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NEW AND EFFECTIVE ROUTE TO β-LACTAMS. THE REACTION OF KETENE SILYL ACETALS WITH SCHIFF BASES PROMOTED BY TITANIUM TETRACHLORIDE

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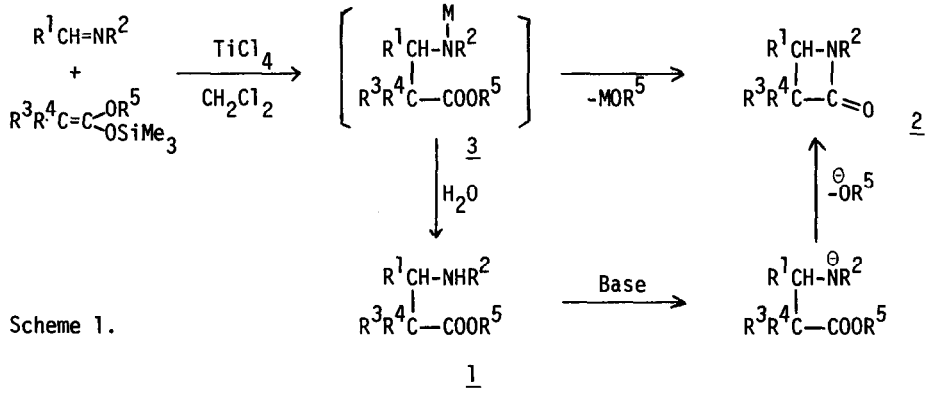
New methods of constructing β-lactam ring are of particular interest in connection with the synthesis of analogues of the naturally occurring anti-biotics such as penicillins, cephalosporins and pachystermines although a variety of synthetic route to β-lactams has been developed.[1] We wish to describe here a new and effective route to β-lactams using the reaction of ketene silyl acetals with Schiff bases promoted by titanium tetrachloride.

It was found that ketene silyl acetals added to Schiff bases in the presence of titanium tetrachloride to give metalated β-amino esters (3), which afforded β-amino esters (1) after hydrolysis or underwent a subsequent cyclization to β-lactams (2). The β-amino ester (1), thus obtained, was easily converted to the corresponding β-lactam (2) in excellent yield by treatment with an appropriate base.



Scheme 1.

A typical procedure is described for the reaction of dimethylketene methyl trimethylsilyl acetal with benzylideneaniline in the presence of titanium tetrachloride: To a 1 *M* solution of

titanium tetrachloride in dichloromethane (20 ml, 20 mmol) was added dropwise a dichloromethane solution (20 ml) of benzylideneaniline (3.62 g, 20 mmol) at ambient temperature with stirring over a period of 10 min. Then, dimethylketene methyl trimethylsilyl acetal (3.48 g, 20 mmol) in dichloromethane (10 ml) was added to the resulting dark-red solution and the mixture was stirred for 1 hr.[2] After the reaction mixture was poured into ice-water for hydrolysis, the organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual crystals were washed with n-pentane on a glass filter to afford 4.79 g (85%) of methyl 2,2-dimethyl-3-phenyl-3-(N-phenylamino)propionate (1a) with sufficient purity. The β-amino ester 1a (4.79 g, 16.9 mmol), thus obtained, was dissolved in tetrahydrofuran (30 ml) and the solution was added to a solution of lithium diisopropylamide (LDA) (17 mmol) in n-hexane-tetrahydrofuran (1:1)(25 ml) at 0°C with stirring. After 10 min, the reaction mixture was poured into ice-water and extracted with dichloromethane. The usual work-up afforded 4.04 g (95%) of crystalline 3,3-dimethyl-1,4-diphenyl-2-azetidinone (2a) with high purity.

Results obtained with a variety of ketene silyl acetals and Schiff bases are summarized in Table 1. As evident in Table 1, it is dependent upon the nature of the substituents of the Schiff base employed whether an intermediate, metalated β-amino ester (3), undergoes the subsequent cyclization to β-lactam (2) or not under the reaction conditions. Namely, when benzylidenemethylamine or alkylidenealkylamine was employed as substrate, the corresponding β-lactam (2) was produced directly in moderate to good yield[3] while the reaction using benzylideneaniline or benzylidenebenzylamine gave the β-amino ester (1) in high yield.

