Tetrahedron Letters, Vol.32, No.1, pp 121-124, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

STUDIES ON N-METALLO IMINES: SYNTHESIS OF N-UNSUBSTITUTED AZIRIDINES FROM N-TRIMETHYLSILYL IMINES AND LITHIUM ENOLATES OF α-HALO ESTERS.

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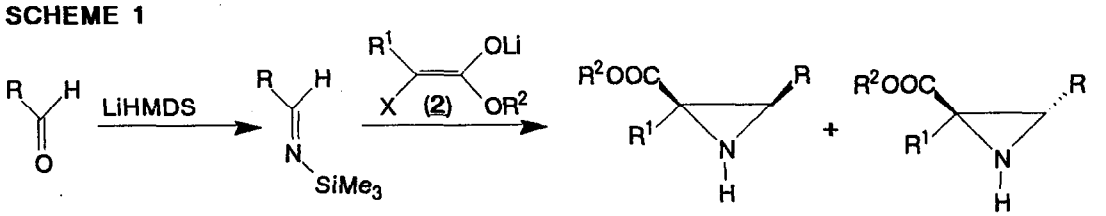
Summary: Addition of lithium enolates of 2-halo carboxylic esters to N-trimethylsilyl imines results in the formation of 1*H* - aziridine derivatives, in the Darzens fashion, with high *cis*-selectivity.

The synthesis of suitably functionalized aziridines is currently of great interest due to the increasing use of these compounds in organic chemistry[1]. In the course of our studies on the synthesis and applications of N-trimethylsilylimines and N-aluminum imines[2] we have recently demonstrated the usefulness of these reagents in the synthesis of β-lactams antibiotics[3], amines[4] and 1,2-amino alcohols[5] . We wish to report our preliminary studies on a convenient "one pot - two steps" synthesis of 1*H*-aziridines starting from N-trimethylsilyl imines (1) and α-halo ester enolates (2) using the synthetic sequence depicted in the Scheme 1.

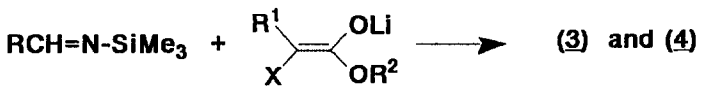
SCHEME 1

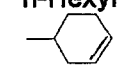


(1) (3) (4)

All the N-trimethylsilyl imines used in this study were prepared by standard methods[6]. In a typical procedure a solution of *t*- butyl 2-chloroacetate (5 mmol, 0.752 g) in THF (10 ml) is added to a solution of LiHMDS (Aldrich) (6 ml of 1 M THF solution) in 100 ml of THF at a temperature below -80°C. The reaction is stirred at the same temperature for 15 min. To this enolate is added by syringe, over a period of 30 min, a previously prepared THF solution of N-trimethylsilylimine of heptanal obtained by treatment of a THF solution of aldehyde (5 mmol) with an equimolar solution of lithium hexamethyl disilylamide (LiHMDSA) in THF at -78°C for 10 min. The temperature is allowed to reach -30°C and the stirring is continued for 2 hrs. At this point 2 ml of H_2O are added, the reaction mixture stirred for further 10 min at the same temperature, and the THF removed under vacuum at room temperature. The residue is treated with pentane and filtered over Celite. The pentane solution is dried ($MgSO_4$) and the solvent removed. The yellow oil is chromatographed over a column of buffered silica gel[7], eluting with hexane/ethyl acetate 8/2. to give (3a) (0.590 g, 52%) as an oil. Following this procedure a number of aziridines could be synthesized (Table 1)[8].

Table 1: Aziridines from ester enolates and silylimines:



Entry	X	R	R^1	R^2	Yield %	Cis/ trans
a	Cl	n-Hexyl	H	*t* -Bu	52	100/0
b	Br	n-Hexyl	H	*t* -Bu	40	100/0
c	I	n-Hexyl	H	*t* -Bu	traces	nd*
d	Br	n-Heptyl	H	*t* -Bu	40	100/0
e	Br	n-Octyl	H	*t* -Bu	40	100/0
f	Br	Cyclohexyl	H	*t* -Bu	10	100/0
g	Br	n-Hexyl	Me	*t* -Bu	60	40/60
h	Br		H	*t* -Bu	25	100/0

*Not determined.

From the results reported it is clear that enolizable as well as nonenolizable N-trimethylsilylimines may be used. As the cyclization reaction takes place at a temperature between -40 and -30 °C, *tert*-butyl ester enolates proved to be more convenient than the corresponding ethyl derivative being more stable toward decomposition.[9]

