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REACTIONS OF KETENE SILVL ACETALS WITH IMINE-COMPLEXES OF TITANIUM TETRACHLORIDE. NEW AND CONVENIENT ROUTES TO 5,6-DIHYDRO-2-PYRIDONES AND 5-AMINO-2-ALKENOATES

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Abstract: The reactions of vinylketene silyl acetals (VKSAs) with imine complexes of $TiCl_4$ give the corresponding 5,6-dihydro-2-pyridones and/or 5-amino-2-alkenoates in good to excellent yields. It is suggested that an addition-cyclization mechanism is operative for the formation of 5,6-dihydro-2-pyridones in this formal cyclocondensation reaction.

The reactions of ketene silyl acetals¹ with various electrophiles in the presence of Lewis acids have spurred considerable interest, e.g., aldol-condensations with aldehydes and acetals,² conjugate additions to α , β -enones,³ alkylations,⁴ and Diels-Alder/cyclocondensation reactions.⁵ We have been interested in the reactions of ketene silyl acetal - TiCl₄ systems. For instance, we have developed an efficient route to β -lactams through the reaction with imines and applied this reaction to highly stereoselective β -lactam synthesis.⁶ We also have reported a novel homocoupling of ketene silyl acetals and their vinyl analogs.⁷ We would like to describe here novel and convenient routes to 5,6-dihydro-2-pyridones⁸ and 5-amino-2alkenoates by the reactions of vinylketene silyl acetals with unactivated imines promoted by titanium tetrachloride and the mechanistic aspects of the reaction.

Conceptually, there are four possible reaction patterns: (i) Diels-Alder cycloaddition, (ii) addition-cyclization giving 3-vinyl- β -lactams, (iii) addition-cyclization giving 5,6-



Entry	1		2		Yie		
	R ¹	R ²		R ⁴	3	4	TOTAL
a	 Н	н	ⁱ Pr	CH ₂ Ph	53[41] ^c	 9[]	62 (99) ^b
b	н	н	Ph	Сн ₂ Рh	20[10] ^c ,d	78[77] ^c ,d	98 (98) ^b
c	н	n	Ph	Ph	0	32[23] ^c	32 (98) ^b
đ	Me	н	ipr	CH2Ph	38[27] ^{c,d}	43[41] ^c ,d	81 (94) ^b
e	Me	н	Ph	CH ₂ Ph	0	94[79] ^c ,d	94 (96) ^b
f	Me	н	Ph	Ph	0	98[89] ^c , ^d	98 (98) ^b
8	н	Me	ⁱ Pr	CH ₂ Ph	96[73] ^c	4[]	100(100) ^b
h	H	Me	Ph	CH2Ph	92[85] ^c	0	92(100) ^b
i	н	Me	Ph	Ph	38[34] ^c	62[40] ^{c.}	100(100) ^b

Table 1. 5,6-Dihydro-2-pyridones (3) and 5-Amino-2-alkenoates (4) obtained by the Reaction of Ketene Silyl Acetals (1) with Imine Complex of Titanium Tetrachloride (2).

^aYield determined by GLC. ^bConversion yield based on the imine consumed. ^cIsolated yield. ^dVKSA was used in excess (4 eq.).

dihydro-2-pyridones and (iv) addition of α - or γ -termini giving 3- or 5- amino-2-alkenoates. Among these possibilities the reaction of a vinylketene silyl acetal (1) with an imine complex of TiCl₄ (2) only gave a 5,6-dihydro-2-pyridone (3) and/or a 5-amino-2-alkenoate (4) (Scheme 1). Typical results are summarized in Table 1.⁹

No products arising from α -addition of a vinylketene silyl acetal (VKSA) (1) to the imine-TiCl₄ complex (2) were obtained at all in all cases examined. Thus, the reaction is extremely regioselective. The ratio of the cyclic (3) to acyclic product (4) is highly dependent on the substitution patterns of both 1 and 2 and also on the reaction conditions.