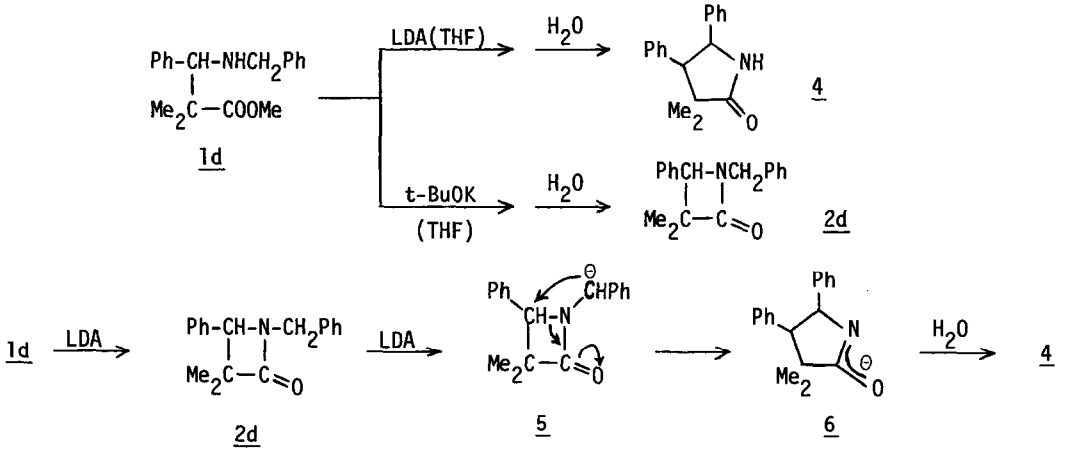
The cyclization of methyl 3-(N-benzylamino)-2,2-dimethyl-3-phenylpropionate (1d), prepared from benzylidenebenzylamine and dimethylketene methyl trimethylsilyl acetal, is worth to be mentioned. The treatment of the β-amino ester 1d with LDA (1 eq.) in tetrahydrofuran resulted in the formation of 3,3-dimethyl-4,5-diphenyl-2-pyrrolidinone (4)[4], i.e., the formation of the corresponding β-lactam 2d could not be observed at all, and the half of the β-amino ester was recovered unchanged. The desired cyclization was successfully achieved by using pottasium t-butoxide as base instead of LDA to give 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (2d) in 77 % yield. The fact may suggest that the benzyl carbanion which was generated from the initially formed β-lactam 2d by the action of the second molecule of LDA undergoes a facile ring enlargement process to afford the pyrrolidinone 4 after hydrolysis via the anion 6, and that

Table 1. β-Amino esters and β-lactams obtained by the reaction of ketene silyl acetals with Schiff bases in the presence of titanium tetrachloride

	R^1	R^2	R^3	R^4	R^5	β-Amino Ester (1) mp(°C) or bp(°C/Torr)	IR(cm^{-1}) ν_{NH}	IR(cm^{-1}) $\nu_{C=O}$	Yield[a] (%)	β-Lactam (2) mp(°C) or bp(°C/Torr)	IR(cm^{-1}) $\nu_{C=O}$	Yield (%)
a	Ph	Ph	Me	Me	Me	122-123	3380	1720	85	150-151[c]	1750	95[b]
b	Ph	Ph	Me	H	Me	79-84[d]	{3430 3350	{1745 1720	83	95-105[d]	1750	90[b]
c	Ph	Ph	$-(CH_2)_5-$		Me	91-92	3370	1720	70	142-143	1750	91[b]
d	Ph	$PhCH_2$	Me	Me	Me	142/0.4	3360	1730	92	141/0.9[e]	1760	77[b]
e	Ph	Me	Me	Me	Me		----------			96/0.6[f]	1750	72[a]
f	^iPr	$PhCH_2$	Me	Me	Me		----------			106/0.3	1755	43[a]
g	Et	PhMeCH	Me	Me	Me		----------			101/0.25[d]	1740	54[a]

a Isolated yield based on the ketene silyl acetal employed b Isolated yield based on the corresponding β-amino ester c Literature value[5]: mp 149.5-150.5°C d A mixture of diastereomers, see Ref. 6 e Literature value[7]: bp 195-205°C/13 Torr f Literature Value[8]: bp 117-121°C/4.6 Torr

the ring enlargement reaction is much faster than the β-lactam formation. In fact, the pyrrolidinone 4 was obtained in 93 % yield on using two equivalents of LDA.



Further studies on these lines are under active investigation.

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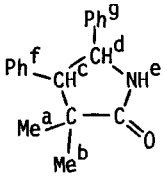
2. The reverse addition, i.e., addition of Schiff base to the mixture of ketene silyl acetal and titanium tetrachloride, did not work well since the coupling of the ketene silyl acetal promoted by titanium tetrachloride giving a substituted succinate predominated over the addition reaction. As to the coupling of ketene silyl acetal promoted by titanium tetrachloride, see S. Inaba and I. Ojima, Tetrahedron Lett., 2009 (1977).

3. The reaction of an alkylidenealkylamine was carried out at initial temperature of -78°C using 10 mmol of a ketene silyl acetal, 20 mmol of a Schiff base, and 15 mmol of titanium tetrachloride in 30 ml of dichloromethane and the reaction mixture was gradually warmed up to ambient temperature. Usually, the reaction was completed within 12 hr.

4. Colorless prisms, mp 166-168°C. IR(KBr disk): 3200 cm^{-1}(ν_{NH}) and 1700 cm^{-1}($\nu_{C=O}$). NMR($CDCl_3$, δ ppm): 0.91 (s, 3H, Me^a), 1.20 (s, 3H, Me^b), 3.12 (d, J=10 Hz, 1H, H^c), 5.00 (d, J=10 Hz, 1H, H^d), 6.92 (broad s, 1H, H^e), and 7.10-7.40 (m, 10H, H^f, H^g). Analysis found: C, 81.57; H, 7.14; N, 5.13%. Calcd. for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28%.



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