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Facile synthesis of α-functionalized vinyl sulfides bearing β-trifluoromethyl group: a highly potential CF_3-containing building blocks

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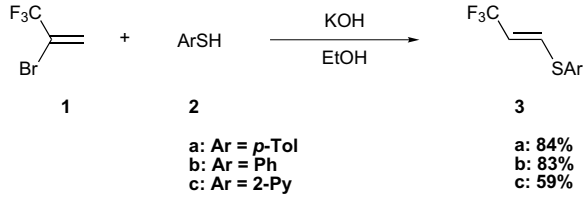
Abstract—The β-(trifluoromethyl)vinylsulfides on treatment with *n*-BuLi/TMEDA were readily lithiated at α-position of the sulfanyl group, and the generated α-lithiovinylsulfides were trapped with a variety of electrophiles to give the corresponding β-trifluoromethyl-α-functionalized vinylsulfides in good to high yields.

Organic fluorine compounds play an important role in various fields such as agrochemicals, pharmaceuticals, polymers and dyes presumably due to their intrinsic properties.[1] In association with these situations, the growing demand for selectively fluorinated organic compounds has requested the development of a new methodology for the selective introduction of fluorine to readily available organic compounds. Among them, the preparation of trifluoromethylated molecules has been of significant subject to chemists from a wide variety of fields.[2] In the course of our study on versatile fluorinated building blocks,[3] we have paid attention to novel trifluoromethylated olefins containing more than one functional group. For instance, two different functional groups could allow to manipulate more complex organic molecules by use of each characteristic feature. One of the straightforward ways to prepare such olefins seemed to be the introduction of additional functional group to trifluoromethylated olefins bearing another functional group in advance. In view of this strategy we sought an appropriate candidate as the starting trifluoromethylated olefin.[4] By literature survey we concluded that β-(trifluoromethyl)vinylsulfide would be the best precursor to our purpose for the reason of both its easy availability and its promising reactivity.[5] In connection of this sulfide, however, some reactions of the corresponding sulfoxide and sulfone have already been reported.[6] The associated report concerning the preparation of α-sulfanylvinyl carbanion and its synthetic application also encouraged us to examine the sulfide.[7] In this Letter, we will report the first convenient synthesis of various α-functionalized-β-(trifluoromethyl)vinylsulfides as highly potential synthetic intermediates.

We initially planned the preparation of three kinds of aryl β-(trifluoromethyl)vinylsulfide. According to the reported procedure for β-(trifluoromethyl)vinylphenyl sulfide,[5] we conducted the reaction of three thiophenols (**2**) and 3,3,3-trifluoro-2-bromopropene (**1**) under the basic conditions. These reactions proceeded smoothly to afford the corresponding aryl vinyl sulfides (**3**) as a mixture of stereoisomers in good to high yields (Scheme 1).[8] The obtained *E*/*Z*-mixtures could be easily separated to each other by column chromatography on silica gel.



Scheme 1. Preparation of aryl β-(trifluoromethyl)vinylsulfide (**3**).

Keywords: Trifluoromethyl group; Vinylsulfide; Functional group; Building block.
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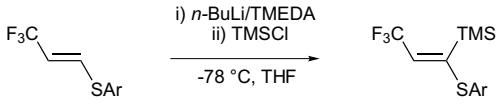
Table 1. Synthesis of (*E*)-aryl β-(trifluoromethyl)-(α-trimethylsilyl)-vinyl sulfide (**4**)[a]

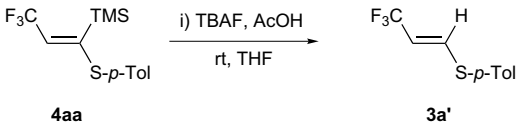


3 **4**

Entry	Vinyl sulfide	Additive	Product[b] (yield, %)
1	**3a**	None	**4aa** (45)
2	**3a**	TMEDA	**4aa** (82)
3	**3b**	TMEDA	**4ba** (90)
4	**3c**	TMEDA	**4ca** (0)

[a] All reactions were conducted in THF at −78 °C.
[b] Isolated yield.

We continued to examine the substitution reaction of the corresponding *E*-sulfides (**3**) using chlorotrimethylsilane (TMSCl) as an electrophile in the next step.[9] Thus, the (*E*)-β-(trifluromethyl)-α-(*p*-tolylsulfanyl)vinyl anion was generated by the successive addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 1.2 equiv) and *n*-BuLi (1.2 equiv) to the *p*-tolyl sulfide (**3a**) in THF at −78 °C for 15 min, and was treated with TMSCl (1.1 equiv) at this temperature for another 15 min to give the desired product in 82% yield (Table 1, entry 2).[10] However, the same reaction was conducted by means of the *Z*-sulfide instead of the *E*-sulfide to afford the corresponding *E*/*Z*-mixtures in poor yields along with a considerable amount of the starting *Z*-sulfide. The reason is not clear at this time. It is noteworthy that the combined use of *n*-BuLi and TMEDA is essential to the successful reaction.[7] The use of *n*-BuLi alone substantially decreased the yield (entry 1). On the contrary to our expectation, the reaction using the corresponding 2-pyridyl sulfide (**3c**) gave no desired product (entry 4). This finding suggested that an electron-withdrawing group attached to sulfur atom did not necessarily stabilize the adjacent vinyl carbanion.



