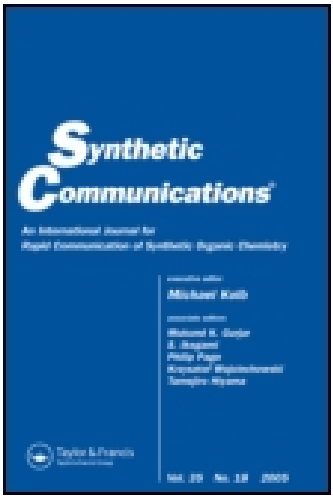

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Seema Kanwar [a] & S. D. Sharma [a]
[a] Department of Chemistry and Centre of Advanced Studies in Chemistry , Punjab University , Chandigarh, India
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Synthesis of β-Lactams: α-Chloro and α-Cyano β-Lactams by Condensation of Imines with Titanium Ester Enolates Derived from Chloro and Cyano Ethyl Acetates

Seema Kanwar and S. D. Sharma
Department of Chemistry and Centre of Advanced Studies in Chemistry, Punjab University, Chandigarh, India

Abstract: α-Cyano and α-chloro β-lactams are obtained in a one-step reaction at a temperature of less than −78°C by condensation of imines with ester enolates derived from ethyl α-cyano and α-chloro acetates.

Keywords: α-Cyano-β-lactams, α-chloro-β-lactams, titanium enolates, ester enolate–imine condensation

The development of efficient approaches to the stereocontrolled synthesis of β-lactams continues to be of crucial importance within the context of the most-employed class of antimicrobial agents, the β-lactam antibiotics.[1–3] As a result of long-standing interest of β-lactams in medicine, biology, and chemistry, many approaches to their stereoselective synthesis have been developed.[4–7] Reaction classes such as metalloester enolate–imine condensations and ketene–imine cycloadditions (Staudinger reaction) are just two examples that have been used extensively. Direct stereospecific approach

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Address correspondence to S. D. Sharma, Department of Chemistry and Centre of Advanced Studies in Chemistry, Punjab University, Chandigarh 160 014, India. Tel.: 91-172-2541435; Fax: 91-172-2545074; E-mail: sdsharmapu@yahoo.com

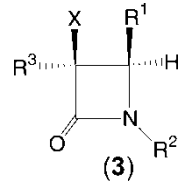
could provide a general route to a greater diversity of β-lactams and would reduce the dependence on other known nonstereospecific methods.

In connection with a series of β-lactams syntheses,[8–13] elaborated in our laboratory in the past few years, especially with those involving condensation of lithium ester enolates and imines,[14] we were interested in the condensation of titanium enolates derived from α-chloro/α-cyano ethylacetates and imines.

For this purpose, the ethyl ester of 2-chloro propanoic acid and 2-cyano propaonic acid were converted into the corresponding enolates and treated with Schiff's base. In the first experiment, ester **1a** was transformed with $TiCl_4$ at -78°C into enolate **2a** and on condensation with aryl aldimines afforded the α-cyano-β-lactam **3a** (Table 1, entry 1). Although it had already been reported[15] that such enolates exist in equilibrium with the ketene **5** or generate carbene **6** through an elimination process (Scheme 1), we observed the formation of β-lactams in moderate yields. This can be attributed to the reactions being performed at -78°C where the titanium ester enolates are quite stable for the pathway favoring β-lactam formation.

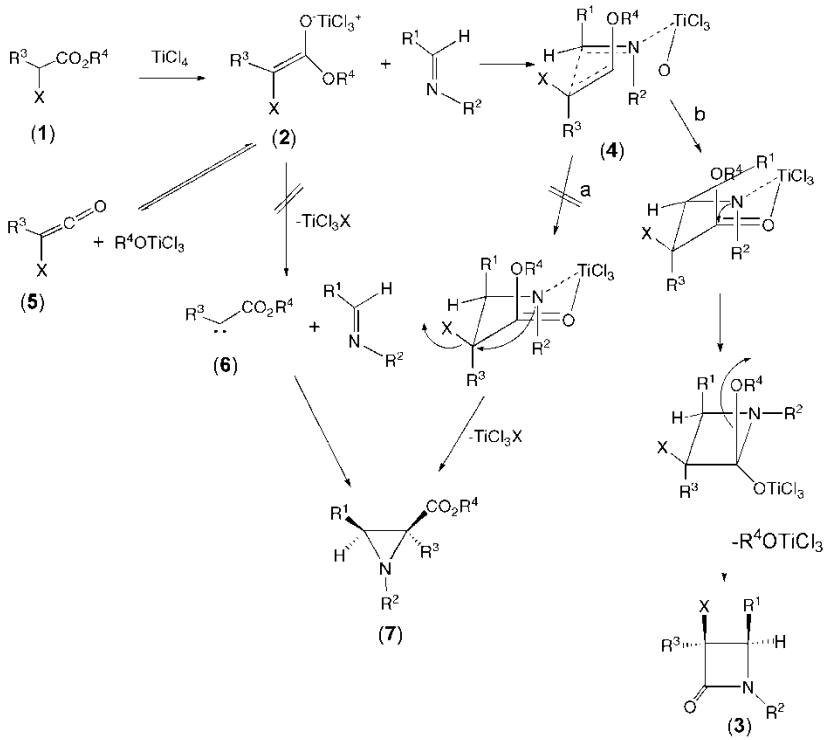
From these results it is clear that enolizable as well as nonenolizable imines may be used. As the cyclization takes place at a temperature below -78°C, titanium enolates are quite stable with regard to decomposition and self-condensation. An interesting feature of this reaction is the complete

