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Regioselective Michael-induced cyclisation of γ- and δ-hydroxy vinyl sulfides and vinyl dithiocarbamates

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Abstract—We herein describe the unprecedented use of heteroaryl vinyl sulfides and vinyl dithiocarbamates as hetero-Michael addition acceptors. Combined chelating and electron-withdrawing effects are postulated to stabilise the transient anionic species and allow smooth Michael-induced ring closure to produce diversely functionalised C-glycosides.
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Intramolecular hetero-Michael addition of oxy-anion species to an α,β-unsaturated electron-withdrawing group (EWG) is a powerful method for the stereo- and regiocontrolled formation of highly functionalised tetrahydrofuran and tetrahydropyran derivatives. This approach has been widely employed as a key-step in the synthesis of complex natural products and is now a standard methodology for the synthesis of C-glycosidic carbohydrate mimics.[1] A wide range of medium to strong EWG has been used for this purpose, including ketones,[2,3] esters,[3,4] thioamides,[5] nitriles,[6] sulfones[7] and sulfoxides.[8] Although the Michael-type intramolecular addition of non-stabilised carbon–metal bonds to α,β-unsaturated, poor-to-moderate EWG is well documented, to our knowledge, no study on the use of alkoxides or other hetero-nucleophiles in combination with such moderate EWG has been undertaken.

In the past decade, we have described several efficient approaches to vinyl-thiofunctionalised polyhydroxylated synthons.[9–11] The resultant library was diverse in terms of electron-withdrawing ability of the various thiofunctions: this offered a good opportunity to seek a threshold in the electron-withdrawing ability needed for an intramolecular hetero-Michael addition as well as to explore new routes to bio-relevant C-glycosides.

The more traditional case in our library of the strong EWGs, such as vinyl sulfones, sulfoxides or sulfimides will be discussed in a separate paper.[12] Herein, we would like to focus on moderate electron-withdrawing thiofunctions such as heteroaryl vinyl sulfides and vinyl dithiocarbamates.

Benzothiazolyl vinyl sulfide **1a**[10] was chosen as a model compound for this study. We found phase-transfer conditions (50% NaOH, CH_2Cl_2, Aliquat 336®)[13] to be efficient and reliable, producing the desired cyclic compound **2a** as a mixture of diastereoisomers.[14] Those optimised conditions were then successfully applied to a range of heteroaryl vinyl sulfides **1b**–**1d** (Scheme 1 and Table 1) to afford the C-glycosides **2b**–**2d**.[15]

All cyclisations were assumed to be highly regioselective as no trace of any tetrahydropyran compound potentially resulting from the addition of the δ-hydroxyl group could be detected. This is presumably due to a kinetic effect: the conformational constraint of the 2,3-*O*-isopropylidene ring would stabilise a pseudo-furano conformation close to the transition state.

In order to investigate the possibility of forming six-membered rings through a hetero-Michael cyclisation, the diol **1a** was mono-*O*-benzylated[16] to give a mixture of regio-isomers **3** and **4**. The δ-hydroxy heteroaryl vinyl sulfide **4** was then subjected to the phase-transfer conditions to cleanly give the C-glycopyranoside **5** as a single diastereoisomer. Extension of the methodology to the synthesis of pyrano C-glycosides thus appeared possible (Scheme 2).

Keywords: Vinyl sulfides; Vinyl dithiocarbamates; Hetero-Michael additions; C-glycosides.
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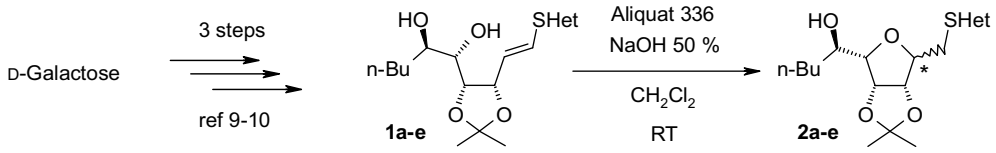
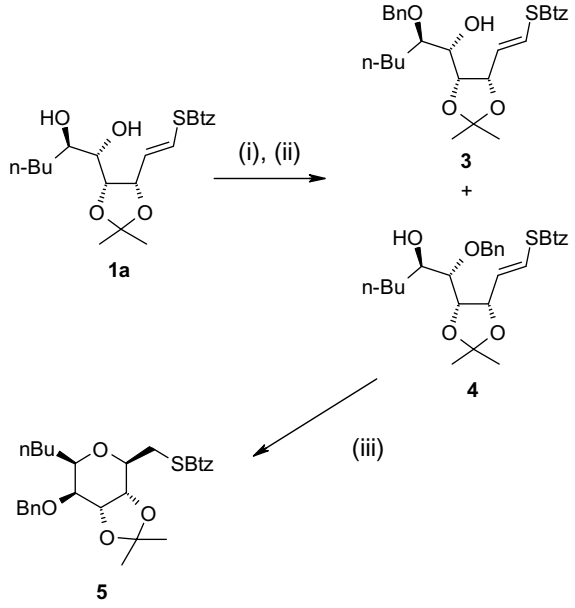


