SYNTHESIS OF THIOPHENE DERIVATIVES BEARING A SILICON ATOM¶

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Abstract——Synthesis of thiophene derivatives containing a silicon atom is described. Silylation of 2-thienylmethyl chloride (**12**) with trichlorovinylsilane or chloro(chloromethyl)dimethylsilane was accomplished by addition of **12** to a mixture of Mg and the former reagent in THF or by addition of a mixture of **12** and the latter reagent to a mixture of Mg in THF to give dichloro(2-thienylmethyl)vinylsilane (**13**) or chloromethyl(dimethyl)(2-thienylmethyl)silane (**18**). The Grignard reagent (**19**) of **18** reacted with carbon dioxide, dimethyl carbonate or benzaldehyde to produce dimethyl(2-thienylmethyl)silylacetic acid (**20**), methyl dimethyl(2-thienylmethyl)silylacetate (**21**) or 2'-[dimethyl(2-thienylmethyl)silyl]-1'-phenylethanol (**22**).

We have recently reported synthesis of 2,2-dimethyl-2-silatetralins having oxygen functional groups (**1**)[1] or alkyl groups (**2**)[2] at the 1-position, polycyclic organosilicon compounds (**3**),[3] and 6-acyl-2-silatetralins (**4**)[4] (Chart1). As a part of our continuing investigation of organosilicons, we are interested in heteroaromatic compounds bearing one or more than silicon atoms, because they might have a promise of new material properties and biological activity. The present paper deals with the synthesis of thiophene derivatives containing a silicon atom, which might be intermediates for synthesis of cyclic heteroaromatic

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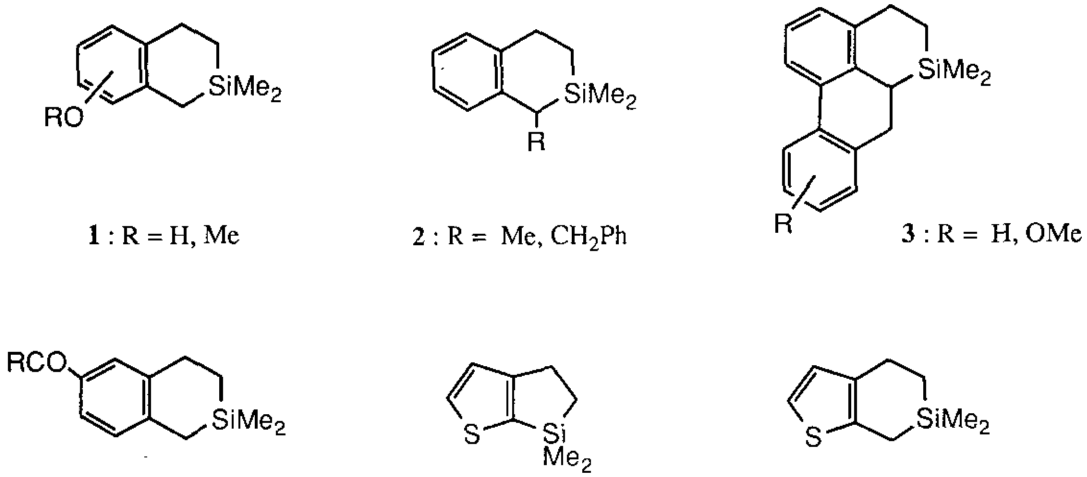
¶ This paper is dedicated to Emeritus Professor Shigeru Oae on the occasion of his 77th birthday.

compounds (eq. **5**, **6**) including a silicon atom.



