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NEW WAYS OF GENERATING ORGANOTIN REACTIVE INTERMEDIATES FOR ORGANIC SYNTHESIS

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Summary

Progress in generating and applying two important organotin reactive species for organic synthesis is reported. - Stannyl radicals $R_3Sn^{\cdot}$, at present the most used tools for free radical synthesis of complicated target molecules, are generally obtained from the hydrides R_3SnH. In a number of cases, however, this is a drawback because of the high radical scavenging power of the latter. New ways of generating $R_3Sn^{\cdot}$, decoupling them from the presence of R_3SnH, are developed and discussed: the spontaneous thermal dissociation of distannanes with bulky substituents, the thermal fragmentation of bisstannyl benzpinacols, the ketone sensitized mild photolysis of simple distannanes, and the mild photolysis of benzyltin compounds such as 9-stannyl-9,10-dihydro anthracene. Examples of advantageous applications, also in combination with adjusted H donors, are given. - Stannyl cations R_3Sn^+ are used as superior leaving groups in electrophilic aromatic ipso substitution. Examples for their application under very mild conditions include the considerable broadening of the scope of the Friedel-Crafts acylation, the Vilsmeier formylation, sulfinations, and sulfonations. The directing influence of certain other substituents can be overcome by this ipso substitution.

Introduction

Organotin chemistry is one of the oldest fields in organometallic chemistry, and a well developed one. After a period in which preparative aspects dominated, mechanistic studies carried out after 1960 revealed that both polar and free radical reactions can easily be effected using organotin compounds[4].

In the last few years free radical reactions have played an important and rapidly increasing part in organic synthesis, no longer mainly in polymerization, but especially for the synthesis of complicated target molecules, often biomolecules. The most used reactive intermediates in doing so are stannyl radicals, mainly $Bu_3Sn^{\cdot}$; dehalogenations of organic chlorides, bromides, and iodides, and also additions to alkenes, dienes, and alkynes are carried out by using them. A main advantage is offered, when the intermediate radicals generated by these routes can undergo desired intra- or intermolecular additions, cycloadditions, or rearrangements before a final stabilization, very often by H donation. Thus, multistep regio-, stereo-, and enantioselective syntheses could be successfully carried out in one-pot procedures with high yields, often by clever handling of the kinetics. Recent and comprehensive reviews are available[5,6].

This present boom in the applications of stannyl radicals has another surprising aspect: the incubation time was a considerable one since the basic organotin radical chemistry leading to it was investigated thoroughly not less than about 25 years ago[4]:

First Use of Radicals $R_3Sn^{\cdot}$

$$R'\text{-Hal} + R_3Sn^{\cdot} \longrightarrow R_3Sn\text{-Hal} + R'^{\cdot}$$

H.G. Kuivila et. al. 1962

$$\text{>C=C<} + R_3Sn^{\cdot} \longrightarrow \text{>C(SnR}_3\text{)-C}^{\cdot}\text{<}$$

W.P. Neumann et. al. 1961

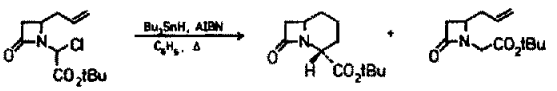
Mostly used: $Me_3Sn^{\cdot}$, $Et_3Sn^{\cdot}$, $Bu_3Sn^{\cdot}$, $Ph_3Sn^{\cdot}$

On the other hand, polar and even ionic reactions involving organotin compounds did not receive such spectacular attention in recent years. Many applications for synthesis have however also been reported. Interesting aspects for the future are offered by the stannyl cations R_3Sn^+, strongly solvated or in the form of contact ion pairs. Again, these aspects are traced by early work, e. g. of C. Eaborn et al.[7,8].

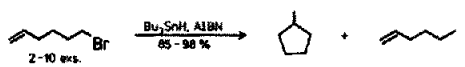
A third group of reactive organotin intermediates, the stannylenes R_2Sn, have also received increasing attention recently with regard to both mechanistic and synthetic aspects[9], but is not treated in the present article.

