Supporting Information

Application of a Double aza-Michael Reaction in a “Click, Click, Cy-Click” Strategy: From Bench to Flow

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**Procedure for Sulfonamides 2.**

To a RB flask containing racemic TBS-protected serine methyl ester (1.1 equiv) was added CH$_2$Cl$_2$ (0.25 M) and Et$_3$N (3 equiv). This mixture was allowed to stir for several minutes until soluble, cooled to 0 ºC, and 2,2-chloroethanesulfonyl chloride (1 equiv) was added drop-wise over several minutes. The solution was slowly warmed to rt, and stirred overnight. The reaction mixture was quenched with 10% HCl and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with saturated aqueous NaHCO$_3$, brine, and dried (Na$_2$SO$_4$). The solution was filtered, and concentrated under reduced pressure to afford crude vinyl sulfonamide 2 as a clear, viscous oil. The crude product was submitted to the following reaction without further purification.

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.57 (dd, $J$ = 16.5, 9.9 Hz, 1H), 6.25 (d, $J$ = 16.5 Hz, 1H), 5.91 (d, $J$ = 9.9 Hz, 1H), 5.21 (d, $J$ = 8.7 Hz, 1H), 4.09 – 4.04 (m, 2H), 3.88 (dd, $J$ = 10.9, 4.0 Hz, 1H), 3.77 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 170.5, 136.5, 126.3, 64.8, 57.6, 52.6, 25.6, -5.5, -5.7.

FTIR (thin film) cm$^{-1}$: 3290, 2955, 2930, 2858, 1749, 1342, 1256, 1138, 1113, 837.

HRMS: calculated for C$_{12}$H$_{26}$NO$_5$SSi (M+H)$^+$ 324.1301; found 324.1288 (TOF MS ES+).

**General Procedure for Tertiary Sulfonamides 3.**

To the crude sulfonamide 2 (1 equiv) was added CH$_3$CN (0.1M) and K$_2$CO$_3$ (1.2 equiv) followed by the dropwise addition of benzyl bromide (1.2 equiv). This mixture was allowed to stir at 60 ºC for 12 – 14 hrs. The reaction was cooled to rt, filtered through a pad of celite/silica and concentrated under reduced pressure to afford crude tertiary sulfonamide 3 as a dark orange oil. The crude product was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1).

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-methylbenzyl)vinylsulfonamido)propanoate (3a):

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.29 (d, $J$ = 8.0 Hz, 2H), 7.12 (d, $J$ = 7.8 Hz, 2H), 6.53 (d, $J$ = 16.6, 9.9 Hz, 1H), 6.21 (d, $J$ = 16.6 Hz, 1H), 5.89 (d, $J$ = 9.9 Hz, 1H), 4.54 (dd, $J$ = 7.0, 4.6 Hz, 1H), 4.49 (d, $J$ = 16.1 Hz, 1H), 4.45 (d, $J$ = 16.1 Hz, 1H), 4.01 (dd, $J$ = 10.8, 7.0 Hz, 1H), 3.96 (dd, $J$ = 10.8, 4.6 Hz, 1H), 3.66 (s, 3H), 2.33 (s, 3H), 0.84 (s, 9H), -0.01 (s, 3H), -0.06 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 170.0, 137.1, 135.6, 134.0, 128.9, 128.0, 126.4, 62.3, 61.4, 52.1, 49.9, 25.7, 21.1, 18.1, -5.7, -5.8.

FTIR (thin film) cm$^{-1}$: 2953, 2930, 2856, 1747, 1342, 1258, 1150, 1119, 837, 777.

HRMS: calculated for C$_{20}$H$_{37}$NO$_5$SSiK (M+K)$^+$ 445.2192; found 445.2184 (TOF MS ES+).

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-methoxybenzyl)vinylsulfonamido)propanoate (3b):

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.33 (d, $J$ = 8.7 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.51 (dd, $J$ = 16.6, 9.9 Hz, 1H), 6.20 (d, $J$ = 16.6 Hz, 1H), 5.88 (d, $J$ = 9.9 Hz, 1H), 4.54 (dd, $J$ = 7.0, 4.8 Hz, 1H), 4.46 (d, $J$ = 15.9 Hz, 1H), 4.42 (d, $J$ = 15.9 Hz, 1H), 4.00 (dd, $J$ = 10.9, 7.1 Hz, 1H), 3.97 (dd, $J$ = 10.9, 4.8 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 0.85 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 170.0, 159.1, 135.7, 129.5, 129.0, 126.3, 113.6, 62.2, 61.3, 55.3, 52.1, 49.6, 25.7, 18.1, -5.7, -5.8.

FTIR (thin film) cm$^{-1}$: 2953, 2932, 2856, 1747, 1512, 1342, 1258, 1150, 1119, 837, 777.

