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THE PREPARATION OF β-LACTAM HOMOENOLATES

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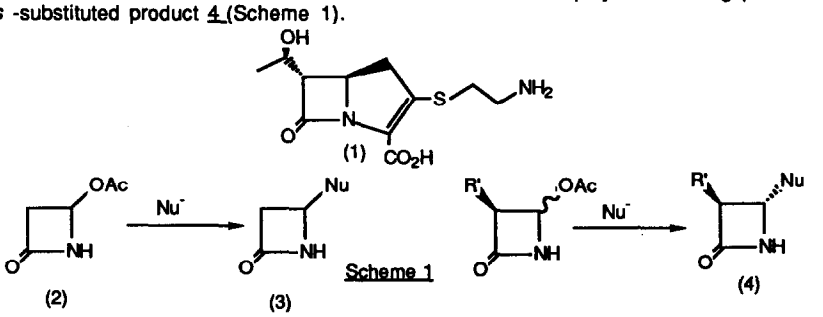
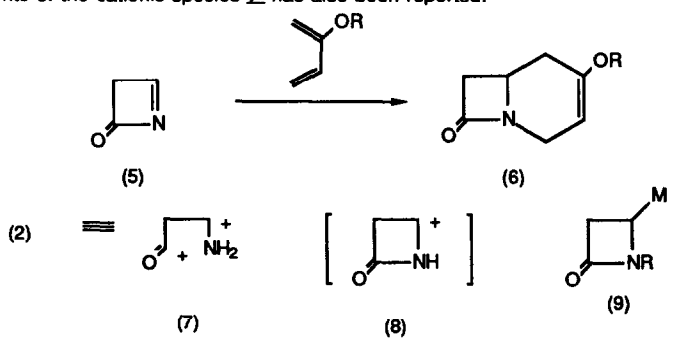
The synthesis of 4-(tri-n-alkylstannyl)azetidin-2-ones has been accomplished via a displacement reaction of 4-substituted azetidin-2-ones with tin centred anions. The utility of these intermediates as homoenolates is presented.

The utilisation of pre-functionalised β-lactams as templates for the construction of mono- and polycyclic β- lactams has now become an established synthetic protocol[1]. With the isolation of β-lactams possessing novel structural types[2] (e. g. Thienamycin, 1) the ability to prepare 4-substituted azetidin-2-ones has become a major synthetic objective[3]. To this end, a number of workers have reported that the readily available[4] 4-acetoxyazetidin-2-one, 2 reacts with a variety of hetero[5a] and carbon centred nucleophiles[5b], affording rapid access to the functionalised substrates 3. Of significant synthetic importance, is the observation[6] that such reactions can proceed with a high degree of stereochemical control when 3,4-di-substituted β-lactams are employed, affording predominantly the *trans* -substituted product 4 (Scheme 1).



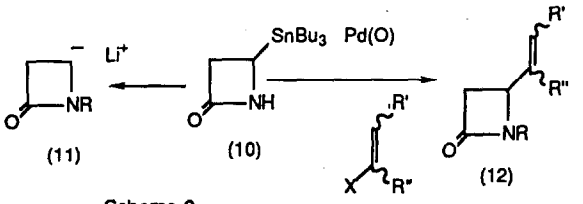
Scheme 1

Recently[7a], the presumed intermediates in these reactions, the azetinones 5 have been captured in hetero Diels-Alder reactions with electron rich dienes, providing a particularly concise approach to the homo-Thienamycin ring system 6. Additionally[7b], the use of functionalised monocyclic β-lactams as synthetic equivalents of the cationic species 7 has also been reported.



