Synthesis S. S. Huang et al. Paper

Convenient Synthesis of 2-(2,2-Difluoroethoxy)-6-(trifluoromethyl)-benzenesulfonyl Chloride, A Key Building Block of Penoxsulam

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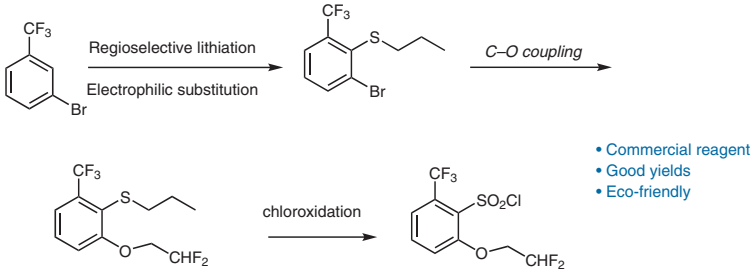

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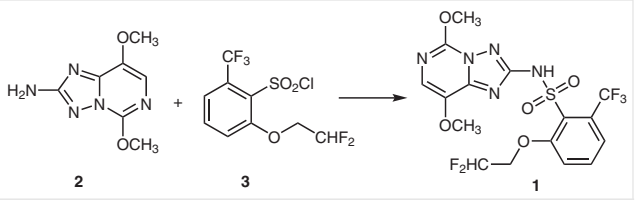
Abstract A convenient and efficient three-step synthesis of 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)benzenesulfonyl chloride, the key building block of penoxsulam, is described. The main features of the synthesis include a regioselective lithiation and subsequent electrophilic substitution starting from commercially available 3-bromobenzotrifluoride to provide (2-bromo-6-(trifluoromethyl)phenyl)(propyl)sulfane, then a copper-catalyzed C–O coupling to introduce the difluoroethoxy moiety and chloroxidation conditions to give the desired sulfonyl chloride.

Key words penoxsulam, regioselective lithiation, benzyne intermediate, C–O coupling, chloroxidation

Penoxsulam, a member of the triazolopyrimidine sulfonamide family, is the active ingredient of Granite, a product developed by Dow AgroSciences.[1] It is a highly effective, broad spectrum, acetolactate synthase (ALS) inhibiting herbicide used to control a wide range of weeds in rice crops. The popularity of this herbicide is probably due to its high weed vs crop selectivity and low toxicity in animals.[2] Therefore, a number of synthetic pathways have been established in the past decade for the preparation of penoxsulam.[3]

Typically, penoxsulam (**1**) has been prepared from the reaction between the corresponding amine **2** and sulfonyl chloride **3** (Scheme 1), which forms the sulfonamide unit.[4] It is obvious that one of the key intermediates of penoxsulam is sulfonyl chloride **3**. Consequently, many efforts have been devoted to the synthesis of sulfonyl chloride **3**. In the original method,[3a] 3-(trifluoromethyl)phenol was protected with chloromethyl methyl ether (MOMCl) first, then the protected phenol was metalated with *n*-BuLi. and quenched with dipropyl disulfide to introduce a thiopropyl moiety. Standard MOM deprotection conditions followed by phenol alkylation afforded the appropriately substituted sulfide, which was converted into the desired sulfonyl chloride **3** through the use of chlorine gas in aqueous acetic acid. After that, Zhang and co-workers reported a method[4b] starting from 4-nitro-2-(trifluoromethyl)aniline which involved bromination, reduction, acetylation, diazotisation, deacetylation, acid hydrolysis, and chlorination. However, the yields of these methods were usually low owing to the tedious processes and many reaction steps (>4). In addition, the documented methods suffer from drawbacks such as the high cost of starting materials,[4b] safety problems of the required diazotisation reaction,[5] and environmental issues of using the heavily polluting sulfur dioxide[6a] and strongly stimulating sulfuryl chloride.[6b,c] To overcome these drawbacks, herein, we report a novel and convenient synthesis of sulfonyl chloride **3** in which a C–O coupling reaction is employed.



Scheme 1 Synthesis of penoxsulam

Our retrosynthetic analysis of sulfonyl chloride **3** is outlined in Scheme 2. Inspired by the renaissance of copper catalysis,[7] we envisioned that the difluoroethyl aryl ether **9** could be constructed by C–O coupling between 2,2-difluoroethanol and aryl bromide **7**, which in turn could be generated from a regioselective lithiation and subsequent electrophilic substitution of the commercially available 3-bromobenzotrifluoride (**4**).