HRMS: calculated for C$_{20}$H$_{33}$NO$_6$SSiK (M+K)$^+$ 482.1435; found 482.1429 (TOF MS ES+).
Methyl 2-((N-benzylvinylsulfonamido)-3-((tert-butyldimethylsilyl)oxy)propanoate (3c):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.25 (m, 1H), 6.54 (dd, $J = 16.6$, 9.9 Hz, 1H), 6.22 (d, $J = 16.6$ Hz, 1H), 5.91 (d, $J = 9.9$ Hz, 1H), 4.59 (dd, $J = 6.9$, 4.2 Hz, 1H), 4.54 (d, $J = 16.5$ Hz, 1H), 4.51 (d, $J = 16.4$ Hz, 1H), 4.03 (dd, $J = 10.8$, 6.9 Hz, 1H), 3.96 (dd, $J = 10.8$, 4.2 Hz, 1H), 3.67 (s, 3H), 0.83 (s, 9H), -0.03 (s, 3H), -0.09 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 170.0, 137.3, 135.4, 128.2, 127.8, 127.4, 126.6, 62.4, 61.5, 52.1, 50.1, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm$^{-1}$: 2953, 2930, 2856, 1745, 1342, 1254, 1150, 1119, 837, 777.

HRMS: calculated for C$_{19}$H$_{35}$N$_2$O$_5$SSi (M+Na)$^+$ 431.2036; found 431.2051 (TOF MS ES+).

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-chlorobenzyl)vinylsulfonamido)propanoate (3d):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J = 8.5$ Hz, 2H), 7.31 – 7.27 (m, 2H), 6.51 (dd, $J = 16.5$, 9.9 Hz, 1H), 6.21 (d, $J = 16.5$ Hz, 1H), 5.93 (d, $J = 9.9$ Hz, 1H), 4.61 (dd, $J = 6.6$, 3.7 Hz, 1H), 4.52 (d, $J = 16.9$ Hz, 1H), 4.49 (d, $J = 16.9$ Hz, 1H), 4.05 (dd, $J = 10.9$, 6.7 Hz, 1H), 3.95 (dd, $J = 10.9$, 3.8 Hz, 1H), 3.69 (s, 3H), 0.82 (s, 9H), -0.02 (s, 3H), -0.09 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 169.9, 136.2, 135.1, 133.1, 129.1, 128.3, 126.9, 62.6, 61.6, 52.2, 49.5, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm$^{-1}$: 2953, 2930, 2856, 1745, 1493, 1342, 1254, 1151, 837, 770.

HRMS: calculated for C$_{19}$H$_{34}$ClN$_2$O$_5$SSi (M+Na)$^+$ 465.1646; found 465.1630 (TOF MS ES+).

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-fluorobenzyl)vinylsulfonamido)propanoate (3e):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 (d, $J = 8.6$, 5.4 Hz, 2H), 7.01 (t, $J = 8.7$ Hz, 2H), 6.51 (dd, $J = 16.5$, 9.9 Hz, 1H), 6.21 (d, $J = 16.5$ Hz, 1H), 5.91 (d, $J = 9.9$ Hz, 1H), 4.60 (dd, $J = 6.8$, 4.0 Hz, 1H), 4.51 (d, $J = 16.5$ Hz, 1H), 4.48 (d, $J = 16.4$ Hz, 1H), 4.03 (dd, $J = 10.9$, 6.8 Hz, 1H), 3.95 (dd, $J = 10.9$, 4.0 Hz, 1H), 3.68 (s, 3H), 0.83 (s, 9H), -0.01 (s, 3H), -0.08 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 170.0, 162.2 (d, $^1$J$_{CF} = 245.5$ Hz), 135.3, 133.2 (d, $^4$J$_{CF} = 3.1$ Hz), 129.5 (d, $^3$J$_{CF} = 8.1$ Hz), 126.7, 115.0 (d, $^2$J$_{CF} = 21.5$ Hz), 62.4, 61.5, 52.2, 49.4, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm$^{-1}$: 2953, 2930, 2856, 1747, 1510, 1342, 1256, 1151, 837, 775.

HRMS: calculated for C$_{19}$H$_{31}$FNO$_5$SSi (M+H)$^+$ 432.1676; found 432.1667 (TOF MS ES+).

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-(trifluoromethyl)benzyl)vinylsulfonamido)propanoate (3f):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.58 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 6.54 (dd, $J = 16.5$, 9.9 Hz, 1H), 6.23 (d, $J = 16.5$ Hz, 1H), 5.96 (d, $J = 9.9$ Hz, 1H), 4.67 (dd, $J = 6.1$, 3.2 Hz, 1H), 4.62 (s, 2H), 4.09 (dd, $J = 10.9$, 6.1 Hz, 1H), 3.94 (dd, $J = 10.9$, 3.2 Hz, 1H), 3.72 (s, 3H), 0.77 (s, 9H), -0.07 (s, 3H), -0.17 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 169.9, 142.3, 134.7, 129.5 (q, $^2$J$_{CF} = 32.5$ Hz), 127.5, 127.3, 126.3 (q, $^1$J$_{CF} = 271.9$ Hz), 125.1 (q, $^3$J$_{CF} = 3.7$ Hz), 62.9, 61.8, 52.3, 49.8, 25.6, 18.0, -6.0, -6.0.

