other multicyclic ring systems. It is expected that in other more complex cases better stereocontrol may be enforced.

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Supplementary Material Available: Complete physical data, including ^{1}H NMR, ^{13}C NMR, IR, and MS, for 15 substances: **4–7**, **9a,b**, **10a,b**, **11–14**, and **15a–c** (5 pages). Ordering information is given on any current masthead page.

Intramolecular Addition of Carbon-Centered Tinthioimidoyl Radicals to Carbon–Carbon Double Bonds. Synthesis of γ- and δ-Thiolactams

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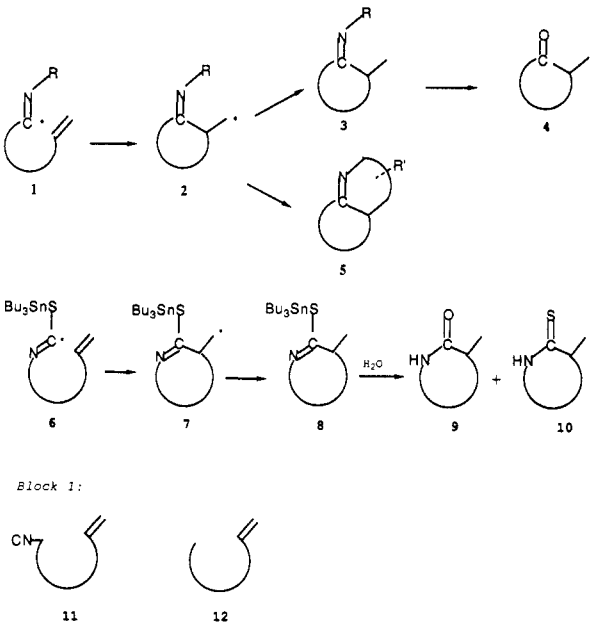
Summary: (Tri-*n*-butyltin)thioimidoyl radicals of type **6**, which were efficiently generated by treatment of alk-3-enyl- and alk-4-enylisothiocyanates with tri-*n*-butyltin hydride and AIBN, underwent exo cyclization to give, after hydrolysis, the corresponding γ- or δ-thiolactams in good to excellent yields.

The formation of cyclic systems through the intramolecular addition of carbon-centered free-radicals to carbon–carbon multiple bonds has been widely exploited in recent years.[1] Educt radicals include a large variety of alkyl, aryl,[2] and ene radicals.[1] To the arsenal of synthetically useful ene radicals, which included vinyl[3] and carbonyl[4] radicals, we recently added imidoyl radicals.[5] We now introduce tinthioimidoyl radicals of type **6**, a novel group of ene radicals, which opens a new avenue for the synthesis of heterocyclic compounds. The difference between the synthetic potential of the previously described[5] imidoyl radicals **1** and that of the tinthioimidoyl radicals **6** is apparent in Scheme I. In imidoyl radicals of type **1** the alkenyl group is linked to the carbon atom of the carbon–nitrogen double bond while in tinthioimidoyl radicals of type **6** the alkenyl group is linked to the nitrogen atom of the carbon–nitrogen double bond. Furthermore, the radical center in **1** is substituted by one heteroatom while in **6** it is substituted by two heteroatoms. Radicals **1** afford cyclic radicals **2**, which carry an exocyclic imine group, and may be transformed into cyclic products of types **4** (via **3**) or **5**.[5] Due to their different structural and functional constitution, tinthioimidoyl radicals **6** may

Scheme I



ring close to cyclic thioimidates **8** (via **7**), which could be subsequently converted into lactams **9** and/or thiolactams **10**. The results described herein provide an interim assessment of the scope and limitation of this reaction for the synthesis of γ- and δ-thiolactams.

Tinthioimidoyl radicals are readily generated through the addition of organotin radicals to isothiocyanates, as in the first step of Barton's method for deamination of primary amines.[6,7] If an analogous degradative process had occurred with tri-*n*-butylthioimidoyl radicals **6** it would produce either isonitriles **11**, by α-elimination, and/or alkene products **12**, by β-elimination. We have previously shown that, provided a multiple bond is judiciously positioned in the molecule, oxycarbonyl radicals undergo 5-exo *or* 6-exo additions rather than degradation to the corresponding desoxy compounds.[4a,f] It was

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(3) The use of vinyl radicals in synthesis was introduced and developed by Stork, see: (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. For other examples see ref 1.

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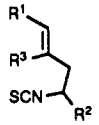
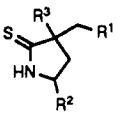
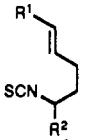
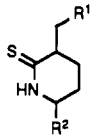
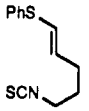
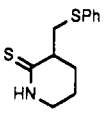
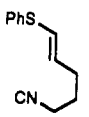
(7) For another reaction involving tinthioimidoyl radicals, see: John, D. I.; Tyrrell, N. D.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1981**, 901.

