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STEREOSPECIFIC SYNTHESIS OF (1*E*,3*Z*)- AND (1*E*,3*E*)-1-TRIMETHYLSILYL-1,3-DIENES BY MEANS OF SEQUENTIAL CROSS-COUPLING REACTIONS

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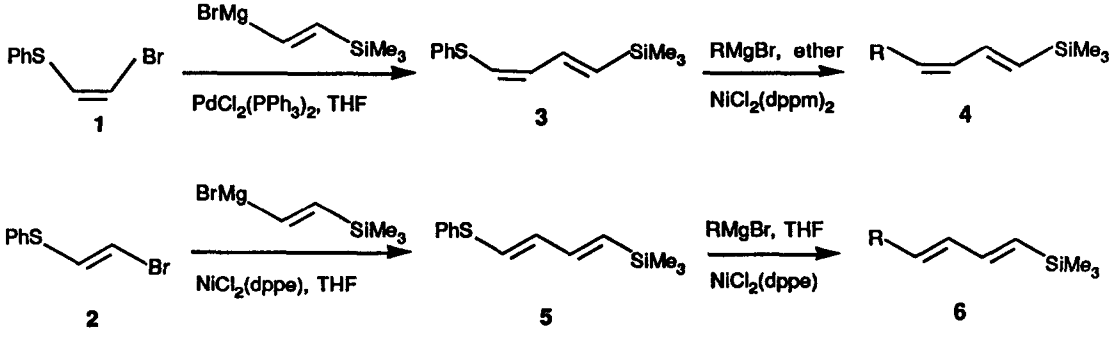
Summary: A new synthesis of stereodefined 1-trimethylsilyl-1,3-dienes is described. The method is based on two sequential coupling reactions between Grignard reagents and the readily available (*Z*)- or (*E*)-1-bromo-2-phenylthioethene, in the presence of transition metal catalysts.

The cycloaddition reactions of 1-silylated-1,3-dienes have received considerable attention from a synthetic point of view.[2-4] Furthermore, these compounds, in analogy with the behaviour of simple vinyl silanes,[2,5] should undergo a variety of substitution reactions of the silyl-group with electrophiles. Indeed, the replacement of such a group with a formyl group has been reported as a convenient route to dienals.[6] The synthesis of 1-silylated-1,3-dienes[2-4,6-11] most frequently requires the Wittig reaction[4] or various elaborations[3] of silylated α,β–unsaturated aldehydes, the condensation reactions of 1-trimethylsilylallyl[6,7] or 1,3-bis(trimethylsilyl)propenyl[8] carbanions with carbonyl compounds, or the hydroalumination of silylated 1,3-diynes.[9] A cross-coupling reaction between vinyl halides and 2-trimethylsilylethenyltrimethylstannane has been also reported.[10] However, the reaction is plagued with homo-coupling and each product would require a different vinylic halide as a starting material.

Herein we report a very convenient route to either the (1*E*,3*Z*)- or the (1*E*,3*E*)-isomer of 1-silylated dienes. The method is based upon our general approach[12] to stereodefined alkenes. Accordingly, the procedure involves two sequential cross-coupling reactions between the readily available (*Z*)- or (*E*)-1-bromo-2-phenylthioethene,[12d,13] **1** and **2**, and Grignard reagents, in the presence of transition metal catalysts, as depicted in the Scheme.

Scheme



dppm=$Ph_2PCH_2PPh_2$ dppe=$Ph_2PCH_2CH_2PPh_2$

The key step of the procedure involves the coupling of compound 1 with (*E*)-2-trimethylsilylethenylmagnesium bromide[14,15] in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$, or the coupling of compound 2 with the same reagent in the presence of $NiCl_2$(dppe), leading to the intermediate dienyl sulphide 3 or 5. The reactions of both (*Z*)- and (*E*)-isomers occurred with high retention of configuration. Indeed, in the reaction of the (*Z*)-isomer the (1*E*,3*Z*)/(1*E*,3*E*) isomers ratio in the product was 96/4 and in the reaction of the (*E*)-isomer the (1*E*,3*E*)/(1*E*,3*Z*) isomers ratio was 98/2.[16]

