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REGIOSELECTIVE TRANSFORMATION OF INTERNAL ALKYNES TO UNSYMMETRICAL KETONES. NOVEL ROUTES TO KEY INTERMEDIATES FOR THE SYNTHESIS OF CARBAPENEM AND CARBACEPHEM SKELETONS

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Summary: *Hydrostannation of the internal alkynes (2,7) with tri-n-butyltin hydride afforded the alkenylstannanes (3,8) regioselectively, from which the ketones (6,11,12), intermediates for the synthesis of carbapenem and carbacephem skeletons, were synthesized.*

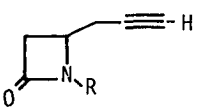
During the course of our synthetic studies on β-lactam antibiotics, we became interested in the conversion of the monosubstituted acetylene (1) to carbapenem and carbacephem skeletons. In these studies, we have found that hydrostannation of internal acetylenes, followed by the conversion of the resulting alkenyltrialkylstannanes to ketones, offers a new useful method for the regioselective synthesis of unsymmetrical ketones from disubstituted acetylenes.[1] In this communication, we wish to report novel synthetic routes to several key intermediates for the synthesis of carbapenem and carbacephem skeletons by utilizing organostannane chemistry.

The versatile intermediate (1b) was efficiently synthesized as follows. Treatment of 4-phenylsulfonylazetidin-2-one[2] with 5 equiv of propargylmagnesium bromide in THF-ether (1:1) at -25° to 0°C for 2 hr gave the monosubstituted acetylene (1a) in 84% yield [IR (neat) 3299, 2125, 1735 cm^{-1}].[3] None of the allenic product was detected in the crude reaction products. Protection of 1a as silyl derivative under the standard conditions afforded 1b quantitatively. The monosubstituted acetylene (1b) was then converted to the lithium acetylide (1.1 equiv of LDA in THF at -78°C), which underwent alkylation to 2b in 82% yield when treated with 1.1 equiv of methyl iodide and HMPA (THF-HMPA, 10:1, initially at -78°C and then gradually warmed to room temperature).

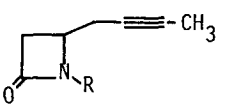
Hydrostannation of the desilylated alkyne (2a), obtained by treatment of 2b with hydrogen chloride in aqueous methanol (94%), was first carried out hopefully to obtain the carbapenem precursor (3a). Treatment of 2a with 1.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN at 91°C for 0.5 hr[4] yielded the alkenyltributylstannanes in 84-88% yield as a mixture of the regioisomers (3a and 4a).[5] Although 1-tributylstannyl-1-alkenes are generally unstable even under slightly acidic conditions, the alkenylstannanes (3,4) were unexpectedly stable and could be purified by silica gel column chromatography without any decomposition.

As we expected, the higher moving major regioisomer (56-59% yield) was found to be the desired alkenylstannane (3a) [PMR ($CDCl_3$,TMS) δ1.74 (broad d, J=6Hz, 3H, CH_3), 6.18 (broad q, J=6Hz, 1H, olefinic proton)], while the more polar isomer (28-29% yield) proved to be the other regioisomer (4a) [PMR ($CDCl_3$,TMS) δ1.88 (broad s, 3H, CH_3), 5.93 (broad t, J=6Hz, 1H, olefinic proton)].[6] From these results, it might be suggested that the regiochemistry of this hydrostannation is governed mainly by the coordinative effect of the lone-pair electrons of nitrogen. The unexpectedly small steric requirement of the tributyltin moiety may be rationalized in terms of the length of the C-Sn bond (*ca.* 2.2 Å). Even in the case of the silylated alkyne (2b), the regioselective hydrostannation took place similarly, giving 3b and 4b in a ratio of *ca.* 3:2 (94% yield).

Conversion of 3a[7] to the corresponding ketone (6) was performed as follows. Epoxidation of 3b with *m*-chloroperbenzoic acid afforded 5 in 88% yield, which was subsequently treated with formic acid (*ca.* 20 equiv) in methylene chloride at room temperature for *ca.* 68 hr. After treatment with lithium hydroxide in aqueous THF,[8] the desired ketone (6) [PMR ($CDCl_3$,TMS) δ1.08 (t, J=8Hz, 3H, CH_3), 2.47 (q, J=8Hz, 2H, CH_2CH_3)] was obtained in *ca.* 70% yield. The



1a: R=H
1b: R=Si≠



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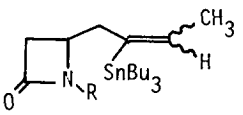
2b: R=Si≠