Part 1. New Ways of Generating Stannyl Radicals

At present, in nearly every case of synthetic application of stannyl radicals, these are generated from hydrides, mostly Bu_3Sn-H, which also act in the same reaction as strong H donors[5,6]. Since this activity is very high (k ~ 2-590 $10^6 M^{-1}s^{-1}$)[5], the intermediate C radical is sometimes trapped before the desired addition or rearrangement mentioned above essential for the synthesis envisaged can occur. In a number of cases, the problems can be diminished or avoided by clever application of kinetics such as use of a large excess of one partner, syringe techniques, or extreme dilution. But in other cases the hydrogen abstraction is still too fast, as in the following two examples[10,11]:



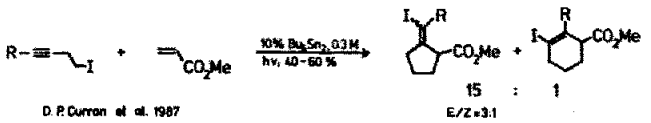
M.D. Bachi et al. 1987 — 0.02 M: 20 % : 50 %; 0.003 M: 50 % : 5 %



Ch. Walling et al. 1972 — 0.355 M: 54 : 46; 0.016 M: 92 : 8

Substantial loss of yield, undesired by-products, more complicated workup and purification have to be tolerated in cases like these.

In other examples, tin hydrides cannot be applied at all, e. g. in the elegant alkyl-vinyl iodide chain reactions[6]:



Here, the stannyl radicals are generated photolytically from hexabutyldistannane. This seems obvious, and is preferred, too, in many cases of spectroscopic work. But, for preparative work severe drawbacks may occur because of

a) the short-wave UV absorption of the distannanes needing hard UV irradiation absorbed also by most of the organic species to be reacted, and present in the mixture,

b) C-Sn splitting besides the desired Sn-Sn splitting ($D_{Sn-Sn} > D_{C-Sn}$) leading to undesired side and following reactions, and products[12]:

Photoreactions of $R_3Sn-SnR_3$

$$R_3Sn-SnR_3 \xrightarrow{h\nu} [R_3Sn-SnR_3]^{T^*} \xrightarrow{k_a} 2\,R_3Sn^{\cdot}$$

$$\downarrow k_b \qquad -2R^{\cdot} \xleftarrow{+2R'Hal} 2\,R_3SnHal$$

$$R_3Sn-SnR_2^{\cdot} + R^{\cdot} \longrightarrow {}^2/_n(R_2Sn)_n + R-R \text{ etc.}$$

R=Me: $k_a > k_b$; R=Et: $k_a \approx k_b$; R = Et, Bu.....

$$+R_6Sn_2 \downarrow S_H2$$

$$R_4Sn + {}^1/_n(R_2Sn)_n \cdot \quad R=Me$$

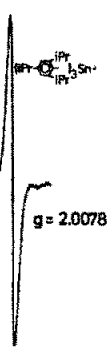
A need for independent ways of generating radicals $R_3Sn^{\cdot}$ is thus present, decoupling them from the inherent presence of tin hydrides. Three possibilities will be discussed.

1.1 Hexaorganodistannanes with Bulky Substituents

Bulky aryl residues have been used in this laboratory[13], to lower the dissociation enthalpy D of the Sn-Sn bond, and therefore to lower the temperature of the (now spontaneous and reversible) dissociation, avoiding the necessity for irradiation:

$$R_3Sn-SnR_3 \overset{T}{\rightleftharpoons} 2\,R_3Sn^{\cdot}$$

R=	T	D_{Sn-Sn} kcal/mol	Raman ν_{Sn-Sn} cm^{-1}
	> 230°C (dec.)	≥ 60	138 (splitting)
	≥ 180°C	49 ±2	102
	≥ 100°C	27 ±2	92
	≥ 20°C	85 ±1	–