1 : R = H, Me

2 : R = Me, CH_2Ph

3 : R = H, OMe

4 : R = Me, Ph, $HO_2C(CH_2)_2$

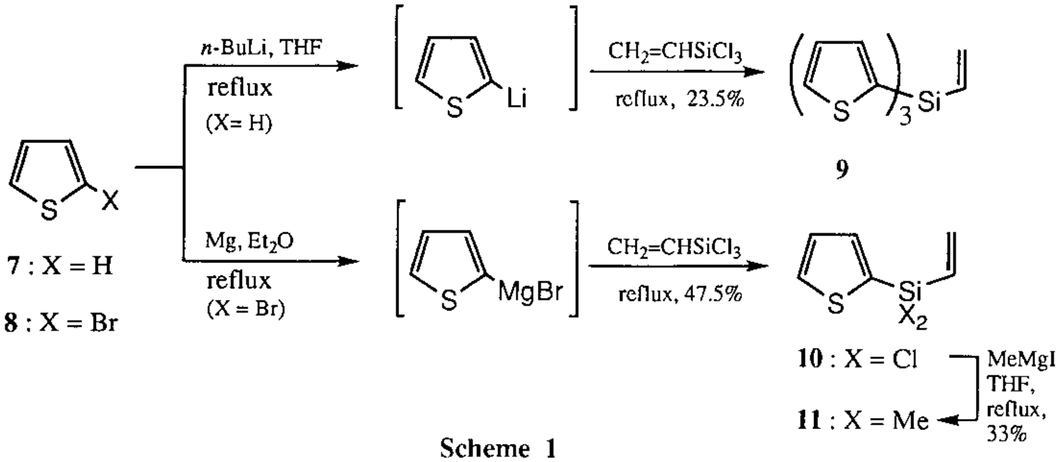
5

6

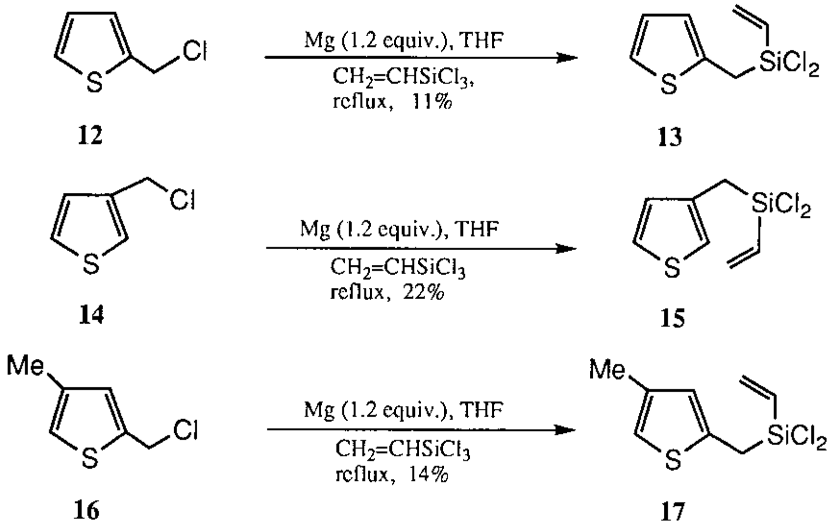
Chart 1

A THF solution of 2-lithiothiophene prepared from thiophene (**7**) and *n*-butyllithium (1 equiv.) was refluxed with trichlorovinylsilane to produce exclusively tri-(2-thienyl)vinylsilane (**9**, bp > 240 °C/14 Torr) in 24% yield. On the other hand, 2-thienylmagnesium bromide generated from 2-bromothiophene (**8**) and Mg in ether in a usual manner reacted with the same reagent to afford dichloro(2-thienyl)-vinylsilane (**10**, bp 83-84 °C/9 Torr) in 47.5% yield,[5] which was converted into the dimethylsilyl compound (**11**, bp 55 °C/5.5 Torr) by the reaction with methylmagnesium iodide in ether (Scheme 1). Structure of **9**, **10**, and **11** was determined on the basis of the spectral evidence (^{1}H-nmr and ms).

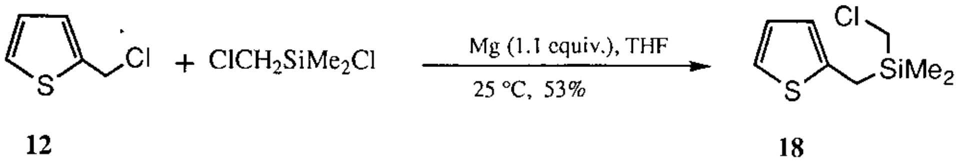
In general, generation of the Grignard reagent from 2-thienylmethyl chloride (**12**) in a usual way is known to be troublesome.[6] After unsuccessful attempts[7] to generate the Grignard reagent, the dichlorosilyl compound (**13**) was prepared, though in low yield. Namely, **12** was added to a mixture[8] of Mg (1.2 equiv.) and trichlorovinylsilane in THF and the reaction mixture was refluxed for 3 h to afford dichloro(2-thienylmethyl)vinylsilane (**13**, bp 88-92 °C/5 Torr) in 11% yield, the ^{1}H-nmr spectrum of which showed a peak due to silylmethylene protons at δ 2.93 (2H, s), peaks due to a vinyl group at δ 6.12-6.31 (3H, m), and peaks due to thienyl ring protons at δ 6.81-6.83, 6.90-6.94, and 7.10-7.12 (each



