Synthesis of Vinyl Sulfonamides Using the Horner Reaction

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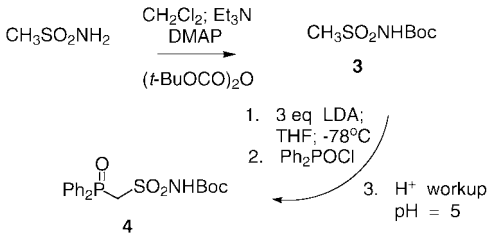
Abstract: A series of vinyl sulfonamides was synthesized using the Horner reaction of aldehydes and diphenylphosphorylmethanesulfonamide. The sulfonamide reagent was easily prepared and can be stored indefinitely. The *trans* orientation about the double bond of the vinyl sulfonamides was the only isomer observed.

Key words: sulfonamides, *E*-alkenes, Horner reaction, aldehydes, ylides

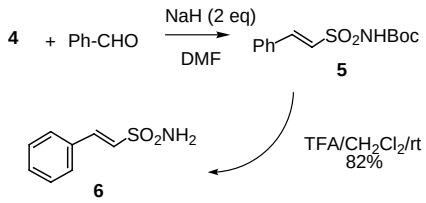
Recently, we were interested in the synthesis of aromatic vinyl sulfonamides as potential drug candidates for anti-inflammatory programs.[2] The sulfonamide is a useful functionality because it can act as a carbonyl bioisostere[3] making key interactions with receptor proteins as well as providing aqueous solubility. Previous routes to vinyl sulfonamides have involved generating the vinyl sulfonate ester,[4] which is then converted to the sulfonyl chloride and subsequently reacted with various amides.[5] Other methods include Heck coupling of the ethylenesulfonamide and aryl chlorides[6] or a Peterson olefination reaction of a silyl-substituted sulfonamide.[7] After reviewing this literature, we found ourselves interested in developing a general route to vinyl sulfonamides that involved minimal steps and utilized readily available starting materials. Herein, we describe the synthesis of a phosphoryl sulfonamide that reacts with aldehydes in a Horner[8] reaction to generate vinyl sulfonamides. We anticipate that this facile method will complement the existing sulfonamide procedures.

The synthesis of the sulfonamide reagent starts with the generation of *tert*-butyl sulfonyl carbamate **3**. We found through initial experiments that a protecting group on the sulfonamide was essential for substrate solubility and facile sulfonamide deprotonation. The synthesis of **3** was straightforward starting with *tert*-butyl pyrocarbonate and commercially available methyl sulfonamide[9] (Scheme 1).



Scheme 1

Treating the Boc-sulfonamide **3** with LDA in THF at –78 °C, followed by addition of diphenylphosphinic chloride at the same temperature provided **4** as a crystalline solid in 78% yield (Scheme 1). When the phosphoryl sulfonamide **4** was mixed with sodium hydride in DMF followed by the addition of benzaldehyde, the only product observed was the Boc-protected vinyl sulfonamide **5** (Scheme 2). This adduct was deprotected using TFA in dichloromethane at room temperature to yield the vinyl sulfonamide **6** in 82% yield (over the two steps).



Scheme 2

We then explored the generality of the reaction and found that a variety of aldehydes yielded the respective vinyl sulfonamides. Sodium hydride and potassium carbonate are effective bases for the deprotonation of the phosphoryl reagent. The Boc deprotection conditions were either TFA in CH_2Cl_2 or hot DMSO,[10] depending on the functionality in the molecule. The overall yields of the sulfonamides for the two step sequence were moderate[11] to good (Table 1). All sulfonamides isolated had the *trans* orientation about the double bond as determined by NMR coupling constants; the *cis* isomer was not observed in any of the examples described. We believe that the preference for the *trans* vinyl sulfonamide is due to steric hindrance encountered in the transition state, which was also observed in the synthesis of vinyl sulfones and sulfides via a phosphonate type reagent.[12] Ketones did not react under these reaction conditions with the phosphoryl reagent.

