Reaction of Silyl Ketene Acetals with *N*-Trimethylsilyl Imines: a Route to *N*-Unsubstituted Azetidin-2-ones

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Reaction of *N*-trimethylsilyl imines with silyl ketene acetals in the presence of ZnI_2 and t-butyl alcohol, followed by treatment *in situ* of the intermediate *N*-silyl β-aminoesters with MeMgBr, leads to *N*-unsubstituted azetidin-2-ones in good yield.

N-Unsubstituted azetidin-2-ones offer major synthetic opportunities in the synthesis of β-lactam antibiotics such as the carbapenems and penams[1] and the monobactams.[2] Routes to such potentially valuable intermediates have hitherto involved either assembly of an *N*-functionalised β-lactam followed by liberation, or degradation of a naturally occurring bicyclic β-lactam.[1] We describe a one-pot procedure for the assembly of a variety of *N*-unsubstituted azetidin-2-ones, based on reaction of *N*-trimethylsilyl imines with silyl ketene acetals.

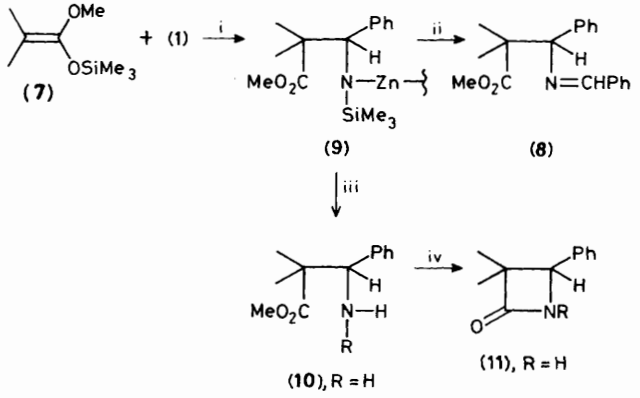
N-Silyl imines, particularly those derived formally from diaryl ketones,[3] have been known for some time;[4] enolisable carbonyl compounds do not lead to pure silyl imines, owing to tautomeric equilibration with enamines. Further, the *N*-trimethylsilyl imine derived from benzaldehyde has been reported[5] to react with diphenylketene to produce 3,3,4-triphenylazetidin-2-one in low yield. Recently, the first direct route[6] to *N*-unsubstituted azetidin-2-ones was described; reaction of certain ester lithium enolates with several *N*-trimethylsilyl imines provided the target compounds directly. A similar sequence employing *N*-aryl imines had been revealed[7] earlier. It is these reports which prompt us to communicate our results.

$$\mathrm{RCHO} \xrightarrow{\text{i, ii, iii}} \mathrm{RCH{=}NSiMe_3}\ (76\text{—}95\%)$$

(**1**), R = Ph
(**2**), R = 2-furyl
(**3**), R = PhCH=CH
(**4**), R = PhC≡C
(**5**), R = $Me_3SiC{\equiv}C$
(**6**), R = $Me_3SiCH{=}CH$

Scheme 1. *Reagents*: i, $LiN(SiMe_3)_2$ (1 equiv.), tetrahydrofuran, 0 °C, 30 min; ii, Me_3SiCl (1 equiv.), 30 min; iii, non-aqueous isolation.

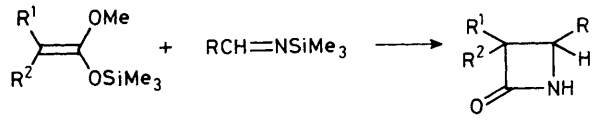
At the outset, a variety of *N*-trimethylsilyl imines, (**1**)—(**6**), was prepared in high yield from the corresponding aldehydes by a modification of published methods (Scheme 1). These imines† were all liquids and, although requiring non-aqueous isolation techniques, could be distilled readily (Kugelrohr).



Scheme 2. *Reagents*: i, ZnI_2 (1 equiv.), Et_2O, 20 °C; ii, (**1**); iii, Bu^tOH (1 equiv.); iv, MeMgBr (3 equiv.).

† These compounds were characterised by high resolution mass spectrometry, and i.r. and ^1H n.m.r. spectroscopy.

Table 1. Preparation of the *N*-unsubstituted azetidinones (**11**).



R^1	R^2	Imine	% Yield of (**11**)	*cis* : *trans*-Ratio
Me	Me	(**1**)	75	
		(**2**)	76	
		(**4**)	78	
		(**6**)	75	
H	H	(**1**)	27[a]	
H	PhO	(**2**)	58	1 : 0.77
Et	H	(**1**)	61	1 : 9[b]
Me	H	(**4**)	82	1 : 3
		(**5**)	62	1 : 1.5
Ph	H	(**5**)	53	1 : 12[b]

[a] Using t-butyldimethylsilyl ketene acetal. [b] Initial additions at −78 °C.

The first catalyst chosen for their reaction with silyl ketene acetals was fluoride ion. Although successful for the direct preparation of certain of the target β-lactams, this sequence occasionally proved irreproducible, possibly owing to the vagaries associated[8] with obtaining catalytically active 'anhydrous' tetrabutylammonium fluoride. Other fluoride sources, such as KF–18-crown-6, proved disappointingly slow in effect, with deleterious side reactions competing.

Alternative activation of the imine component with a Lewis acid was initially attempted using $TiCl_4$, a reagent employed successfully in a related reaction[9,10] with *N*-aryl and *N*-alkyl imines. This and a variety of other Lewis acids proved to be of limited utility, but it was observed that reaction between the ketene acetal (**7**) and the imine (**1**) in the presence of ZnI_2 produced the imino ester (**8**) in high yield (Scheme 2). On the assumption that this had been formed by competitive transamination between unchanged imine (**1**) and the metalloamide (**9**), the same reaction was performed in the presence of one equivalent of a weak proton source, t-butyl alcohol. Gratifyingly, this yielded, on isolation, solely the β-amino ester (**10**) in high yield. Further, treatment of the reaction mixture prior to work-up with MeMgBr[11] gave, on isolation, the *N*-unsubstituted azetidin-2-one (**11**) in a yield of 75%.

Employing this general technique of complexation of the imine with ZnI_2 in diethyl ether, followed by immediate and sequential addition of the ketene acetal and t-butyl alcohol, and, after 2—3 h, of MeMgBr, the range of β-lactams‡ shown in Table 1 was obtained. A certain *trans*-stereoselectivity was observed, in contrast to the *cis*-stereoselectivity which prevails when ester lithium enolates are employed. The full synthetic potential of several of these β-lactams is under active investigation.

We thank the S.E.R.C. for financial support, and A. McLeod for some initial experiments.

Received, 4th February 1985; Com. 153

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‡ These compounds were fully characterised by elemental analysis, mass spectrometry, and i.r. and ^1H n.m.r. spectroscopy.