Table 1. α-Cyano and α-chloro-β-lactams from ester enolate–imine condensation reaction



(**3**)

Entry	X	R^1	R^2	R^3
3a	CN	C_6H_5	$C_6H_4OCH_3$(p)	H
3b	CN	$C_6H_4OCH_3$(p)	$C_6H_4OCH_3$(p)	H
3c	CN	piperonyl	$C_6H_4OCH_3$(p)	H
3d	CN	$CH{=}CHC_6H_5$	$C_6H_4OCH_3$(p)	H
3e	CN	$C_6H_4OCH_3$(p)	$CH_2CH(OH)CH_3$	H
3f	CN	C_6H_5	$CH_2CH(OH)CH_3$	H
3g	Cl	C_6H_5	$C_6H_4OCH_3$(p)	H
3h	Cl	$C_6H_4OCH_3$(p)	$C_6H_4OCH_3$(p)	H
3i	Cl	piperonyl	$C_6H_4OCH_3$(p)	H
3j	Cl	$CH{=}CHC_6H_5$	$C_6H_4OCH_3$(p)	H
3k	Cl	$C_6H_4OCH_3$(p)	$CH_2CH(OH)CH_3$	H
3l	Cl	C_6H_5	$CH_2CH(OH)CH_3$	H
3m	Cl	$C_6H_4OCH_3$(p)	$CH_2CH_2C_6H_5$	H



Scheme 1.

absence from the reaction mixture of products containing the aziridine ring **7**, an outcome of a faster addition–elimination reaction (path b) versus the intramolecular nucleophilic displacement of the halogen atom (path a), as shown in Scheme 1. In strong contrast to the previous report,[16] the present trichloro titanium enolate effected the formation of 3-cyano and 3-chloro-2-azetidinone in a stereospecific manner. This unprecedented selectivity is quite noteworthy and can be explained reasonably in terms of the relatively weak ionic but moderate Lewis acid character of the intermediary titaniumamide **4**. Accordingly, preferential attack of titanium amide to the ester part was smoothly achieved chemoselectively. It can also be argued that the success of this reaction is the result of the difference in the electrophilicity of carbons of the titanium enolate involved as well as the stability of the product formed.

Although there is possibility of formation of two isomers, the reaction is highly cis-stereoselective and no traces of trans isomer were detected. These facts are consistent with a Zimmerman–Traxler transition state[17] of the addition of the ester enolate to Schiff's base, followed by ring closure via elimination of the acyclic intermediate. In the proposed mechanism, the geometry of enolate[18] and of the Schiff's base is assumed to be E.

EXPERIMENTAL PROCEDURE

All melting points (mp, °C) are uncorrected. The FT-IR spectra were recorded on a Perkin-Elmer model 1430 spectrophotometer and were calibrated against polystyrene. Only the principal peaks of interest are reported and expressed in cm^{-1}. ^1H NMR spectra were recorded on a 300-MHz Bruker AC 300F spectrometer. Chemical shifts are expressed as δ values (ppm) downfield from tetramethylsilane (TMS). Elemental analysis (C, H, N) was recorded using a Perkin-Elmer 2400 (C, H, N) elemental analyzer. Thin-layer chromatography was performed using TLC-grade silica gel (G) and was developed in an atmosphere of iodine vapors.

Typical Procedure for Preparation of β-Lactams (3a–3m)

Titanium tetrachloride (0.1 mmol) was added to the appropriate ethyl ester (0.1 mmol) in dry THF (10 mL) under a nitrogen atmosphere, and the reaction mixture was cooled to −78°C. After 15 min, triethylamine (0.11 mmol) was added and stirred for 30 min at −78°C, followed by addition of Schiff's base (0.05 mmol) in dry THF (5 mL). The reaction mixture was stirred for 5–6 h and then at rt overnight, quenched by the addition of saturated ammonium chloride solution, and filtered. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to obtain oily material, which was purified by column chromatography on silica gel by using ethyl acetate:hexane (20 : 80).