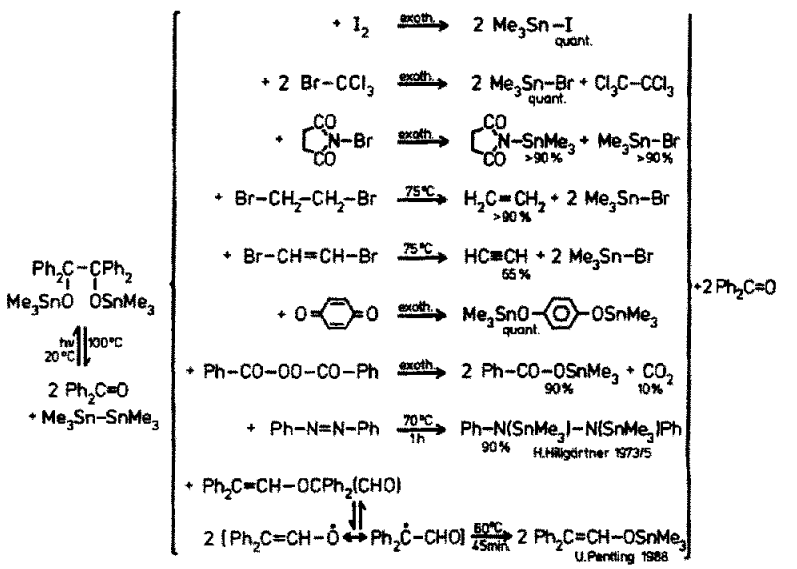
The reactivity of these bulky stannyl radicals is sufficiently high towards non-bulky molecules, e. g. for halogen abstraction. The desired reaction can be then completed by addition of an H-donor of adjusted strength and concentration, such as THF or cumene, leaving enough time for the intermediate C radical to, for example, cyclize.

For example, the tris(triethylphenyl)stannyl radical whose ESR signal appears in the

solution of the distannane above 100 °C, reacts completely at 140 °C in o-xylene with 6-bromo-1-hexene (which gives unsatisfactory results with Bu_3SnH[11] as mentioned above) yielding exclusively the desired ring closure to methyl cyclopentane, after 3.5 hrs; no hexene-1 is formed (GLC). Besides, an excess of bromohexene no longer has to be used, which facilitates the workup. As another test reaction, the elegant formal addition of an alkane to an olefin[14] could be effected by the same stannyl radical using 1-bromohexane and acrylonitrile to give 1-cyanooctane.

1.2 Bisstannyl Pinacols and O-Stannyl Ketyls

The bis-trimethylstannyl benzpinacol is prepared conveniently from benzophenone and the distannane, and can easily be stored for use. Upon warming it is split reversibly into stannyl ketyls, but irreversibly into benzophenone and stannyl radicals (giving distannane in the absence of reactive partners) above 60 °C (better at 100 °C)[15]. Typical reactions of stannyl radicals are obtained in the presence of appropriate partners, surprisingly often at low temperatures or even exothermally:

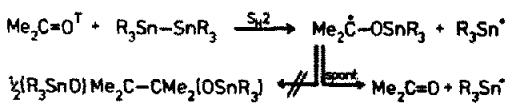


It can be concluded that in many cases the partners attack the bisstannyl benzpinacol directly, the latter acting as a stabilized ("canned"), easily available stannyl radical. This versatile source can be used for synthesis, also in combination with H donors of appropriate strength such as cumene or THF[16]. Stannyl radicals of this origin have also been applied very recently for additions to C≡N groups[17].

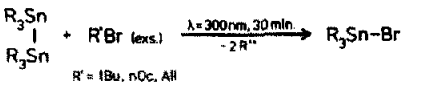
If a thermal procedure for the generation of stannyl radicals under mild conditions is preferred, the bisstannyl benzpinacol described is of advantage. The corresponding tributylstannyl derivative, which could be of interest because of the lower toxicity of tributyltin compounds compared with the trimethyl ones, and because of the precursors available technically on a large scale, is however hard to prepare by the same route from benzophenone and hexabutyldistannane.

If a mild photochemical method for the generation of stannyl radicals can be accepted, no isolation of the bisstannyl pinacol is necessary. First we irradiated a solution of benzophenone (total absorption $\leq$ 380 nm, E_T = 69 kcal/mol), the distannane, and the compound to be attacked by stannyl radicals. If an H donor is necessary, it can be admixed (e. g. THF or cumene). After some time we observed a deposit of free benzpinacol on the wall of the flask.

