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REGIOSPECIFIC SYNTHESIS OF AROMATIC COMPOUNDS VIA ORGANOMETALLIC INTERMEDIATES

II. 1,3,5-(TRIMETHYLMETAL(IV))BENZENE COMPOUNDS

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Summary

Sequential metal–halogen exchange reactions between n-C_4H_9Li and 1,3,5-tribromobenzene and reaction at each step with $(CH_3)_3M^{IV}Cl$ (M^{IV} = Si, Ge, Sn) has provided a 1,3,5-(trimethylmetal(IV))benzene compound. This class of compounds can be synthesized either through a step-wise procedure, where the various intermediates are isolated, or in a continuous metal–halogen exchange process without isolation of various intermediates.

Introduction

We have recently reported the synthesis and reaction of 3,5-dibromophenyllithium (I) [1]. In that study we have suggested and demonstrated, in part, the possibility of sequential metal–halogen exchange reactions on the remaining bromines to yield organolithium intermediates capable of reacting with various substrates to yield poly-substituted benzene compounds. In our continuing studies on regiospecific synthesis of aromatic compounds via organometallic intermediates we are now reporting our findings on sequential metal–halogen exchange reactions between n-C_4H_9Li and 1,3,5-tribromobenzene leading to the synthesis of 1,3,5-trisubstituted benzene compounds.

Results and discussion

For purposes of experimental simplicity our studies in this area have been limited to nonfunctional substituent groups, e.g., $(CH_3)_3Si$, $(CH_3)_3Ge$, and $(CH_3)_3Sn$.

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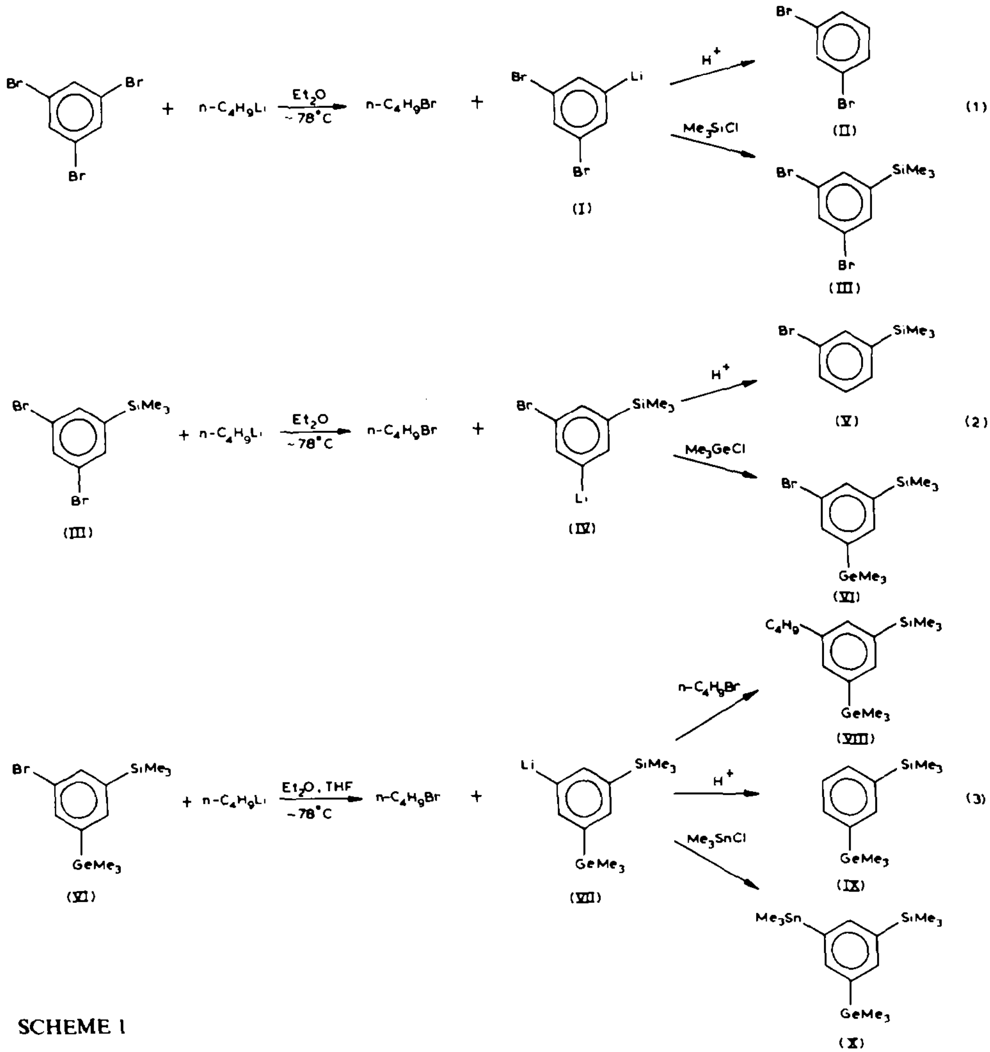
These 1,3,5-trisubstituted benzene compounds were prepared as shown in Scheme 1.



