Synthesis of Novel 2-Substituted 1,1-Difluoro-3-phenylthio-1,3-butadienes *via* Indium-mediated 1,4-Debromofluorination Reaction

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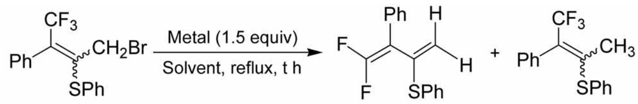
1,3-Butadienes are valuable synthetic intermediates for the formation of ring and multifunctionalized systems in organic synthesis.[1] Especially, 1,1-difluoro-1,3-butadienes are useful building blocks for the synthesis of *gem*-difluoro or mono-fluoro substituted compounds.[2-5] Introduction of phenylthio group to 1,1-difluoro-1,3-butadienes could provide a more wide range of utilization because of the transformation of phenylthio functionality. Although there has been several reports on the preparation of 1,1-difluoro-1,3-butadienes, to the best of our knowledge, however, there has been no report on the preparation of phenylthio substituted 1,1-difluoro-1,3-butadienes. Huang *et al.* reported on the synthesis of 1,1-difluoro-2-siloxy-1,3-butadiene from the reaction of trifluoroacetyltriphenylsilane with vinylmagnesium bromide.[6] Difluorinated Danishefsky's diene was also prepared from Mg(0)-promoted selective C-F bond cleavage of trifluoromethyl enone.[5] Double dehydrobromination of 1,3-dibromo-1,1-difluorinated compounds with DBU afforded 1,1-difluoro-1,3-butadienes.[7] Wittig reaction of 3,3-difluoroallyltriphenylphosphonium bromide with aldehydes also gave 1,1-difluoro-1,3-butadienes.[8] Ichikawa *et al.* prepared 1,1-difluoro-1,3-butadienes from the reaction of 2,2-difluorovinylboranes with 1-alkenyl halides in the presence of copper(I) iodide and a palladium catalyst.[9] Palladium-catalyzed cross-coupling reactions of 1,1-difluorohomoallenyl bromide with aryl iodides, aryl boronic acids and terminal alkynes provided the corresponding 1,1-difluoro-1,3-butadienes.[10] 1,1-Difluoro-4,4-bis(dimethylamino)-1,3-butadienes were also synthesized from the treatment of 1,1-difluoro-4,4-bis(dimethylamino)ethane with ethyl propiolate.[11] Recently, Burton *et al.* reported that 1,1-difluoro-1,3-butadienes were prepared from the coupling reactions of α-bromo-β,β-difluorostyrenes with vinylboronic acid in the presence of Pd catalyst.[12] Herein, we wish to report the first preparation of 2-substituted 1,1-difluoro-3-phenylthio-1,3-butadienes *via* indium-mediated 1,4-debromofluorination reaction of 3-phenylthio substituted 1-bromo-4,4,4-trifluoro-2-butenes.

Recently, we reported that 1-bromo-4,4,4-trifluoro-3-phenyl-2-phenylthio-2-butene (**3a**) were prepared in two steps from 3,3-bis(phenylthio)-1,1,1,2,2-pentafluorobutane (**1**).[13] We examined the 1,4-debromofluorination reaction of **3** with metals, such as Zn, Zn(Cu), Mg and In, to give the corresponding 2-substituted 1,1-difluoro-3-phenylthio-1,3-butadienes **4**. When **3a** was treated with Zn in refluxing THF for 4 hours, only reduced product **2a** was obtained in 39% GC yield. The same reaction was performed with Zn(Cu) in refluxing THF for 3 hours to give the desired product **4a** in 35% GC yield along with **2a** in 13% GC yield. Mg-mediated debromofluorinaton reaction in refluxing THF for 18 hours afforded **4a** and **2a** in 41% and 20% GC yields, respectively. Treatment of **3a** with In in refluxing THF for 4 hours resulted in the formation of **4a**[14] in 79% GC yield and only trace amount of **2a** was observed. The use of other solvents such as ether, CH_3CN, DME, diglyme and triglyme did not provide the better results. The results of these reactions are summarized in Table 1.

