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CARBONYL-INITIATED CYCLIZATION OF TETRAALKYLSTANNANES

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SUMMARY: Trimethylstannyl alkanal and alkanone compounds undergo a five- or six-membered carbocyclization or an internal redox process upon activation with select Lewis acids.

Work in our laboratory has been directed at developing the potential of the carbon-tin σ bond as a latent nucleophile for the internal formation of carbon-carbon bonds with *in situ* generated carbon-centered electrophiles.[1-3] In this Communication, we report the adaptation of Lewis acid-activated carbonyl centers as the electrophilic partners for the formation of five- and six-membered rings [eg. 1 → 2 (X = -$SnMe_3$, n = 3,4)] by this methodology, thereby effecting an acid-mediated equivalent of the internal Barbier[4,5] or related halocarbonyl reductive cyclization reactions.[6] During the course of our investigations, Fleming and Rowley published an elegant study on the stereochemistry of electrophilic substitution at the stannane carbon in the formation of a substituted cyclopentanol ring by the cyclization of a 5-trimethylstannylpentanal.[7] This Comunication outlines the scope of the trialkylstannyl-alkyl carbonyl cyclization reaction.

1 2

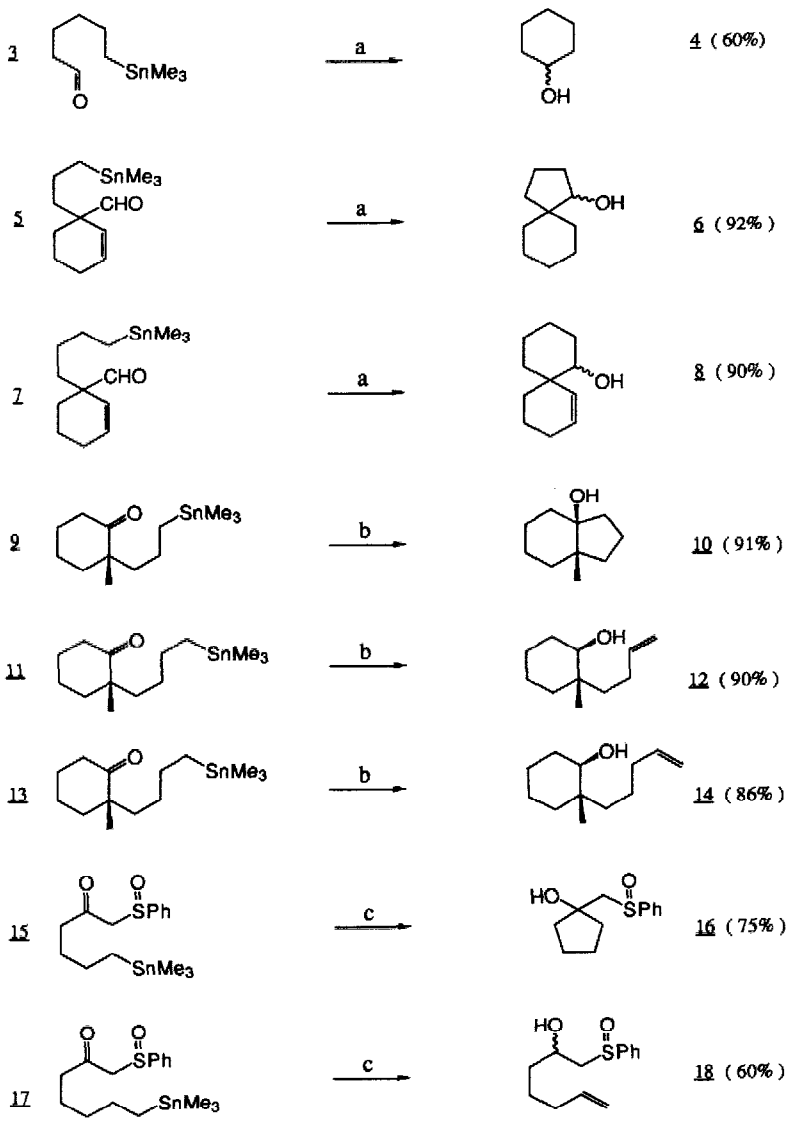
Our data for the Lewis acid-mediated transformation of eight trimethylstannyl alkanal and alkanone substrates are compiled in the Table.[8] Examination of the Table illustrates several recurring themes for internal cyclizations of trialkylstannane substrates: both the mode of reaction and its facility are functions of the size of the ring being formed, the substitution pattern of the electrophilic site and the Lewis acid employed to initiate the reaction. In aldehyde initiated reactions (Table: 3, 5 and 7), carbon-carbon bond formation proceeded smoothly in all instances providing good yields of the desired five- and six-membered rings. The cyclization of trimethylstannyl aldehydes 5 and 7 provided the spiro-

cyclic carbinols as ~1:1 diastereomeric mixtures at 0oC, indicating an insensitivity to the differential steric features of the adjacent cyclohexene ring in the approach of the trimethylstannylalkyl group to the carboxaldehyde function.