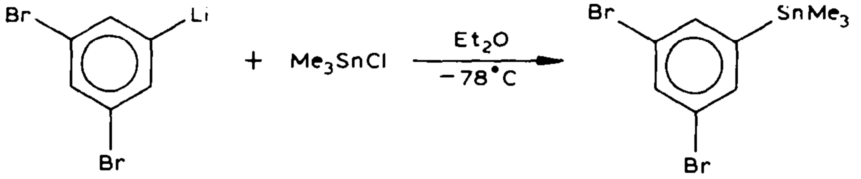
SCHEME 1

In this series of reactions the intermediate III and VI were isolated, characterized and subsequently used in the next sequential synthesis step. The organolithium intermediates I, IV and VII were further characterized by hydrolysis to yield the protonated products II, V and IX. Since the organolithium compound I is temperature sensitive, all organolithium synthesis were carried out at −78°C. The metal–halogen exchange reactions were nearly quantitative as determined by gas chromatography analyses of hydrolyzed aliquot samples. In diethyl ether as the solvent media, the rates of metal–halogen exchange reactions are relatively fast for the formation of the organolithium compounds I and IV. For compound VI, however, with only one remaining bromine, the metal–halogen exchange reaction in diethyl ether is very slow. Under this condition, the slowly formed organolithium compound VII partially reacts with the exchange compound, n-C_4H_9Br, to form the butylated derivative VIII as an undesirable by-product prior to derivatization with

$(CH_3)_3SnCl$. In order to avoid this side reaction, the rate of the metal–halogen exchange reaction between VI and n-C_4H_9Li can be increased by performing the reaction in a mixture of diethyl ether and tetrahydrofuran. In this solvent combination the exchange reaction takes place rapidly and compound VII reacts with $(CH_3)_3SnCl$ faster than with n-C_4H_9Br. In this manner, formation of the butylated product VIII is minimized. The derivatization with the $(CH_3)_3MCl$ (M = Si, Ge and Sn) gave high yields of substitution products at each step. It was observed, however, that derivatization with $(CH_3)_3SiCl$ at −78°C is a slow process. Higher temperatures, e.g., −25°C were used to increase the rate of reaction. The reactions of the organolithium compounds with either $(CH_3)_3SnCl$ or $(CH_3)_3GeCl$ at −78°C are rapid.

Compound X was thus synthesized in three separate steps as outlined in eq. 1–3. It was of interest to us to determine whether compound X could be prepared more conveniently by a one-step procedure without isolation of the various intermediates. We have found that by sequential and alternate additions of equivalent molar quantities of n-C_4H_9Li, $(CH_3)_3SiCl$, n-C_4H_9Li, $(CH_3)_3GeCl$, n-C_3H_9Li and $(CH_3)_3SnCl$, the desired product X could be synthesized in good yield. The course of the reaction was followed at each step by withdrawing an aliquot sample, hydrolysis of the sample and mass spectral gas chromatographic analyses. The products at each step were confirmed by comparison with the products resulting from the sequence described in eq. 1–3.

