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A highly stereoselective preparation of CF_3-substituted 1-aryl-1,2-diphenylethenes: application to the synthesis of panomifene

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Abstract—β-CF_3-α,β-diphenylvinyl sulfide **3a** was prepared stereoselectively in 77% yield from the reaction of **2** with phenyllithium at room temperature for 5 h. Oxidation of **3a** with MCPBA afforded the corresponding vinyl sulfone **4a**, in which (*E*)-**4a** can be crystallized in a mixture of CH_2Cl_2 and hexane. The addition–elimination reaction of (*E*)-**4a** with phenyllithium having substituents on the benzene ring provided **5a–j** in 51–82% yields stereospecifically. Similarly, the treatment of (*E*)-**4a** with *p*-chloroethoxyphenyllithium in the presence of 12-crown-4 (20 mol %) at −10 °C, followed by slowly warming to room temperature, resulted in the formation of the corresponding panomifene precursor **6** in 82% yield.

Triarylethene unit is a key framework in many nonsteroidal antiestrogens, which exhibit mammary tumor inhibiting properties.[1] Tamoxifen, the most attractive one among compounds having triarylethene framework, is a drug in widespread clinical use for the treatment of all stages of hormone dependent breast cancer.[2] Only the *Z*-isomer of tamoxifen has the antiestrogenic activity required for clinical use, whereas the *E*-isomer has estrogenic properties, which would oppose the action of tamoxifen.[3] Panomifene, a CF_3-substituted tamoxifen-like compound, exhibits antiestrogenic and tumor inhibiting activities superior to those of tamoxifen in the only *E* isomer.[4] Therefore, highly stereocontrolled synthesis of the *E*-isomer of panomifene is a quite important subject in recent years. Several methods for the stereocontrolled preparation of panomifene have been documented in previous literatures since the first patent.[4] Simig and co-workers, prepared panomifene via the highly stereoselective dehydration[5] of 3,3,3-trifluoro-1-{4-[2-(methoxymethoxy)ethoxy]phenyl}-1,2-diphenylpropan-1-ol (diastereoisomer ratio = 7.9:1), which was formed from the reaction of α-(trifluoromethyl)-phenylacetic acid[6,7] with 4-[2-(methoxymethoxy)ethoxy]phenylmagnesium bromide. Recently, a novel method for the preparation of panomifene was accomplished via the Pd-catalyzed cross-coupling reaction of aryl iodides with β-CF_3-substituted alkenyl boronates, generated high stereoselectively from the reaction of dichlorohydrines with 3 equiv of aryllithium,[8,9] followed by treatment with $(Bpin)_2$.[10] Konno also prepared panomifene via the Suzuki–Miyaura cross-coupling reaction of phenylboronic acid with α-CF_3-substituted alkenyl iodides formed from a highly regio- and stereoselective carbocupration of trifluoromethylated internal alkynes, followed by treatment with iodine.[11] However, these methods suffer from tedious procedure, low-yield preparation, and not easy availability of starting material. In this communication, we wish to describe a simple and highly stereoselective preparation of CF_3-substituted 1-aryl-1,2-diphenylethenes from the β-CF_3-α,β-diphenylvinyl sulfone and apply this method to prepare antiestrogenic drug panomifene.

It has been reported that β-CF_3-α,β-diphenylvinyl sulfone **4a** (*E*:*Z* = 30:70) prepared via two steps from 1,1-bis(phenylthio)-2,2,3,3,3-pentafluoropropylbenzene[12] was reacted with *p*-methoxyphenyllithium (1.1 equiv) in ether at room temperature for 5 h to afford the corresponding CF_3-substituted 1-aryl-1,2-diphenylethene derivative **5a** (*E*:*Z* = 40:60).[13] Although *E*-stereoselectivity for the formation of **5a** was not accomplished in this reaction, it was found that *E*-stereoselectivity was