Scheme 1

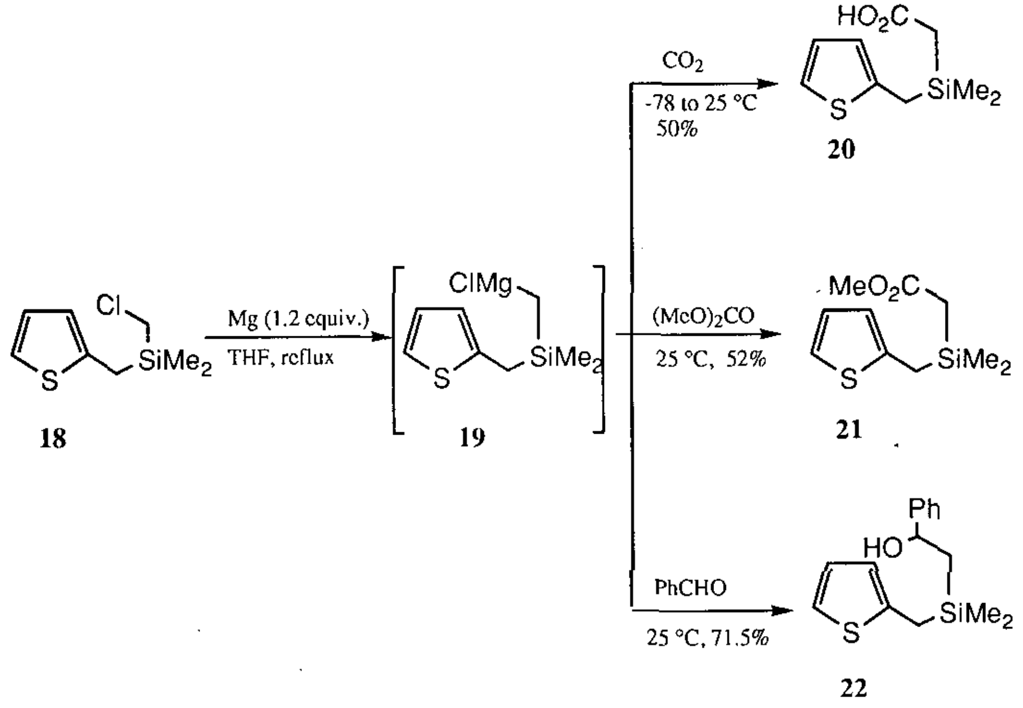


Scheme 2



Scheme 3

1H, m). Similarly, 3-thienylmethyl chloride (**14**) or 4-methyl-2-thienylmethyl chloride (**16**) produced the corresponding dichlorovinylsilanes (**15** or **17**) in 22 or 14% yield (Scheme 2). Their structure was characterized by the spectral evidence (^{1}H-nmr and ms). Since dichloro(2-thienylmethyl)vinylsilane (**13**) was prepared by addition of **12** to a mixture of Mg and trichlorovinylsilane in THF, this methodology was applied to the reaction of **12** with chloro(chloromethyl)dimethylsilane. In this case, however, as a mixture of Mg and chloro(chloromethyl)dimethylsilane gives the Grignard reagent, a solution of **12** and chloromethylsilyl reagent in THF was added to a mixture of Mg in THF at 0 °C and the reaction mixture was stirred at 25 °C for 2 h. Usual work-up produced the expected silyl compound (**18**, bp 93-95 °C/3 Torr) in 53% yield, the spectral (^{1}H-nmr and ms) data of which supported well the structure (Scheme 3). With chloromethyl(dimethyl)(2-thienylmethyl)silane (**18**) in hand, the reaction of **18** with carbon dioxide or carbonyl compounds *via* the Grignard reagent (**19**) was performed. Treatment of **18** with Mg in THF in a usual way generated the Grignard reagent, which was cooled at -78 °C and reacted with crashed dry-ice solid. The reaction mixture raised gradually to 25 °C and usual work-up of the reaction mixture gave a silylacetic acid (**20**) in 50% yield. Similarly, the reaction of **19** with dimethyl carbonate or benzaldehyde in THF at 25 °C afforded a methyl silylacetate (**21**) or 1'-phenyl-2'-silylethanol (**22**) in 52 or