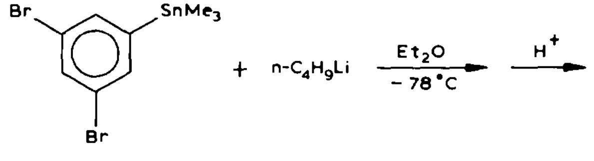
The order of introducing the $(CH_3)_3M$ (M = Si, Ge and Sn) substituent is very important. Under the experimental conditions employed, the CH_3Si, Aryl–Si, CH_3–Ge and Aryl–Ge bonds did not react with n-C_4H_9Li during the metal–halogen exchange. We have found, however, that the CH_3–Sn and Aryl–Sn bonds do undergo cleavage by n-C_4H_9Li. Cleavage of a C–Sn bond by organolithium reagents has been previously noted by other investigators [2,3]. We have found, as an example, that if the $(CH_3)_3Sn$ substituent is the first group introduced, the product 3,5-dibromotrimethylstannylbenzene (XI) is formed in high yield.



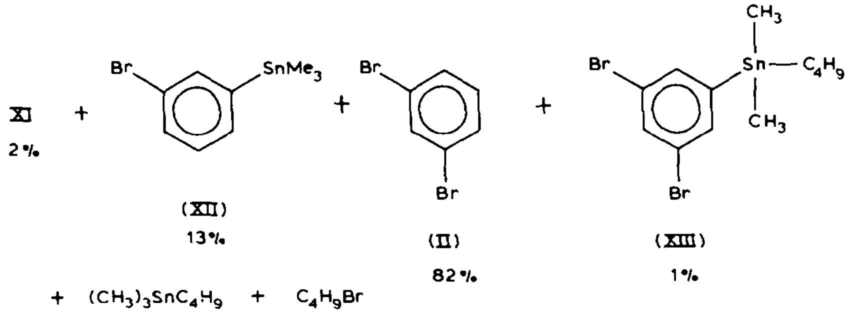
(4)

(XI)

A subsequent metal–halogen exchange reaction between n-C_4H_9Li and XI, however, gave the following products (expressed in GC area percent).



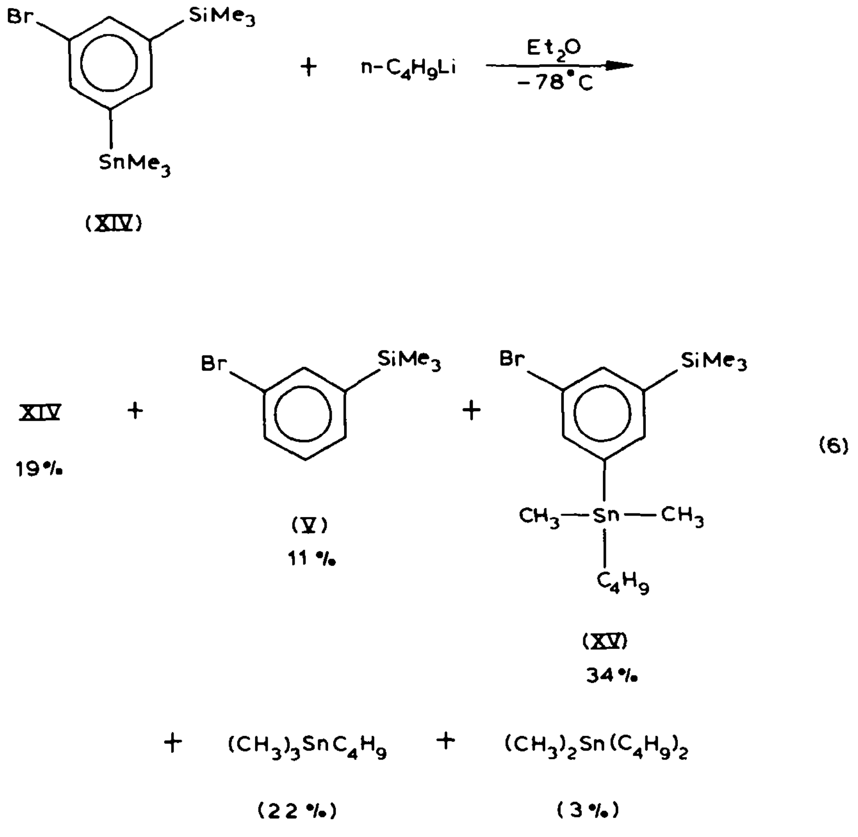
(XI)



(5)

The reaction products XII, II and XIII were identified by gas chromatography (retention time) and gas chromatography/mass spectrometry analyses. From this data it can be seen that the predominant reaction is that of Aryl–Sn cleavage resulting in compound II. The other fragment from the cleavage reactions, $(CH_3)_3SnC_4H_9$, was also observed. Some metal–halogen exchange did occur which produced, after hydrolysis, compound XII. The ratio of II/XII (82/13) definitely indicates the preference of Aryl–Sn cleavage over metal–halogen exchange in compound XI. Formation of compound XIII also indicates a small amount of cleavage of a CH_3–Sn bond [2,3] by n-C_4H_9Li.

