# Thioimidate *N*-Oxides: From Nature to Synthetic Pathways

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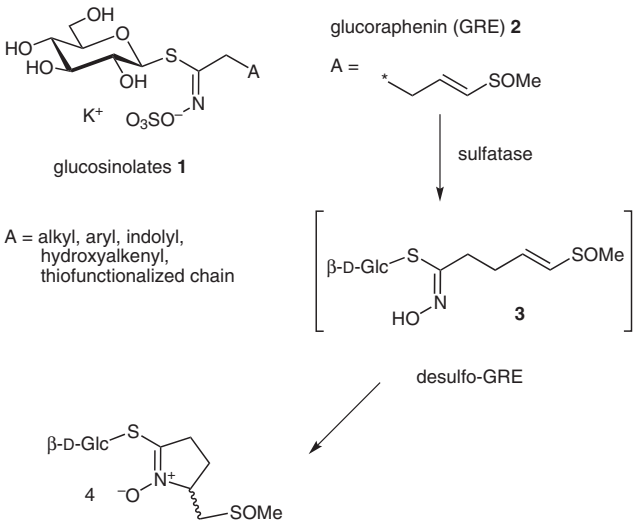
**Abstract:** Inspired by the unexpected reactivity of desulfated naturally occurring glucoraphenin, methods to synthesize thioimidate *N*-oxides (TIO) have been devised on simple or carbohydrate templates. Either through halocyclization or under Mitsunobu conditions, the starting thiohydroximates cyclized to generate efficiently the corresponding TIO.

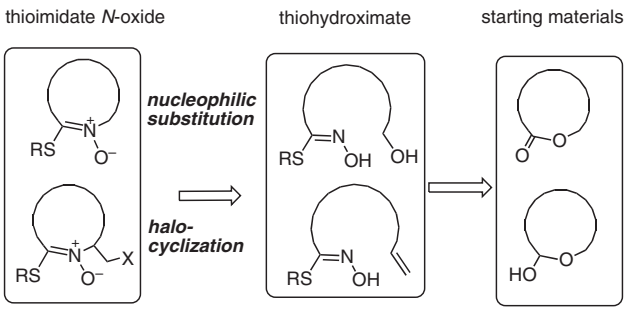
**Key words:** carbohydrates, cyclization, heterocycles, azasugars, thio function

Along our journey for studying sulfur-containing secondary metabolites, glucosinolates have been a cornerstone in the disclosure and development of original chemical moieties. Glucosinolates **1** (GL) are remarkable for their homogeneous structure: a hydrophilic β-D-glucopyrano framework bearing an O-sulfated anomeric (*Z*)-thiohydroximate moiety connected to a fairly hydrophobic aglycon side chain (Scheme 1).[1] Those molecules are heavily involved in human and animal nutrition, having shown impact on health status either as chemopreventive agents, antioxidant activities[2a] or by inducing antinutritional effects on livestock.[2b] This latter aspect has led to establishing standard procedures (EU official method ISO-9167-1) for determining the amount of GL in *Brassicaceae*, notably in rapeseed.[3] This method is based on preliminary enzymatic desulfation of GL, followed by HPLC analysis of the resulting more stable desulfo-GL. We have recently reported the unique behavior of glucoraphenin (4-methylsulfinylbut-3-enyl GL) **2**, whose desulfo-counterpart **3** is readily converted into an unprecedented cyclic thioimidate *N*-oxide **4** (Scheme 1).[4]

This can be explained by intramolecular concerted Michael addition of the thiohydroximate moiety of **3** onto the vinyl sulfoxide acceptor. The originality of this rare thioimidate *N*-oxide function prompted us to design preparative synthetic methods, as a prerequisite to evaluate the chemical potential and reactivity scope of thioimidate *N*-oxides.[4b] The formation of a cyclic thioimidate *N*-oxide could be controlled by avoiding direct attack on an electrophilic carbon. We chose to introduce a thiohydroximate function at one end of the chain and an activable moiety at the other end. Two possibilities for the latter were first explored: using either an alkenyl group to perform halocyclization or a hydroxyl group prior to nucleophilic substitution (Scheme 2).




