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BIFUNCTIONAL ANNULATING REAGENTS: STUDIES ON THE UTILITY OF NOVEL TIN BASED ANNULATING REAGENTS IN THE PREPARATION OF SIX AND SEVEN MEMBERED RINGS

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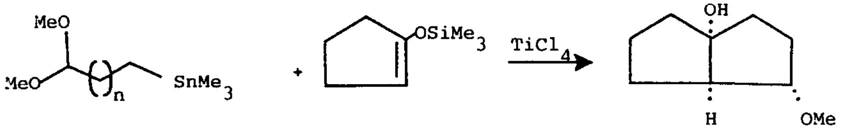
Summary: The acetal stannanes (2) and (3) have been prepared and shown to be of limited use for the preparation of six and seven-membered rings due to an enhanced ability to undergo an alternative β-elimination reaction. A tentative explanation for this enhancement is presented.

Having introduced the acetal stannane (1) as a one pot bifunctional annulating reagent for the preparation of cyclopentanes[1] it seemed worthwhile to study the use of this strategy for the preparation of six and seven-membered rings.



(1) n = 1

(2) n = 2

(3) n = 3

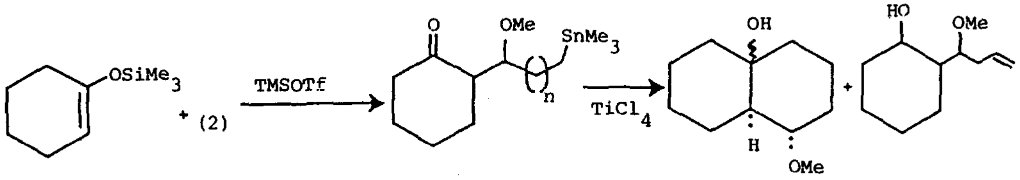
For this we required the synthesis of the two higher homologues (2) and (3). The potential cyclohexane precursor (2) is best obtained by one of two series of reactions[2], the first of which involves conversion of the readily available bromacid (4) to the aldehyde and formation of the acetal. Grignard reagent formation and quenching with chlorotrimethyltin then gave the required stannane (2). An alternative route involves displacement of the acetal chloride (5) by trimethylstannyl lithium, which gives 61% of (2). This latter method is also readily applied to the homologue of (5) to provide the stannane (3) in 71% yield.

$$\underset{(4)}{Br(CH_2)_3CO_2H} \xrightarrow[\text{iii.MeOH/H}^+]{\text{i. BH}_3\text{SMe}_2 \quad \text{ii. Swern}} Br(CH_2)_3CH(OMe)_2 \xrightarrow[Me_3SnCl]{Mg} (2)$$

$$\underset{(5)}{(MeO)_2CH(CH_2)_3Cl} + Me_3SnLi \longrightarrow (2)$$

$$NC(CH_2)_4Cl \xrightarrow[\text{ii.MeOH/H}^+]{\text{i. DiBAlH}} (MeO)_2CH(CH_2)_4Cl + Me_3SnLi \longrightarrow (3)$$

The reaction of (2) with the O-silylated enolate of cyclohexanone in the presence of trimethylsilyltrifluoro methane sulphonate (TMSOTf) formed the expected ketone (6) which we know to be the intermediate in these annulation reactions. Upon treatment with titanium tetrachloride we observed the expected decalin (7)[3] but combined with the alcohol (8), which was in marked contrast to our previous observations on cyclopentannulation. Furthermore upon repeating this reaction with the stannane (3) we only observed formation of the alkenyl alcohol (9), and finally an attempt at a spirocyclization reaction[4] using the enol (10) also gave a mixture of products.

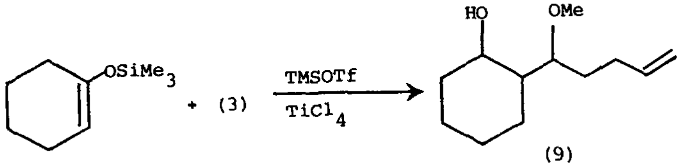


(6) n = 2

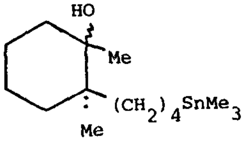
(14) n = 3

(7) 35%

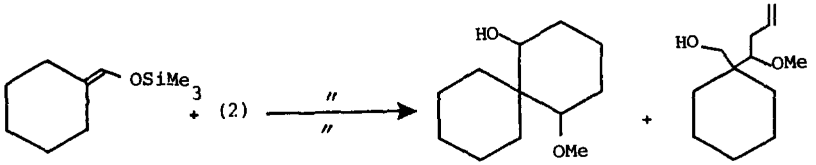
(8) 32%



(9)



(11)

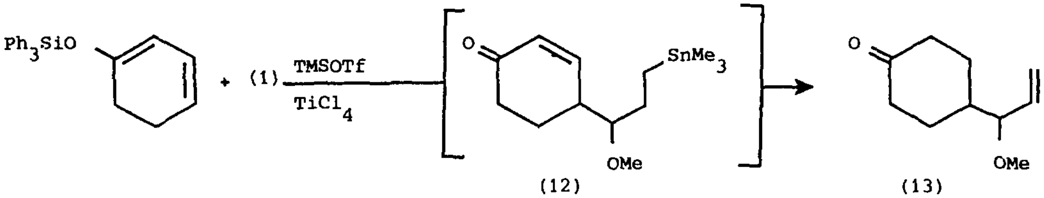


(10)

23%

34%

These observations were not totally unexpected due to Macdonalds observati upon carbon-tin mediated cyclizations of alcohols such as (11)[5]. However we were surprised when the γ-substituted enone (12), prepared in situ from a triphenylsilyl dienol ether[6], gave, with Ti



(12)

(13)

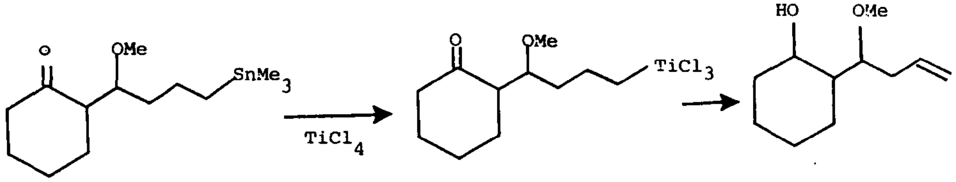
+ 10% α isomer

67%

only the alkene (13)[7] corresponding to a β-elimination reaction with concurrent reduction of the enone.