Another example of preferential Sn–C bond cleavage to metal–halogen exchange by n-C_4H_9Li was seen in the reaction between compound XIV and n-C_4H_9Li (expressed in GC area percent).



(6)

In this reaction, no metal–halogen exchange took place. Aryl–Sn (forming V) and CH_3–Sn (forming XV) cleavage were the primary reactions noted.

Since the C–Sn bond as demonstrated in eq. 5 and 6 is subject to n-C_4H_9Li cleavage, the $(CH_3)_3Sn$ substituent must be introduced into the 1,3,5-trisubstituted benzene at the last stage. Under this condition the product X containing the $(CH_3)_3Sn$ group is not exposed to any potential reaction with n-C_4H_9Li.

Conclusion

The synthesis of compound X demonstrates the feasibility of sequential multiple metal–halogen exchange reactions. Such a process can be either a stepwise (eq. 1–3) or a one-step process, wherein the various intermediates are not isolated. Only $(CH_3)_3Si$, $(CH_3)_3Ge$, and $(CH_3)_3Sn$ substituents were introduced in this study. It is quite likely that other metal- or metalloidal–carbon bond formations may be possible during the last step of the sequential reaction (see eq. 3, Scheme 1) since they will not be exposed to any further n-C_4H_9Li. The introduction of functional groups, e.g., CO_2H, C(O)H, $C(O)CH_3$, $C(O)CF_3$, SH, etc., similarly can be accomplished as demonstrated in our other studies.

Experimental

General comments

All reactions were carried out in flame-dried glassware under an atmosphere of pre-purified dry nitrogen. Infrared spectra were recorded using a Perkin–Elmer model 521 or 621 spectrophotometer as KBr wafers or neat liquids. GC analyses were performed on Perkin–Elmer model Sigma I instrument using a 6ft, 10% SE-30 on chromosorb W column. The GC/MS analyses were performed on a du Pont model 21-490 mass spectrometer using chemical ionization mode. Only peaks for the major isotopes of bromine, germanium and tin: ^{79}Br, ^{81}Br, ^{74}Ge, ^{118}Sn, are reported in Table 1. The yields reported are isolated yields except for those performed on small quantities were such yields were determined by GC using internal standards. Empirical response factors products were determined separately using standard solutions. All new principal products were characterized by elemental, mass spectral and infrared analysis. Analytical data for all isolated compounds are given in Table 1. All the temperatures reported are uncorrected. Anhydrous diethyl ether and tetrahydrofuran were dried by distillation from lithium aluminum hydride prior to use.

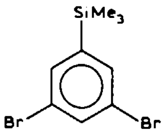
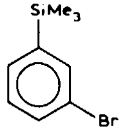
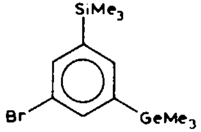
Synthesis of (3,5-dibromophenyl)trimethylsilane (III) and (3,5-dibromophenyl)trimethyltin (XI)

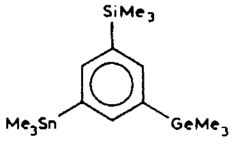
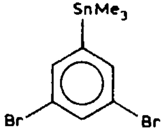
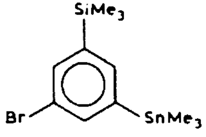
Into a diethyl ether (1200 ml) solution of 1,3,5-tribromobenzene (77.0 g, 244 mmol) was added at −78°C n-butyllithium (99.2 ml 2.46 *M* in hexane, 244 mmol) during a 30 min period. After an additional 30 min of stirring a white slurry of the organolithium compound I was formed. To this mixture was added $(CH_3)_3SiCl$ (28.3 g, 261 mmol) in anhydrous ether (50 ml) over a 20 min period. Removal of aliquot samples for GC analyses over a period of 20 min indicated a slow rate of reaction and therefore the temperature was raised to −25°C. After 1 h at −25°C, a GC analysis indicated maximum product (III) formation and therefore the reaction