1-(4-Methoxy-phenyl)-2-oxo-4-phenyl-azetidine-3-carbonitrile (3a). Oil (45%); IR: $\nu = 1770\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.75 (s, 3H, OCH_3), 5.01 (d, 1H, C_3H, $J = 4.5$ Hz), 6.23 (d, 1H, C_4H, $J = 4.5$ Hz), 6.85–7.51 (m, 9H, ArH). Anal. calcd. for $C_{17}H_{14}N_2O_2$: C, 73.38; H, 5.04; N, 10.07. Found: C, 73.05; H, 4.95; N, 10.39.

1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidine-3-carbonitrile (3b). Oil (48%); IR: $\nu = 1775\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.96 (d, 1H, C_3H, $J = 4$ Hz), 5.23 (d, 1H, C_4H, $J = 4$ Hz), 6.72–7.25 (m, 8H, ArH). Anal. calcd. for $C_{18}H_{16}N_2O_3$: C, 70.3; H, 5.19; N, 9.09. Found: C, 70.00; H, 4.99; N, 9.29.

2-Benzo[1,3]dioxol-5-yl-1-(4-methoxy-phenyl)-4-oxo-azetidine-3-carbonitrile (3c). Oil (36%); IR: $\nu = 1772\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.85 (s, 3H, OCH_3), 5.11 (d, 1H, C_3H, $J = 4.3$ Hz), 5.25 (d, 1H, C_4H, $J = 4.3$ Hz), 6.16 (s, 2H, OCH_2O), 7.12–7.34 (m, 7H, ArH). Anal. calcd. for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.35; N, 8.70. Found: C, 66.99; H, 4.15; N, 8.89.

1-(4-Methoxy-phenyl)-2-oxo-4-styryl-azetidine-3-carbonitrile (3d). Solid (35%), mp 141–142°C; IR: $\nu = 1777\,cm^{-1}$; β-lactam (C═O); ^1H NMR

($CDCl_3$; δ/ppm): 3.73 (s, 3H, OCH_3), 4.85 (d, 1H, C_3H, $J = 4.5$ Hz), 5.01 (dd, 1H, C_4H, $J = 4.5$ Hz and 7 Hz), 6.19 (dd, 1H, NCHCH, $J = 7$ Hz and 15 Hz) 6.53 (d, 1H, CHC_6H_5, $J = 15$ Hz), 6.82–7.51 (m, 9H, ArH). Anal. calcd. for $C_{19}H_{16}N_2O_2$: C, 75.00; H, 5.26; N, 9.21. Found: C, 74.89; H, 5.12; N, 9.51.

1-(2-Hydroxy-propyl)-2-(4-methoxy-phenyl)-4-oxo-azetidine-3-carbonitrile (3e). Oil (39%); IR: $\nu = 1760\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 1.21 (d, 3H, CH_3), 3.51–3.82 (m, 2H, NCH_2), 3.73 (s, 3H, OCH_3), 4.02 (m, 1H, CHOH), 4.20 (d, 1H, C_3H, $J = 3.9$ Hz), 4.51 (d, 1H, C_4H, $J = 3.9$ Hz) 6.91–7.25 (m, 4H, ArH). Anal. calcd. for $C_{14}H_{16}N_2O_3$: C, 64.62; H, 6.15; N, 10.76. Found: C, 64.11; H, 5.89; N, 10.95.

1-(2-Hydroxy-propyl)-2-oxo-4-phenyl-azetidine-3-carbonitrile (3f). Oil (40%); IR: $\nu = 1772\,cm^{-1}$; β-lactam (C═O)]; ^1H NMR ($CDCl_3$; δ/ppm): 1.23 (s, 3H, $CHCH_3$), 3.51 (m, 2H, NCH_2), 4.21 (m, 1H, CHOH), 4.25 (d, 1H, C_3H, $J = 4.32$ Hz), 4.65 (d, 1H, C_4H, $J = 4.32$ Hz), 7.12–7.34 (m, 5H, ArH). Anal. calcd. for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17. Found: C, 67.56; H, 5.81; N, 12.35.

