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Regioselective N-vinylation of cyclic thionocarbamates through a vinyl bis-sulfone methodology

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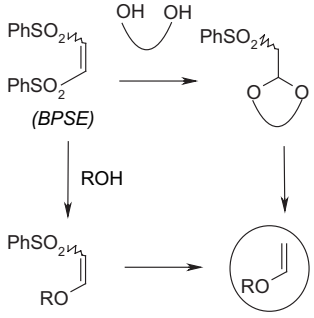
Abstract—A vinyl bis-sulfone Michael type approach towards heteroatom vinylation was applied on nitrogen derivatives. Cyclic thionocarbamates—mainly 1,3-oxazolidine-2-thiones—were converted into their N-vinyl counterparts; the procedure proved particularly efficient in the case of carbohydrate-derived complex structures.

1,2-Bis-(phenylsulfonyl)ethylidene (BPSE) is recognized as a useful reagent in organic synthesis, in particular for cycloadditions[1] or Michael type reactions.[2] In recent years, our group has developed a broad study of BPSE and its application in carbohydrate chemistry.[3] A double Michael addition on BPSE involving a carbohydrate partner led to the formation of a phenylsulfonylethylidene (PSE) acetal, a new protective device in carbohydrate chemistry,[4] with promising properties owing especially to its remarkable resistance against acidic media. Further studies were centered on the selective opening of PSE acetals under reductive desulfonylation conditions, to produce vinyl ethers.[5] A parallel study on selective mono-Michael additions on BPSE of both hydroxyl and thiol groups was also performed with the aim of producing—after reductive desulfonylation—vinyl ethers and vinyl sulfides connected to mono-saccharide templates (Scheme 1).[6]

In asymmetric synthesis, vinyl ethers are useful synthons for the development of stereoselective cycloadditions.[7] Our two-step process is both efficient and smooth enough to be applied to complex structures like saccharidic compounds. In contrast with O-vinyl derivatives, N-vinyl amide- or carbamate-type structures have only been occasionally synthesized on complex templates and mostly applied in biopolymer development.[8] Simple N-vinylated derivatives have been prepared following various pathways through elimination processes,[9] catalytic transetherification,[10] acetylene addition,[11] Curtius rearrangement,[12] enamine acylation,[13] copper- or palladium-mediated vinyl transfer.[14] The Peterson-type approach to enamides developed by Fürstner et al.[15] is also worth mentioning. Developing a convenient new methodology to introduce a vinyl group on nitrogen is nevertheless attractive with respect to enamine chemistry and its chiral applications. This preliminary report delivers preliminary results about the extension of our vinyl bis-sulfone methodology to the synthesis of N-vinylated cyclic thionocarbamates.



Scheme 1. Vinyl ether formation starting with BPSE.

Keywords: Oxazolidinethione; Oxazinethione; Carbohydrate; BPSE; N-Vinylation.
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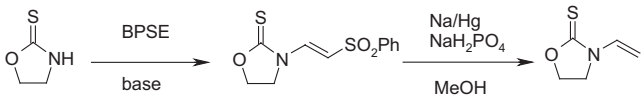
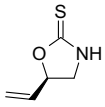
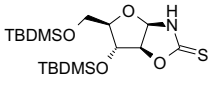
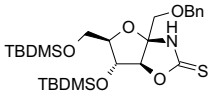
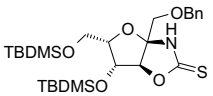
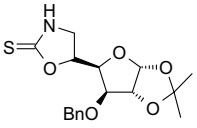
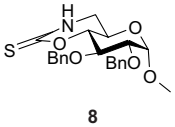
A number of naturally-occurring 1,3-oxazolidine-2-thiones (OZT) originate from important vegetable metabolites known as glucosinolates;[16] various aspects of the chemical behaviour of such OZT have been previously investigated in our group.[17] In other respects, carbohydrate-based OZT are readily obtainable through condensation of thiocyanic acid with free sugars: such more complex chiral OZT have proven useful in elaborating a range of biologically relevant molecules.[18]

Our vinylation process was tested on a selection of both simple and more complex OZT (Scheme 2). The Michael type addition on BPSE was applied to parent OZT[19] 1, *epi*-goitrin[20] **2** (an enantiopure derivative), tetrahydro-1,3-oxazine-2-thione[19] **3** and finally sugar-derived thionocarbamates **4**–**8** (Table 1).[18b,21]



Scheme 2. Two-step sequence to N-vinyl OZT.