In conclusion, we have developed a novel and expedient route to vinyl sulfonamides. The protected phosphoryl sulfonamide **4** is easily prepared and following deprotonation readily reacts with a variety of aldehydes. Removal of the Boc group is straightforward using standard deprotection conditions. We anticipate that this procedure will complement the existing methods for vinyl sulfonamide

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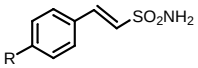
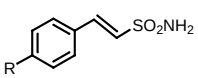
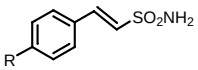
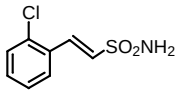
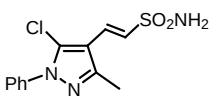
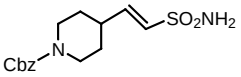
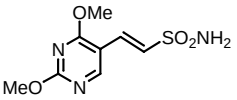
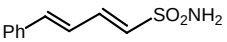
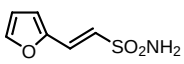
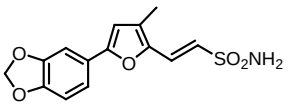
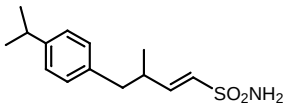
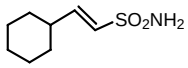
Table 1 Synthesis of Vinyl Sulfonamides

Product			Deprotection Method[a]	Yield (%)[b]
7	R = OMe		A	54
8	R = Me		A	78
9	R = Cl		A	59
10			A	63
11			B	74
12			B	73
13			A	72
14			A	46
15			B	26
16			B	79
17			A	46
18			A	57

[a] A = TFA/CH_2Cl_2, r.t.; B = DMSO/heat.
[b] Isolated yields after column chromatography on silica gel.

synthesis providing an additional route to generate functionally distinct molecules.

Reagents and solvents were purchased from Aldrich as HPLC grade whenever possible. NMR spectra were recorded on a Bruker DPX 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS with reference to internal solvent. Analytical TLC was performed using Analtech silica gel plates (250 microns) with a fluorescent indicator present. Flash chromatography was conducted using EM Science silica gel 60 (230–400 mesh).

***tert*-Butyl[(diphenylphosphoryl)methyl]sulfonyl Carbamate (4)**
To a solution of diisopropylamine (3.21 g, 31.76 mmol) in THF (32 mL) at –78 °C under N_2 was added *n*-BuLi in hexanes (12.29 mL, 30.73 mmol). The mixture was warmed to 0 °C for 1 min, then re-cooled to –78 °C. A solution of **3** (2.00 g, 10.24 mmol) in THF (22 mL) was added dropwise. After 8 min, diphenylphosphinic chloride (2.42 g, 10.24 mmol) was added dropwise. After 90 min, H_2O (100 mL) was added and the mixture was warmed to r.t. Additional H_2O (100 mL) was added and the mixture was washed with EtOAc (250 mL). The aqueous layer was brought to pH 5 with 5% aq HCl. The white precipitate was filtered and dried in vacuo to yield 3.14 g of **4** (78%); mp 221.0–224.0 °C.

IR (KBr): 3434, 2980, 1730, 1140 cm^{-1}.

^1H NMR (DMSO-d_6, 300 MHz): δ = 1.42 (9 H, s), 4.92 (2 H, d, *J* = 9.7 Hz), 7.57 (6 H, m), 7.84 (4 H, m), 11.59 (1 H, s).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 27.6, 50.9, 51.7, 82.0, 128.5, 128.6, 130.4, 130.5, 130.6, 131.5, 132.0, 132.1, 132.9, 150.7.

LSI-MS: *m*/*z* = 396 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{22}NO_5PS$: C, 54.68; H, 5.61; N, 3.54. Found: C, 54.84; H, 5.65; N, 3.58.

Vinyl Boc-Sulfonamides; General Procedure
To a well–stirred solution of the reagent **4** (0.8 mmol) in DMF at 0 °C was added NaH (2.04 mmol). The reaction was allowed to warm to r.t. and stirred for 30 min. The aldehyde (0.98 mmol) was then added at once and the reaction was stirred overnight at r.t. H_2O (50 mL) was added to the reaction and the mixture was extracted with EtOAc (50 mL). The organic solution was washed with 2% aq HCl, H_2O, brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo to give the crude product.