3-Chloro-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (3g). Solid (42%), mp 116–118°C; IR: $\nu = 1750\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.78 (s, 3H, OCH_3), 4.55 (d, 1H, C_3H, $J = 4.4$ Hz), 4.95 (d, 1H, C_4H, $J = 4.4$ Hz), 6.95–7.45 (m, 9H, ArH). Anal. calcd. for $C_{16}H_{14}NO_2Cl$: C, 66.78; H, 4.87; N, 4.87. Found: C, 66.52; H, 4.56; N, 4.96.

3-Chloro-1,4-bis-(4-methoxy-phenyl)-azetidin-2-one (3h). Solid (38%), mp 125–126°C; IR: $\nu = 1755\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.78 (d, 1H, C_3H, $J = 4.5$ Hz), 5.28 (d, 1H, C_4H, $J = 4.5$ Hz), 6.87–7.51 (m, 8H, ArH). Anal. calcd. for $C_{17}H_{16}NO_3Cl$: C, 64.25; H, 5.03; N, 4.40. Found: C, 64.11; H, 4.89; N, 4.61.

4-Benzo[1,3]dioxol-5-yl-3-chloro-1-(4-methoxy-phenyl)-azetidin-2-one (3i). Solid (37%), mp 140–142°C; IR: $\nu = 1754\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.52 (d, 1H, C_3H, $J = 3.9$ Hz), 4.90 (d, 1H, C_4H, $J = 3.9$ Hz), 5.95 (s, 2H, OCH_2O), 7.01–7.55 (m, 8H, ArH). Anal. calcd. for $C_{17}H_{17}N_2O_4Cl$: C, 60.99; H, 5.08; N, 4.18. Found: C, 60.78; H, 4.89; N, 4.36.

3-Chloro-1-(4-methoxy-phenyl)-4-styryl-azetidin-2-one (3j). Solid (42%), mp 148–149°C; IR: $\nu = 1760\,cm^{-1}$; β-lactam (C═O); ν=1620 cm^{-1}; (C = C); ^1H NMR ($CDCl_3$; δ/ppm): 3.83 (s, 3H, OCH_3), 4.59 (d, 1H, C_3H, $J = 4$ Hz), 4.89 (dd, 1H, C_4H, $J = 4$ Hz and 6 Hz), 6.19 (dd, 1H, NCHCH, $J = 9$ Hz and 14 Hz), 6.53 (d, 1H, CHC_6H_5, $J = 14$ Hz), 6.99–7.53 (m, 9H, ArH). Anal. calcd. for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.10; N, 4.47. Found: C, 68.61; H, 4.93; N, 4.72.

3-Chloro-1-(2-hydroxy-propyl)-4-(4-methoxy-phenyl)-azetidin-2-one (3k). Oil (44%); IR $\nu = 1760\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 1.33 (d, 3H, CH_3), 2.75 (d, 2H, NCH_2, $J = 7.5$ Hz), 3.35 (m, 1H, CHOH), 3.81 (s, 3H, OCH_3), 4.11 (d, 1H, C_3H, $J = 4.1$ Hz), 4.71 (d, 1H, C_4H, $J = 4.1$ Hz), 6.89–7.05 (m, 4H, ArH). Anal. calcd. for $C_{13}H_{16}NO_3Cl$: C, 57.88; H, 5.93; N, 5.19. Found: C, 57.74; H, 5.81; N, 5.35.

3-Chloro-1-(2-hydroxy-propyl)-4-phenyl-azetidin-2-one (3l). Oil (40%); IR: $\nu = 1756.3\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 1.35 (d, 3H, CH_3), 2.92 (d, 2H, CH_2N), 3.41 (m, 1H, CHOH), 4.09 (d, 1H, C_3H, $J = 4.5$ Hz), 4.69 (d, 1H, C_4H, $J = 4.5$ Hz), 6.89–7.25 (m, 5H, ArH). Anal. calcd. for $C_{12}H_{14}NO_2Cl$: C, 60.13; H, 5.85; N, 5.86. Found: C, 60.09; H, 5.79; N, 5.98.

3-Chloro-4-(4-methoxy-phenyl)-1-phenethyl-azetidin-2-one (3m). Oil (41%); IR: $\nu = 1752.5\,cm^{-1}$; β-lactam (C═O); ^1H NMR ($CDCl_3$; δ/ppm): 2.56 (t, 2H, $CH_2C_6H_5$), 3.13 (t, 2H, NCH_2), 3.82 (s, 3H, OCH_3), 4.24 (d, 1H, C_3H, $J = 4.5$ Hz), 4.59 (d, 1H, C_4H, $J = 4.5$ Hz), 7.21 (m, 9H, ArH). Anal. calcd. for $C_{18}H_{18}NO_2Cl$: C, 68.46; H, 5.71; N, 4.44. Found: C, 68.61; H, 5.46; N, 4.56.

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