**Scheme 1** Structure of glucosinolates and unexpected desulfation of glucoraphenin **2** resulting in a cyclized TIO




**Scheme 2** Two routes to prepare a thioimidate *N*-oxide

At first, we used natural alkenyl glucosinolates (Scheme 1), sinigrin (A = ethenyl), gluconapin (A = prop-2-enyl), and epiprogoitrin (A = 1-hydroxyprop-2-enyl) which fulfilled our requirements and gave us rapidly the opportunity to test the terminal alkene approach. To reach the desired thiohydroximate templates, standard enzymatic desulfation was performed,[3] providing the corresponding desulfoglucosinolates **5a–c** in quantitative yield (Scheme 3). Prior to the halocyclization step, the OH groups of the sugar ring were masked in a two-step sequence: standard per-O-acetylation of **5a–c** followed by selective deprotection of the *N*-hydroxyimino group using hydrazinium acetate. All reactions proceeded smoothly,

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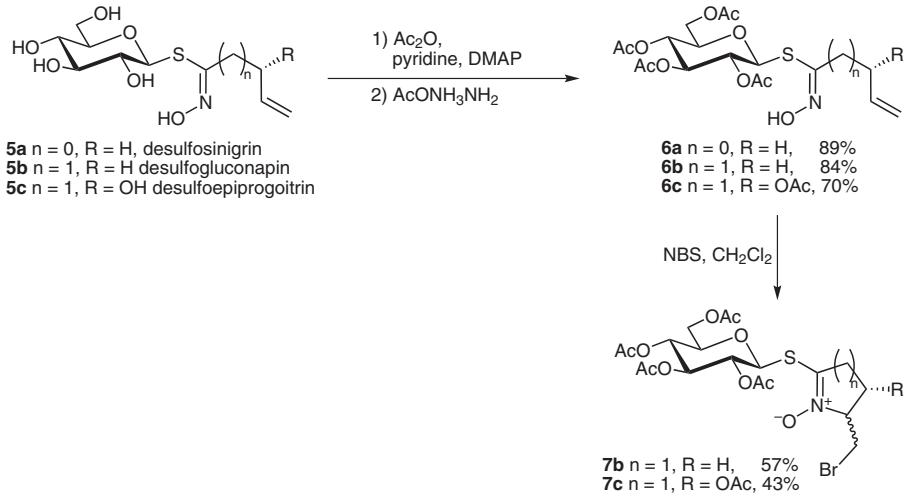


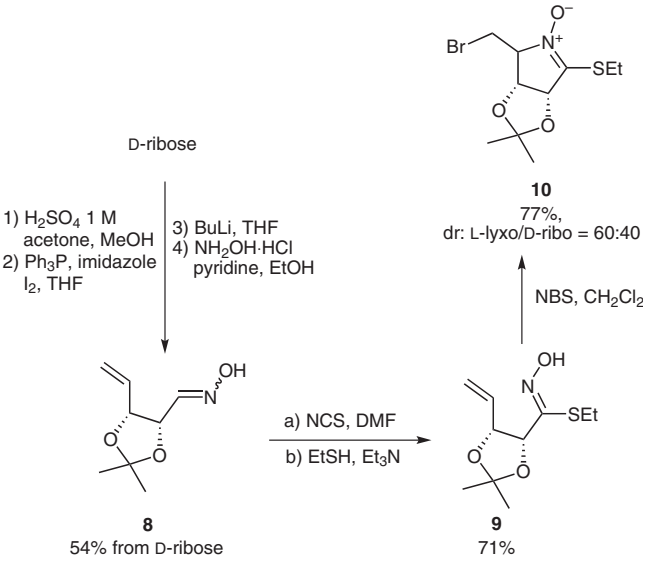

**Scheme 3** TIO derived from desulfoglucosinolates through halocyclization

giving (70–94% yield) thiohydroximates **6a–c**, which were further submitted to the halocyclization conditions previously established by Grigg[5] and Jäger.[6] On reaction with NBS in dichloromethane, protected desulfosinigrin **6a** only led to degradation products. In contrast, desulfo-GL **6b** and **6c** readily underwent *5-exo-trig* bromocyclization to give glucosyl thioimidate-*N*-oxides **7b** and **7c** in 57% and 43% yield, respectively. Those compounds appeared rather unstable and degradation occurred at room temperature.

