http://dx.doi.org/10.5012/bkcs.2012.33.2.379

Preparation of 2,2-Difluoro-1-arylethenylstannane as a Precursor of 1,1-Diaryl-2,2-difluoroethenes

Hyo Young Lee, Jong Hee Jeon, Sung Lan Jeon, and In Howa Jeong*

*Department of Chemistry and Medical Chemistry, Yonsei University, Wonju 220-710, Korea. *E-mail: jeongih@yonsei.ac.kr*
Received October 11, 2011, Accepted December 5, 2011

Key Words : 2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate, Arylation, 2,2-Difluoro-1-arylethenyl *p*-toluenesulfonate, Stannylation, 2,2-Difluoro-1-arylethenylstannane

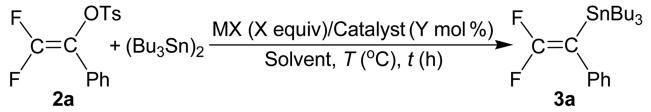
gem-Difluoroolefins have attracted much attention because they show chemical reactivities toward nucleophiles[1,2] and are useful intermediate for the synthesis of fluorinated organic compounds *via* addition-elimination reaction.[3] They are also important class of potential mechanism-based inhibitors[4] and have been known to behave as a bioisostere for carbonyl group.[5] The synthesis of *gem*-difluoroolefins can be mainly achieved by two generalized methods such as Wittig and related reaction, and metalation and related chemistry.[6,7] However, Wittig methodology was not suitable for the preparation of 1,1-diaryl-2,2-difluoroethenes because of the poor reactivity of the diaryl ketones.[8-11] One straightforward route to 1,1-diaryl-2,2-difluoroethenes is to use 2,2-difluoroethenylmetal reagents. Among these reagents, one of the promising precursors to *gem*-difluoroolefins is 2,2-difluoroethenylstannane reagents which can be utilized as cross-coupling reaction at stannyl site. Although numerous methods for the preparation of 2,2-difluoroethenylmetal reagents have been well documented in the previous literatures,[12-15] methods for the preparation of 2,2-difluoroethenylstannane reagents have been quite limited, in which 1,1-diaryl-2,2-difluoroethenes can be easily prepared by the Stille cross-coupling reaction. Percy *et al.* reported a method for the synthesis of 2,2-difluoro-1-tributylstannylethenyl diethylcarbamate from the reaction of 2,2-difluoro-1-lithioethenyl diethylcarbamate with tributylstannyl chloride.[16,17] 2,2-Difluoro-1-tributylstannylethenyl ethers were prepared in a similar manner and their cross-coupling with aryl iodides, followed by cleavage of ether linkage provided difluoromethyl ketones.[18,19] Burton *et al.* synthesized 2,2-difluoroethenylstannane from the reaction of 2,2-difluoroethenyltriethylsilane with tributylstannyl chloride in the presence of KF.[20] He also prepared 2,2-difluoro-1-bromoethenylstannane from the reaction of 1,1-dibromo-2,2-difluoroethene with tributyltin chloride in the presence of Zn metal.[21] We reported a method for the preparation of 2,2-difluoro-1-phenylethenylstannane from the stannylation of sulfonyl group in 2,2-difluoro-1-phenylethenylsulfone and its arylation to give 1,1-diaryl-2,2-difluoroethenes.[22] Alkenylation and alkynylation of 2,2-difluoro-1-phenylethenylstannane provided the corresponding 1,1-difluoro-1,3-butadienes[23] and 1,1-difluoro-1,3-enynes.[24] Recently, efficient synthesis of 2,2-diaryl-1,1-difluoroethenes can be achieved by consecutive cross-coupling reactions of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate.[25] However, a general preparation of 1-aryl-2,2-difluoroethenylstannane which is a better coupling partner of arylation as compared to 1-aryl-2,2-difluoroethenyltosylate[25] has not been reported in the previous literature. Herein, we wish to report a general method for the preparation of 1-aryl-2,2-difluoroethenylstannane which should be a nice precursor to 1,1-diaryl-2,2-difluoroethenes.

2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (**1**) was easily prepared in 90% yield from the reaction of 2,2,2-trifluoroethyl *p*-toluenesulfonate with 2.2 equiv of LDA in THF at −78 °C, followed by treatment with tributylstannyl chloride.[25] Then, the cross-coupling reaction of **1** with aryl iodides in the presence of 10 mol % $Pd(PPh_3)_4$ and 10 mol % CuI in DMF at 80 °C for 10-20 hours afforded the 2,2-difluoro-1-arylethenyl *p*-toluenesulfonate **2** in moderate to excellent yields.[25]

We attempted the stannylation of tosylate functional group of **2**. When 2,2-difluoro-1-phenylethenyl *p*-toluenesulfonate (**2a**) was reacted with 1.2 equiv of hexabutyldistannane in the presence of 5 mol % of $Pd(PPh_3)_4$ and 5 equiv of LiCl in DMF at 100 °C for 6 h, the desired product **3a** was observed in a trace amount and starting material was recovered. The longer reaction time and increase of LiCl up to 30 equivalent afforded the similar result. The reaction was performed in the presence of 5 equiv of LiBr instead of LiCl to give **3a** in 45% yield, in which the reaction completed in 8 hours. The dramatically increased yield (60% yield) of **3a** was achieved by the use of 10 equiv of LiBr in this reaction. However, when the higher equiv of LiBr was used in the reaction, the yield of **3a** decreased. Increase of $Pd(PPh_3)_4$ up to 10 mol % did not cause to increase the yield of **3a**. Reaction of **2a** with 1.2 equiv of hexabutyldistannane in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 equiv of LiBr in THF at reflux temperature for 8 hours afforded the desired product **3a** in a trace amount and most of starting material was recovered. Reaction did not improve even though 30 equiv of LiBr was used in this reaction. The use of a mixture of $PdCl_2(PPh_3)_4$ and X-Phos as a ligand in the reaction also did not give the observation of **3a**. After monitoring of the reaction under the different solvent, different equiv of LiBr and catalyst (Table 1), we found that the use of 5 mol % of $Pd(PPh_3)_4$ and 10 equiv of LiBr in DMF at 100 °C for 8 hours provided **3a** in 60% isolated yield.