0022-3263/90/1955-3442$02.50/0

Table I. Cyclization of Alkenyl Isothiocyanates with *n*-Bu_3SnH and AIBN

entry	isothiocyanates	conditions[a]	products (yield, %)	[E/Z][b]
				
1	**13**: R^1 = Me; R^2 = CO_2Me; R^3 = H	a	**25** (94)	[1/1]
2	**14**: R^1 = Ph; R^2 = CO_2Me; R^3 = H	a	**26** (89)	[1/1.66]
3	**15**: R^1 = H; R^2 = CO_2Me; R^3 = Me	a	**27** (80)	-
4	**16**: R^1 = H; R^2 = CO_2Me; R^3 = CO_2CMe_3	a	**28** (94)	[1/4.5]
5	**17**: R^1 = R^2 = R^3 = H	b	**29** (70)	-
6	**18**: R^1 = R^2 = H; R^3 = Me	b	**30** (40)	-
				
7	**19**: R^1 = H; R^2 = CO_2Me	b	**31** (nil)	
8	**20**: R^1 = Ph; R^2 = CO_2Me[c]	b	**32** (75)	*d*
9	**21**: R^1 = SPh; R^2 = CO_2Me[c]	b	**33** (90)	[1.75/1]
10	**22**: R^1 = CO_2CMe_3; R^2 = CO_2Me	b	**34** (93)	[1.26/1]
11	**23**: R^1 = SPh; R^2 = Ph[c]	c	**35** (69)	[12/1]
			 	
12	**24**: R^1 = SPh; R^2 = H[c]	c	**36** (17)	**37** (37)
13		d	**36** (33)	**37** (23)
14		e	**36** (64)	**37** (5)

[a] Reactions were performed with ca. 1 mmol of isothiocyanate in dry degased toluene (c = 0.02 M), *n*-Bu_3SnH (1.15 equiv), and AIBN (0.15 equiv) under the following conditions: (a) 75 °C, 20–40 min; (b) 75 °C, 1–4 h; (c) 75 °C, 7 h; (d) 30 °C, Pyrex flask, sunlight, 2 h; (e) 10 °C, Pyrex flask, 100-W high-pressure mercury lamp with Corning glass filter no. 5850 (major transmitance 280–490 nm), 8 h. All reactions were monitored by TLC and flash chromatographed on a silica gel column (Merck, Kiesilgel 60, 230–400 mesh). [b] Determined by ^1H NMR. [c] Mixture of cis and trans isomers. [d] Diastereoisomeric ratio was not assigned.

therefore reasonable to expect that the thioimidoyl radicals **6**, which are isoelectronic to oxycarbonyl radicals, will undergo a similar ring closure. In order to test the proposed method we included in this study isothiocyanates derivatives of α-amino carboxylic acid esters. These compounds are particularly prone to competitive homolytic deamination, which would be favored by the formation of a stabilized radical intermediate in a position α to an alkoxycarbonyl group, as does occur in the deamination of isonitrile derivatives of various amino acid esters.[8]

Isothiocyanates **13–24** were prepared by standard methods;[9,10] the corresponding amino acid esters were obtained through alkylation of *N*-(diphenylmethylene)-glycine methyl esters, or through Wittig reactions involving the adduct of this compound with acrolein.[11,12] The isothiocyanates **13–24** (0.02 M in toluene) were treated with tri-*n*-butyltin hydride (1.15 equiv) and AIBN (0.15 equiv), and the products were chromatographed over silica gel as specified in Table I. Products analysis indicates that isothiocyanates **13–18** produce tinthioimidoyl radicals of type **6**, which undergo 5-exo cyclization to tinthioimidates of type **8**. Spontaneous hydrolysis during chromatography occurred at the Sn–S bond, giving the corresponding γ-thiolactams **25–30** related to thiolactams **10**. Methyl thiopyroglutamates **25–28** were obtained in excellent yield; oxo analogues related to **9** were not detected. The regiochemistry of cyclization is not altered when a substituent (R^3) is introduced on the double bond at the site of addition of the ene radical (entries 3, 4, and 6), even when this substituent (entry 4) would accelerate the endo addition by polar, steric, and thermochemical factors.[13,14] It seems that the dominant directing factor in this, as in many other cyclizations, is a stereoelectronic factor.[15] Comparison of the data in entries 1 and 3 with that of entries 5 and 6 indicates that the cyclization is accelerated by a substituent R^2 in the position α to the nitrogen atom.[16] The 6-exo cyclization occurring with isothiocyanates **20–24** is highly regioselective. However, as it is slower than the 5-exo cyclization encountered with compounds **13–18**, it requires activation of the double bond. Indeed, compound **19** which bears a nonactivated double bond failed to cyclize. Comparison of the data in entries 9 and 11 with that in entries 12–14 indicates that the accelerating effect of a substituent R^2 is more pronounced in the 6-exo than in the 5-exo cyclization. Thus in the absence of such a substituent as in compound **24** degradation competes with cyclization. At standard reaction conditions the isonitrile **37** was obtained as the major product while the thiolactam **36** was obtained as the minor product. However, due to the difference in the entropic factor for cyclization vs that for degradation, the thiolactam **36** was obtained as the major product when the reaction was performed at 10 °C (entry 14).