Table 1. N-vinylsulfones and N-vinyl derivatives

OZT	N-phenylsulfonyl vinyl OZT	N-vinyl OZT
 1	**9** (80%)	**17** (86%)[b]
 2	**10** (93%)	**18** (75%)[b]
 3	**11** (91%)	**19** (13%)[b]
 4	**12** (91%)	**20** (76%)[a]
 5	**13** (70%)	**21** (98%)[a]
 6	**14** (72%)	**22** (96%)[a]
 7	**15** (98%)	**23** (64%)[b]
 8	**16** (72%)	**24**[b]

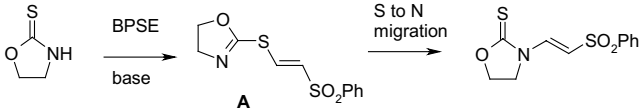
[a] Reaction performed at rt.
[b] Reaction performed at −30 °C for less than 1 h.

Condensation of Michael acceptors on a five-membered ring lactam has previously been attempted by Knapp and Levorse,[22] using sodium hydride as a base. Unfortunately, in our case those conditions proved unsuccessful. Screening miscellaneous basic reagents—triethylamine, pyridine, diisopropylethylamine (DIEA), DBU—allowed us to establish optimized conditions for condensing BPSE on the cyclic thionocarbamates **1**–**8**: a combination of DIEA and the phase transfer agent Bu_4NBr in DMF afforded 70–90% yields of the N-phenylsulfonylvinyl derivatives **9**–**16**, respectively (Table 1).[23]

As expected from previous studies,[17a] N-regioselectivity was observed, no trace of isomeric 2-phenylsulfonylvinylthio-derivative **A** (Scheme 3) could be detected in the reaction medium using our protocol. Furthermore, the addition–elimination process leading to **9**–**16** was stereospecific, in harmony with previous results from our laboratory and the formerly postulated mechanism.[6,7] However, for compounds **7** and **8**, S-phenylsulfonylvinyl derivatives (**A**) could be detected when reduced time conditions (1.5 h) were applied. In the specific case of oxazinethione **8**, a complete S-selectivity was observed after 1.5 h, producing a 75% isolated yield of the S-vinylated isomer of **16**. In contrast, applying the general protocol[23] only gave N-selectivity and compound **16** was obtained in 72% yield. These results suggested a Michael type addition on sulfur for the first stage then an S to N transfer of the vinylsulfone residue during the mechanism process (Scheme 3).

The previously established sodium amalgam reduction conditions[5a,6a] were implemented to desulfonylate the N-phenylsulfonylvinyl derivatives in order to produce the corresponding N-vinylated compounds. When applied to the simplest structures **9**–**11**, reduction at room temperature failed to deliver the expected N-vinyl derivatives. However by lowering the temperature, the N-vinyl OZT **17** was obtained in good yield whereas precursor **11** mainly returned oxazinethione **3** together with a disappointing 13% yield of N-vinyl oxazinethione **19**.

Extension of the reduction procedure[24] to heavier carbohydrate-based structures **12**–**15** produced the corresponding N-vinylated OZT **20**–**23** in 64–98% yields (Table 1); in the case of oxazinethione **16**, degradation was mostly observed in the course of the reductive process. This final result points out the patent unstability of N-vinyl oxazinethiones **19** and **24** as compared with N-vinyl OZT **20**–**22**, for which no degradation was observed even at room temperature.



Scheme 3. Tentative mechanism.

In summary, we have disclosed a simple, smooth and effective two-step sequence based on our vinyl bis-sulfone methodology to produce N-vinylated OZT: (i) regioselective Michael-type N-phenylsulfonylvinylation; (ii) chemoselective reduction. The enantiopure substrates of type **18** and **20**–**23** are currently tested in stereoselection transfer through cycloaddition processes and palladium-catalyzed reactions.