In studies of ketone initiated transformations (Table: 9, 11, 13, 15 and 17), the mode of reaction was dependent upon the ring size of the potential product carbocycle.[1-3] Carbon-carbon bond formation was the sole process observed in the formation of five-membered carbocycles, whereas β-hydride transfer was the predominant process observed in the attempted cyclization to form six- and seven-membered rings (>98:2). The stereochemical outcome of either cyclization (eg. 10) or β-hydride transfer (eg. 12 and 14) was in accord with our prior studies of structurally related trimethylstannane-mediated processes.[1-3] A sensitive balance between steric factors and stereoelectronic constraints must underlie the striking and consistent ring-size dependent differences in the reaction pathways for tri-substituted electrophiles.[2,7] Our data suggest that the formation of carbon-carbon bonds is the intrinsically preferred mode of reaction for five-, six- and seven-membered ring systems when the electrophilic site is singly or doubly substituted and suitable stannophilic counterions are present to associate with the incipient trimethylstannyl cation. However, when cyclization is attempted to tri-substituted electrophilic sites, steric and stereoelectronic constraints must possess differential influences on the course of reaction depending upon ring size. In the reactions of 5-trimethylstannyl alkanones, either the steric influence of an additional substituent at the electrophilic site is small or the energy cost for attainment of the stereoelectronically allowed transition state for internal hydride transfer in the five-membered ring is large and thus carbon-carbon bond formation remains the sole reaction pathway observed. Importantly, that β-hydride transfer is an accessible reaction pathway for 5-membered systems (and therefore can fulfill any stereoelectronic requirement) has been demonstrated by Fleming and Rowley in the attempted cyclization of a sterically encumbered carbon-tin center.[7] However, in the reactions of 6-trimethylstannyl alkanones, the pathway leading to cyclization presumably encounters enhanced steric demands (relative to cyclization at a less substituted site) that are sufficient to promote the β-hydride transfer process, which must readily accomodate the stereoelectronic constraints in a six- and larger-membered ring. The underlying source of the striking difference in the preferred mode of reaction between 5- and higher ring systems as a function of electrophile substitution pattern is fundamental to all trialkylstannylalkyl-mediated cyclizations and to related processes with different carbon-metal (or metalloid) bonds[cf. 5] and is the subject of continuing investigation.

We have found that efficient reaction of these trimethylstannyl carbonyl substrates is dependent on the Lewis acid: aldehydes (3, 5 and 7) produced the highest yields with $EtAlCl_2$, ketones (9, 11 and 13) with Et_2AlCl, and α-sulfoxoketones (15 and 17) with $TiCl_4$. The alkylaluminum chloride reagents were the most successful at maintaining a balance between initiation of reaction and inhibition of dehydration of the resultant alcohol, as noted by Snider and co-workers in ene reactions.[9] In this context, the formation of the secondary and tertiary carbinol upon treatment of 15 and 17 with a strong Lewis acid ($TiCl_4$) is notable and may reflect the stability of a chelated intermediate which prevents further reaction of the titanium alkoxide reaction product. In addition, the use of Et_2AlCl to initiate aldehyde

Table



(a) $EtAlCl_2$ (2.5 eq), CH_2Cl_2, 0°C; (b) Et_2AlCl (2.5 eq)/toluene, CH_2Cl_2, 0^0C; (c) $TiCl_4$ (10 eq), CH_2Cl_2, 0^0C.

cyclization resulted in varying amounts of ethyl group addition to the carbonyl moiety for the three aldehydes examined.

This tetraalkystannane-mediated carbonyl cyclization complements existing halocarbonyl reductive methods, which proceed under strongly reducing or nucleophilic conditions, and extends the reange of carbonyl substrates available to the carbocyclization strategy embodied by the transformation 1 to 2 to include aldehyde and α-sulfoxocarbonyl compounds.

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8. All new compounds were characterized by infrared, mass, ^{1}H nmr (360 MHz) and ^{13}C nmr (90 MHz) spectroscopy. The cyclization products in the Table (with the exception of 6 and 18) were correlated with an independently synthesized material (4, 10, 12, 14, 16) or with an authentic synthetic derivative obtained by subsequent transformation (8). All yields represent isolated materials and are not optimized. Syntheses of the trimethylstannylalkyl carbonyl substrates will be described in a Full Paper.

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