The 1,4-debromofluorination reactions of various 3-aryl substituted 1-bromo-4,4,4-trifluoro-2-phenylthio-2-butenes **3b-i** with In in refluxing THF under the optimized condition afforded the corresponding 2-aryl-1,1-difluoro-3-phenylthio-1,3-butadienes **4b-4i** in 60-83% yields. 3-Alkyl substituted 1-bromo-4,4,4-trifluoro-2-phenylthio-2-butenes **3j** and **3k** also provided the corresponding 2-alkyl-1,1-difluoro-3-phenylthio-1,3-butadienes **4j** and **4k** in 40% and 63% yields, respectively. A trace amount of reduced products **2** were observed in these reactions. These reactions were summarized in Table 2.

2,3-Bis(phenylthio)-1,1-difluoro-1,3-butadiene (**9**) was also prepared in four steps from **5**. Since **5** was not reacted at all with sodium benzenethiolate even under refluxing condition, **5** was oxidized to give a reactive vinyl sulfone **6**[15]

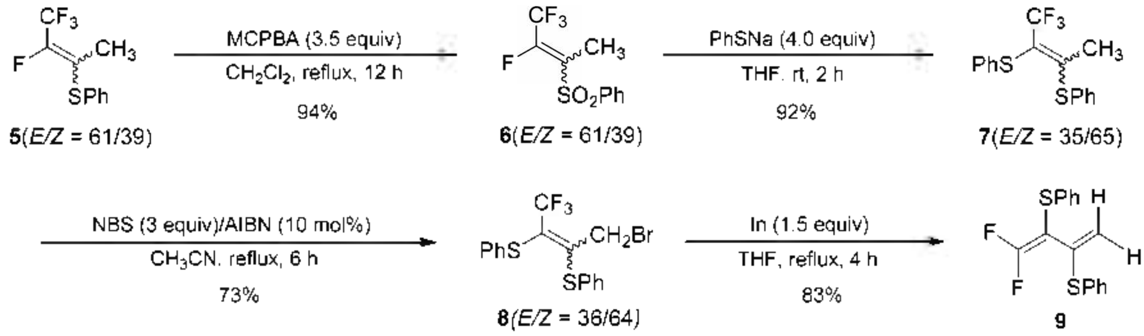
Table 1. 1,4-Debromofluorination reactions of 2-phenylthio substituted 1-bromo-4,4,4-trifluoro-2-butenes **3a** with metals



3a **4a** **2a**

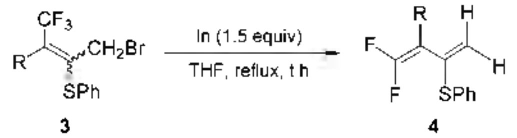
entry	M	Solvent	t	Yield (%)[a]	
				4a	**2a**
1	Zn	THF	4	0	39
2	Zn(Cu)	THF	3	35	13
3	Mg	THF	18	41	20
4	In	THF	4	79	1
5	In	ether	1	0	0
6	In	CH_3CN	1	37	12
7	In	DME	4	16	5
8	In	diglyme	2	26	9
9	In	triglyme	1	58	8

[a]GC yield.