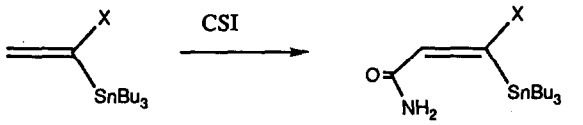
In all of these reports, reaction proceeds *via* an incipient cationic species 8. We considered that the synthetic utility of templates such as 2 could be significantly enhanced if functionalisation at C-4 could be achieved *via* the synthetic equivalent of a carbanionic or masked carbanionic intermediate 9 . Hence intermediates such as 9 could then serve as synthetically useful Umpoled[8] reagents not only for the

elaboration of bi-cyclic ß-lactams but as a general route for the preparation of novel non-protienogenic ß-amino acids[9]. We sought therefore a method for the synthesis of the tin substituted ß-lactams 10 , as we believed that such intermediates could serve as a source of the homoenolate[10] anions 11 (*via* transmetallation) or could be utilised in palladium mediated coupling[11] reactions with a variety of aryl/vinyl halides to afford the func tionalised substrates 12 (Scheme 2). Given that there is a paucity[12] of stereochemical information relating to the course of the palladium catalysed processes, we considered that such an undertaking could also provide valuable mechanistic information on these coupling reactions.



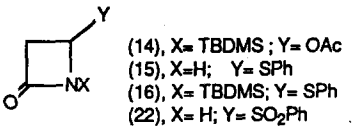
Scheme 2

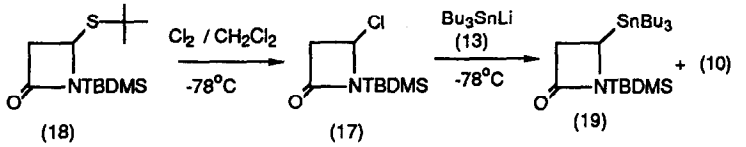
The recent report by Nativi[13] prompts us to communicate our findings in this area. Our initial[14] attempts to prepare tin-functionalised ß-lactams via a cycloaddition reaction between CSI and variously functionalised vinyl stannanes either led to the formation of acyclic materials in high yield (Scheme 3; X = SPh) or to complex reaction mixtures
(Scheme 3; X = H).



Scheme 3

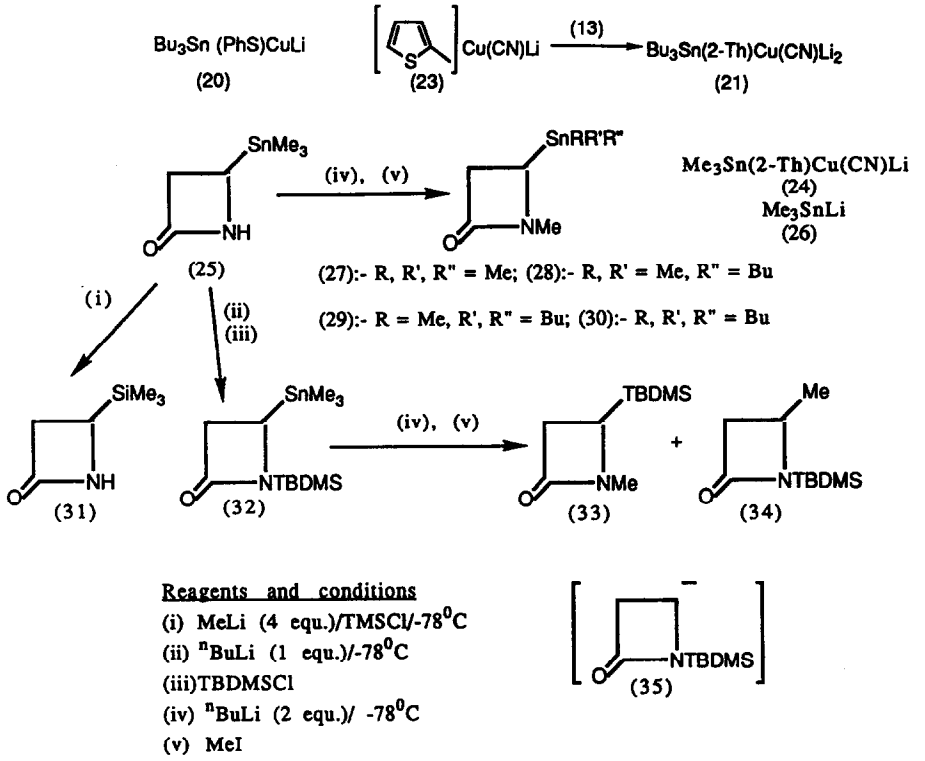
Accordingly the reaction of tin centred nucleophiles with a number of 4-substituted azetidin-2-ones was next investigated. However, reaction of the tin anion[15] 13 with a variety of 4-substituted ß-lactams (14, 15, 16) even at low temperatures merely led to the disruption of the ß-lactam ring. Encouragingly, reaction of the highly reactive and somewhat unstable 4-chloro derivative[16] 17 (readily available from the thioether 18) at low temperatures (-78°C) afforded a chromatographically separable[17] mixture of the desired tin substituted ß-lactams 10 and 19 in moderate overall yield (30%, 10:19= 1:2).