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23. General protocol for the Michael addition: a 0.2 M DMF solution of the thionocarbamate (1 equiv) was prepared under Ar in anhydrous conditions. After cooling at 0 °C, DIEA (2 equiv) then *E*-BPSE (1 equiv) were added together with 0.1 equiv of Bu_4NBr. After a slow return to room temperature and overnight stirring, the solution was extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$. Removing the solvent and chromatography of the residue afforded the desired *E*-compound. Fully satisfactory spectroscopic data were obtained for all new compounds. Selected data for compound **9**: mp = 57–59 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.84–4.00 (m, 2H, H-4a and -4b); 4.62–4.77 (m, 2H, H-5a and -5b); 5.95 (d, 1H, J_{vic} = 13.5 Hz, H-2′); 7.47–7.65 (m, 3H, *meta*, *para*-H–$PhSO_2$); 7.80–7.95 (m, 2H, *ortho*-H–$PhSO_2$); 8.35 (d, 1H, H-1′). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ (ppm) 45.6 (C-4); 67.9 (C-5); 113.1 (C-2′); 127.2 (2*CH–*ortho*-$PhSO_2$); 129.4 (2*CH–*meta*-$PhSO_2$); 133.4 (CH–*para*-$PhSO_2$); 136.7 (C-1′); 141.1 (C_{IV}–$PhSO_2$); 187.0 (C=S). MS (Ionspray®) *m/z*: 270 $(M+H)^+$; 292 $(M+Na)^+$. Selected data for compound **13**: $[\alpha]_D$ −88 (*c* 1.02, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) −0.12, −0.07, 0.07, 0.11 (4s, 12H, CH_3Si); 0.78, 0.85 (2s, 18H, $(CH_3)_3C$); 3.37 (dd, 1H, $J_{6b,5}$ = 6.6 Hz, J_{gem} = 11.0 Hz, H-6b); 3.47 (dd, 1H, $J_{6a,5}$ = 4.4 Hz, H-6a); 3.53 (d, 1H, J_{gem} = 11.0 Hz, H-1b); 3.88 (d, 1H, H-1a); 3.99–4.06 (m, 1H, H-5); 4.38 (d, 1H, J_{gem} = 12.3 Hz, CH_2–Ph); 4.46 (dd, 1H, $J_{4,3}$ = 1.9 Hz, H-4); 4.49 (d, 1H, CH_2–Ph); 4.86 (d, 1H, H-3); 6.70 (d, 1H, J_{vic} = 14.1 Hz, H-2′); 7.15–7.24 (m, 2H, H–Ar); 7.28–7.38 (m, 3H, H–Ar); 7.46–7.65 (m, 3H, *meta*, *para*-H–$PhSO_2$); 7.86–7.92 (m, 2H, *ortho*-H–$PhSO_2$); 8.02 (d, 1H, H-1′). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ: (ppm) −5.5, −5.4, −4.9, −4.8 (CH_3Si); 17.9, 18.2 ($(CH_3)_3C$); 25.7, 25.8 ($(CH_3)_3C$); 61.0 (C-6); 66.6 (C-1); 73.7 (CH_2–Ph); 76.1 (C-4); 88.8 (C-5); 91.7 (C-3); 100.8 (C-2); 116.2 (C-2′); 127.5, 127.7, 128.4, 128.8 (CH–Ar); 129.4 (2*CH–*meta*-$PhSO_2$); 133.4 (C-1′); 136.6 (C_{IV}–Ar);141.4 (C_{IV}–$PhSO_2$); 185.4 (C=S). MS (Ionspray®) *m/z* 706.5 $(M+H)^+$. IR (NaCl) *v* 1748 (C=S), 1625 (C=C), 1384, 1145 (SO_2) cm^{-1}.
24. General protocol for reductive desulfonylation. The N-vinylsulfone (1 equiv) was dissolved in THF–MeOH (1:1 v/v). NaH_2PO_4 (25 equiv) and Na/Hg 5% (25 equiv) were added and the solution stirred at room temperature until completion of the reaction. The heterogeneous solution was filtered, extracted with CH_2Cl_2, washed with water, dried over K_2CO_3; removing the solvent in vacuo afforded the N-vinyl derivative, which was pure enough for further uses. Selected data for compound **21**: $[\alpha]_D$ −97 (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 0.03, 0.10, 0.12 (3s, 12H, CH_3Si); 0.86, 0.87 (2s, 18H, $(CH_3)_3C$); 3.40 (dd, 1H, $J_{6b,5}$ = 8.2 Hz, J_{gem} = 10.7 Hz, H-6b); 3.51–3.60 (m,

1H, H-6a); 3.55 (d, 1H, J_{gem} = 10.4 Hz, H-1b); 3.98–4.10 (m, 2H, H-1a, H-5); 4.43–4.62 (m, 3H, CH_2–Ph, H-4); 4.78 (dd, 1H, $J_{2'Z,\,2'E}$ = 0.9 Hz, $J_{2'Z,1'}$ = 9.4 Hz, H-2′); 4.84–4.88 (m, 1H, H-3); 5.20 (dd, 1H, $J_{\,2'E,1'}$ = 16.3 Hz, H-2′); 6.86 (dd, 1H, H-1′); 7.22–7.41 (m, 5H, H–Ar). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ (ppm) −7.3, −7.2, −6.8, −6.7 (CH_3Si); 15.9, 16.3 ($(CH_3)_3C$); 23.7, 23.9 ($(CH_3)_3$ *C*); 59.5 (C-6); 64.5 (C-1); 71.5 (*C*H_2–Ph); 74.4 (C-4); 86.9 (C-5); 89.0 (C-3); 99.9 (C-2); 101.4 (C-2′); 125.9, 126.1, 126.8 (CH–Ar); 127.5 (C-1′); 135.1 (C_{IV}–Ar); 183.8 (C═S). MS (Ion-spray®) *m/z*: 566,0 $(M+H)^+$; 588,0 $(M+Na)^+$. IR (NaCl): 1642 (C═C), 1748 (C═S), 2949 (═CH_2) cm^{-1}.