A New Method for the Synthesis of (*E*) and (*Z*)-Trifluoromethylated 1,2-Diphenylethene Derivatives

In Howa Jeong,* Young Sam Park, Sang Tae Oh, and Bum Tae Kim†

Department of Chemistry, Yonsei University, Wonju 220-710, Korea
†Korea Research Institute of Chemical Technology, Daejeon 305-606, Korea
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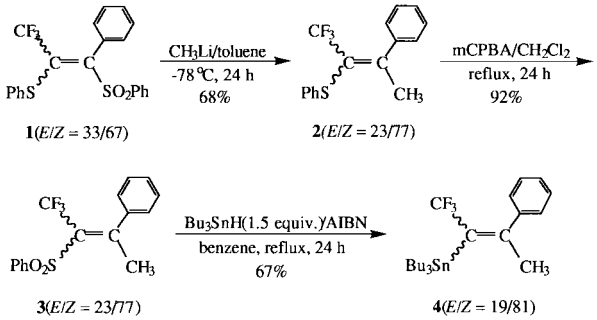
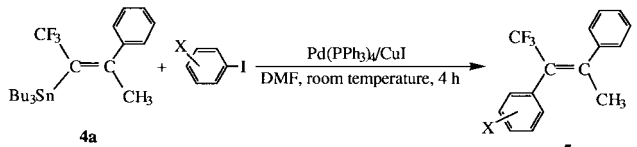
It has been well known that diphenylethene derivatives such as diethylstibestrol and dienestrol are useful mammary tumor inhibitors.[1,2] Replacement of alkyl or vinyl group in those compounds by trifluoromethyl substituent resulted in the enhancement of binding affinity as well as estrogenic activity.[3] However, the method for the preparation of trifluoromethylated diphenylethene derivatives has one drawback such as synthesis of only symmetrical bis(trifluoromethyl)diphenylethene derivatives.[3] Recently, we developed a new method for the synthesis of α-trifluoromethylated β-methyl-β-phenylvinyltin which is a quite useful building block for the synthesis of unsymmetrical trifluoromethylated diphenylethene derivatives. Although α-trifluoromethylvinylmetal reagents bearing proton, fluorine or ethoxy group at β-position have been synthesized, there has been no report on the synthesis of α-(trifluoromethyl)vinylmetal reagents bearing methyl or phenyl group at β-position. Generally, α-(trifluoromethyl)-vinyllithium reagents are easily decomposed to difluoroallene *via* defluorination even at low temperature.[4] However, β,β-difluoro-α-(trifluoromethyl)vinyllithium was quite stable at -78 °C and utilized to react with aldehydes or ketones to give the corresponding allylic alcohols.[5] A stable α-(trifluoromethyl)vinylzinc reagent was prepared from the reaction of 2-bromotrifluoropropene with Zn(Ag) in the presence of TMEDA and underwent the coupling reactions with aryl and vinyl halides in the presence of palladium catalyst, but the coupling reaction with acyl chlorides was failed.[6,7] Burton successfully synthesized β,β-difluoro-α-(trifluoromethyl)vinylzinc reagents and performed the coupling reactions with aryl halides.[8] Jiang also prepared β-ethoxy-α-(trifluoromethyl)-vinylzinc reagents which underwent a coupling reaction with aryl iodides.[9] Although α-(trifluoromethyl)vinyltin reagent was prepared in recent years from the reaction of 2-bromotrifluoroisopropene with lithium tributylstannate in the presence of CuI and utilized for the cross-coupling with acyl halides to give α-(trifluoromethyl)vinyl ketones,[10,11] there has been no report on the preparation of β-methyl-β-phenyl-α-(trifluoromethyl)vinyltin and a cross-coupling reaction with aryl iodides, in which trifluoromethylated diphenylethene derivatives can be obtained. Thus, we wish to describe a new and efficient method for the preparation of novel β-methyl-β-phenyl-α-(trifluoromethyl)vinyltin reagent and cross coupling reactions with aryl iodides to give trifluoromethylated diphenylethene derivatives in this communication.