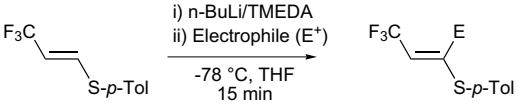
4aa **3a'**

Scheme 2. Desilylation of **4aa** by means of TBAF.

Although it is well accepted that alkenyl anions have a tendency toward their configuration with retention to a high degree,[11] we determined the configuration of the product as follows. We conducted the desilylation of the product (**4aa**) by means of TBAF in the presence of a small amount of acetic acid (Scheme 2). The GC–MS analysis of the crude reaction mixture gave a single peak. The structural assignment of this desilylated sulfide was performed on the basis of the comparison of both the ^{1}H NMR spectrum and the GC–MS analysis. The spectrum and retention time of the desilylated sulfide (**3a**′) were identical with those of the parent sulfide (*E*-**3a**). We therefore confirmed the *E* configuration of the product (**4aa**).

Under the similar conditions, a variety of electrophiles were employed for this substitution reaction to evaluate the scope of the functionalization of *E*-**3a**. These results are summarized in Table 2. As seen in Table 2, most

Table 2. Synthesis of (*E*)-β-(trifluoromethyl)-α-functionalized vinyl *p*-tolyl sulfide (**4a**)[a]



E-**3a** **4a**

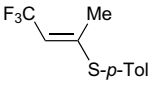
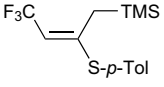
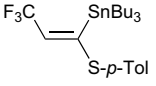
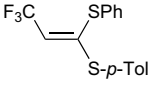
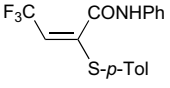
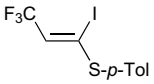
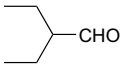
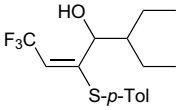
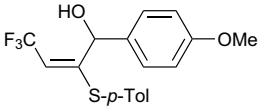
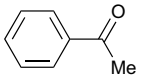
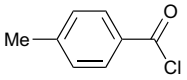
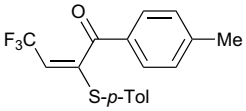
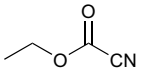
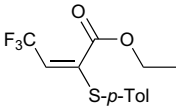
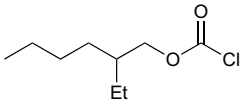
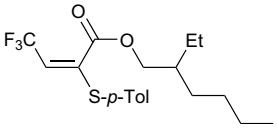
Entry	Electrophile	Product		Yield[b] (%)
1	MeI		**4ab**	83
2[c]	$TMSCH_2I$		**4ac**	91
3	Bu_3SnCl		**4ad**	81
4	$PhSS(O)_2Ph$		**4ae**	95
5	PhNCO		**4af**	54

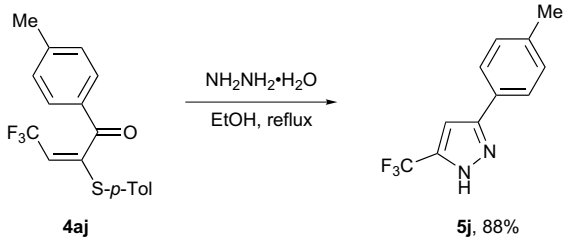
Table 2 (*continued*)

Entry	Electrophile	Product		Yield[b] (%)
6	I_2		**4ag**	91
7			**4ah**	98
8			**4ai**	86
9		—	—	NR
10			**4aj**	79
11			**4ak**	60
12			**4al**	76

[a] All reactions were conducted using *E*-**3a** (1 equiv) with electrophiles (1.1 equiv) at −78 °C for 15 min.
[b] Isolated yield.