The diastereoisomeric ratio of the disubstituted thiolactams shown in Table I was determined by ^1H NMR analysis. The influence of substituents R^2 and R^3 on the E/Z ratio is consistent with that observed in the cyclization

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of analogously substituted alkenyl radicals. It was reported that a substituent at position 3 of 5-hexenyl radicals favors the formation of the *Z* product of 5-exo cyclizations[17] while a substituent at position 3 of a 6-heptenyl radical favors the *E* product of 6-exo cyclizations.[18] These observations were supported by force field calculations.[19]

In summary, the *n*-Bu_3SnH/AIBN-induced cyclization of alkenylisothiocyanates constitutes a general and efficient method for the preparation of γ-thiolactams, and a useful method for the preparation of suitably substituted δ-thiolactams.

Acknowledgment. We thank the Minerva Foundation (Munich, Germany) for financial support.

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Apical-Equatorial Orientation of the Six-Membered Ring in P(V) Models of Enzymatically Formed cAMP-Nucleophile Adducts. Relationship to the Basic Hydrolysis of cAMP

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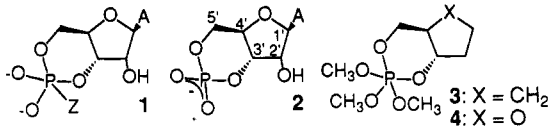
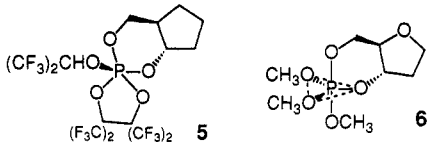
Summary: Results of a low-temperature ^{13}C NMR study of **4**, an X-ray crystal structure of **5**, and ^1H NMR results for **4** and **5** which show both model compounds to have the P(V) 1,3,2-dioxaphosphorinane ring attached apical/equatorial to phosphorus and in a twist rather than chair conformation are reported and discussed relative to the enzymic and particularly the basic chemical hydrolysis of cAMP.

Pentacovalent phosphorus, P(V), adducts (**1**) have been proposed as intermediates both in the phosphodiesterase-catalyzed hydrolysis[1] of cAMP (**2**) to 5′-AMP and in the activation by cAMP of protein kinases[2] on coordination of cAMP with the active site of the regulatory subunit. As a guide to an understanding of the biological systems, several nonenzymic P(V) model systems have been prepared[3,4] of which one can ask: (1) Is the structure trigonal bipyramidal or square pyramidal about phosphorus? (2) Is the six-membered (1,3,2-dioxaphosphorinane) ring attached to P(V) diequatorial or apical/equatorial? (3) For apical/equatorial attachment, is the O5′ or O3′ atom apical? (4) What is the conformation (chair or nonchair) of that ring?



Puzzlingly different answers to question **2** have been presented in certain systems. Thus, it has been calculated by CNDO/2 methods that a pentacovalent adduct from cAMP with ring *diequatorial* is about 25 kcal/mol *lower* in energy than its apical/equatorial alternative.[2c] Furthermore, in a ^{13}C NMR study[2a] the MeO signals of **4** (X = O) failed to decoalesce at −88 °C, whereas, at the same temperature, **3** (X = CH_2) showed two MeO resonances, the lower field one (two equatorial MeO's) being of twice the intensity of the higher field peak (one apical MeO). The result for **3** is clearly indicative of *apical/equatorial* 1,3,2-dioxaphosphorinane ring attachment. The lack of decoalescence for **4**, which with X = O more closely resembles a cAMP P(V) adduct, was interpreted[2a] to mean that the corresponding ring of **4** is by contrast quite likely *diequatorial*. This conclusion is consistent with the CNDO/2 calculations.[2c]

In this report we present high-field variable-temperature studies of **4** which dispel the notion that its P(V)-containing 1,3,2-dioxaphosphorinane ring is diequatorial. Also reported is an X-ray structure[5] of the model system **5**



which shows the apical and equatorial positions of the O5′ and O3′ ring atoms, respectively, to be attached to near-TBP P(V) contained in a *twist* form 1,3,2-dioxaphosphorinane ring. These findings, although important by themselves, lead as well to a better understanding of the regiochemistry of the nonenzymic, base-catalyzed ring opening of cAMP.

Selected ^{13}C NMR spectra for **4**[5] obtained at 125 MHz over the temperature range 25 to −113 °C in CD_2Cl_2 are displayed in Figure 1. Just as was found with **3** at 22.6 MHz,[2a] **4** also reaches a slow exchange limit at which the low-field equatorial MeO's are twice as intense as the higher field, apical one[6] which means that *the 1,3,2-diox-*

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(5) Phosphorane **5** was prepared by the method of ref 2a in >95% purity as assessed by ^1H and ^{13}C NMR spectroscopy.
(6) This chemical shift relationship between apical and equatorial methoxy groups has been defined in van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 215.

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