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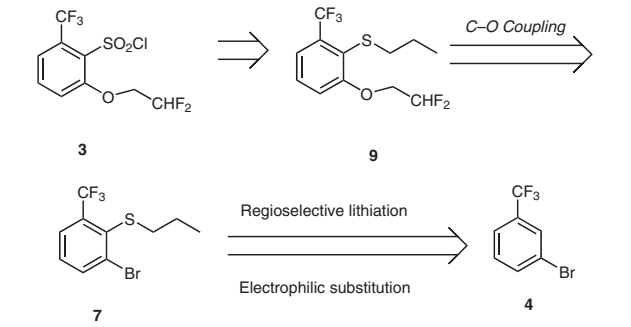
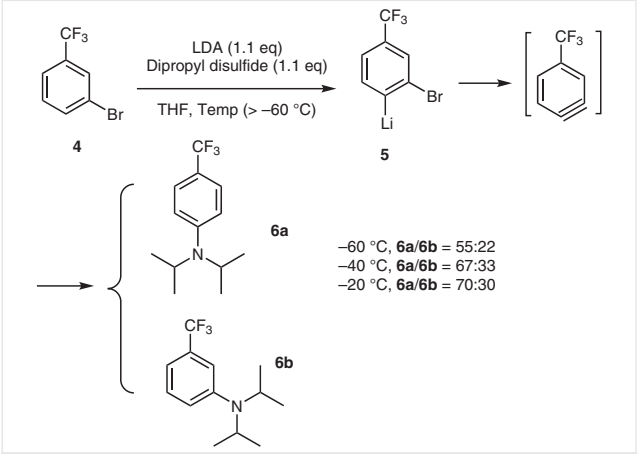
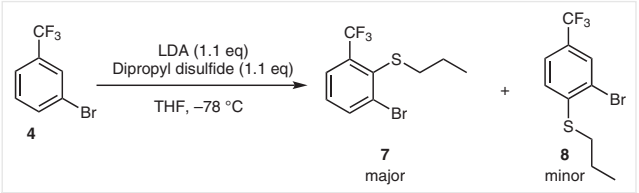


Scheme 2 Retrosynthetic analysis of the sulfonyl chloride building block **3**

Initially, we used 3-bromobenzotrifluoride (**4**) as starting material to carry out the lithiation step. Generally, if two lithiation-directing groups are placed meta to one another, lithiation nearly always occurs between them.[8] However, when the lithiation reaction was performed at a temperature of –40 °C, the main products we obtained were two aniline derivatives, **6a** and **6b** (Scheme 3), probably due to lithiation occurring at the uncongested ortho position to Br to form the lithium salt of the 1,2,5-trisubstituted benzene **5**, which then forms a benzyne intermediate by elimination of LiBr at >–60 °C,[9] followed by in situ reaction with diisopropylamine to provide the aniline derivatives **6a** and **6b**. Given that the temperature can dramatically affect the regioselectivity of the lithiation step, compound **4** was then sequentially treated with LDA and dipropyl disulfide at –78 °C (Scheme 4). To our delight, the reaction proceeded smoothly, with lithiation occurring mainly between CF_3 and Br, and the desired sulfide **7** was obtained in good yield (71% isolated yield).



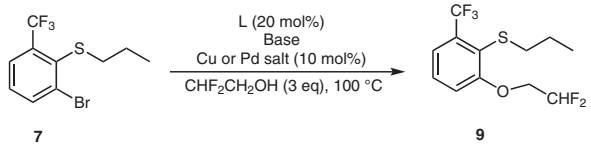
Scheme 3 Side reaction of the lithiation step and aniline formation through a benzyne intermediate



Scheme 4 Synthesis of compound **7**

With (2-bromo-6-(trifluoromethyl)phenyl)(propyl)-sulfane (**7**) in hand, we set out to explore the reaction between aryl bromide **7** and 2,2-difluoroethanol. As shown in Table 1, we first checked the documented palladium-catalyzed C–O coupling conditions and found no target product.[10] Then, we turned to a copper-mediated C–O coupling reaction in the presence of different ligands, for example