Thus in contrast to Macdonald[5] we observe a) competitive β-elimination via a 5-membered transition state during cyclization at a disubstituted cationic centre (derived from the enol (10)), b) exclusive β-elimination during an attempted five-membered ring formation (enone (12)), and c) no control of the course of the reaction by varying the electrophilic catalyst.[8]

It seemed appropriate to study these processes further, so as to explain the contrast between our own observations of these attempted reactions with Macdonalds observations on the previously unprecedented β-elimination of tin hydride[9]. Clearly the difference between the two sets of reactants is the presence of the residual methoxy group in our examples and so it may be that this group is influencing the outcome of our reactions. High field nmr (270 MHz) studies at -30°C of the reaction of the ketone (6) with $TiCl_4$ has given a limited insight into the reaction.[10] As the reaction proceeded we observed a decrease in the C-$SnMe_3$ peak at δ 0.69, plus two broad peaks at δ 3.11 and δ 3.42. In addition the methoxy peaks (two diastereoisomers) initially at δ 3.22 and δ 3.28 move downfield by ca. 1.0 ppm, suggesting deshielding is occurring due to complexation of the oxygen in either an inter or intra-molecular manner. After a further period the peaks at δ 3.11 and δ 3.42 decrease whilst signals at δ 5.26 and δ 5.81 corresponding to the alkene signals of (8), appear. In addition the peak at δ 0.69 increases and that at δ-0.1 disappears completely. By comparison with the literature values of δ 0.69 for the protons of Me_3Sn-Cl and of δ 3.12 and δ 3.5 for the methylene protons of ethyltitanium trichloride[11] we have drawn a tentative conclusion from our observations. It appears possible that the β-elimination of tin hydride in our examples goes via a Sn-Ti exchange, the first example of which has recently been described,[12] to form an intermediate (15) which displays the nmr signals at δ 3.11 and δ 3.42 for the methylene next to titanium. The previously observed exchange[12] required the presence of an electron donating group to help stabilise the transition state for exchange and it is possible that the methoxy group functions in this way. After exchange the chelated side chain may be held in a more rigid conformation from which intramolecular hydride transfer is preferred over direct attack. This could explain the apparently greater ease of β-elimination in our examples compared to those of Macdonald, since β-elimination at a σ-bonded C-transition metal centre is a much more facile process[13].



(6) (15)

However, despite possibly providing some insight into their mode of reactivity, the acetal stannanes (2) and (3) are clearly of limited utility for the preparation of six and seven-membered rings. These observations have therefore led us to investigate a series of related allylsilane based acceptor-donor annulation reagents.[4,14]

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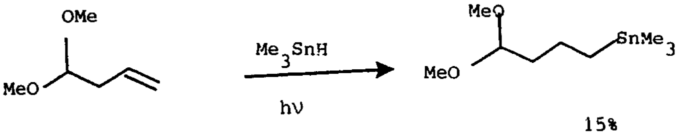
REFERENCES AND NOTES

1. T.V. Lee and K.A. Richardson, *Tetrahedron Letters*, 1985, 26, 3629.
2. A third preparation of these compounds using hydrostannation, is shown below, unfortunately the low yields precluded its use.



3. Two bridgehead isomers were formed in a 3:2 ratio, but separation has not yet been achieved.
4. T.V. Lee, K.A. Richardson and D.A. Taylor, *Tetrahedron Letters*, 1986, 27, 5021.
5. T.L. Macdonald, S. Mahalingam and D.E. O'Dell, *J. Amer. Chem. Soc.*, 1981, 103, 6767 and references therein.
6. S. Murata, M. Suzuki and R. Noyori, *J. Amer. Chem. Soc.*, 1980, 102, 3248 and I. Fleming and T.V. Lee, *Tetrahedron Letters*, 1981, 22, 705.
7. All new products gave satisfactory analytical and/or spectral data.
8. A wide range of electrophilic catalysts were tried ($TiCl_4$, $TiCl_4/TiOPr_4$, BF_3, $AlCl_3$, Et_2AlCl) with only TMSOTf plus $TiCl_4$ giving clean reactions.
9. For a subsequent example of this mode of reaction see E. Murayama, M. Vematsu, H. Nishio and T. Sato, *Tetrahedron Letters*, 1984, 25, 313.
10. Similar nmr studies were performed on the ketone (14) and the aldehyde derived from (10) + (2). These results are less clear but a similar pattern of reactivity is observed.
11. J. Hanlan and J.D McCorvan, *Can. J. Chem.*, 1972, 50, 747.
12. W.R. Baker, *J. Org. Chem.*, 1985, 50, 3942.
13. M. Bottrill, P.D. Gavens, J.W. Kelland and J. McMeeking, Vol. 3 p.433 of *Comprehensive Organometallic Chemistry*, (Eds. G. Wilkinson, F.G.A. Stone and E.W. Abel), Pergamon (1982) and R.P.A. Sneeden and H.H. Zeiss, *Organometallic Chem.*, 1970, 22, 713.
14. Following communication.

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