FTIR (thin film) cm$^{-1}$: 2955, 2932, 2855, 2858, 1747, 1344, 1327, 1151, 1124, 1067, 837, 773.

HRMS: calculated for C$_{20}$H$_{36}$F$_3$NO$_5$SSiNa (M+Na)$^+$ 504.1464; found 504.1460 (TOF MS ES+).

Methyl 2-((N-(4-methylbenzyl)vinylsulfonamido)acrylate (4):

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.18 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 7.9$ Hz, 2H), 6.73 (dd, $J = 16.5$, 9.9 Hz, 1H), 6.31 (d, $J = 16.6$ Hz, 1H), 6.27 (s, 1H), 6.02 (d, $J = 9.9$ Hz, 1H), 5.68 (s, 1H), 4.50 (s, 2H), 3.79 (s, 3H), 2.33 (s, 3H).
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(prop-2-yn-1-yl)vinylsulfonamido)propanoate (6):
To the crude sulfonamide 2 (1 equiv) was added DMF (0.1M), K$_2$CO$_3$ (2 equiv) and NaI (2 equiv) followed by the addition of propargyl bromide (1.5 equiv). This was allowed to stir at 60 °C for 14 hrs. The reaction was cooled to rt and filtered through a pad of celite/silica and concentrated to afford crude tertiary sulfonamide 3 as a dark orange oil. The crude product was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1) to provide the product as pale yellow oil (79%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.61 (dd, $J = 16.5, 9.9$ Hz, 1H), 6.28 (d, $J = 16.5$ Hz, 1H), 5.95 (d, $J = 9.9$ Hz, 1H), 4.59 (m, 1H), 4.27 (dd, $J = 18.5, 2.4$ Hz, 1H), 4.22 (dd, $J = 18.5, 2.4$ Hz, 1H), 4.18 (dd, $J = 9.1, 3.6$ Hz, 1H), 4.15 (dd, $J = 9.1, 2.4$ Hz, 1H), 3.75 (s, 3H), 2.26 (t, $J = 2.4$ Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 169.7, 135.6, 126.8, 80.0, 71.8, 62.8, 60.9, 52.3, 35.4, 25.7, 18.1, -5.7, -5.9.

FTIR (thin film) cm$^{-1}$: 3275, 2959, 1745, 1339, 1146, 972, 737, 565.

HRMS: calculated for C$_{15}$H$_{27}$NO$_5$SiNa (M+Na)$^+$ 384.1277; found 384.1256 (TOF MS ES+).
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(vinylsulfonamido)propanoate (2)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-methylbenzyl)vinylsulfonamido)propanoate (3a)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-methoxybenzyl)vinylsulfonamido)propanoate (3b)
Methyl 2-(N-benzylvinylsulfonamido)-3-((tert-butyl-dimethylsilyl)oxy)propanoate (3c)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-chlorobenzyl)vinylsulfonamido)propanoate (3d)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-fluorobenzyl)vinylsulfonamido)propanoate (3e)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(4-(trifluoromethyl)benzyl)vinylsulfonamido)propanoate (3f)
Methyl 2-(N-(4-methylbenzyl)vinylsulfonamido)acrylate (4):
Methyl 5-cyclopentyl-2-(4-methylbenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5a)
Methyl 2-(4-methoxybenzyl)-5-octyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5b**)

![Chemical Structure](image)

![1H NMR Spectrum](image)

![13C NMR Spectrum](image)
Methyl 2-benzyl-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5c)
Methyl 2-benzyl-5-(4-fluorobenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5d)
Methyl 2-(4-chlorobenzyl)-5-(4-methoxybenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5e)
Methyl 2-(4-chlorobenzyl)-5-phenethyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5f)
Methyl 2-(4-fluorobenzyl)-5-isobutyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5g)
Methyl 5-benzyl-2-(4-(trifluoromethyl)benzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5h)
Methyl 3-((tert-butyldimethylsilyl)oxy)-2-(N-(prop-2-yn-1-yl)vinylsulfonamido)propanoate (6)
Methyl 5-butyl-2-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7a)
Methyl 5-butyl-2-((1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7b)
Methyl 2-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7e)
Methyl 5-benzyl-2-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7d)
Methyl 5-benzyl-2-((1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7e)
Methyl 5-benzyl-2-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7f)
Methyl 5-(2-hydroxyethyl)-2-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7g)
Methyl 2-((1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7h)
Methyl 2-((1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (7i)