Table 1 Copper (or Palladium)-Catalyzed C–O Coupling[a]



Entry	Ligand (L)	Base	Catalyst	Yield[b] (%)
1	PPh_3	Cs_2CO_3 (2 eq)	$Pd(OAc)_2$	NR
2[c]	–	NaH (3 eq)	–	NR
3	1,10-phenanthroline	Cs_2CO_3 (2 eq)	CuI	NR
4[d]	*N*,*N*′-diphenethyloxalamide	*t*-BuONa (1.5 eq)	CuI	NR
5	8-hydroxyquinoline	K_3PO_4 (1.5 eq)	CuI	NR
6[e]	–	CHF_2CH_2ONa (3 eq)	CuBr	68

[a] Reaction conditions: CHF_2CH_2OH (3 eq), ligand (20 mol%), catalyst (10 mol%), 100 °C, 24 h.
[b] NR = no reaction.
[c] At 70 °C in THF.
[d] At 80 °C in the presence of 4 Å molecular sieves in 1,4-dioxane.
[e] In the presence of ethyl formate (2 eq) and LiCl (1 eq).

1,10-phenanthroline,[11] 8-hydroxyquinoline[12] or *N*,*N*′-diphenethyloxalamide.[13] Unfortunately, all reactions proceeded sluggishly and showed almost no activity, probably due to the sterically bulky mercaptopropyl substituent at the ortho position. Finally, we performed the reaction with sodium 2,2-difluoroethoxide as nucleophile, CuBr/ethyl formate as catalyst system and lithium chloride as additive in the presence of neat 2,2-difluoroethanol.[14] In this case, the reaction proceeded well to give the desired difluoroethyl aryl ether **9** in good yield (68% isolated yield).

After the successful introduction of the difluoroethoxy group, we aimed to convert the propyl sulfide group of **9** into the corresponding sulfonyl chloride (Scheme 5). Following the method developed by Nishiguchi and coworkers,[15] which involves the combination of *N*-chlorosuccinimide and dilute hydrochloric acid, the desired sulfonyl chloride **3** was obtained in good yield (76% isolated yield). The ^{1}H and ^{13}C NMR spectra were in good agreement with the reported data of compound **3**. This method is more eco-friendly than using sulfuryl chloride[6c] or chlorine.[16,17]

Scheme 5 Synthesis of compound **3**

In conclusion, the convenient and efficient synthesis of 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)benzenesulfonyl chloride (**3**) has been achieved by using regioselective lithiation, electrophilic substitution and a copper-catalyzed C–O coupling as key steps, followed by a chloroxidation reaction. The synthetic method provides a facile, eco-friendly, and economical approach to the preparation of the sulfonyl chloride building block of penoxsulam.

All reagents were used as purchased. Flash column chromatography was performed over silica gel (100–200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on an Avance (Bruker) 400 MHz Nuclear Magnetic Resonance Sspectrometer, and were referenced to the internal solvent signals. High-resolution mass spectra (ESI-HRMS) were obtained on a micrOTOF-Q II (Bruker) spectrometer. IR spectra were recorded using a Nicolet 5700 FTIR apparatus. TLC was performed using silica gel.

(2-Bromo-6-(trifluoromethyl)phenyl)(propyl)sulfane (7)

To a solution of 3-bromobenzotrifluoride (**4**; 4.5 g, 20 mmol) in THF (50 mL) was added LDA (11 mL, 22 mmol, 2 M in THF/heptane) over a period of 10 min at –78 °C. After stirring for 45 min at this temperature, dipropyl disulfide (3.3 g, 22 mmol) was added. The mixture was stirred for 2 h at rt, then saturated NH_4Cl solution (30 mL) was added, followed by extraction with EtOAc (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography on silica gel to give **7** as a colorless oil; yield: 4.3 g (71%).

IR: 2968, 2924, 1403, 1307, 1194, 1169, 1133, 794, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 2.80 (t, *J* = 7.4 Hz, 2 H), 1.56 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.92, 136.52 (q, *J* = 29 Hz), 134.72, 129.43, 126.04 (q, *J* = 6 Hz), 124.49, 121.77, 38.76, 22.73, 13.50.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}BrF_3S$: 298.9711; found: 298.9726.