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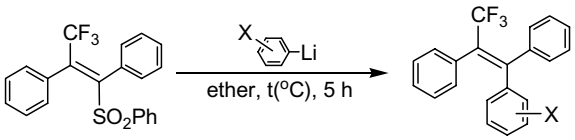
increased in the formation of **5a** from the addition–elimination reaction of **4a** with *p*-methoxyphenyllithium. This result prompted us to attempt another approach to prepare **4a** in high *E*-stereoselectivity. We started with 1,1,3,3,3-pentafluoro-2-phenylpropene **1**.[14,15] Although **1** undergoes direct addition–elimination reaction twice with substituted phenyllithium to provide CF_3-substituted 1-aryl-1,2-diphenylethene derivatives, this approach is not highly stereoselective.[15] Treatment of **1** with sodium phenylthiolate in THF at room temperature for 12 h resulted in the formation of vinyl sulfide **2** (*E*:*Z* = 85:15) in 71% yield. The high *E*-stereoselectivity for the formation of **2** can be rationalized by thermodynamic stabilities of two carbanion intermediates [A] and [B] arising from the addition of **1** with sodium phenylthiolate, in which intermediate [A] is thermodynamically more stable than intermediate [B] because of larger electrostatic repulsion between CF_3 and phenylthio groups in [B] than that between CF_3 and fluorine groups in [A].[16,17] When **2** was reacted with 2 equiv of phenyllithium in THF at room temperature for 5 h, β-CF_3-α,β-diphenylvinyl sulfide **3a** (*E*:*Z* = 89:11) was obtained in 77% yield. Subsequent oxidation of **3a** with MCPBA provided the corresponding vinyl sulfone **4a** (*E*:*Z* = 89:11) in 87% yield. The formation of **3a** from **2** is a crucial step to give *E*-isomer of **4a** high stereoselectively. The reaction of **4a** with *p*-methoxyphenyllithium (1.1 equiv) in ether at room temperature for 5 h to afford the corresponding CF_3-substituted 1-aryl-1,2-diphenylethene derivative **5a** (*E*:*Z* = 93:7) in 78% yield. Pure *E*-isomer of **4a** can be obtained in 92% yield by recrystallization of **4a** (*E*:*Z* = 89:11) in a mixture of CH_2Cl_2 and hexane. However, we could not have a X-ray crystallographic data for pure *E*-isomer of **4a** because of crystal problem of **4a**.

Assignment of (*E*)-β-CF_3-α,β-diphenylvinyl sulfone **4a** was established by assigning the isomers of β-CF_3-α-methoxyphenyl-β-phenylvinyl sulfone **4b**, in which the methoxy protons arranged to the same side with benzene ring are more shielded than those arranged to the other side.[18] Therefore, the methoxy protons in *E*-isomer appears at $\delta = 3.83$ ppm in ^{1}H NMR, whereas the methoxy protons in *Z*-isomer appears at $\delta = 3.64$ ppm. As a result of the chemical shift of methoxy group, CF_3 fluorine in *E*-isomer was observed at $\delta = -58.47$ ppm, whereas the peak of CF_3 fluorine in *Z*-isomer appears at −53.87 ppm. The reaction of pure (*E*)-**4a** with phenyllithium substituted by bromo, chloro, fluoro, ethyl, methyl, and methoxy on the benzene ring provided stereospecifically the corresponding *E*-isomer of 1-aryl-1,2-diphenylethenes **5a**–**j** in 51–82% yields. The results of these reactions are summarized in Table 1. Stereoisomers of **5** were assigned in a similar manner as shown in the determination of stereoisomer **4a**.