Scheme 4

71.5% yield (Scheme 4). Their structure was supported well by spectral (^{1}H-nmr and ms) data, in which each ms spectrum of **20** and **21** showed characteristically a peak at *m/z* 75 [base peak, $(Me_2SiOH)^+$] and 89 [93%, $(Me_2SiOMe)^+$], respectively.

For the purpose of the synthesis of cyclic silicon-containing heteroaromatic compounds (eq. **5**, **6**) intramolecular Friedel-Crafts reaction of **10**, **13**, **15**, and **17** in the manner similar to that reported previously[1] was performed. In remarkable contrast to arylmethyl(dichloro)vinylsilanes,[1] however, cyclization did not take place.

In conclusion, silicon-containing thiophene derivatives were synthesized by the modified Grignard reaction, though the reaction conditions could not be optimalized.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General—All boiling points are uncorrected. Ir spectra were taken with a Hitachi model 260-10 spectrophotometer in neat state. ^{1}H-Nmr spectra were recorded on a JEOL model EX-270 spectrometer in $CDCl_3$ solution using Me_4Si or $CHCl_3$ as an internal standard. Ms were measured on a Hitachi M-80 or M-80A spectrometer. HRms were measured on a Hitachi M-80 spectrometer. The column chromatography was carried out on silica gel. The extract was dried over anhydrous $MgSO_4$.

Materials—THF was distilled from sodium wire and benzophenone prior to use. *n*-BuLi-hexane solution was purchased from Kanto Chemical Co. Inc., and titrated before use.

Tri-(2-thienyl)vinylsilane (9). *n*-BuLi (1.6M in hexane, 18.75 ml, 0.03 mol) was added dropwise to a stirred solution of thiophene (**7**, 2.35 ml, 0.03 mol) in THF (20 ml) at 25 °C under Ar over a period of 5 min and the reaction mixture was refluxed for 4 h. The 2-lithiothiophene solution obtained above was added to a solution of trichlorovinylsilane (3.81 ml, 0.03 mol) in THF (50 ml) over a period of 5 min, and the whole was refluxed for 2 h. After the reaction was quenched with saturated aq. $NaHCO_3$ solution, the solvent was removed *in vacuo* to give a residue, to which was added saturated aq. $NaHCO_3$ solution and the product was taken up in ether. The ether extract was washed with brine. The oily residue obtained on removal of the solvent *in vacuo* was purified by column chromatography with hexane-AcOEt = 10 : 1 to give the title compound (**9**, 0.75 g, 23.5%, >bp 240 °C/14 Torr). ^{1}H-Nmr δ : 5.91-6.01 [1H, m, (*trans*)CH(*H*)=CHSi], 6.29-6.36 [1H, m, (*cis*)C*H*(H)=CHSi], 6.56-6.70 (1H, m, CH_2=C*H*Si), 7.22-7.25, 7.42-7.44, 7.70-7.73 (each 1H, m, C_4H_3S). Ms *m/z* : 304 (M^+); HRms *m/z* calcd for $C_{14}H_{12}S_3Si$ (M^+) : 303.9870, found : 303.9867.