Nevertheless, the above results strengthened our resolve to develop more accessible models based on carbohydrate frameworks.

With a view to improving the stability of our structures, we turned to a carbohydrate template (Scheme 4). Starting with D-ribose, the acyclic aldoxime **8** could be obtained in four steps with a 34% overall yield.[6b,7] The thiohydroximate function was more smoothly introduced, compound **9** being isolated in 71% yield.[8] NBS-induced halocyclization afforded the ethyl thioimidate *N*-oxide **10** in 77% yield. After standing for a few days at room temperature, compound **10** also revealed some instability, whereas no major degradation was observed when kept at –18 °C: thus a carbohydrate template approach is favorable in the synthesis of TIO.

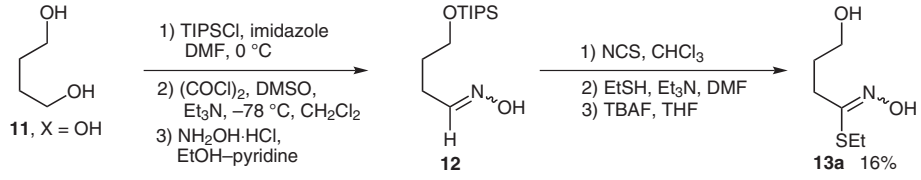
Our second path to generate TIO involved nucleophilic substitution of an activated terminal alcohol. Mono-*O*-silylation of butane-1,4-diol (**11**) followed by Swern oxidation then aldoxime formation afforded in 42% yield precursor **12**,[9] which could be converted into the ethyl




**Scheme 4** Halocyclization on more simple thiohydroximate templates

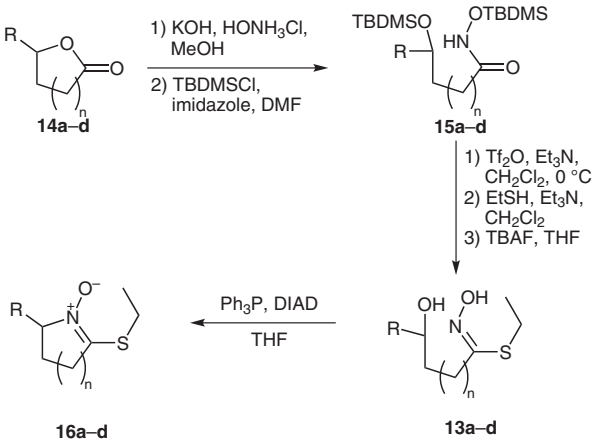
thiohydroximate **13a** albeit in relatively poor yield (Scheme 5).[10]

We thus moved to a new sequence in order to shorten the process. A range of four lactones, γ-butyrolactone (**14a**), γ-valerolactone (**14b**), δ-valerolactone (**14c**), and ε-caprolactone (**14d**), was selected for conversion into hydroxamic acids, which were readily protected in the form of bis-*O*-silylated derivatives **15** (Scheme 6). The overall yields (44–57%, Table 1) are in a reasonable range, taking into




**Scheme 5** The nucleophilic displacement approach (pathway 1)

account the sensitivity of *O*-TBDMS-protected hydroxamic acids to silica gel chromatography. The following critical synthetic step to deliver ethyl thiohydroximates **13** was performed using a protocol developed by Carreira et al.[11] to generate nitrile oxides. Condensation was effected in a two-step sequence: formation of the triflated hydroximates, then condensation with ethanethiol under basic conditions. Obtained in ca. 80% yield, the intermediate O-silylated thiohydroximates were then deprotected using standard TBAF conditions, and the thiohydroximate precursors **13** were obtained in 65–75% yields. It can be noted from example **13a** how much shorter and more efficient this last sequence is.