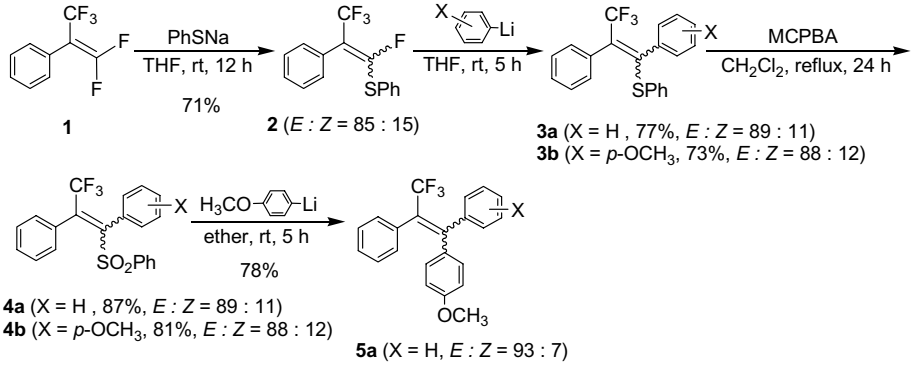
Table 1. Preparation of (*E*)-CF_3-substituted 1-aryl-1,2-diphenylethenes **5**

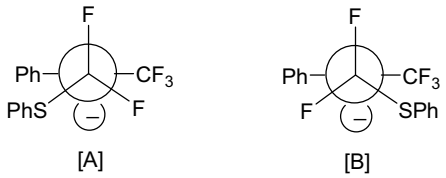


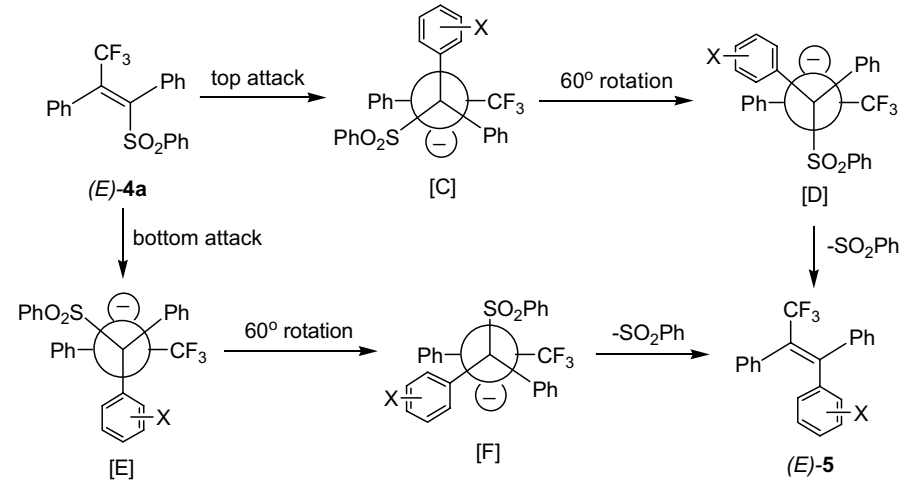
(E)-**4a** **5**

Compound no	X	*t* (°C)	Yield (%)[a]	*E*/*Z*[b]
5a	*p*-OCH_3	25	78	99/1
5b	*p*-CH_3	25	74	99/1
5c	*p*-C_2H_5	25	75	99/1
5d	*p*-Cl	25	79	99/1
5e	*p*-Br	0→25	77	99/1
5f	*p*-CF_3	−5→25	82	99/1
5g	*p*-SCH_3	25	78	99/1
5h	*m*-F	−50→25	51	99/1
5i	*m*-Cl	25	69	99/1
5j	*m*-CF_3	0→25	56	99/1

[a] Isolated yield.
[b] *E*/*Z* ratio was determined by ^{1}H and ^{19}F NMR spectroscopic analysis.







The stereospecificity for the formation of **5** can be explained by the formation of stable carbanion intermediate followed by elimination of sulfonyl group. The conformational intermediates [C] and [E] could be formed from top and bottom attack of the substituted phenyllithium on (*E*)-**4a**, respectively. Rotation of these two intermediates by 60° would result in two reasonably stable conformational intermediates [D] and [F], which quickly undergo the elimination of sulfonyl group to give (*E*)-**5**. The high *E*-stereoselectivity for the formation of **3** can also be explained in a similar manner as shown in the formation of (*E*)-**5**.