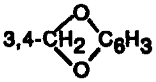
To obtain various (1*E*,3*Z*)- or (1*E*,3*E*)-1-trimethylsilyl-1,3-dienes, it was sufficient to react respectively the intermediate 3 or the intermediate 5 with different Grignard reagents in the presence of Ni-phosphine catalysts. Due to a complete retention of configuration in the second cross-coupling reaction, the stereoisomeric purities of the final products were equals to those of the intermediate dienyl sulphides. However, it is worth noting that in the case of the (1*E*,3*Z*)-isomers the choice of the catalyst is critical. Indeed, poor results are obtained performing the reactions in THF in the presence of $NiCl_2$(dppe) as a catalyst. For instance, the reaction of 3 with *n*-$C_6H_{13}MgBr$ and 3% of $NiCl_2$(dppe) led to diene 4 (R=*n*-C_6H_{13}) with (1*E*,3*Z*)-stereochemical purity of 70% as evidenced by capillary GLC. After unsuccessful attempts with $NiCl_2$(dppp) [dppp=1,3-bis(diphenylphosphino)propane] , $NiCl_2$(dppf) [dppf=1,1'-bis(diphenylphosphino)ferrocene], and $NiCl_2(PPh_3)_2$ in THF and in ether, good results were obtained using $NiCl_2(dppm)_2$[17] in ether as a solvent. The relevant data are summarized in the Table.

The following procedure for the synthesis of (1*E*,3*Z*)-7-phenyl-1-trimethylsilyl-1,3-heptadiene 4 [Table, R=$C_6H_5(CH_2)_3$] is representative. $PdCl_2(PPh_3)_2$ (0.28 g, 0.4 mmol) was placed in a dry, nitrogen flushed, 100 ml flask equipped with a magnetic stirrer and a solution of (*Z*)-1-bromo-2-phenylthioethene 1 (2.0 g, 9.3 mmol) in anhydrous THF (30ml) was added. A solution of (*E*)-2-trimethylsilylethenylmagnesium bromide in THF (35 ml, 13.8 mmol) was then added dropwise to the stirred suspension at room temperature under nitrogen. After reaction completion (3h), the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were washed with water and dried over Na_2SO_4. After removal of the solvent by evaporation, the residue was taken up in a minimum of petroleum ether and passed through a short Florisil column, with petroleum ether as eluant, in order to remove the catalyst. The solvent was evaporated in vacuo and the product 3, isolated in 82% yield after flash chromatography (silica gel, petroleum ether as eluant), was characterized by GC/mass-spectrometry analysis.[18] The stereochemistry of the double bonds was ascertained from the ^{1}H-NMR coupling constants between the vinylic protons.[18] The second cross-coupling reaction was performed by adding a 0.76 M solution of 3-phenylpropylmagnesium bromide in Et_2O (15.8 ml, 12 mmol) to a stirred suspension containing dichlorodi[1,1-bis-(diphenylphosphino)methane]nickel(II) (0.22 g, 0.24 mmol) and (1*E*,3*Z*)-4-phenylthio-1-trimethylsilyl-1,3-butadiene 3 (0.94 g, 4 mmol) in anhydrous Et_2O (10 ml) at room temperature under nitrogen. The mixture was stirred for 48h, then quenched with saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with 10% aqueous NaOH and with H_2O, and dried over Na_2SO_4. The catalyst was removed as described above and the product 4 was isolated in 71% yield after flash chromatography (silica gel, petroleum ether). Structural assignement was ascertained by ^{1}H-NMR spectroscopic data and GC/MS.[18]

In conclusion, the procedure described here should provide a highly stereospecific route to doubly stereodefined conjugated 1-silylated-dienes starting with the two isomers of a common precursor. Furthermore, besides representing a crucial step of our procedure, the synthesis of 4-phenylthio-1-trimethylsilyl-1,3-dienes

TABLE: Cross-coupling Reactions of (1*E*,3*Z*)- or (1*E*,3*E*)-4-Phenylthio-1-trimethylsilyl-1,3-butadiene with Grignard Reagents in the Presence of Nickel-Phosphine Complexes as Catalysts[a]

$$\underset{(\,3 \text{ or } 5\,)}{\text{PhS-CH=CH-CH=CH-SiMe}_3} + \text{RMgBr} \xrightarrow{\text{cat., r.t.}} \underset{(\,4 \text{ or } 6\,)}{\text{R-CH=CH-CH=CH-SiMe}_3}$$

Substrate	R	Solvent	Catalyst	Reaction time(h)	Yield%[b] 4 (1*E*,3*Z*)	6 (1*E*,3*E*)
5 (1*E*,3*E*)	C_6H_5	THF	$NiCl_2(dppe)$	5		75
3 (1*E*,3*Z*)	C_6H_5	Ether	$NiCl_2(dppm)_2$	27	88	
5 (1*E*,3*E*)	n-C_5H_{11}	THF	$NiCl_2(dppe)$	4		78
3 (1*E*,3*Z*)	n-C_5H_{11}	Ether	$NiCl_2(dppm)_2$	26	60	
5 (1*E*,3*E*)	n-C_6H_{13}	THF	$NiCl_2(dppe)$	3		86
3 (1*E*,3*Z*)	n-C_6H_{13}	Ether	$NiCl_2(dppm)_2$	45	65	
5 (1*E*,3*E*)	$C_6H_5(CH_2)_3$	THF	$NiCl_2(dppe)$	6		75
3 (1*E*,3*Z*)	$C_6H_5(CH_2)_3$	Ether	$NiCl_2(dppm)_2$	48	71	
5 (1*E*,3*E*)	n-C_4H_9	THF	$NiCl_2(dppe)$	3		84
5 (1*E*,3*E*)	$THPO(CH_2)_7$	THF	$NiCl_2(dppe)$	2		70
5 (1*E*,3*E*)	 3,4-$(OCH_2O)C_6H_3$	THF	$NiCl_2(dppe)$	5		72