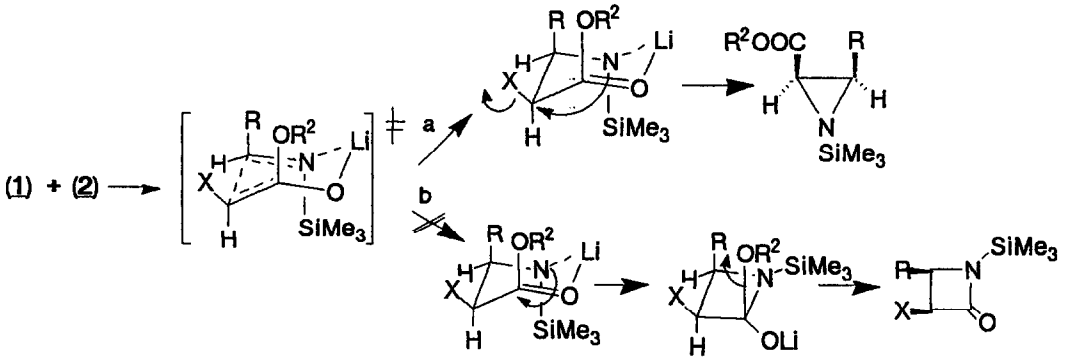
The reaction is highly *cis*-stereoselective[10], no traces of the *trans* isomer could be detected except in the case of an a-alkylsubstituted halo-ester (entry **g**)[11]. These facts are consistent with a Zimmerman-Traxler transition state[12] of the addition of the ester enolate to the N- trimethylsilylimine, followed by ring closure *via* intramolecular

nucleophilic displacement of the acyclic intermediate (Scheme 2). In the proposed mechanism, the geometry of the enolate[13] and of the silylimine[14] is assumed to be E.

An interesting feature of this reaction is the complete absence from the reaction mixture of products containing the β-lactam ring as outcome of a faster intramolecular nucleophilic displacement of the halogen atom (Scheme 2 *path a*) *versus* the addition-elimination reaction (*path b*)[15].

Mechanistic aspects as well as the application of this technology to the synthesis of homochiral aziridines are now actively investigated and will be reported in due course.

Scheme 2



Acknowledgement: We gratefully acknowledge the "Progetto Finalizzato Chimica Fine e Secondaria II" and Ministero Pubblica Istruzione (Fondi 60%) for generous support.

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7 The buffered silica gel was prepared suspending 150g of silica gel (Merck, 200-400 Mesh) in 500 ml of a phosphate buffer solution (pH6.8). After stirring for 2 h, the silica gel was filtered and dried at 120°C overnigh

8 Yields are reported for isolated chromatographically pure products and have not been optimized. ^{1}H NMR, ^{13}C NMR and GC/MS spectra were enterely consistent with the assigned structures Selected data as follow: (3a) I.r. (cm^{-1}, film) 3250, 1721. M.S. 185, 168.^{1}H NMR ($CDCl_3$ 200 MHz) 0.8 (3 H, t); 1.2-1.65 (19 H, m; NH); 2.05 (1 H, m); 2.45 (1 H, d, J=6.3 Hz). ^{13}C 170.00 (s); 81.60 (s); 38.62 (d); 35.37(d); 31.60 (t); 28.96 (t); 28.94 (t); 28.00 (q); 27.78 (t); 22.47 (t); 13.94 (q). (3f) I.R. (cm^{-1} CCl_4) 3250, 1720, 1225. ^{1}H NMR 1.0-1.8 (m, 20 H and NH); 1.95 (m, 1 H); 2.3 (d, J=6.1 Hz, 1H) . ^{13}C NMR 170.38 (s); 81.58 (s); 43.64 (d); 36.89 (d); 35.04 (d); 31.46 (t); 30.95 (t); 27.74 (q); 25.85 (t); 25.27 (t); 25.23 (t). MS (m/e) 169, 152, 124. (3g) I.R. (film) 3250, 1717, 1216. ^{1}H NMR ($CDCl_3$) 0.8 (t, 3 H); 1.15-1.6 (m, 22 H and NH); 2.15 (m, 1 H). 13C NMR ($CDCL_3$) 173.85 (s); 81.39 (s); 43.28 (d); 38.75 (s); 31.68 (t); 28.98 (t); 28.85 (t); 27.85 (q); 27.48 (t); 22.46 (t); 13.91 (q); 13.83 (q). M.S. (m/e) 185, 140.(4g) I.r. (film, cm^{-1}) 3250, 1717, 1216. ^{1}H NMR ($CDCl_3$) 0.8 (3 H, t); 1.75 (1 H, m); 1.1-1.5 (m, 22 H and NH). ^{13}C NMR ($CDCl_3$): 171.71 (s); 81.43 ((s); 46.26 (d); 40.69 (s); 31.73 (t); 29,00 (t); 28.42 (t); 27.93 (t); 22.50 (t); 20.32 (q); 13.95 (q). M.S.(m/e) 185, 140. (3h) I.R. (cm^{-1} CCl_4) 3230, 1725, 1220. ^{1}H NMR ($CDCl_3$) 1.2-2.1 (m, 17 H and NH); 2.55 (m, 1 H); 5.6 (m, 2 H). ^{13}C NMR ($CDCl_3$) 170.00 (s); 127.13 (d); 125.01 (d); 81.67 (s); 43.10 (10); 35.27 (d); 32.86 (d); 29.35 (t); 28.03 (q); 26.99 (t); 24.25 (t). M.S. (m/e) 208, 167, 122.

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(Received in UK 31 October 1990)