Dichloro(2-thienyl)vinylsilane (10). A solution of 2-bromothiophene (**8**, 1.9 ml, 0.02 mol) in dry ether (4 ml) was added dropwise to a stirred mixture of Mg (0.59 g, 0.024 g atom) in dry ether (10 ml) and the reaction mixture was refluxed for 1 h under Ar. The Grignard reagent thus obtained was added to a stirred solution of trichlorovinylsilane (2.54 ml, 0.02 mol) in dry ether (40 ml) and the whole was refluxed for 2.5 h under Ar. Work-up similar to that noted for **9** gave an oily residue, which was distilled *in vacuo* to afford the title compound (**10**, 1.98 g, 47.5%, bp 83-84 °C/9 Torr). ^{1}H-Nmr δ : 6.12-6.44 (3H, m, CH_2=CHSi), 7.26 (1H, dd, *J* = 3.5, 4.5 Hz, 4-H), 7.58 (1H, dd, *J* = 1, 3.5 Hz, 3-H), 7.79 (1H, dd, *J* = 1, 4.5 Hz, 5-H).

Dimethyl(2-thienyl)vinylsilane (11). To the methylmagnesium iodide solution [prepared from MeI (12 ml, 0.19 mol), Mg (5.63 g, 0.23 g atom), and dry ether (100 ml) in a usual manner] was added a solution of **10** (10.0 g, 0.048 mol) in dry ether (100 ml) and the mixture was refluxed for 1 h. The reaction was quenched with 1N HCl and the organic phase was separated. The aqueous phase was extracted with ether. The combined ether extract was washed successively with saturated aq. $Na_2S_2O_3$ solution, brine, saturated aq. $NaHCO_3$ solution, and brine. Removal of the solvent afforded an oily residue, which was distilled *in vacuo* to produce (**11**, 2.60 g, 33%, bp 55 °C/5.5 Torr). ^{1}H- Nmr δ : 5.77 [1H, dd, *J* = 4, 20 Hz, (*trans*)C*H*(H)=CHSi], 6.05 [1H, dd, *J* = 4, 15 Hz, (*cis*)CH(*H*)=CHSi], 6.33 [1H, dd, *J* = 15, 20 Hz, CH(H)=C*H*Si], 7.20-7.68 (3H, m, C_4H_3S). Ms *m/z* : 168 (M^+); HRms *m*/*z* calcd for $C_8H_{12}SSi$ (M^+) : 168.0428, found : 168.0438.

2-Thienylmethyl Chloride (12). To a solution of 2-thienylmethanol[9] (5.71 g, 0.05 mol) in dry CH_2Cl_2 (50 ml) were added dropwise pyridine (6.04 ml, 0.075 mol) and $SOCl_2$ (5.45 ml, 0.075 mol) in this order and the reaction mixture was stirred at 25 °C for 10 min. The reaction was quenched with ice-cold water and the product was taken up in CH_2Cl_2. The CH_2Cl_2 extract was washed with saturated aq. $NaHCO_3$ solution and brine. Removal of the solvent gave an oily residue, which was distilled *in vacuo* to leave the title compound (**12**, 4.67 g, 71.3%), bp 91-92 °C/35 Torr (lit.,[10] bp 78-82 °C/18 Torr).

Dichloro(2-thienylmethyl)vinylsilane (13). A solution of **12** (6.60 g, 0.05 mol) in THF (100 ml) was added dropwise to a mixutre of Mg (1.46 g, 0.06 g atom) and trichlorovinylsilane (6.35 ml, 0.05 mol) in THF (100 ml) containing a small pieces of I_2 at 25 °C under Ar over a period of 0.5 h and the whole was refluxed with stirring for 3 h. After a precipitate obtained by filtration was washed with ether, evaporation of the solvent produced an oily residue, which was distilled *in vacuo* to afford the title compound (**13**, 1.17 g, 11%, bp 88-92 °C/4 Torr). ^{1}H-Nmr δ : 2.93 (2H, $C_4H_3SCH_2Si$), 6.12-6.31 (3H, m, CH_2=CHSi), 6.81-6.83, 6.90-6.94, 7.10-7.12 (each 1H, m, C_4H_3S). Ms *m*/*z* : 222 (M^+); HRms *m*/*z* calcd for $C_7H_8{}^{35}Cl_2SSi$ (M^+): 221.9493, found : 221.9488.