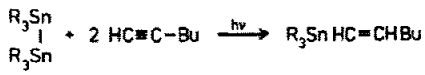
The best procedure, we think, is the use of acetone (total absorption $\leq$ 330 nm, E_T = 80 kcal/mol), perhaps as solvent, and an irradiation at 300 nm. Also λ = 350 nm is effective, but needs more time. The unstable bisstannyl pinacol is not formed, but the triplet acetone reacts easily with the distannane via an S_H2 mechanism to give the desired stannyl radicals smoothly, without C-Sn splitting or side reactions known from the short-wave length irradiation of the distannane alone, as mentioned above:



Thus the acetone is a sensitizer for the smooth and complete transformation of the distannane into 2 R_3Sn radicals. We checked their preparative use by the following two model systems:



Me_2CO / R_6Sn_2	Solvent	Yield [%] R_3SnBr
0.0	hexane	2-19
0.5	hexane	42-81
75.0	acetone	100

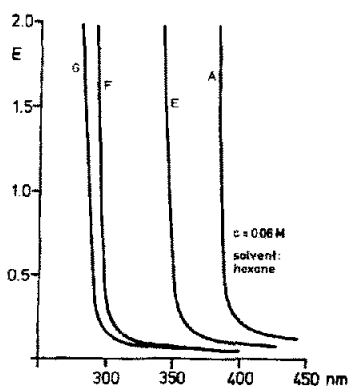


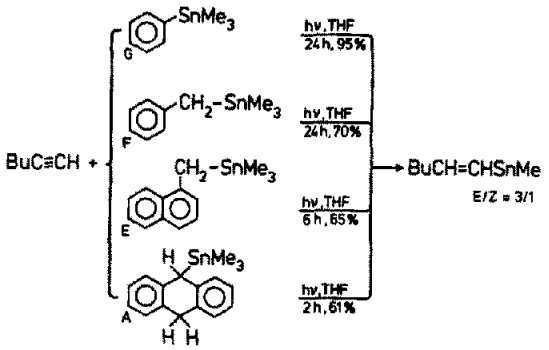
		Yield [%] Adduct
0.5	pentane	26
14.0	acetone	40
3.0	THF	95

In the former case, both the distannane and the alkyl bromide react quantitatively when acetone is used as the solvent. The latter shows the satisfying hydrostannation of a non-activated alkyne, and the importance of the nature of the H donor.

1.3 Stannyl Radicals from Benzylic Precursors

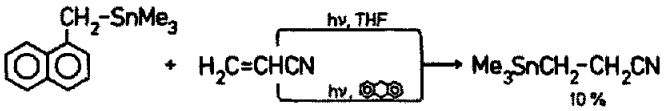
Based on the low dissociation enthalpy of R_3Sn-benzyl and R_3Sn-allyl compounds[4], and the easy splitting off of R_3Sn radicals during irradiation at the absorption wavelength of the π-system, we looked for related derivatives with longer wavelengths and/or more intense absorption. As a test reaction the hydrostannation of 1-hexyne has been used[2] and THF as the H donator:

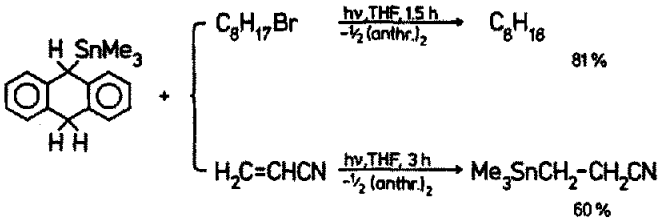




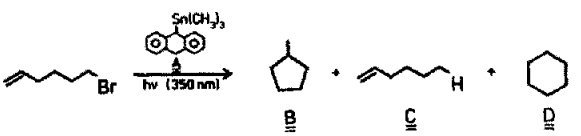
As can be seen, the α-trialkylstannylmethyl naphthalene E needs, under the same conditions, only one fourth of the irradiation time of F for a comparable yield, but 9-trialkyl-

stannyl-9,10-dihydroanthracene A works even better, as to be expected from its longer-wave length absorption (λ_{max} = 255 nm) with the remarkable tailing up to 400 nm (see above)at a preparatively realistic concentration. A soft irradiation at 350-400 nm is sufficient to cleave A, allowing the presence of almost all of the organic reaction partners to be considered here as partners for $R_3Sn^{\cdot}$. In the following test reactions, different H donors and sources for $R_3Sn^{\cdot}$ are used. Again, A is the most promising.