β-Methyl-β-phenyl-α-(trifluoromethyl)vinyltin can be synthesized *via* 3 steps from the reaction of 3,3,3-trifluoro-1-phenyl-1-phenylsulfonyl-2-phenylthiopropene (**1**).[12] The reaction of **1** with methyllithium (1.5 equiv.) in toluene at -78 °C for 24 hours afforded an isomeric mixture (*E* : *Z* = 23 : 77) of 1,1,1-trifluoro-3-phenyl-2-phenylthio-2-butene (**2**)[13] in 68% yield. Oxidation of **2** with mCPBA (2.5 equiv.) in methylene chloride at reflux temperature for 24 hours resulted in the formation of 1,1,1-trifluoro-3-phenyl-2-phenylsulfonyl-2-butene (**3**)[14] in 92% yield. The oxidation reaction proceeded with retention of configuration at the double bond. When **3** was reacted with tributyltin hydride (1.5 equiv.) and catalytic amount of AIBN in benzene at reflux temperature for 24 hours, finally, β-methyl-β-phenyl-α-(trifluoromethyl)vinyltin (**4**)[15] reagent was obtained in 67% yield as an isomeric mixture (*E* : *Z* = 19 : 81) which was isolated by column chromatography. The assignment of stereoisomers of **2**, **3** and **4** was based on the chemical shift of CF_3 in ^{19}F NMR. Generally, the CF_3 fluorines which are arranged to the same side with benzene ring (*E* isomer) are more shielded than those arranged to the other side (*Z* isomer).[16] Therefore, the chemical shifts of *E* isomers of **2**, **3** and **4** are -57.58, -54.56 and -51.91 ppm, whereas the chemical shifts of *Z* isomers of **2**, **3** and **4** are -56.32, -51.85 and -50.09 ppm.



It has been well known that the cross-coupling reaction *via* vinyltin group is a useful tool for the carbon-carbon bond formation.[17] Therefore, the reactions of (*E*)-β-methyl-β-phenyl-α-(trifluoromethyl)vinyltin (**4a**) with aryl iodides in the presence of several palladium catalyst were examined to give the corresponding coupling products **5**. The cross-coupling reaction was well proceeded by using a mixture of 10 mol% $Pd(PPh_3)_4$ and 10 mol% CuI in DMF. The reaction was completed in 4 hours at room temperature. The adopted

Table 1. The cross-coupling reactions of **4a** with aryl iodides

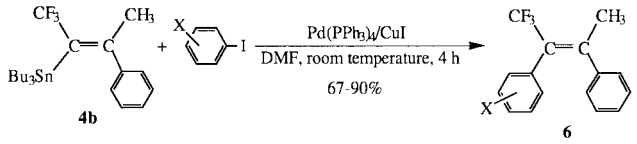


4a **5**

Compound No.	X	Yield (%)[a]
5a	H	80
5b	*p*-Br	74
5c	*p*-OCH_3	85
5d	*p*-CH_3	84
5e	*p*-NO_2	78
5f	*p*-CF_3	83
5g	*m*-Br	77
5h	*m*-OCH_3	79
5i	*m*-CH_3	86
5j	*m*-NO_2	80
5k	*m*-CF_3	82

[a]Isolated yields.

reaction condition tolerated substituents such as bromo, methoxy, methyl, nitro or trifluoromethyl group on *para* or *meta*-position of benzene ring. However, the coupling reaction with aryl iodides bearing a methoxy or methyl on *ortho*-position of benzene ring, was unsuccessful under the same reaction conditions, whereas a reduced product and dimerization product (butadiene) were formed as major products. The results of the coupling reactions of **4a** with aryl iodides are summarized in Table 1. Similarly, (*Z*)-β-methyl-β-phenyl-α-(trifluoromethyl)vinyltin (**4b**) also underwent the coupling reaction with aryl iodides to give (*E*)-1,1,1-trifluoro-2-aryl-3-phenyl-2-butene (**6**) in 67-90% isolated yields under the same reaction condition.



4b **6**

A typical reaction procedure for the preparation of **5d** is as follows. To a DMF (5 mL) solution of *p*-iodotoluene (0.090 g, 0.42 mmol) and (*E*)-β-methyl-β-phenyl-α-(trifluoromethyl)-vinyltin (0.118 g, 0.33 mmol) are added $Pd(PPh_3)_4$ (10 mol%) and CuI (10 mol%), and the reaction mixture was stirred at room temperature for 4 hours under argon atmosphere. After the reaction mixture was quenched with water and then washed with 5% KF solution and brine, the solution was extracted with ether twice. The ether solution was dried and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (20 : 1) provided 0.077 g of (*Z*)-1,1,1-trifluoro-2-(4'-methyl)phenyl-3-phenyl-2-butene (**5d**) in 84% yield. **5d**: oil; ^{1}H NMR ($CDCl_3$) δ 7.37-6.83 (m, 9H), 2.30 (s, 3H), 2.15 (q, J = 2.3 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ -56.74 (s, 3F); MS, *m*/*z* (relative intensity) 276 (M^+, 100), 261 (59), 241 (38), 207 (40), 192 (75), 165 (19), 115 (21), 77 (20), IR (neat) 3025, 2957, 2925, 1443, 1331, 1263, 1113, 924, 762, 699 cm^{-1}.

