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A New Method for the Preparation of Perfluoroalkylated Triphenylethylene Derivatives

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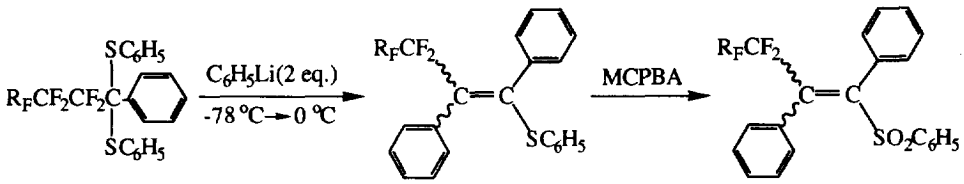
Abstract : The reaction of perfluoroalkylated dithioketals **1** with 2.1 equiv. of phenyllithium afforded the corresponding vinyl sulfides **2** in good yields. Treatment of vinyl sulfones **3**, obtained from the oxidation of **2**, with phenyllithium derivatives resulted in the formation of perfluoroalkylated triphenylethylenes **4**.

It has been well known that triphenylethylene unit is one of the most important frameworks of many nonsteroidal antiestrogens,[1] which exhibit mammary tumor inhibiting properties *via* binding to the estrogen receptor. Tamoxifen is the most excellent representative of these types of compounds and is a drug in clinical use for the treatment of mammary tumor.[2] There have been many efforts to develope a new compound, exhibiting the stronger mammary tumor inhibiting properties than Tamoxifen.[3-7] One of the possible approaches is to introduce fluorine into the alkyl group in alkyl triphenylethylene. A couple of papers suggested that introduction of fluorinated alkyl group instead of alkyl group in alkyl triphenylethylene system generally enhanced the estrogen receptor affinity due to good lipophilicity of perfluorinated alkyl group and thus mammary tumor inhibiting properties could be raised.[6,7] A number of methods for the stereoselective preparation of nonfluorinated triphenylethylene derivatives including Tamoxifen have been well documented in previous literatures,[8-11] whereas there are only limited reports on the synthesis of fluorinated ones[7,12] and these methods have disadvantages such as low yields, lack of generalization and tedious procedure. Especially, perfluoroalkylated triphenylethylene derivatives can not be easily accessible by using the previous method.[12] Thus, we wish to describe a new and efficient method for the preparation of perfluoroalkylated triphenylethylene derivatives in this communication.

Recently, we have developed a general and an efficient method for the preparation of perfluorinated dithioketals.[13] Thus, the starting materials, 2,2,3,3,3-pentafluoro-1,1-bis(phenylthio)propylbenzene(**1a**) and 2,2,3,3,4,4,4-heptafluoro-1,1-bis(phenylthio)propylbenzene(**1b**), can be prepared from the reaction of pentafluoroethyl phenyl ketone and heptafluorobutyrophenone with thiophenol in the presence of $AlCl_3$ at -78 °C for 20 hours. The reactions of **1a** and **1b** with 2.1 equiv. of phenyllithium at -78 °C, followed by warming to 0 °C, afforded the E and Z isomeric mixtures of trifluoromethylated and pentafluoroethylated diphenylvinyl sulfides **2a** and **2b** in 87% and 83% yields. The reaction pathway seems likely that the initial attack on sulfur atom by phenyllithium provides a carbanion bearing the perfluoroalkyl group, which quickly undergo β-dehydrofluorination to give β-fluoro-β-perfluoroalkylvinyl sulfide. This reactive vinyl sulfide quickly undergoes the addition-elimination reaction with phenyllithium presented in solution as soon as it was formed.

Since the phenylthio group has an excellent potential for the carbon-carbon bond formation,[14] we performed the reaction of **2a** with phenylmagnesium bromide in the presence of Ni(II) catalyst such as $NiCl_2$(dppp) and $NiCl_2(PPh_3)_2$. Unfortunately, the coupling product, trifluoromethylated triphenylethylene, was not obtained under the various reaction conditions, but the only starting material was recovered. With a convenient

route to the trifluoromethylated triphenylethylene, we decided to examine the possibility of addition-elimination pathway of perfluoroalkylated diphenylvinyl sulfones, which can be prepared *via* oxidation of **2**, with phenyllithium reagents. Thus, trifluoromethylated and pentafluoroethylated diphenylvinyl sulfones **3a** and **3b** were prepared *via* the reaction of **2a** and **2b** with MCPBA in 87% and 83% yields.