Since the preparation of panomifene via demethylation of **5a**, followed by chloroethylation and amination is tedious procedure,[10] direct addition–elimination reaction of (*E*)-**4a** with *p*-chloroethoxyphenyllithium should provide a simple and efficient method for the preparation of panomifene precursor **6**. Therefore, the reaction of (*E*)-**4a** with *p*-chloroethoxyphenyllithium was carried out under the similar reaction condition, but the reaction was not proceeded at all and starting material was recovered quantitatively. Addition of TMEDA (2 equiv) in this reaction did not make any difference, but the use of HMPA (2 equiv) resulted in the formation of **6** in 58% yield based on 70% conversion of **4a**. When **4a** was reacted with *p*-chloroethoxyphenyllithium in ether in the presence of catalytic amount of 12-crown-4 (20 mol %) at −10 °C for 1 h, followed by slowly warming to room temperature and then stirring for 12 h, desired product **6** was obtained in 82% yield. Subsequent amination of **6** with 2-aminoethanol in 2-methoxyethanol at reflux temperature for 2 h afforded panomifene **7** in 82% yield.

A typical reaction procedure for the preparation of **6** is as follows. A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum, and nitrogen tee connected to an argon source was charged with *p*-chloroethoxyiodobenzene (0.169 g, 6.0 mmol) and ether (5 mL) and then cooled to −10 °C. *n*-BuLi (4.0 mmol, 2.5 M solution in hexane) was slowly added into flask and then the mixture was stirred at −10 °C for 1 h. (*E*)-**4a** (0.388 g, 1.0 mmol) dissolved in 1 mL of THF and 12-crown-4 (20 mol %) were added at −10 °C and then the reaction mixture was stirred at −10 °C for 1 h, followed by slowly warming to room temperature. After the reaction mixture was allowed to stir at room temperature for 12 h and then quenched with 1 N HCl, the reaction mixture was extracted with ether twice. The ether solution was dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (10:1) provided 0.330 g of **6** (*E*:*Z* = 99:1) in 82% yield. (*E*)-**6**: mp 108–109 °C: ^{1}H NMR ($CDCl_3$) δ 7.34–7.24 (m, 10H), 6.82 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 3.71 (t, J = 5.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −55.98 (s, 3F); MS, *m*/*z* (relative intensity) 404 (M^++2, 33), 402 (M^+, 100), 270 (16), 253 (9), 239 (14), 215 (6), 183 (6), 165 (6); IR (KBr) 3057, 2929, 1604, 1508, 1328, 1246, 1171, 1140, 1110, 826, 761, 705 cm^{-1}. Anal. Calcd for $C_{23}H_{18}ClF_3O$: C, 68.64; H, 4.51. Found: C, 68.51; H, 4.47.

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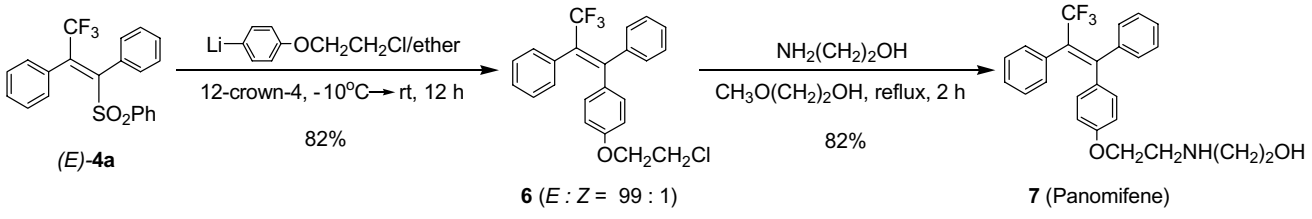

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