(Continued on p. 156)

TABLE 1

ANALYSES OF COMPOUNDS

Compound	B.p. (°C/mmHg)	Isolated yield (GC) (%)	M.W. (Mass spec.) (found)	IR (cm^{-1})	Analysis (Found (Calcd.) (%))		
					C	H	Br
 (III)	62/0.008 [a]	84 (96)	306 $C_9H_{12}Si^{79}Br_2$ 308 $C_9H_{12}Si^{79}Br^{81}Br$ 310 $C_9H_{12}Si^{81}Br_2$	2958, 2900, 1562 1535, 1380, 1248 830, 727, 668	34.95 (35.08)	3.81 (3.93)	51.59 (51.87)
 (V)	113/6.0 [b]	75 (89)	228 $C_9H_{13}Si^{79}Br$ 230 $C_9H_{13}Si^{81}Br$		47.21 (47.16)	5.64 (5.72)	34.82 (34.87)
 (VI)	116-117/2.0	81 (94)	346 $C_{12}H_{21}Si^{79}Br^{74}Ge$ 348 $C_{12}H_{21}Si^{81}Br^{74}Ge$	2952, 2902, 1530 1242, 1100, 850 827, 748, 726 600	41.52 (41.67)	6.09 (6.12)	23.32 (23.10)

 (X)	96-98/0.2	69 (81)	M-CH$_3$ 415 C$_{14}$H$_{27}$Si^{74}Ge^{118}Sn	2952, 2900, 1252 1240, 1226, 850 826, 750, 595	42.18 (41.92)	7.16 (7.04)	- -
 (XI)	106/0.4 [c]	88 (98)	M-CH$_3$ 383 C$_8$H$_9$^{79}Br$_2$^{118}Sn 385 C$_8$H$_9$^{79}Br^{81}Br^{118}Sn 387 C$_8$H$_9$^{81}Br$_2$^{118}Sn	2980, 2910, 1544 1530, 1088, 844 668, 530	27.20 (27.11)	3.07 (3.03)	39.95 (40.09)
 (XIV)	97/0.24	72 (88)	M-CH$_3$ 375 C$_{11}$H$_{18}$Si^{79}Br^{118}Sn 377 C$_{11}$H$_{18}$Si^{81}Br^{118}Sn	2955, 2903, 1528 1366, 1244, 1095 525	37.15 (36.77)	5.40 (5.40)	20.25 (20.39)

[a] M.p., 39–40°C; lit. ref. 4, m.p., 40–41°C. [b] Ref. 5. [c] M.p. 30–31°C.

mixture was hydrolyzed with 2 *N* HCl, the organic layer phase separated and dried over $MgSO_4$. Distillation of the mixture yielded (3,5-dibromophenyl)trimethylsilane (III) [4] (63.1 g, 84%). See Table 1. Compound XI was prepared under similar conditions for III except the reaction temperature and hydrolysis were performed at −78°C. Five minutes after addition of $(CH_3)_3SnCl$, a GC analysis indicated completion of reaction. See Table 1.

Synthesis of (3-bromophenyl)trimethylsilane (V) [5]

To a diethyl ether (150 ml) solution of III (4.0 g, 13.0 mmol) at −78°C was added n-butyllithium (7.5 ml of 2.20 *M* in hexane, 16.5 mmol). After stirring at −78°C for 30 min, the reaction mixture was hydrolyzed with 2 *N* HCl solution at 0°C, the organic layer was phase separated and dried over $MgSO_4$. Distillation at reduced pressure yielded compound V. See Table 1.

Synthesis of [3-bromo-5-(trimethylgermyl)phenyl]trimethylsilane (VI)

To a diethyl ether (240 ml) solution of III (6.50 g, 21.1 mmol) was added n-butyllithium (8.8 ml of 2.40 *M* in hexane, 21.1 mmol) at −78°C. After stirring at −78°C for 10 min, an aliquot sample was hydrolyzed and GC analysis indicated complete conversion of III to V. After an additional 10 min, $(CH_3)_3GeCl$ (3.70 g, 24.2 mmol) was added dropwise. The reaction was stirred for an additional 1.5 h. The reaction mixture was hydrolyzed at −78°C with ethanol (10 ml) containing concentrated HCl (4.0 ml). The reaction mixture was then poured into diluted HCl (200 ml), phase separated and the organic layer dried with $MgSO_4$. After aspiration of the solvent, the residue was distilled under reduced pressure to yield the product VI. See Table 1.