Scheme 1. Hetero-Michael cyclisation of γ,δ-hydroxy heteroaryl vinyl sulfides to furano derivatives.[15]

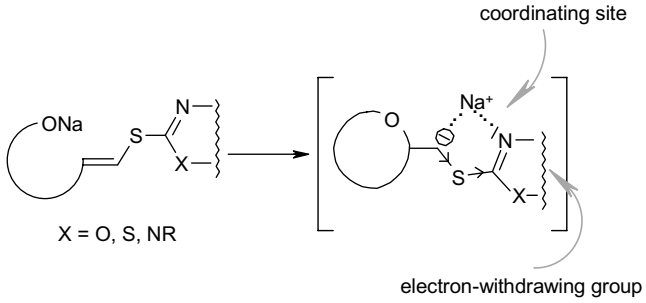
Table 1. Hetero-Michael cyclisation of γ,δ-hydroxy heteroaryl vinyl sulfides to furano derivatives[15]

Heteroaryl (Het)	2-Benzothiazolyl	2-Benzoxazolyl	2-Thiazolinyl	1-Phenyltetrazolyl	2-Pyridyl
Cyclised product	**2a**	**2b**	**2c**	**2d**	**2e**
Isolated yields (%)	58	60	60	54	—



Scheme 2. Hetero-Michael cyclisation of a δ-hydroxy heteroaryl vinyl sulfide into a pyrano derivative. (i) Bu_2SnO, toluene, Δ; (ii) BnBr, *n*-Bu_4NBr, **3**: 45%, **4**: 38%; (iii) Aliquat 336®, NaOH 50%, CH_2Cl_2, 72%.

The Michael-acceptor ability of our heteroaryl vinyl sulfides could be explained by a synergy of two distinct influences (Scheme 3). First, the electron-withdrawing ability of the intracyclic heteroatoms decreases the electron density at sulfur, improving its ability to stabilise the intermediate carbanion. Secondly, the basic nitrogen atom further stabilises the carbanion by coordinating the metal counter-cation. However, this chelation effect does not seem to be sufficient by itself to substantially improve the Michael acceptor ability: no cyclisation product was observed in the case of the pyridyl sulfide **1e**, which presents a potentially coordinating nitrogen atom but displays more moderate electron withdrawing ability. This hypothesis was supported by the inability of methyl- or phenyl vinyl sulfide counterparts to undergo cyclisation, whatever the basic conditions applied.

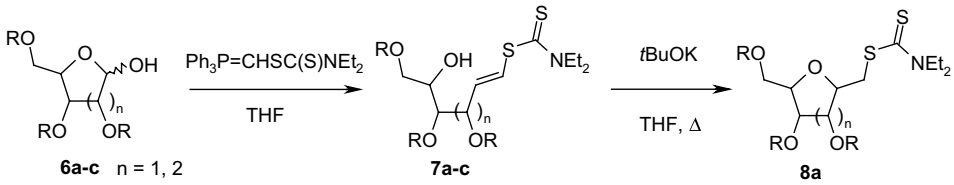


Scheme 3. Hypothesised origin of the hetero-Michael acceptor ability of heteroaryl vinyl sulfides.

We assumed that other thiofunctions meeting the two criteria of our hypothesis could be involved in hetero-Michael cyclisation. Dithiocarbamates were selected as promising substrates for preliminary exploration: a thiocarbonyl group usually acts as an efficient coordinating site and the thiocarboxamide moiety has a strong electron-withdrawing ability. Applying the Wittig-based methodology previously described for the synthesis of saccharidic methyl- and phenyl vinyl sulfides,[11] sugar lactols **6a**–**c** were condensed with a suitably functionalised phosphorane[17] to produce nearly quantitative yields of the desired ring-opened vinyl dithiocarbamates **7a**–**c** (Scheme 4).

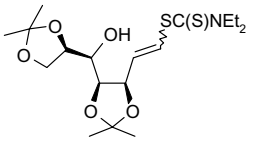
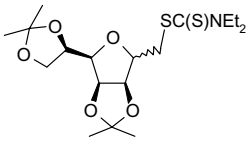
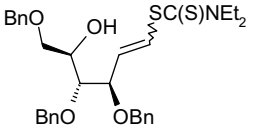
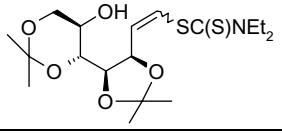
The dithiocarbamate moiety was found to be fairly base-sensitive: when subjected to the phase transfer conditions, all three compounds **7a**–**c** led to complex degradation mixtures. However, simple anhydrous conditions (*t*BuOK, THF, 50 °C, 18 h) induced successful cyclisation to C-furanoside **8a** of compound **7a**—which is structurally close to heteroaryl sulfides **1a**–**d**—but totally failed for **7b** and **7c** (Table 2).[18]

This latter result supports the hypothesis of a strong template effect of the isopropylidene ring during the cyclisation process of **1a**–**d** and **7a**. By forcing the alkoxide precursor to adopt a conformation close to



Scheme 4. Synthesis and hetero-Michael cyclisation of γ- and δ-hydroxy vinyl dithiocarbamates.