Dichloro(3-thienylmethyl)vinylsilane (15). The title compound (**15**, 2.43 g, 22%, bp 117-120 °C/21 Torr) was obtained by the reaction of **14**[11] (6.60 g, 0.05 mol) in THF (100 ml) with Mg (1.46 g, 0.06 g atom) and trichlorovinylsilane (6.35 ml, 0.05 mol) in THF (50 ml) at reflux (2.5 h) followed by work-up similar to that noted for **13**. ^{1}H-Nmr δ : 2.75 (2H, s, $C_4H_3SCH_2Si$), 6.08-6.23 (3H, m, CH_2=CHSi), 6.90-7.34 (3H, m, C_4H_3S). Ms *m*/*z* : 222 (M^+); HRms *m*/*z* calcd for $C_7H_8{}^{35}Cl_2SSi$ (M^+): 221.9493, found : 221.9485.

Dichloro(4-methyl-2-thienylmethyl)vinylsilane (17). The title compound (**17**, 0.72 g, 14%, bp 114-116 °C/5.5 Torr) was obtained by the reaction of **16**[12] (3.07g, 0.021 mol) in THF (20 ml) with Mg (0.6 g, 0.025 g atom) and trichlorovinylsilane (2.66 ml, 0.026 mol) in THF (40 ml) at reflux (2.5 h) followed by work-up similar to that noted for **13**. ^{1}H-Nmr δ : 2.20 (3H, s, Me), 2.86 (2H, s, $C_4H_3SCH_2Si$), 6.16-6.19 (2H, m, CH_2=CHSi), 6.23-6.31 (1H, m, CH_2=CHSi), 6.62, 6.60 (each 1H, s, 3- and 5-H). Ms *m/z* : 236 (M^+); HRms *m/z* calcd for $C_8H_{10}{}^{35}Cl_2SSi$ (M^+): 235.9649, found : 235.9656.

Chloromethyl(dimethyl)(2-thienylmethyl)silane (18). (1) A solution of **12** (1.32 g, 0.01 mol) and chloro(chloromethyl)dimethylsilane (1.1 ml, 0.0083 mol) in THF (3 ml) was added dropwise to a stirred suspension of Mg (0.26 g, 0.011 g atom) in THF (40 ml) containing a small pieces of I_2 at 0 °C over a period of 10 min and the mixture was refluxed for 0.5 h. After the reaction was quenched with water, the product was taken up in ether. The ether extract was washed with 10% HCl and brine. Removal of the solvent gave an oily residue, which was distilled *in vacuo* to leave the title compound (**18**, 0.5 g, 24.8%, bp 100-105 °C/15.5 Torr). ^{1}H-Nmr δ : 0.17 (6H, s, $SiMe_2$), 2.45 (2H, s, $SiCH_2Cl$), 2.80 (2H, s, $C_4H_3SCH_2Si$), 6.64-6.65, 6.88-6.91, 6.99-7.02 (each 1H, m, C_4H_3S). Ms *m/z* : 204 (M^+); HRms *m/z* calcd for $C_8H_{13}{}^{35}ClSSi$ (M^+): 204.0195, found : 204.0197.

(2) **12** (1.32 g, 0.01 mol) and chloro(chloromethyl)dimethylsilane (1.1 ml, 0.0083 mol) in THF (3 ml), and Mg (0.26 g, 0.011 g atom) in THF (40 ml) were used. The reaction was carried out according to the procedure noted above except at reflux (the reaction mixture was stirred at 25 °C for 2 h). Work-up similar to that noted above gave an oily residue, which was purified by column chromatography (silica gel, 60 g) with hexane to afford the title compound (**18**, 0.9 g, 53%, bp 93-94 °C/3 Torr). The ^{1}H-nmr spectrum was well identical to that of the product obtained in (1).