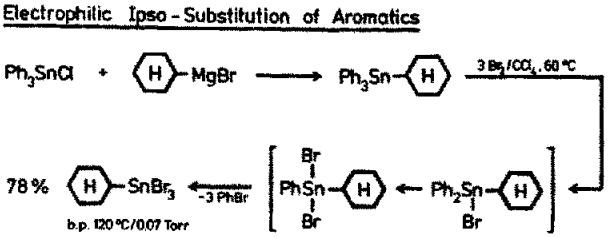
This encouraged us to try to resolve certain of the problems left by the application of hydrides R_3Sn-H because of the very rapid hydrogen abstraction (see above). Whereas 6-bromo-1-hexene gave, with Bu_3Sn-H, considerable amounts of the undesired 1-hexene C besides the expected ring closure product B[11], A in combination with THF as an H donor gave a good yield of B, and a relation B/C better than 99/1. Moreover, no or only a slight excess of the bromohexene had to be used, in contrast to the 2-10 fold excess necessary earlier. This seems encouraging for a wider use of this source A for stannyl radical generation:



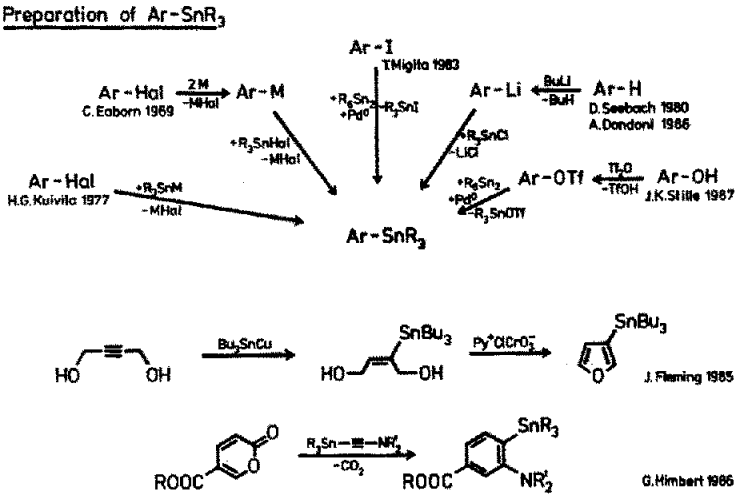
[A]	[RBr]	solvent	yield [%] B	C	D	ratio B/C
0.10	0.150	benzene	44	0	0	100/0
0.05	0.075	THF/0c	88	<1	<2	>99/1
0.11	0.081	THF	73	<1	<2	>99/1

Part 2. Stannyl Cations as Leaving Groups in Electrophilic Aromatic Ipso Substitutions

A few years ago we required cyclohexyltin tribromide. Not having been able to reproduce the reports in the literature, we succeded finally in its preparation starting from triphenyl cyclohexyltin, and realized that this is in fact an electrophilic ipso substitution of the stannyl group by bromine, the stannyl group proving to be a powerful leaving group rendering superfluous any catalyst in this case:

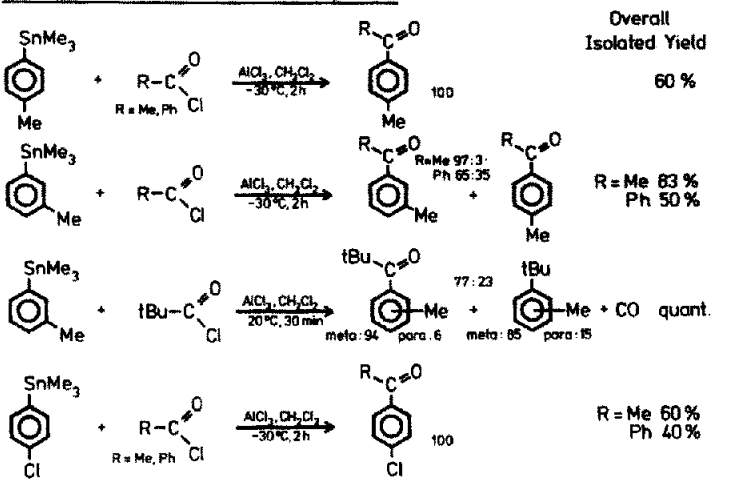


There are several reports on analogous electrophilic replacements of stannyl groups at an aromatic moiety scattered in the literature, beginning with C. Eaborn's work[7,8]. However, neither a systematic investigation on this type of reaction exists nor, to our knowledge, a review. So we looked for further applications, especially since aryltin compounds are now accessible more easily than before[7,18-24]:



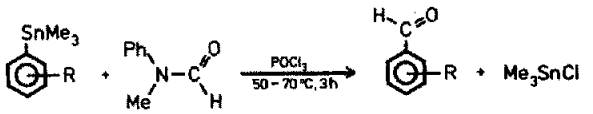
Thus, the Friedel-Crafts acylation can be carried out even at -30 °C within 30 min, the acceleration being $>10^2$. The o,p-directing activity of a Me group is overcome by the potent m-R_3Sn leaving group (R = Me or Bu): the m-acyl derivative is obtained in a new regioselective way by ipso substitution. Even the disactivated chlorobenzene reacts > 60 times faster than toluene, with R_3Sn as the leaving group. A few examples will illustrate this application:

Tin-Mediated Friedel-Crafts Acylation



The Vilsmeier formylation, though accepted as "the most common method for the formylation of aromatic rings"[25], has until now been restricted to highly activated species such as amines and phenols. However, using the stannyl-mediated ipso substitution, benzene itself reacts at room temperature, and also the disactivated chlorobenzene, and a regioselective meta formylation with respect to a Me group is easily carried out, too:

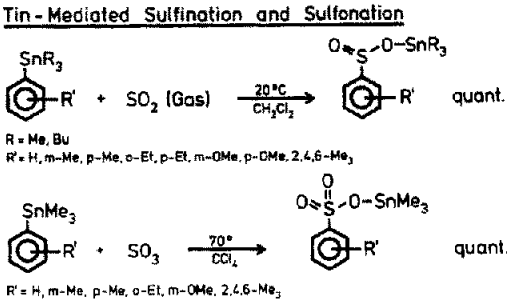
Tin-Mediated Vilsmeier-Formylation



Substituent R	H	p-Me	m-Me	p-OMe	o-OMe	p-Cl
Yield [%]	56	70	55	96	79	10

Besides the halogenation mentioned above (obtained without a catalyst like $AlHal_3$), other examples include the smooth reaction with SO_2 or SO_3 giving the stannylesters of aryl sulfinic or sulfonic acids. No acid is needed, and very mild conditions can be used. This route also seems promising for other ipso substitutions.

Tin-Mediated Sulfination and Sulfonation



The stannyl group in these reactions evidently acts as a potent leaving group superior to hydrogen by several powers of 10. In addition, it seems to increase the overall π-electron density of the aromatic nucleus enhancing the formation of a π complex which might precede the ipso substitution. Lastly, it may form an intermediate complex with the reagents containing π electrons via pentacoordination at the tin, thus promoting the substitution[26].

Acknowledgements

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Experimental Section

All experiments have been carried out under dry welding argon as protective gas.

Part 1:

Hexakis(2,4,6-triethylphenyl)distannane was prepared following ref.[13]. Preparation of bis-(trimethylstannyl)benzpinacol and its typical reactions are carried out according to ref.[15].

The irradiations were carried out in a Rayonet Reactor RPR 100, Southern New England Ultraviolet Comp., Hamden, CT/USA at 300 nm (lamps RPR-3000 Å) or at 350 nm (lamps RPR-3500 Å) in Duran or Pyrex Schlenk tubes or NMR tubes.

Acetone-Sensitized Photolysis of Distannanes. - A 0.1 M solution of Me_6Sn_2 or Bu_6Sn_2 and 5 mol/mol alkyl bromide R'Br (R' = tBu, nOc, All) in a hexane/acetone mixture 1/1 is irradiated at 300 nm. After 30-240 min, dependent on the kind of tube, the distannane has disappeared (titration with I_2/benzene), and > 98% of Me_3SnBr or Bu_3SnBr are found (GLC), as well as a mixture of the products from the alkyl radical: alkane/alkene/dimer. The same result is obtained with distannane: nOcBr = 1:2. The irradiation time is 8 times longer for λ = 350 nm.