(2-(2,2-Difluoroethoxy)-6-(trifluoromethyl)phenyl)(propyl)sulfane (9)

To a freshly prepared solution of CHF_2CH_2ONa (from 0.69 g metallic Na) in CHF_2CH_2OH (30 mL) was added CuBr (0.14 g, 1 mmol), LiCl (0.43 g, 10 mmol), **7** (3.0 g, 10 mmol) and HCOOEt (1.48 g, 20 mmol). The mixture was stirred at 100 °C for 48 h. Then, H_2O (10 mL) was added and the mixture was diluted with MTBE (50 mL), filtered, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to give **9** as a yellow oil; yield: 2.0 g (68%).

IR: 2967, 2924, 1436, 1307, 1132, 1050, 800 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H), 7.08 (m, 1 H), 6.23 (tt, *J* = 55.0, 4.0 Hz, 1 H), 4.30 (td, *J* = 12.9, 4.0 Hz, 2 H), 2.87 (t, *J* = 7.4 Hz, 2 H), 1.62–1.53 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.44, 135.31 (q, *J* = 29 Hz), 129.13, 124.43, 122.03, 120.23 (q, *J* = 7 Hz), 115.98, 113.37 (t, *J* = 240 Hz), 68.38 (t, *J* = 30 Hz), 36.85, 23.00, 13.32.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}F_5OS$: 301.0680; found: 301.0695.

2-(2,2-Difluoroethoxy)-6-(trifluoromethyl)benzenesulfonyl Chloride (3)

To a solution of NCS (3.45 g, 26 mmol, 5 eq) in CH_3CN (20 mL) was added **9** (1.55 g, 5.2 mmol). Then, aq 2 M HCl (13 mL, 5 eq) was slowly added. The reaction mixture was stirred at rt overnight, quenched with aq saturated Na_2CO_3, then extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography on silica gel to give **3** as a white powder; yield: 1.3 g (76%); mp 70 °C.

IR: 2924, 1480, 1440, 1307, 1050, 898, 800 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (t, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 6.22 (tt, *J* = 54.8, 4.1 Hz, 1 H), 4.39 (td, *J* = 12.4, 4.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.89, 136.25, 132.07, 130.00 (q, *J* = 34 Hz), 123.09, 121.41 (q, *J* = 7 Hz), 120.36, 119.65, 112.76 (t, *J* = 240 Hz), 69.63 (t, *J* = 30 Hz).

HRMS (APCI, sulfonyl chloride **3** derivatised with NH_3/H_2O before detection): *m*/*z* [M + H]$^+$ calcd for $C_9H_8F_5NO_3S$: 306.0218; found: 306.0227.

***N*,*N*-Diisopropyl-4-(trifluoromethyl) aniline (6a) and *N*,*N*-Diisopropyl-3-(trifluoromethyl) aniline (6b)**

To a solution of 3-bromobenzotrifluoride (**4**; 4.5 g, 20 mmol) in THF (50 mL) was added LDA (11 mL, 22 mmol, 2 M in THF/heptane) over a period of 10 min at –20 °C. After stirring for 45 min at this temperature, dipropyl disulfide (3.3 g, 22 mmol) was added. The mixture was

stirred for 2 h at rt, then saturated NH_4Cl solution (30 mL) was added, followed by extraction with EtOAc (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography on silica gel to give **6a** and **6b** as colorless oils.

6a

Yield: 3.1 g (63%).

IR: 2973, 2930, 1607, 1582, 1497, 1403, 1307, 865, 777, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 3.89 (m, 2 H), 1.29 (d, *J* = 8.0 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.37, 125.85 (q, *J* = 4 Hz), 125.18 (q, *J* = 261 Hz), 117.52, 117.12, 114.77, 47.36, 20.98.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}F_3N$: 246.1464; found: 246.1472.

6b

Yield: 1.3 g (27%).

IR: 2973, 2930, 1607, 1583, 1498, 1403, 1307, 865, 777, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.0 Hz, 1 H), 7.03 (s, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 3.83 (m, 2 H), 1.25 (d, *J* = 8.0 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.35, 130.87 (q, *J* = 31 Hz), 128.85, 125.99, 123.28, 120.27, 113.51 (q, *J* = 4 Hz), 113.39 (q, *J* = 4 Hz), 47.56, 21.15.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}F_3N$: 246.1464; found: 246.1470.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690617.

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