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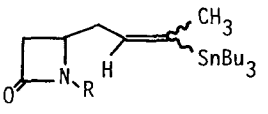
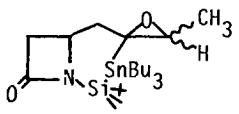
3b: R=Si≠



4a: R=H
4b: R=Si≠



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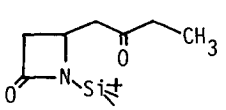

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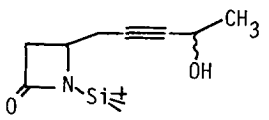

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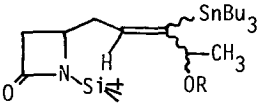
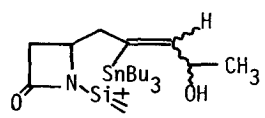


8a: R=H
8b: R=Ac



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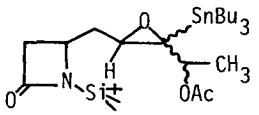

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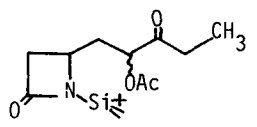

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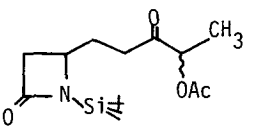

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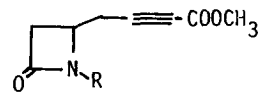
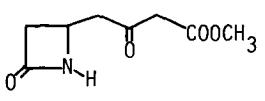


13a: R=H
13b: R=Si≠



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ketone (6) should be useful for the construction of the biologically interesting 1-carbapen-2-em ring system.[9] Furthermore, the use of different alkyl halides at the step (1b→2b) would allow for potential introduction of alternative substituents at the position 2 (carbapenem numbering).

Next, the monosubstituted alkyne (1b) was converted to the propargylic alcohol (7) by the coupling reaction with acetaldehyde (1.2 equiv of LDA in THF at -78°C, then 2 equiv of acetaldehyde) in 71% isolated yield (17% recovery of 1b). With the aim of synthesizing the carbacephem precursor (8a),[10] hydrostannation of 7 was attempted. In this case, we anticipated that the alkenylstannane (8a) would be mainly formed owing to the stronger coordinative ability of the hydroxyl group to the tin atom. Indeed, treatment of 7 with 1.5 equiv of tri-*n*-butyltin hydride in the presence of a catalytic amount of AIBN at 100-105°C for 20 min provided the desired alkenylstannane (8a)[5] [PMR ($CDCl_3$,TMS) δ6.08 (broad t, J=7Hz, 1H, olefinic proton)] in 77% yield together with a small amount of the other regioisomer (9)[5] [PMR ($CDCl_3$,TMS) δ6.07 (broad d, J=7Hz, 1H, olefinic proton)] (14% yield).[6] The desired alkenylstannane (8a) was converted to the acetate (8b)[11] in 75% yield, followed by treatment with *m*-chloroperbenzoic acid to give the epoxide (10). Reaction of 10 with formic acid in methylene chloride at room temperature for 2.7 hr resulted in the clean formation of two products. One of the products, obtained in 50% overall yield from 8b, was found to be the keto-acetate (11) [PMR ($CDCl_3$,TMS) δ1.08 (t, J=8Hz, 3H), 2.14 (s, 3H), 2.51 (q, J=8Hz, 2H), 5.01, 5.10 (two t, J=4Hz, 1H),[12] while the structure of the other product (37% yield from 8b) proved to be the expected keto-acetate (12) [PMR ($CDCl_3$,TMS) δ1.39 (d, J=7HZ, 3H), 2.14 (s, 3H), 5.07 (q, J=7HZ, 1H)]. Although we could not succeed in the exclusive formation of either 11 or 12, both of the keto-acetates (11,12) should be useful for the construction of the carbacephem skeletons.[13]

Finally, in order to demonstrate the further versatility of the intermediate (1), transformation of 1b to the β-keto ester (14), which is a known intermediate for the synthesis of the carbapenem ring system,[14] was attempted. Thus, the monosubstituted acetylene (1b) was first converted to the acetylenic ester (13b) in 56% isolated yield (23% recovery of 1b) by treatment of the lithium acetylide with methyl chloroformate in THF at -78°C.[15] Regiospecific hydration of the desilylated acetylenic ester (13a) was conducted by treatment with a catalytic amount of mercuric acetate in aqueous methanol containing sulfuric acid at room temperature for 24 hr to afford the desired β-keto ester (14) in 28% isolated yield (49% yield based on the recovered 13a (44%)).