Table 2. Synthesis and hetero-Michael cyclisation of γ- and δ-hydroxy vinyl dithiocarbamates

Starting lactol **6**	Vinyl dithiocarbamate **7**	Yield (*E*:*Z*)	Cyclised C-glycoside **8**	Yield
a		94% (70:30)		76% 1*R*:1*S* 65:35
b		96% (20:80)	*Degradation*	—
c		92% (10:90)	*Degradation*	—

the transition state, this effect could dramatically enhance the kinetics of the hetero-Michael addition. We suppose that in the case of much less rigid **7b** and **7c**, side-reactions leading to the degradation of the starting material proceed faster than the cyclisation pathway.

In conclusion, we have developed and experienced novel thiofunctionalised Michael acceptor systems for synthesising C-glycosides. Further exploration of this chemistry is currently performed and results will be reported in due course.

Acknowledgements

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14. Interestingly, during our attempts to optimise the conditions for the cyclisation of **1a**, it was found that addition of a stoichiometric amount of various electrophiles could be beneficial to the reaction in terms of the yield. The best results were obtained with tosyl chloride, which dramatically raised the yield up to 88%. This 'electrophilic assistance' seemed to be limited to the benzothiazolyl moiety and could not be extended to the other heteroaryl derivatives: γ,δ-epoxy derivatives were the major products obtained in the tosyl chloride-activated reaction of **1b**–**e** in phase transfer conditions.
15. Cycloadducts were not readily separable except for **2c**, with a 2:1 diastereoisomeric ratio. Selected data for the major (2*R*)-C-glycoside **2c**: $[\alpha]_D^{25}$ +7 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ, 0.93 (br t, 3H, Bu), 1.32, 1.50 (2s, 6H, *i*Prd), 3.16 and 3.31 (2dd, AB system, J_{gem} = 13.7 Hz, J_{1b-2} = 7.5, J_{1a-2} = 7.2, H-1a, H-1b), 3.41 (t, 2H, J_{vic} = 8.0, H-5 thiazoline), 3.73 (dd, 1H, J_{4-5} = 3.8, H-5), 3.96 (m, 1H, H-6), 4.21 (t, 2H, J_{vic} = 8.0, H-4 thiazoline), 4.35 (t, 1H, H-2), 4.73 (m, 2H, H-3 and H-4). ^{13}C NMR (75.1 MHz, $CDCl_3$) δ 14.0 (Bu), 25.8, 27.6

(*i*Prd), 32.7 (C-1), 35.8 (C-5 thiazoline), 64.0 (C-6), 70.2 (C-4 thiazoline), 81.4 (C-2), 82.3, 83.0 (C-3, C-4), 84.8 (C-5), 115.0 (CMe_2), 165.1 (C-2 thiazoline). HRMS: $C_{16}H_{27}NO_4S_2$: calcd 361.1381; found 361.1366.

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18. Selected data for the major (2R)-C-glycoside **8a**: $[\alpha]_D^{25}$ +65 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.23–1.32 (m, 6H, CH_2CH_3), 1.35, 1.37, 1.43, 1.49 (4s, 12H, *i*Prd), 3.48 (dd, 1H, $J_{4-5} = 3.2$, $J_{5-6} = 7.9$, H-5), 3.57 (dd, 1H, $J_{gem} = 13.9$, $J_{1b-2} = 7.9$, H-1b), 3.69 (dd, 1H, $J_{1a-2} = 5.8$, H-1a), 3.71–3.81 (m, 2H, CH_2CH_3), 3.87 (ddd, 1H, $J_{2-3} = 3.2$, H-2), 3.95–4.12 (m, 4H, CH_2CH_3, H-7a, H-7b), 4.39 (dt, 1H, $J_{6-7} = 5.3$, H-6), 4.70–4.76 (m, 2H, H-3, H-4). ^{13}C NMR (125.2 MHz, $CDCl_3$) δ 11.7, 12.6 (CH_2CH_3), 24.8, 25.4, 25.9, 27.1 (2*i*Prd), 35.0 (C-1), 46.9, 49.8 (CH_2CH_3), 67.1 (C-7), 73.2 (C-6), 80.4 (C-2), 80.9 (C-4), 81.4 (C-3), 81.9 (C-5), 109.2, 112.7 (2CMe_2), 195.4 (C=S). HRMS: $C_{18}H_{31}NO_5S_2$: calcd. 405.1644; found 405.1631.