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12. Spectroscopic data of **1** is as follows. **1**: mp 94-96 °C; ^{1}H NMR ($CDCl_3$) δ 7.90-6.85 (m, 15H); ^{19}F NMR ($CDCl_3$) δ -53.58 (s, 3F, *Z*-isomer), -54.50 (s, 3F, *E*-isomer); MS, *m*/*z* (relative intensity) 420 (M^+, 17), 239 (100), 210 (78), 186 (67), 109 (77), 77 (72), 65 (42), 51 (38); IR (KBr) 3061, 2962, 1726, 1581, 1476, 1445, 1260, 1146, 753, 689 cm^{-1}.
13. Spectroscopic data of **2** is as follows. **2**: mp 56-57 °C; ^{1}H NMR ($CDCl_3$) δ 7.61-7.10 (m, 10H), 2.41 (q, J = 2.2 Hz, 3H, *Z*-isomer), 2.21 (q, J = 2.1 Hz, 3H, *E*-isomer); ^{19}F NMR ($CDCl_3$) δ -56.32 (s, 3F, *Z*-isomer), -57.58 (s, 3F, *E*-isomer); MS, *m*/*z* (relative intensity) 294 (M^+, 100), 225 (53), 210 (41), 165 (27), 147 (91), 115 (43), 109 (20), 77 (38), 51 (35); IR (KBr) 3118, 2988, 1716, 1660, 1541, 1507, 1457, 1151, 1086, 742, 699 cm^{-1}.
14. Spectroscopic data of **3** is as follows. **3**: mp 107-109 °C; ^{1}H NMR ($CDCl_3$) δ 8.08-7.98 (m, 2H), 7.66-7.07 (m, 8H), 2.63 (q, J = 1.5 Hz, 3H, *Z*-isomer), 2.37 (q, J = 2.3 Hz, 3H, E-isomer); ^{19}F NMR ($CDCl_3$) δ -51.85 (s, 3F, *Z*-isomer), -54.56 (s, 3F, *E*-isomer); MS, *m*/*z* (relative intensity) 326 (M^+, 8), 260 (25), 241 (19), 221 (19), 184 (19), 164 (32), 146 (14), 125 (18), 115 (71), 91 (14), 103 (16), 77 (100), 51 (59); IR (KBr) 3063, 2926, 1736, 1593, 1490, 1446, 1292, 1152, 1030, 764, 691 cm^{-1}.
15. Spectroscopic data of **4** is as follows. **4a** (*E*-isomer): oil; ^{1}H NMR ($CDCl_3$) δ 7.32-7.06 (m, 5H), 2.26 (q, J = 2.7 Hz, 3H), 1.71-0.83 (m, 27H); ^{19}F NMR ($CDCl_3$) δ -51.91 (s, 3F); MS, *m*/*z* (relative intensity) 419 (M^+-56, 6), 399 (14), 253 (5), 177 (7), 147 (100), 127 (6), 121 (5), 69 (4), 57 (3); IR (neat) 3021, 2956, 2853, 1595, 1463, 1273, 1134, 1075, 763, 700 cm^{-1}. **4b** (*Z*-isomer): oil; ^{1}H NMR ($CDCl_3$) δ 7.38-6.69 (m, 5H), 2.12 (q, J = 2.2 Hz, 3H), 1.67-0.76 (m, 27H); ^{19}F NMR ($CDCl_3$) δ -50.09 (s, 3F); MS, *m*/*z* (relative intensity) 419 (M^+-56, 3), 399 (11), 253 (9), 177 (8), 147 (100), 127 (8), 121 (8), 69 (7), 57 (6); IR (neat) 3020, 2957, 2924, 2854, 1595, 1463, 1273, 1134, 1074, 763, 700 cm^{-1}.
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