Optimized reaction condition was applied to prepare a

Table 1. Stannylation of 2,2-difluoro-1-phenylethenyl *p*-toluenesulfonate (**2a**) with $(Bu_3Sn)_2$



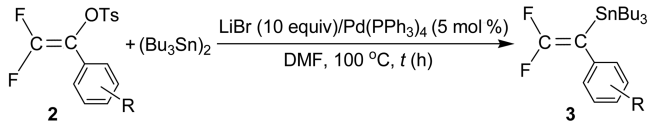
Entry	Solvent	MX	X	Catalyst	Y	T (°C)	t (h)	Yield (%)[a]
1	DMF	LiCl	5	$Pd(PPh_3)_4$	5	100	6	-[b]
2	DMF	LiCl	5	$Pd(PPh_3)_4$	5	100	20	-[b]
3	DMF	LiCl	30	$Pd(PPh_3)_4$	5	100	6	-[b]
4	DMF	LiBr	5	$Pd(PPh_3)_4$	5	100	8	45
5	DMF	LiBr	10	$Pd(PPh_3)_4$	5	100	8	60
6	DMF	LiBr	20	$Pd(PPh_3)_4$	5	100	8	20
7	DMF	LiBr	10	$Pd(PPh_3)_4$	10	100	8	58
8	THF	LiBr	10	$Pd(PPh_3)_4$	5	reflux	8	-[b]
9	THF	LiBr	30	$Pd(PPh_3)_4$	5	reflux	8	-[b]
10	THF	LiBr	10	$PdCl_2(PPh_3)_4$[c]	5	reflux	8	-[b]

[a]Isolated yield. [b]Trace amount of product was observed and starting material was recovered. [c]X-Phos was added as a ligand.

variety of 2,2-difluoro-1-arylethenylstannane **3b-n** *via* reaction between hexabutyldistannane and **2** having fluoro, chloro, bromo, methoxy, methyl, trifluoromethyl and nitro on the benzene ring. Except for the 2,2-difluoro-1-arylethenyl *p*-toluenesulfonate having electron-donating group (CH_3, OCH_3) on the benzene ring attached to double bond, the desired products **3** were obtained in 58-67% isolated yields (Table 2). The longer reaction time (14 hours) was required for the reaction with 2,2-difluoro-1-arylethenyl *p*-toluenesulfonate having electron-donating group or *o*rtho-substituent, with relatively low yields (31-45%).

A typical reaction procedure for the preparation of **3e** is as follows. A 15 mL two-neck round bottom flask equipped with a magnetic stirrer bar, glass stopper and reflux condenser connected to an argon source was charged with LiBr (0.869 g, 10 equiv) and 5 mol % $Pd(PPh_3)_4$ and then a solution of hexabutyldistannane (0.696 g, 1.2 equiv) in 3 mL of DMF was added by dropwise to the mixture. Then, DMF (2 mL) solution of **2a** (0.340 g, 1 mmol) was added. After the reaction mixture was heated at 100 °C for 24 hours, the reaction mixture was cooled to room temperature and then quenched with water. The reaction mixture was extracted with ether twice, washed with 5% KF and brine, dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of *n*-hexane and ethyl acetate (20:1) provided **3e** (0.188 g) in 41% yield. **3e**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91-6.89 (d, J = 8.8 Hz, 2H), 6.76-6.74 (d, J = 8.8 Hz, 2H), 3.69 (s, 3H), 1.45-1.36 (m, 6H), 1.26-1.18 (m, 6H), 0.92-0.88 (m, 6H), 0.84-0.77 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (dd, J = 314, 271 Hz), 129.6, 128.5, 114.2, 113.8, 84.9 (dd, J = 51, 13 Hz), 55.1, 28.2, 27.2, 13.6, 10.5; ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −74.95 (d, J = 41.4 Hz, 1F), −78.11 (d, J = 41.4 Hz, 1F); MS, *m/z* (relative intensity) 460 (M^++1, 1), 403 (20), 253 (100), 177 (39), 139 (31), 57 (18). Anal. Calcd for $C_{21}H_{34}F_2OSn$: C, 54.93; H, 7.46. Found: C, 54.71; H, 7.40.

Table 2. Preparation of 2,2-difluoro-1-arylethenylstannane **3**



Compound no.	R	t (h)	Yield (%)[a]
3a	H	8	60
3b	*p*-F	8	62
3c	*p*-Cl	8	67
3d	*p*-Br	8	63
3e	*p*-OCH_3	14	41
3f	*p*-CH_3	14	45
3g	*p*-NO_2	6	61
3h	*m*-F	8	65
3i	*m*-Cl	8	64
3j	*m*-Br	8	58
3k	*m*-OCH_3	14	40
3l	*m*-CH_3	14	42
3m	*m*-CF_3	6	64
3n	*o*-OCH_3	14	31

[a]Isolated yield.

Acknowledgments. This work was supported by the Basic Research Grant (2010-0016792) funded by the National Research Foundation of Korea.

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