Dimethyl(2-thienylmethyl)silylacetic Acid (20). Excess of crashed dry-ice solid was added carefully to a cold (-78 °C in dry-ice-acetone bath) solution of the Grignard reagent (**19**)[prepared from **18** (1.02 g, 0.005 mol) and Mg (0.15 g, 0.006 g atom) in THF (4.5 ml) by refluxing for 3 h]. The reaction mixture raised gradually to 25 °C. 10% HCl was added to a residue obtained on removal of the solvent *in vacuo* and the product was taken up in ether. The ether phase was extracted with saturated aq. $NaHCO_3$ solution and the aq. alkaline solution was acidified with 10% HCl. The product was taken up again in ether. The ether extract was washed with brine. Removal of the solvent gave the title compound (**20**, 0.53 g, 50%) as an oil. ^{1}H-Nmr δ : 0.20 (6H, s, $SiMe_2$), 1.98 (2H, s, $SiCH_2CO_2H$), 2.45 (2H, s, $C_4H_3SCH_2Si$), 6.65-6.70, 6.88-6.91, 6.99-7.02 (each 1H, m, C_4H_3S). Ir : 2970, 1690 cm^{-1}. Ms *m/z* : 214 (M^+), 75 [base peak, $(Me_2SiOH)^+$]; HRms *m/z* calcd for $C_9H_{14}O_2SSi$ (M^+): 214.0184, found :

214.0189.

Methyl Dimethyl(2-thienylmethyl)silylacetate (21). To a solution of the Grignard reagent (**19**) [prepared from **18** (1.02 g, 0.005 mol), Mg (0.15 g, 0.006 g atom) and THF (5.5 ml) by refluxing for 3 h] was added dimethyl carbonate (0.42 ml, 0.005 mol) and the mixture was stirred at 25 °C for 9 h. The residue obtained on removal of the solvent was diluted with ether. The ether solution was washed with 10% HCl, saturated aq. $NaHCO_3$ solution, and brine. The solvent was evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography (silica gel, 60 g) with $CHCl_3$ to produce the *title compound* (**21**, 1.19 g, 52%) as an oil. ^{1}H-Nmr δ : 0.15 (6H, s, $SiMe_2$), 1.95 (2H, s, $SiCH_2CO_2$-Me), 2.41 (2H, s, $C_4H_3SCH_2Si$), 3.64 (3H, s, OMe), 6.64-6.65, 6.88-6.91, 6.99-7.01 (each 1H, m, C_4H_3S). Ir : 1720 cm^{-1}; ms *m/z* : 227 (M^+-1), 197, 155, 131 (base peak), 89 [93%, $(Me_2SiOMe)^+$].

2'-[Dimethyl(2-thienylmethyl)silyl]-1'-phenylethanol (22). Benzaldehyde (0.51 ml, 0.005 mol) was added to a solution of the Grignard reagent (**19**)[prepared from **18** (1.02 g, 0.005 mol), Mg (0.15 g, 0.006 g atom) and THF (4 ml) by refluxing for 3 h] and the mixture was stirred at 25 °C for 0.5 h. After filtration of a precipitate, the residue obtained on removal of the solvent was diluted with ether. Work-up of the ether solution similar to that noted for **20** afforded an oily residue, which was purified by column chromatography (silica gel, 60 g) with hexane : EtOAc = 5 : 1 to produce the title compound (**22**, 0.99 g, 71.5%) as an oil. ^{1}H-Nmr δ : -0.03, 0.04 (each 3H, s, $SiMe_2$), 1.22, 1.33 (each 1H, dd, J = 8, 15 Hz, $SiCH_2CH$), 1.83 (1H, s, OH), 2.27 (2H, s, $C_4H_3SCH_2Si$), 4.86 [1H, t, J = 7.6 Hz, Ph-$CH(OH)CH_2$], 6.58-6.60, 6.83-6.90, 6.98-7.00 (each 1H, m, C_4H_3S), 7.27-7.37 (5H, m, C_6H_5). Ir : 3400 cm^{-1}; ms *m/z* : 258 (M^+-H_2O); HRms *m/z* calcd for $C_{15}H_{18}SSi$ (M^+-H_2O): 258.0899, found : 258.0882.

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7. Although the reaction of **12** with large excess (10 or more than equiv.)[1] of Mg in THF at 25 °C or reflux was performed, the Grignard reagent could not be generated.
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12. 4-Methyl-2-thienylmethyl chloride (**16**, bp 84-85 °C/17 Torr) was prepared from 4-methyl-2-thiophenemethanol[13] in the manner similar to that noted for **12**. ^{1}H-Nmr δ : 2.22 (3H, s, Me), 4.74 (2H, s, $MeC_4H_2SC\mathit{H}_2Cl$), 6.87, 6.89 (each 1H, s, $MeC_4\mathit{H}_2S$).
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