Given the instability of the ß-lactam 17 (ß-lactam 17 was prepared *in situ* immediately prior to use) we sought a suitable modification of the above substitution reaction which would enable the introduction of the tin moiety into more complex ß-lactams without the necessity of preparing highly reactive intermediates.

Unfortunately, reaction of the tin cuprate[18] 20 with the ß-lactams (2, 14, 15, 16) led either to recovery of starting material or to complete disruption of the ß-lactam ring. We were encouraged however by recent reports by Lipshutz[19] who has demonstrated the significant synthetic advantages of utilising higher order mixed organo cuprates in a number of substitution reactions. We therefore decided to prepare the higher order tin cuprate[20] 21 in the hope that it would effect the desired substitution reaction with a less reactive substrate.



Reagents and conditions

(i) MeLi (4 equ.)/TMSCl/-78^{0}C

(ii) ^{n}BuLi (1 equ.)/-78^{0}C

(iii)TBDMSCl

(iv) ^{n}BuLi (2 equ.)/ -78^{0}C

(v) MeI

Gratifyingly, not only did reaction of the higher order tin cuprate 21 with the 4-chloroazetidi-2-one 17 proceed in slightly higher overall yield (35%, 19:10 = 1:5) but displacement at C-4 of the stable sulphone[4] 22 resulted in the isolation of the ß-lactam 25 in only moderate yield (31%), whereas reaction of the sulphide 15 with the anion 26 (3 equ., THF, 48 hrs., RT) proved to be more synthetically useful (45% yield of 25). This result complements Nativi's findings in that displacement reactions are indeed possible and in marginally higher yieldsusing simple tin anions on 4-(phenylthio)azetidin-2-ones. Having developed a general route to tin-functionalised ß-lactams such as 10 and 25 a study of their reactivity was undertaken. In contrast to Nativi's findings on the acylation of such substrates all attempts to perform palladium catalysed coupling reactions on the tin-substituted ß-lactams 10, 19, 25 and 32 with vinyl / aryl halides met with little success, although their transmetallation chemistry to afford reactive homoenolates appears to be more promising. Attempted transmetallation of the lactam 25 (^{n}BuLi, 2 equ. -78^{0}C, 5 min.) followed by reaction with methyl iodide merely afforded the N-methyl ß-lactam 27 (26%) and the products 28 (6%), 29 (4%) and 30 (7%), presumably via a redistribution process. However, exposure of the N-protected ß-lactam 32 to ^{n}BuLi (1 equ., -78^{0}C, 3 mins.) followed by a methyl iodide quench afforded an inseparable mixture of products containing the C-4 functionalised ß-lactams 33 and 34. It is reasonable to suggest that both products arise *via* the homoenolate 35 which then undergoes both intra- and intermolecular alkylation. In order to circumvent problems arising from protecting group instability, the generation of the di-anion 11 was next attempted. *In situ* generation of the supposed di-anion 11 (R = Li)(MeLi, 1.4 M in ether, 4 equ., -78^{0}C, 60 min.) in the presence of chlorotrimethylsilane (4.5 equ.) afforded 4-trimethylsilylazetidi-2-one [21], 31, in fair overall yield (53%) after chromatography [22]. To our knowledge this represents the first report of the generation and trapping of an otherwise unstablilised carbanion [23] at C-4 of a monocyclic ß-lactam.