Deprotection of Vinyl Boc-Sulfonamides; General Procedures
Method A: CH_2Cl_2 (20 mL) and TFA (6 mL) were added to the Boc-sulfonamide (ca. 1 mmol) and the reaction mixture was stirred for 1–2 h (disappearance of the starting material was monitored by TLC). The solvent and TFA were then removed via evaporation, and H_2O (30 mL) was added. The solution was neutralized with aq 20% NaOH solution and extracted with CH_2Cl_2. The resulting organic solution was washed with brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo, followed by purification via column chromatography on silica gel (EtOAc–hexane, 40:60) provided the respective vinyl sulfonamide.

Method B: The Boc-sulfonamide (ca. 1 mmol) was dissolved in DMSO (5 mL) and heated to 80 °C (disappearance of the starting material was monitored by TLC). Upon completion, the reaction was cooled, poured into H_2O (25 mL) and extracted with EtOAc (3 × 30 mL). Evaporation of the solvent in vacuo, followed by purification via column chromatography on silica gel (EtOAc–hexane, 50:50) provided the respective vinyl sulfonamide.

(*E*)-2-Phenylethenesulfonamide (6)
Solid; yield: 0.115 g (82%); mp 144 °C.

IR (KBr): 3337, 3240, 1624, 1450, 1284, 1194 cm^{-1}.

^1H NMR (DMSO-d_6, 300 MHz): δ = 7.10 (2 H, s), 7.22 (1 H, d, *J* = 15.5 Hz), 7.3 (1 H, d, *J* = 15.5 Hz), 7.44 (3 H, m), 7.68 (2 H, m).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 128.1, 128.9, 130.1, 130.3, 132.9, 136.4;

HRMS (EI): *m*/*z* calcd for $C_8H_9NO_2S$: 183.0354; found: 183.0359.

(*E*)-2-(4-Methoxyphenyl)ethenesulfonamide (7)
Solid; yield: 0.145 g (54%); mp 126–148 °C.

IR (KBr): 1514, 1312 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.80 (3 H, s), 6.98 (2 H, d, *J* = 8.8 Hz), 7.03 (2 H, s), 7.07 (1 H, d, *J* = 15.4 Hz), 7.26 (1 H, d, *J* = 15.5 Hz), 7.63 (2 H, d, *J* = 8.8 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 55.7, 114.8, 125.7, 128.2, 130.3, 136.7, 161.2.

EIMS: *m*/*z* = 213 $(M)^+$.

Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.36; H, 5.23; N, 6.69.

(*E*)-2-(4-Methylphenyl)ethenesulfonamide (8)
Solid; yield: 0.248 g (78%), mp 161.4–162.8 °C.

IR (KBr): 3328, 3244, 1606, 1315, 1132 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.4 (3 H, s), 4.8 (2 H, br s), 6.88 (1 H, d, *J* = 15.4 Hz), 7.21 (2 H, d, *J* = 8.1 Hz), 7.38 (2 H, d, *J* = 8.1 Hz), 7.51 (1 H, d, *J* = 15.4 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 21.9, 126.3, 128.7, 130.0, 130.2, 141.2, 142.0.

EI-MS: *m*/*z* = 197 $(M)^+$.

Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.8; H, 5.62; N, 7.10. Found: C, 55.15; H, 5.61; N, 7.11.

(*E*)-2-(4-Chlorophenyl)ethenesulfonamide (9)
Solid; yield: 0.159 g (59%); mp 189.5–189.9 °C.

IR (KBr): 3374, 3262, 1329, 1136 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.16 (2 H, s), 7.25 (1 H, d, *J* = 15.6 Hz), 7.35 (1 H, d, *J* = 15.6 Hz), 7.47 (2 H, d, *J* = 8.6 Hz), 7.73 (2 H, d, *J* = 8.6 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 128.9, 129.9, 131.1, 131.9, 134.6, 135.1.

