supplementary Material Available: Spectral details for compounds **3–12**, **14-19**, **21**, and **23** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Lewis acid promoted [2 + 2] cycloaddition reactions of trimethylsilyl enol ethers and electron-deficient acetylenes give cyclobutenes. The same reaction with enones does not yield cyclobutanes. Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248, 253. For thermal [2 + 2] cycloadditions, see: Oppolzer, W.; Loosli, H. R. *Helv. Chim. Acta* **1974**, *57*, 2605. Alder, A.; Bellus, D. *J. Am. Chem. Soc.* **1983**, *105*, 6712. Hall, H. K.; Ykman, P. *J. Am. Chem. Soc.* **1975**, *97*, 800. For photochemical [2 + 2]cycloadditions to trimethylsilyl enol ethers, see: Pak, C.; Okamoto, H.; Sakurai, H. *Synthesis* **1978**, 589.

(9) We have previously observed that electrophilic catalysis can divert a [2 + 4] cycloaddition into a [2 + 2] pathway. Magnus, P.; Schultz, J. *Tetrahedron Lett.* **1986**, *27*, 655. It is also possible that the reaction involves a radical cation mediated cyclization. Bauld, N. L.; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon, R. A., Jr.; Reynolds, D. W.; Wirth, D. D.; Chiou, H. S.; Marsh, B. K. *Acc. Chem. Res.* **1987**, *20*, 371.