On the basis of the arguments presented above, it might be concluded that 1 is a useful synthon for the construction of the carbapenem and carbacephem skeletons. Synthesis of optically active 1 is now under investigation. Furthermore, it can be suggested that hydrostannation of internal alkynes offers a useful method for the regioselective synthesis of ketones.

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References and Notes

1) Regioselective conversion of internal alkynes to unsymmetrical ketones by hydroboration-oxidation is well known, see P.F.Hudrlik and A.M.Hudrlik, Ed. by S.Patai," The Chemistry of the carbon-carbon triple bond," Part 1, pp. 199-273, John Wiley & Sons, New York, N. Y., 1978.

2) K.Clauss, D.Grimm, and G.Prossel, Justus Liebigs Ann. Chem., 539 (1974).

3) A method for the carbon-extension reactions of azetidin-2-ones at the 4-position is reported, see T.Kobayashi, N.Ishida, and T.Hiraoka, J. Chem. Soc., Chem. Commun., 736 (1980).

4) E.Negishi," Organometallics in Organic Synthesis," Vol.1, p. 410, John Wiley & Sons, New York, N. Y., 1980.

5) The stereochemistry of the alkenylstannanes (3,4,8,9) has not been determined.

6) Further addition of tri-*n*-butyltin hydride and a small amount of AIBN, followed by heating, did not produce any change on the product ratio.

7) The alkenylstannane (3a) could be protected as *t*-butyldimethylsilyl derivative to give 3b in *ca.* 80% yield.

8) Since a half of the crude reaction products was found to be the formate (15), the hydrolysis procedure was required.

9) For the closely related work, see A.J.G.Baxter, K.H.Dickinson, P.M.Roberts, T.C.Smale, and R.Southgate, J. Chem. Soc., Chem. Commun., 236 (1979); L.Cama and B.G.Christensen, Tetrahedron Lett., 2013 (1980).

10) Introduction of an oxygen functionality to the 6-membered ring seems to be essential for antibacterial activities of carbacephem series, see P.G.Sammes," Topics in Antibiotic Chemistry," Vol. 4, p. 87, John Wiley & Sons, New York, N. Y., 1980.

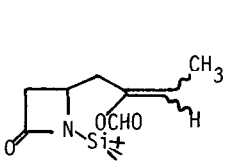
11) Direct conversion of 8a to the corresponding ketones (11 and 12, Ac=H) gave the rather complex reaction products. The alkenylstannane (8a) could be protected as MEM ether, however, even in this case, transformation of the MEM ether to the ketones (11 and 12, $Ac=CH_2OCH_2CH_2OCH_3$) afforded the unsatisfactory result.

12) The mechanism of the formation of 11 may be explained as shown in 16. This type of migration should find general utility in the direct conversion of 17 to 18.

13) For the closely related work, see R.N.Guthikonda, L.D.Cama, and B.G.Christensen, J. Am. Chem. Soc., 96, 7584 (1974).

14) R.W.Ratcliffe, T.N.Salzmann, and B.G.Christensen, Tetrahedron Lett., 31 (1980); T.N. Salzmann, R.W.Ratcliffe, and B.G.Christensen, Tetrahedron Lett., 1193 (1981); N.Ikota, H.Shibata, and K.Koga, Heterocycles, 14, 1077 (1980); S.Oida A.Yoshida, and E.Ohki, Chem. Pharm. Bull., 28, 3494 (1980); and related papers, T.N.Salzmann, R.W.Ratcliffe, B.G. Christensen, and F.A.Bouffard, J. Am. Chem. Soc., 102, 6161 (1980); D.G.Melillo, I.Shinkai, T.Ryan, and M.Sletzinger, Tetrahedron Lett., 2783 (1980); T.Kametani, S.-P.Huang, T.Nagahara, and M.Ihara, Heterocycles, 16, 65 (1981).

15) It is important that a THF solution of the lithium acetylide is gradually added to methyl chloroformate in THF. The corresponding benzyl ester could be similarly obtained in 52% yield by treatment with benzyloxycarbonyl chloride.



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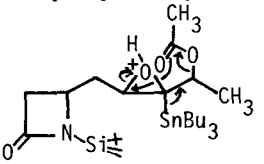

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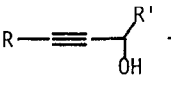

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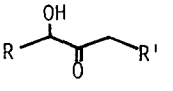

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