Synthesis trimethyl[3-(trimethylgermyl)-5-(trimethylstannyl)phenyl]silane (X)

Into a reaction flask containing the intermediate VI (3.0 g, 8.67 mmol) dissolved in anhydrous ether (60 ml) and tetrahydrofuran (60 ml) was added n-butyllithium (3.90 ml of a 2.4 *M* hexane solution, 9.36 mmol) at −78°C. After 20 min, at which time a GC analysis indicated a complete metal–halogen exchange, a solution of $(CH_3)_3SnCl$ (2.20 g, 11.0 mmol) in anhydrous diethyl ether (25 ml) was added over a period of 5 min. After an additional 45 min at −78°C the reaction mixture was hydrolyzed with 2 *N* HCl (100 ml). The organic layer was separated, dried over $MgSO_4$ and aspirated under vacuum leaving a residue of products which by GC/MS analysis indicated the desired product X, 81% (GC area percent). The compound was identified by GC retention time and GC/MS analysis and compared to the product X prepared as described below. The GC/MS analysis also indicated the following minor products:

(a) IX (Sn–Aryl cleavage due to the excess n-butyllithium used);

(b) [3-butyl-5-(trimethylgermyl)phenyl]trimethylsilane (VIII) (product from reaction between $n\text{-}C_4H_9Br$ and VII);

(c) [3-trimethylgermyl-5-(dimethylbutylstannyl)phenyl]trimethylsilane (product from $Sn{-}CH_3$ cleavage due to the excess n-butyllithium used).

The structure of the minor products a → c are suggested as a result of the mass spectral analysis which had the proper parent ion and fragmentation peaks. In product c, the butyl group is on the Sn as indicated by the presence of the fragmentation peak, $(Sn(CH_3)_2C_4H_9)^+$.

If the above reaction is carried out in diethyl ether solvent, the metal–halogen exchange reaction is very slow. Under this condition the organolithium intermediate VII reacts preferentially with n-C_4H_9Br prior to derivatization with $(CH_3)_3SnCl$ to yield [3-butyl-5-(trimethylgermyl)phenyl]trimethylsilane (VIII) as the major product.

Synthesis of X (sequential one-step synthesis)

A solution of n-butyllithium (4.20 ml of 2.40 *M* in hexane 10.1 mmol) was added dropwise over a period of 30 min to a rapidly stirred suspension of 1,3,5-tribromobenzene (3.15 g, 10.0 mmol) in diethyl ether (80 ml) at −78°C. After an additional 30 min, a GC analysis indicated complete formation of I. To this solution $(CH_3)_3SiCl$ (1.10 g, 10.1 mmol) was added. Since the rate of reaction with $(CH_3)_3SiCl$ at −78°C is slow the reaction mixture was allowed to warm to −25°C and kept for 20 min. An aliquot sample was removed and a GC analysis showed a 96% (GC area percent) yield of compound III. After cooling the reaction mixture to −78°C, n-butyllithium (4.20 ml of 2.40 *M* in hexane, 10.1 mmol) was added. The reaction mixture was stirred at −78°C for an additional 20 min. GC analysis indicated complete conversion of compound III into compound V. $(CH_3)_3GeCl$ (1.55 g, 10.1 mmol) was added and the reaction was stirred for 10 min before an aliquot sample was removed for a GC analysis which showed the formation of compound VI in 93% (GC) area percent). Into the reaction mixture was added anhydrous tetrahydrofuran (60 ml) and n-butyllithium (4.20 ml of 2.40 *M* in hexane, 10.1 mmol). After stirring at −78°C, a GC analysis of an aliquot sample showed complete conversion of VI into compound IX. A solution of $(CH_3)_3SnCl$ (2.20 g, 11.0 mmol) dissolved in diethyl ether (15 ml) was added and the reaction mixture was stirred for an additional 15 min. The reaction mixture was then hydrolyzed at −78°C with 2 *N* HCl, the organic layer separated, dried over $MgSO_4$ and concentrated by removal of the solvent. GC analysis of the residue indicated the desired product X in 81% (GC area percent) yield. A number of smaller components (1–4%) were also indicated. Distillation of the reaction mixture produced pure X. See Table 1. The ^1H NMR showed a complex multiplet in the aromatic region consistent with an ABC pattern for the three-ring hydrogens with differing chemical shifts. In the methyl region, three singlets were observed at 0.28, 0.30 and 0.39 ppm (downfield from TMS) for the CH_3 groups on the various M substituents.