EI-MS: *m*/*z* = 217 $(M)^+$.

Anal. Calcd for $C_8H_8NClO_2S$: C, 44.14; H, 3.70; N, 6.43. Found: C, 44.43; H, 3.87; N, 6.27.

(*E*)-2-(2-Chlorophenyl)ethenesulfonamide (10)
Solid; yield: 0.172 g (63%); mp 132.0–134.2 °C.

IR (KBr): 3319, 3242, 1469, 1444 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.27 (2 H, s), 7.37 (1 H, d, *J* = 15.4 Hz), 7.45 (2 H, m), 7.57 (1 H, m), 7.63 (1 H, d, *J* = 15.5 Hz), 7.93 (1 H, dd, *J* = 7.2, 2.1 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 127.8, 128.4, 130.0, 130.6, 130.8, 131.6, 131.7, 133.3, 133.5.

EI-MS: *m*/*z* = 217 $(M)^+$.

HRMS (EI): *m*/*z* calcd for $C_8H_8ClNO_2S$ $(M)^+$: 216.9964; found: 216.9965.

(*E*)-2-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethenesulfonamide (11)
Solid; yield: 0.273 g (74%); mp 176 °C.

IR (KBr): 3397, 3271, 1626, 1138 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.43 (3 H, s), 6.41 (2 H, s), 6.9 (1 H, d, *J* = 15.7 Hz), 7.3 (1 H, d, *J* = 15.7 Hz), 7.47 (2 H, m), 7.52 (3 H, m).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 13.9, 111.8, 124.8, 126.9, 127.8, 128.6, 129.1, 137.4, 149.2.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{12}ClN_3O_2S$: 297.0339; found 297.0338.

Benzyl 4-[*(E)*-2-(aminosulfonyl)ethenyl]piperidine-1-carboxylate (12)
Solid; yield: 0.208 g (73%); mp 87 °C.

IR (KBr): 3346, 1694, 1138 cm$^{-1.}$

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.38 (2 H, m), 1.75 (2 H, m), 2.35 (1 H, m), 2.84 (2 H, m), 4.23 (2 H, m), 5.03 (2 H, s), 5.12 (2 H, s), 6.33 (1 H, dd, *J* = 15.2, 1.4 Hz), 6.73 (1 H, dd, *J* = 15.2, 6.4 Hz), 7.35 (5 H, m).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 30.3, 37.6, 43.5, 67.2, 127.9, 128.1, 128.5, 129.5, 136.7, 146.4, 155.2.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}N_2O_4S$: 324.1144; found: 324.1144.

(*E*)-2-(2,4-Dimethoxypyrimidin-5-yl)ethenesulfon-amide (13)
Solid; yield: 0.138 g (72%); mp 172.6–173.4 °C.

IR (KBr): 3297, 3230, 2965, 1622, 1597, 1548, 1477 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.95 (3 H, s), 4.04 (3 H, s), 7.08 (2 H, s), 7.25 (2 H, s), 8.70 (1 H, s).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 54.4, 54.9, 108.3, 127.9, 130.9, 160.2, 164.9, 168.1.

EIMS: *m*/*z* = 245 $(M)^+$.

HRMS (EI): *m*/*z* calcd for $C_8H_{11}N_3O_4S$ $(M)^+$: 245.0470; found 245.0471.

(1*E*,3*E*)-4-Phenylbuta-1,3-diene-1-sulfonamide (14)
Solid, yield: 0.123 g (46%); mp 194.2–195.4 °C.

IR (KBr): 3333, 3239, 1622, 1591, 1449, 1314 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 6.70 (1 H, m), 7.06 (5 H, m), 7.35 (3 H, m), 7.54, (2 H, br d, *J* = 6.9 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 125.2, 127.5, 129.2, 129.3, 133.1, 136.3, 137.2, 140.0.

EI-MS: *m*/*z* = 209 $(M)^+$.

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.64; H, 5.43; N, 6.58.