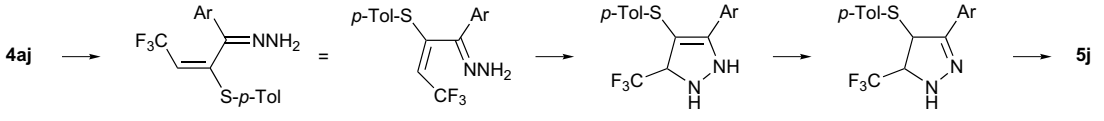
reactions proceeded well to give the corresponding products in good to high yields except for acetophenone (entry 9). These results have indicated that the β-(trifluoromethyl)-α-sulfanylvinyl anion should provide important β-(trifluoromethyl)vinyl intermediates in organic synthesis. It is noteworthy that the sulfanyl group should play an important role of these substitution reactions in comparison with the corresponding sulfonyl group.[4]

Finally, utilization of the product was preliminarily investigated. The reaction of α,β-unsaturated ketone (**4aj**) with hydrazine monohydrate was conducted in ethanol under reflux conditions. On the contrary to our expectation, the corresponding 3-*p*-tolyl-5-(trifluoromethyl)-1*H*-pyrazole was obtained as a desulfurization product (**5j**) in 88% yield (Scheme 3).[12] Although the detailed reaction mechanism is not clear at present, the plausible mechanism of the formation of **5j** was depicted in Scheme 4.



Scheme 3. Synthesis of pyrazole (**5j**).

In summary, we have demonstrated the convenient synthesis of **4aa**–**4al** as highly promising trifluoromethylated building blocks. Since most of these products have a variety of functional groups, they should be applied to cyclization, cross-coupling reaction, reduction, for example, to lead to more complex trifluoromethylated compounds that were not easily accessible. Further studies on their synthetic utility are under progress in our laboratory.



Scheme 4. Plausible mechanism for the formation of **5j**.

Acknowledgement

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8. Preparation of **3a**: A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with 20 mL of ethanol and potassium hydroxide (0.64 g, 11.4 mmol). To the stirred solution was successively added 4-methylbenzenethiol (1.30 g, 10.5 mmol) and 3,3,3-trifluoro-2-bromopropene (1.3 mL, 12.5 mmol) at 0 °C. The mixture was gradually warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride, and the organic layer was separated from the mixture. The resulting aqueous layer was extracted with hexane three times. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. The resulting oily residue was purified by silica gel chromatography (hexane as eluant) to give *E*-**3a** as colorless oil (1.69 g, 74%) and *Z*-**3a** as a white solid (0.22 g, 10%). Compound *E*-**3a**: $R_f = 0.68$ (hexane); ν_{max} (neat)/cm^{-1} 1619, 1300, 1279, 1119, 938, 832, 810; δ_H ($CDCl_3$) 2.38 (3H, s), 5.32 (1H, dq, *J* 15.2, 6.4), 7.11 (1H, dq, *J* 15.2, 2.0), 7.20–7.40 (4H, m); δ_F ($CDCl_3$) −63.4 (1F, dd, *J* 6.6, 2.7); GC–MS *m*/*z* 218 (84, M^+), 217 (18), 134 (80), 123 (37), 91 (100), 77 (51), 69 (47), 65 (79); Anal. Calcd for $C_{10}H_9F_3S$: C, 55.03; H, 4.16. Found: C, 55.12; H, 4.16. Compound *Z*-**3a**: $R_f = 0.50$ (hexane); δ_H ($CDCl_3$) 2.36 (3H, s), 5.60 (1H, dq, *J* 11.0, 8.6), 6.82 (1H, dq, *J* 11.0, 0.9), 7.10–7.40 (4H, m); δ_F ($CDCl_3$) −61.1 (1F, d, *J* 7.4).
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10. Preparation of **4aa**: To a solution *E*-**3a** (84.0 mg, 0.385 mmol) in THF (2 mL) under argon was added TMEDA (74 μL, 0.46 mmol) at room temperature, and the whole mixture was cooled to −78 °C. After being stirred for 10 min at this temperature, to this mixture was added *n*-BuLi (2.71 M in hexane solution, 170 μL, 0.46 mmol) dropwise via syringe. After being stirred for 10 min, TMSCl (54 μL, 0.42 mmol) was added to the solution, and the whole mixture was stirred for 15 min. The reaction was quenched with water at this temperature and extracted with hexane/ether = 3/1. After the usual work-up, the residue was purified by Florisil chromatography (hexane as eluant) to give 91.7 mg of **4aa** as pale yellow oil in 82% yield: ν_{max} (neat)/cm^{-1} 1585, 1276, 1135, 1109, 847, 817; δ_H ($CDCl_3$) 0.35 (9H, s), 2.43 (3H, s), 5.25 (1H, q, *J* 9.0), 7.25–7.40 (4H, m); δ_F ($CDCl_3$) −56.9 (3F, d, *J* 10.0); GC–MS *m*/*z* 290 (0.5, M^+), 141 (48), 107 (47), 91 (21), 77 (55), 73 (100), 65 (17); Anal. Calcd for $C_{13}H_{17}F_3SSi$ C, 53.76; H, 5.90. Found: C, 53.87; H, 5.78.
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