Reaction of n-butyllithium with (3,5-dibromophenyl)trimethyltin (XI)

To a diethyl ether (60 ml) solution of XI (2.85 g, 7.15 mmol) was added n-butyllithium (3.0 ml of 2.40 *M* in hexane, 7.20 mmol) at −78°C. After stirring at −78°C for 30 min, the reaction mixture was hydrolyzed with 2 *N* HCl, the organic layer was separated and dried over $MgSO_4$. GC analysis indicated a mixture of the following aromatic products in GC area percent: (a) 1,3-dibromobenzene (II), (82%); (b) (3-bromophenyl)trimethyltin (XII) (13%); (c) unreacted starting material XI (2%) and (d) (3,5-dibromophenyl)dimethylbutyltin (XIII) (1%). The products were characterized by GC/MS analysis and their GC retention time.

Synthesis of [3-bromo-5-(trimethylstannyl)phenyl]trimethylsilane (XIV)

To a diethyl ether (250 ml) solution of III (7.20 g, 23.4 mmol) at −78°C was added n-butyllithium (10.5 ml of 2.30 *M* in hexane, 24.2 mmol) dropwise with stirring over 15 min. After stirring the mixture at −78°C for 20 min, a solution of

$(CH_3)_3SnCl$ (5.50 g, 27.6 mmol) in anhydrous diethyl ether (10 ml) was added over a 5 min period and stirred for an additional 30 min. The reaction mixture was then hydrolyzed by the addition of cold, dil HCl solution. The organic layer was phase separated and dried over $MgSO_4$. The solvent was removed by aspiration under vacuum and the residue was analyzed by GC. Distillation of the concentrated mixture at reduced pressure yielded XIV. See Table 1.

Attempted synthesis of compound X from [3-bromo-5-(trimethylstannyl)phenyl]-trimethylsilane (XIV)

To a diethyl ether (80 ml) solution of XIV (1.50 g, 3.83 mmol) was added n-butyllithium (1.6 ml of 2.40 *M* in hexane, 3.84 mmol) at −78°C. Periodic removal of aliquot samples, hydrolysis with 2 *N* HCl and GC analyses indicated no metal–halogen exchange to have taken place as evidenced by the absence of n-C_4H_9Br or 1-trimethylsilyl, 3-trimethylstannylbenzene. After stirring the reaction at −78°C for an additional 21 h, the reaction mixture was hydrolyzed with 2 *N* HCl, the organic layer separated, dried over $MgSO_4$ and concentrated. GC/MS analysis indicated the following compounds expressed in GC area percent: n-$C_4H_9Sn(CH_3)_3$ (22%); (n-$C_4H_9)_2Sn(CH_3)_2$ (3%); V (11%); unreacted XIV (19%) and XV (34%). Numerous other minor unidentified products were also present.

References

1 L.S. Chen, G.J. Chen and C. Tamborski, J. Organomet. Chem., 215 (1981) 281.

2 D. Seyferth, M.A. Weiner, L.G. Vaughan, G. Raab, D.E. Welch, H.M. Cohen and D.L. Alleston, Bull. Soc. Chim. Fr., (1963) 1364 (review).

3 D. Seyferth, F.M. Armbrecht, Jr., R.L. Lambert, Jr. and W. Tronich, J. Organomet. Chem., 44 (1972) 299.

4 R.A. Benkeser, R.A. Hickner, D.I. Hoke and O.W. Thomas, J. Am. Chem. Soc., 80 (1958) 5289.

5 R.A. Benkeser and H.R. Krysiak, J. Am. Chem. Soc., 76 (1954) 599.