(*E*)-2-(2-Furyl)ethenesulfonamide (15)
To a well-stirred solution of **4** (1.02 g, 2.6 mmol) in H_2O (8 mL) were added K_2CO_3 (0.899 g, 6.5 mmol) and furfural (0.22 mL, 2.6 mmol) at r.t. The mixture was warmed to reflux and stirred overnight. The mixture was cooled to r.t., diluted with EtOAc (50 mL) and filtered through a plug of silica gel capped with anhyd $MgSO_4$. The filtrate was evaporated in vacuo to afford the crude product. Method B was used for the deprotection of the Boc-sulfonamide (0.117 g, 26%); mp 151.1–151.6 °C.

IR (KBr): 3399, 3283, 1631, 1300, 1134 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.45 (1 H, br s), 6.48 (1 H, dd, *J* = 3.4, 1.8 Hz), 6.62 (1 H, d, *J* = 1.8 Hz), 6.83 (1 H, d, *J* = 15.1 Hz), 7.22 (1 H, d, *J* = 15.1 Hz)), 7.49 (1 H, d, *J* = 1.8 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 112.1, 115.0, 125.6, 125.9, 144.7, 148.6.

EI-MS: *m*/*z* = 173 $(M)^+$.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09; Found: C, 41.88; H, 4.08; N, 8.09.

(*E*)-2-[5-(1,3-Benzodioxol-5-yl)-3-methyl-2-furyl]ethenesulfonamide (16)
Solid; yield: 0.2 g (79%); mp 199 °C.

IR (KBr): 1501, 1479 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.14 (3 H, s), 6.07 (2 H, s), 6.86 (1 H, d, *J* = 15.1 Hz), 6.89 (1 H, s), 6.98 (1 H, d, *J* = 8.1 Hz), 7.03 (2 H, s), 7.11 (1 H, d, *J* = 15.1 Hz), 7.32 (1 H, dd, *J* = 8.1, 1.7 Hz), 7.39 (1 H, d, *J* = 1.7 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 9.79, 101.3, 104.5, 108.7, 109.5, 118.3, 121.7, 123.5, 125.1, 127.7, 143.6, 147.6, 147.8, 154.1.

EI-MS: *m*/*z* = 307 $(M)^+$.

Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.7; H, 4.27; N, 4.56. Found: C, 54.49; H, 4.23; N, 4.49.

(*E*)-4-(4-isopropylphenyl)-3-methylbut-1-ene-1-sulfonamide (17)

Solid; yield: 0.156g (46%); mp 84–86 °C.

IR (KBr): 3327, 3241, 2957, 1321, 1131 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08 (3 H, d, *J* = 6.3 Hz), 1.23 (6 H, d, *J* = 6.9 Hz), 2.64 (4 H, m), 2.88 (1 H, m), 4.63 (2 H, br s), 6.25 (1 H, dd, *J* = 15.1, 1.0 Hz), 6.78 (1 H, dd, *J* = 15.1, 6.7 Hz), 7.04 (2 H, d, *J* = 8.1 Hz), 7.15 (2 H, d, *J* = 8.0 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 18.5, 24.0, 33.7, 37.6, 41.7, 126.5, 128.9, 129.1, 136.3, 147.0, 148.8.

EI-MS: *m*/*z* = 267 $(M)^+$.

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92; N, 5.24. Found: C, 62.64; H, 7.76; N, 5.18.

(*E*)-2-Cyclohexylethenesulfonamide (18)

Solid; yield: 0.137 g (57%); mp 89–92 °C.

IR (KBr): 3349, 2923, 1324, 1137 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.23 (5 H, m), 1.74 (5 H, m), 2.17 (1 H, m), 4.75 (2 H, br s), 6.31 (1 H, dd, *J* = 15.2, 1.5 Hz), 6.77 (1 H, dd, *J* = 15.2, 6.5 Hz).

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 26.0, 26.2, 31.8, 40.0, 128.4, 149.8.

EI-MS: *m*/*z* = 189 $(M)^+$.

Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99; N, 7.40. Found: C, 50.89; H, 7.95; N, 7.31.

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