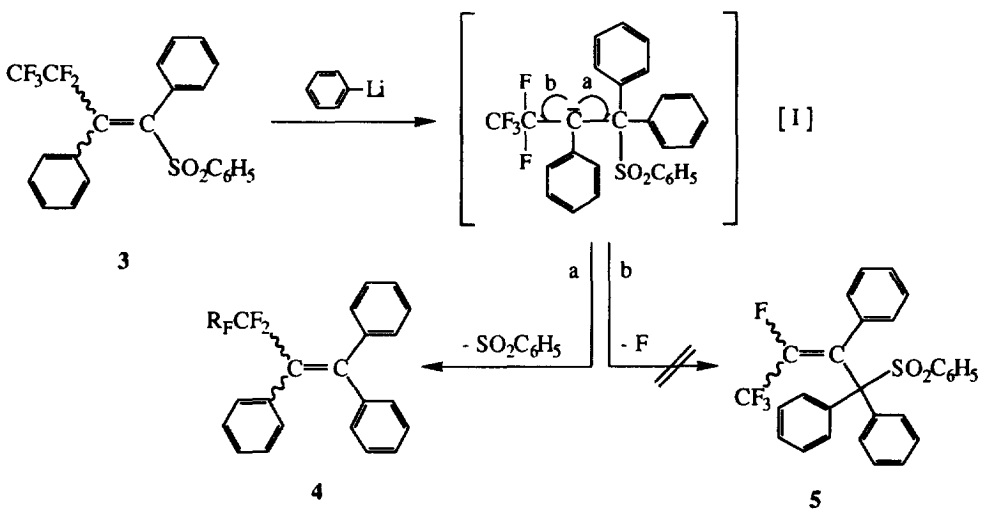


1a, $R_F = F$
1b, $R_F = CF_3$

2a, $R_F = F$
2b, $R_F = CF_3$

3a, $R_F = F$
3b, $R_F = CF_3$

Subsequent treatment of **3a** with 1.1 equiv. phenyllithium in ether at room temperature for 24 hours resulted in the formation of trifluoromethylated triphenylethylene **4a** in 83% yield. The similar reactions between **3a** and phenyllithium reagents bearing a substituent on the benzene ring afforded the E and Z isomeric mixtures (E : Z = 40 : 60) of the corresponding trifluoromethylated triphenylethylene derivatives **4b-j** in 50-78% yields. Assignment of the isomers of **4b-j** was established by assigning the isomers of **4f**, in which the chemical shift of the methoxyl group in ^1H NMR provides a useful diagnosis which allows tentative assignment of the geometry of triaryl-substituted alkenes. Generally, the methoxyl protons which are arranged to the same side with benzene ring are more shielded than those arranged to the other side.[15] When **3b** was reacted with 1.1 equiv. of phenyllithium reagent under the same reaction condition, pentafluoroethylated triphenylethylene **4k** was obtained in 74% yield. In spite of the good leaving ability of fluoride from the intermediate [I] ($CF_3CF_2 >> CF_3$),[16] S_N2' product **5** was not detected in this reaction.



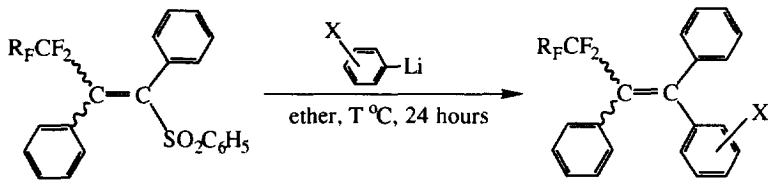
3

4

5

Similarly, the reaction of **3b** with phenyllithium reagents bearing a substituent on the benzene ring provided the E and Z isomeric mixtures (E : Z = 35 : 65) of the corresponding pentafluoroethylated triphenylethylene derivatives **4l-n** in 67-71% yields. The results of these reactions are summarized in Table 1.

Table 1. Reaction of β-Perfluoroalkylated Vinyl Sulfones **3** with Phenyllithium Reagents



3 **4**

Compound No.	R_F	X	T (°C)	**4**, Yields(%)[a,b]
4a	CF_3	H	25	83
4b	CF_3	4-CH_3	25	71
4c	CF_3	4-C_2H_5	25	70
4d	CF_3	4-Cl	25	63
4e	CF_3	4-Br	0→25	77
4f	CF_3	4-CH_3O	25	68
4g	CF_3	3-CF_3	0→25	50[c]
4h	CF_3	4-CF_3	-5→25	78[d]
4i	CF_3	3-F	-40→25	53
4j	CF_3	3-Cl	-10→25	63
4k	CF_3CF_2	H	25	74
4l	CF_3CF_2	4-Br	0→25	68
4m	CF_3CF_2	4-CH_3	25	71
4n	CF_3CF_2	4-CH_3O	25	67

[a]Isolated yields. [b]All products except for **4a** and **4k** are E and Z isomeric mixture.
[c]Starting material(15%) was recovered. [d]Starting material(17%) was recovered.

A typical reaction procedure for the preparation of **4f** is as follows. To a ether(5 ml) solution of 4-iodoanisole (0.702 g, 3.0 mmol) was added n-BuLi (2.5 mmol) at room temperature, and the reaction mixture

was stirred at room temperature for 30 min. under argon atmosphere. The solution of 3,3,3-trifluoro-1,2-diphenyl-1-phenylsulfonylpropene(0.194 g, 0.5 mmol) dissolved in ether(1 ml) was added and then the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was treated with aqueous HCl solution (3%) and extracted with ether twice. The ether solution was dried and chromatographed on SiO_2 column. Elution with hexane provided 3,3,3-trifluoro-1-(4'-methoxyphenyl)-1,2-diphenylpropene **4f** in 68% yield. **4f** : mp 97-99 °C ; ^{1}H NMR($CDCl_3$) δ 7.32-6.49 (m, 14H), 3.70 (s, 3H, Z-isomer), 3.63 (s, 3H, E-isomer); ^{19}F NMR($CDCl_3$) δ -55.86 (s, 3F), -56.15(s, 3F); MS, m/z (relative intensity) 354(M^+, 100), 285 (12), 270 (17), 253 (16), 195 (19), 165 (14), 157 (12), 119 (12); IR(KBr) 3097, 2956, 1737, 1606, 1505, 1487, 1305, 1250, 1200, 1171, 1100, 1020, 810, 750, 690 cm^{-1}.

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