Hydrostannation. - A 3 fold excess of 1-hexyne is added to a 0.1 M solution of R_6Sn_2 in THF/acetone 1/1. Irradiation of the mixture at 300 nm for 1 h yields 1-trialkylstannyl-1-hexene quantitatively (GLC), Z:E ~ 1:3.

9-Trimethylstannyl-9,10-dihydroanthracene A. - 0.15 mol of BuLi in hexane are added dropwise to 18.0 g (0.1 mol) 9,10-dihydroanthracene in 250 mL of Et_2O at 0°C. After stirring overnight, the mixture is added slowly to 30.0 g (0.15 mol) of Me_3SnCl in 100 mL Et_2O at 0°C. After aqueous workup, the product is separated from anthracene by dissolving it in 50 mL $CHCl_3$. Recrystallization from EtOH yields 47% of A, m. p. = 103°C (slightly contaminated by anthracene). The analytical and spectral data confirm the structure.

Reaction of A with 6-bromo-1-hexene. - A 0.11 M THF solution of A, 1.5 mol/mol of the bromohexene and 3% n-octane (as internal standard for the GLC) are irradiated at 350 nm. After 20 h, 88% of B, 0.8% of C, and 2% of D are obtained (GLC).

Part 2:

Acylations. - 20 mmol of the stannane in 10 mL dry CH_2Cl_2 are added to a stirred solution of 30 mmol $AlCl_3$ and 30 mmol acyl chloride in 20 mL dry CH_2Cl_2 at -30°C. The mixture is stirred for 2 h, warmed to 20°C and hydrolysed by adding it to 50 g ice. The aqueous phase is extracted twice with 10 mL CH_2Cl_2. The combined organic layers are dried with sodium sulfate and the solvent is evaporated. The residue is distilled at 15 torr to yield the corresponding ketone, whose isomer distribution is determined by GLC.

Formylations. - The mixture of 30 mmol $POCl_3$, 10 mmol of the stannane and 30 mmol N-phenyl-N-methylformamide is heated to 70°C for 3 h, then hydrolysed by 25 g ice and adjusted to pH 6 by adding 10% NaOH/water. The aqueous layer is extracted three times with 20 mL ether. The combined organic layers are dried with sodium sulfate, evaporated and fractionated at 15 torr.

Sulfinations. - Dry SO_2 is bubbled through 10 mmol of the stannane in 5 mL of dry CH_2Cl_2 at 20°C until the reaction is complete (^{1}H-NMR). The solvent is removed at 15 torr and the oily residue is taken up in $CDCl_3$. Structure and yield of the product are determined by ^{13}C NMR. R = Me, R' = 3-Me: ^{1}H NMR (CH_2Cl_2) δ 0.80 (s, 9H, $^2J_{H,Sn}$ = 70 Hz), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 1.5 (q, $^1J_{C,Sn}$ = 521 Hz), 21.3 (q); ^{119}Sn NMR ($CDCl_3$) δ + 18.0. R = Me, R' = 4-OMe: ^{1}H NMR (CH_2Cl_2) δ 0.70 (s, 9H, $^2J_{H,Sn}$ = 70 Hz), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 1.4 (q, $^1J_{C,Sn}$ = 523 Hz), 55.2 (q). Selected values.

Sulfonations. - 10 mmol of the stannane are added to a solution of 11 mmol SO_3 (prepared by heating 65% oleum) in dry CCl_4 at 20°C. The mixture is refluxed for 1-2 h. The product is isolated by evaporation of the solvent. Spectroscopic determination by ^{1}H and ^{13}C NMR. R = H: ^{1}H NMR (CH_2Cl_2) δ 0.70 (s, 9H, $^2J_{H,Sn}$ = 68 Hz); ^{13}C NMR (DMSO) δ 1.9 (q, $^1J_{C,Sn}$ = 511 Hz). R = 3-Me: ^{1}H NMR (CH_2Cl_2) δ 0.65 (s, 9H, $^2J_{H,Sn}$ = 69 Hz), 2.53 (s, 3H); ^{13}C NMR (DMSO) δ (q, $^1J_{C,Sn}$ = 509 H), 20.9 (q). Selected values.

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