As shown in Table 1, the introduction of a methyl group to the 2-position of 1 (1B: $R^1=Me$, $R^2=H$) gives rise to the selective formation of acyclic products (Entries d-f), while the 3methyl VKSA (1C: $R^1=H$, $R^2=Me$) and the parent VKSA (1A: $R^1=R^2=H$) give cyclic products with high selectivity (Entries a, g, h). When a phenyl group is attached to the nitrogen of an imine, 1A and 1C give acyclic compounds (4) as the major product (Entry i) or the exclusive product (Entry c). These observations may provide important information for the understanding of the mechanism of the reaction. There are two conceivable mechanisms which can accommodate these results, viz., (i) there are two competitive reactions which give a cyclic product (3) and an acyclic product (4) independently where the cyclic product (3) is formed via Diels-Alder cycloaddition while the acyclic product (4) is yielded by a simple nucleophilic γ -addition of VKSA (1) and (ii) there is a common intermediate complex for both the cyclic and acyclic products and 3 is formed through an addition-cyclization process.

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We looked closely at the dependency of the product distribution on the reaction temperature: It was found that a combination which gave a cyclic product (3h) in a virtually exclusive manner under the standard reaction conditions⁹ afforded an acyclic product (4h) selectively (4h/3h=4) (initial E/Z ratio of 1C is 0/100)¹⁰ when the reaction was quenched at the temperatures lower than -50 °C regardless of the reaction time before the quenching. It is more important to note that the GLC-monitoring of the reaction under the standard reaction conditions disclosed the gradual formation of the cyclic product (3h) and the decrease of the acyclic product (4h) where the total yield of the two products remained virtually constant. The results, together with the substituent effects mentioned above imply the existence of a common intermediate for the reaction although more detailed mechanistic study is necessary.

Further investigations on the mechanism and the application of this reaction are actively underway.

Acknowledgment: The generous support from National Science Foundation (CHE-8309935) is gratefully acknowledged.

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 - 8. A part of this work was presented at the 4th International Conference on Organic Synthesis (IUPAC), Aug. 22-27, Tokyo, Japan (1982); K. Hirai and I. Ojima, Abstracts, A-II-2105. While our research was in progress, Danishefsky reported a non-catalyzed Diels-Alder reaction of an exocyclic vinylketene sily/ actetal with an imine. See ref. 5f, 5i.
 - 9. A typical experimental procedure is as follows: A solution of benzylidenebenzylamine (1.00 mmole, 161 mg) in 5 ml CH₂Cl₂ was treated with 1 ml of 1M TiCl₄ in CH₂Cl₂ at -78°C and allowed to stir until the temperature dropped to ca. -100°C. The vinylketene silyl acetal (1C) derived from methyl 3-methylcrotonate (2.00 mmole, 372 mg) in 10 ml CH₂Cl₂ was then added dropwise. After the addition was complete, the reaction mixture was removed from the cold bath and allowed to warm slowly to room temperature over a period of 3-4 hours. The reaction mixture was then quenched with water, extracted with CH₂Cl₂, dried over anhydrous sodium sulfate, and solvent evaporated to give a crude product. The GLC analysis of the crude product showed (92% yield) the exclusive formation of N-benzyl-4methyl-6-phenyl-5,6-dihydro-2-pyridone (3h). The crude product was purified on a silica gel column to give 237 mg of 3h (85% yield). Satisfactory analytical data for identification were obtained for all products listed in Table 1.
- 10. The E/Z ratio for 1A and 1B is ca. 1/1. However, 1C was formed extremely selectively. The Z-structure of 1C was unambiguously assigned based on the comparison of its spectral ¹H NMR data with the reported ones: C. P. Casey, C. R. Jones, and H. Tsukuda, J. Org. Chem., <u>46</u>, 2089 (1981).

(Received in USA 18 August 1986)