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Synthesis of 4-(Trimethylsilyl)- and 4-(Tributylstannyl)-2-azetidinones and some of their Applications to β-Lactam Chemistry

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Summary. *Silylcupration and stannylcupration of 4-acetoxy-2-azetidinones gave the corresponding silyl- and stannyl-β-lactams. The first results on the reactivity of these products with electrophiles are reported: 4-(tributylstannyl)- 2-azetidinone undergoes the palladium catalyzed coupling with electrophiles allowing an "umpolung" acylation of the position 4 of the β-lactam ring.*

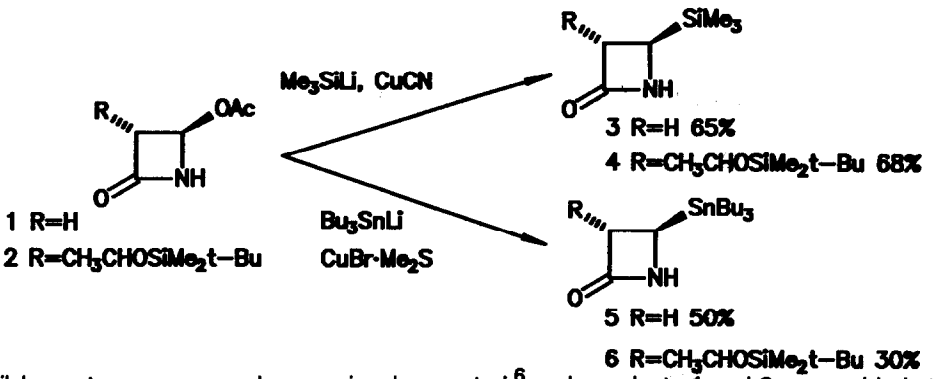
The chemistry of the β-lactam ring is continuously developing and great efforts have been made to search for new methodologies and reagents suitable for the preparation of β-lactam antibiotics.[1]

Organosilicon reagents have been used mainly as protecting groups of the -OH or -NH functionalities or during the formation of the heterocyclic ring.[2] Several 3-(trimethylsilyl)-2-azetidinones have been reported to be formed by silicon migration[3] or by silylation of the ring after treatment with LDA.[4]

Analogously, organostannanes (mainly allylstannanes) have been used to introduce allylic groups on the heterocyclic ring system[5].

We report here the preparation of 4-(trimethylsilyl)- and 4-(tributylstannyl)-2-azetidinones (compounds **3**, **4**, **5** and **6** respectively) and our first results concerning their possible use as synthetic buildings blocks in β-lactam chemistry.

The introduction of the group IVB elements was performed by silyl- and stannylcupration of 4-acetoxy-2-azetidinones **1** and **2**, as reported in the following scheme.

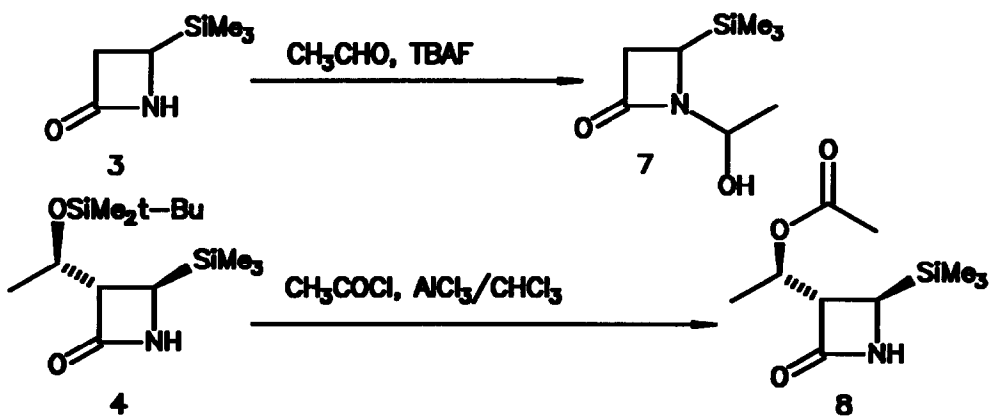


The silylcuprate was prepared as previously reported,[6] and products **1** and **2** were added at -30°C, followed by warming to room temperature, stirring for two hours and aqueous workup.[7] Stannylcupration was done using tributylstannyllithium (from tributylstannane and LDA in THF) and CuBr.Me_2S in THF[8] at -50°C for three hours followed by quenching with an NH_4Cl solution at -30°C and a rapid workup[7].

In both cases the cuprates were the reagents of choice. Attempts to directly use the silyl- or stannyllithium derivatives gave worse results: with trimethylsilyllithium traces of **3** were obtained together with several by-products, whereas we did not observe any reaction using tributylstannyllithium. However in both cases better yields were obtained using at least a two fold excess of the cuprate reagents with respect to **1** or **2**. The introduction of the organometallic framework on **2** was stereocontrolled giving the *trans* derivatives **4** and **6** as evidenced by ^1H NMR analysis ($J_{3,4}$ = 3 Hz, typical of a 3-4 *trans* relationship in a β-lactam ring).[9]

Products **3** and **4** proved to be very stable and could be handled without any problem, whereas **5** and **6** were more prone to decomposition under strong hydrolytic conditions.

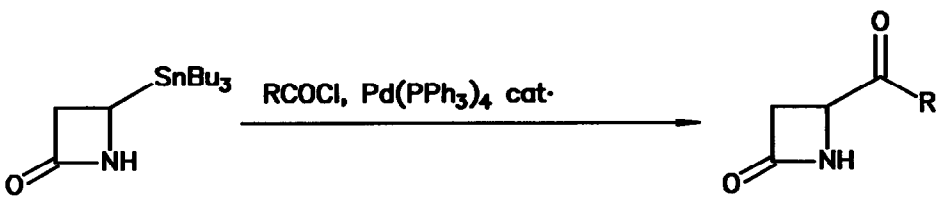
Many attempts were made to replace the trimethylsilyl group with an electrophile using either a Lewis acid activated electrophile or in the presence of fluoride ions. Nevertheless the only remarkable results were the reactions of the -NH group of **3** with acetaldehyde in the presence of TBAF and the acylation of the -$OSiMe_2$t-Bu group of **4** using acetyl chloride and $AlCl_3$ in $CHCl_3$.



Product **7** was isolated in 65% yield as a single diastereoisomer with the opposite stereochemistry of the product obtained by reaction of **3** with LDA and quenching with acetaldehyde.[10] Product **8** was isolated in 90% yield after column chromatography on silica gel.

Compounds **5** and **6** were less hydrolytically stable as expected on the basis of the presence of the α-heterosubstituted C-Sn bond.[11]

Product **5** underwent the Stille palladium catalyzed coupling reaction[12] with acylchlorides to give the products reported in the following scheme.



5 **9** R=$C_6H_5CH_2$

10 R=$(CH_3)_2CHCH_2$

In this case we obtained an acylation of the position 4 of a β lactam ring with an "umpolung" functionalisation that gives products generally obtained only by ring closure or manipulation of other functional groups.[13]

Some extensions of this methodology applied to the synthesis of other β-lactam derivatives are currently under way in our laboratories.

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