Scheme 1

Table 2. Preparation of 2-aryl (or alkyl)-1,1-difluoro-3-phenylthio-1,3-butadienes **4**



Compound	R	t	Yield (%)[a]
4a	C_6H_5	4	70
4b	*p*-MeOC_6H_4	2	73
4c	*p*-MeC_6H_4	2.5	83
4d	*p*-FC_6H_4	2	74
4e	*p*-ClC_6H_4	4	68
4f	*p*-BrC_6H_4	2	79
4g	*m*-$CF_3C_6H_4$	2	60
4h	*m*-$CF_3C_6H_4$	2.5	79
4i	*m*-BrC_6H_4	2	74
4j	CH_3	3.5	40
4k	*n*-C_4H_9	3.5	63

[a]Isolated yield.

which was treated with sodium benzenethiolate (4 equiv) in THF at room temperature for 2 hours to give an isomeric mixture (*E*/*Z* = 35/65) of 2,3-bis(phenylthio)-1,1,1-trifluoro-2-butene (**7**) in 92% yield. After optimization of reaction condition for the allylic bromination of **7**, an isomeric mixture (*E*/*Z* = 36/64) of 2,3-bis(phenylthio)-1-bromo-4,4,4-trifluoro-2-butene (**8**) was obtained in 73% yield from the reaction of **7** with NBS (3.0 equiv) and AIBN (10 mol%) in refluxing CH_3CN for 6 hours. Treatment of **8** with In (1.5 equiv) in refluxing THF for 4 hours resulted in the formation of **9**[16] in 83% yield (Scheme 1). The 2-substituted 1,1-difluoro-3-phenylthio-1,3-butadienes **4** and **9** were found to be sensitive under light and thus underwent polymerization after purification. Therefore, these dienes have to be stored in ether at 0 °C for further reactions.

In conclusion, 1,4-debromofluorination reactions of 2-phenylthio substituted 1-bromo-4,4,4-trifluoro-2-butenes **3** and **8** to give the corresponding 2-substituted 1,1-difluoro-3-phenylthio-1,3-butadienes **4** and **9** were established with Indium in refluxing THF for 2-4 hours.

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14. A typical reaction procedure for the preparation of **4a** is as follows. A 15 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with **3** (0.80 mmol), In (1.20 mmol), and 3 mL of THF. After the reaction mixture was heated to reflux for 4 hours, the reaction mixture was quenched with 1 M HCl. The reaction mixture was extracted with ether twice, dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with *n*-hexane provided **4a** (0.153 g, 70%). **4a** : oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 8H), 7.19-7.17 (m, 2H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (dd, J = 295, 291 Hz), 137.9 (dd, J = 4, 4 Hz), 133.7, 132.1, 131.5, 128.9, 128.7, 128.3, 128.2, 127.7, 119.3, 95.4 (dd, J = 19, 18 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −84.56 (d, 1F, J = 22.6 Hz), −87.02 (d, 1F, J = 22.6 Hz); MS, m/z (relative intensity) 274 (M^+, 90), 253 (100), 241 (8), 221 (9), 196 (10), 183 (34), 164 (89), 145 (33), 135 (12), 127 (16), 115 (46), 109 (7), 89 (8), 77 (7), 65 (9), 51 (6); IR (neat) 3060, 1601, 1583, 1477, 1440, 763, 744, 692 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_2S$: C, 70.05; H, 4.41. Found: C, 69.79; H, 4.35.
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16. Spectroscopic data of **9**: oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 10H), 5.41 (s, 1H), 5.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (dd, J = 291, 291 Hz), 137.0 (t, J = 4 Hz), 134.1, 133.4, 133.2, 132.6, 130.3, 129.5, 129.1, 128.1, 127.2, 121.1, 89.8 (t, J = 20 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −74.87 (d, J = 7.5 Hz, 1F), −75.89 (d, J = 7.5 Hz, 1F); MS, m/z (relative intensity) 306 (M^+, 100), 285 (12), 273 (16), 253 (19), 215 (17), 196 (43), 179 (31), 164 (42), 147 (72), 135 (30), 133 (31), 127 (48), 109 (49), 91 (18), 77 (25), 65 (32), 51 (17); IR (neat) 3060, 3020, 1692, 1583, 1478, 1439, 1275, 1024, 1009, 741, 689 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_2S_2$: C, 62.72; H, 3.95. Found: C, 62.45; H, 3.90.