a) A 2/1 molar ratio of Grignard reagent to substrate was used for reactions in THF (a 3/1 ratio for reactions in ether). 3 mol% of $NiCl_2(dppe)$ or 2 mol% of $NiCl_2(dppm)_2$ with respect to the Grignard reagent were used; b) yields refer to products purified by flash chromatography (silica gel, eluted with petroleum ether); satisfactory ^{1}H-NMR and mass spectra were obtained for all new compounds.

is also important in itself since it provides a convenient preparation of dienes having silicon and sulfur functionalities which are both useful. Synthetic applications of these dienes are under investigation in our laboratory.

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15) 1-Trimethylsilyl-2-bromoethene is commercially available (Fluka) in an (*E*)/(*Z*) 87/13 ratio. The mixture was distilled two or three times on a Fisher column MMS 202 at 50-52°C/56 mbar and fractions enriched in (*Z*)-isomer were collected. Then (*E*)-isomer was recovered and purified by straightforward distillation (b.p. 54-55°C/56 mbar; stereoisomeric purity 98-99%).

16) The isomers with (1*Z*)-configuration were also produced (ca 2%), partially due to the presence of (*Z*)-1-trimethylsilyl-2-bromoethene in the starting material.[15] However, preliminary experiments performed with Grignard reagent deriving from (*Z*)/(*E*)-mixtures of 1-trimethylsilyl-2-bromoethene revealed that our procedure is not suitable for the stereospecific synthesis of (1*Z*)-isomers. Indeed, in the reactions of both compounds **1** and **2** the extent of (1*Z*)-dienes was much lower than that expected on the basis of the (*Z*)-content of the starting mixture. Isomerization of Grignard reagents deriving from (*Z*)-olefins in similar cross--coupling processes has been reported: M. Zembayashi, K. Tamao, and M. Kumada, *Tetrahedron Lett.*, **1975**, 1719.

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18) ^{1}H-NMR spectra were recorded on a Varian XL 200, 200 MHz, in $CDCl_3$ as solvent. GC/mass-spectrometry analysis were performed on a Hewlett-Packard 5890A Gas Chromatograph equipped with HP-17 capillary column, 25 m, and Hewlett-Packard Mass Selective Detector MSD 5970B.

(1*E*,3*Z*)-4-Phenylthio-1-trimethylsilyl-1,3-butadiene **3**, ^{1}H-NMR data: δ 0.24 (s, 9H, Me_3Si), 6.09 (d, 1H, $J_{1,2}$=18.2 Hz, **1-H**), 6.32 (d, 1H, $J_{3,4}$=9.3 Hz, **4-H**), 6.4 (dd, 1H, $J_{2,3}$=9.3 Hz, $J_{3,4}$=9.3 Hz, **3-H**), 7.07 (dd, 1H, $J_{1,2}$=18.2 Hz, $J_{2,3}$=9.3 Hz, **2-H**), and 7.29-7.48 ppm (m, 5H). Mass spectral data: *m/e* 234 (M^+,11), 219 (4), 157 (27), 109 (14), 73 (100).

(1*E*,3*Z*)-7-Phenyl-1-trimethylsilyl-1,3-heptadiene **4**, ^{1}H-NMR data: δ 0.18 (s, 9H, Me_3Si), 1.75-1.90 (m, 2H), 2.29-2.41 (m, 2H), 2.73 (t, 2H, J=7.6 Hz), 5.54 (dt, 1H, J=7.6 Hz, $J_{3,4}$=10.6 Hz, **4-H**), 5.93 (d, 1H, $J_{1,2}$=18.3 Hz, **1-H**), 6.13 (dd, 1H, $J_{2,3}$=10.6 Hz, $J_{3,4}$=10.6 Hz, **3-H**), 6.86 (dd, 1H, $J_{1,2}$=18.3 Hz, $J_{2,3}$=10.6 Hz, **2-H**), and 7.2-7.4 ppm (m, 5H). Mass spectral data: *m/e* 244 (M^+, 5), 229 (13), 170 (23), 153 (9), 135 (12), 91 (44), 73 (100).

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