Given the ready availability and stability of the sulphone 22 and the sulphide 15 we anticipate that the synthesis of a number of tin substituted ß-lactams will result. We are currently investigating the generality of this process in related heterocyclic ring systems and delineating the synthetic utility of the derived aminomethylstannanes as precursors to functionalised homoenolates.

General Procedure:- Preparation of tin cuprate 21.

To a solution of di-isopropylamine (0.15ml, 0.95 mmol) in anhydrous THF (5ml) under an atmosphere of nitrogen at 0°C was added n-BuLi (0.62 ml, 1.6 Mol. soln. in hexane, 0.95 mmol). The resulting mixture was stirred for a period of 5 minutes and freshly redistilled tri-n-butyl tin hydride (0.25 ml, 0.95 mmol) was added. After 15 minutes at 0°C the resultant pale green solution was cooled to -78°C and lithium 2-thienylcyanocuprate 23 (3.8 ml, 0.25 Mol. soln. in THF (Aldrich), 0.95 mmol) was added dropwise. After stirring for an additional period of 15 minutes at -78°C the higher order tin cuprate 21 was used without further delay.

Preparation of β-lactam 10.

To a solution of the freshly prepared cuprate 21 (20 mmol) at -78°C was added 4-phenylsulphonylazetidin-2-one 22 (2.0g, 9.5 mmol). The mixture was allowed to warm up to -10°C and then recooled to -78°C . Ammonium hydroxide/saturated ammonium chloride (1:9, 10 ml) was added and the mixture allowed to warm up to room temperature. The reaction mixture was extracted with ether (3 X 100ml) and the combined extracts washed with brine (1 X 50 ml), dried ($MgSO_4$) and evaporated to dryness. Flash chromatography (7% ethyl acetate in dichloromethane) of the residue afforded the β-lactam as a yellow/green oil (1.36 g, 40%). Selected spectroscopic data:- ir 3220, 1746 cm^{-1}; ^1H nmr ∂ ($CDCl_3$, 300 MHz)) 0.9 (15H, m), 1.3 (6H, m), 1.5 (6H, m), 3.0 (1H, ddd, J=15, 3, 1.4 Hz), 3.35 (1H, ddd, J=15, 5.9, 1.5 Hz), 3.45 (1H, dd, J= 5.9, 3 Hz), 5.9 (1H, brd. exch.); m/e (M+1) $C_{15}H_{32}NOSn$ requires 362.1505; found 362.1512.; microanalysis $C_{15}H_{31}NOSn$ requires C, 49.8; H, 8.85; N,4.3; Sn 33.1%. Found C, 50.05; H, 8.7; N, 3.9; Sn, 32.95%.

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(21) M.p. 49-51°C,(Lit[13].49-51); ^1H nmr ($CDCl_3$, 200 MHz) ∂ 0.058 (9H, s), 2.77 (1H, ddd, J = 14.4, 2.2, 2.2 Hz), 3.04 (1H, dd, J = 6.2, 2.5 Hz), 3.14 (1H, ddd, J = 14.4, 6.1, 1.3 Hz), 5.85 (1H, brd. s); ir ν_{max} 3239, 1746cm^{-1}; m/e (CI, NH_3) 161 (M + 18, 100%), 144 (M + 1, 58%), 102 (33%).

(22) Presumably the intermediate N,C-bis TMS derivative undergoes facile N-desilylation upon work-up and chromatography.

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