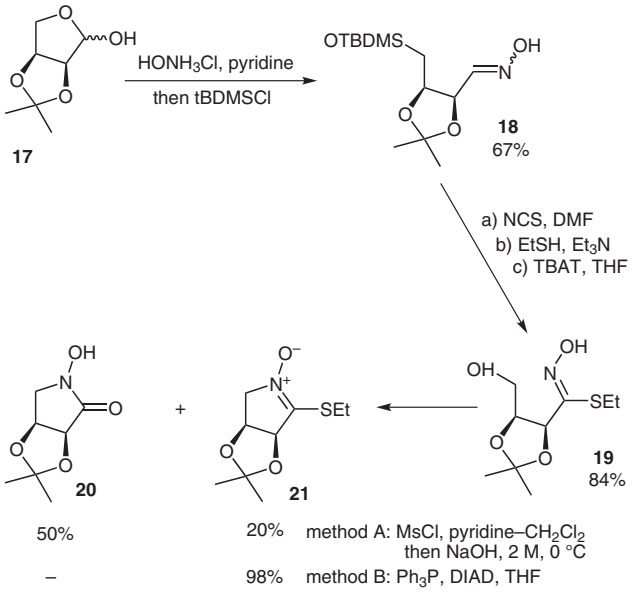

**Scheme 6** The nucleophilic displacement approach (pathway 2)

**Table 1** From Lactone Opening to Thiohydroximates and TIO

| Lactone | Hydroxamic acid (yield, %) | Thiohydroximate (yield, %) | TIO (yield, %) | Overall yield (%) |
|---|---|---|---|---|
| **14a** n = 1, R = H | **15a** 45 | **13a** 65 | **16a** 35 | 10 |
| **14b** n = 1, R = Me | **15b** 57 | **13b** 74 | **16b** 79 | 33 |
| **14c** n = 2, R = H | **15c** 51 | **13c** 75 | **16c** | – |
| **14d** n = 3, R = H | **15d** 44 | **13d** 71 | **16d** | – |

Our major concern being to prevent hydrolysis of the cyclic TIO into an *N*-hydroxylactam, we postulated that a mild neutral reaction protocol might be appropriate. Mitsunobu conditions were thus applied to thiohydroximates **13** and the internal nucleophilic displacement produced interesting results. While six- or seven-membered rings did not form (neither **16c** nor **16d** were detected in the reaction medium), the five-membered ring TIO **16a** and **16b** were obtained in 35% and 79% yield, respectively. This dramatic improvement in reactivity might be attributed to a stabilization effect related to the ring size; in addition, the considerable yield increase observed from **16a** to **16b** is likely to derive from some transition-state stabilization effect in the methyl-branched precursor **13b**.[12]

The above synthetic approach to TIO was further extended to carbohydrate-type templates, to increase the ring-closure yield and stability of the TIO. We have explored in parallel both synthetic sequences previously examined to access a suitable template, carrying a thiohydroximate at one end and a free alcohol at the other end. The lactone approach starting with 2,3-*O*-isopropylidene-D-erythronolactone proved unsuccessful, as we were unable to isolate the hydroxamic acid whatever the conditions used. On the contrary, easy one-pot conversion of 2,3-*O*-isopropylidene-L-erythrose (**17**)[13] into the aldoxime **18**[6b,14] allowed a four-step, efficient access (67% overall yield) to the thiohydroximate **19** (Scheme 7).[15] Final de-O-silylation proved more efficient using tetrabutylammonium tetrafluoroborate (TBAT) instead of standard TBAF. Two different ring-closing procedures were then applied. Method A involved mesyl activation of the primary alcohol prior to application of basic conditions to induce intramolecular cyclization. Sodium hydrogencarbonate proved inefficient, leading to rapid hydrolysis to afford the hydroxylactam **20** in 70% yield. Sodium hydroxide allowed formation of TIO **21** as the minor product (20% yield) together with **20** (50% yield). Method B used the Mitsunobu procedure: under those conditions, the expected TIO **21** was obtained in nearly quantitative yield.[16]




**Scheme 7** The nucleophilic displacement approach (pathway 3)

In conclusion, initially inspired by a standard analytical protocol used for determining the glucosinolate content in plants, we have explored two approaches for the synthesis of thioimidate *N*-oxides. The halocyclization studied revealed some stability problems, when using complex (glucosyl **6b**, **6c**) precursors. This could be overcome by using a D-ribose-derived template, from which a fairly stable TIO **10** could be readily prepared.

The intramolecular nucleophilic substitution approach also proved inadequate when applied to simple frameworks, whereas the use of a carbohydrate scaffold combined with an application of the Mitsunobu methodology proved most efficient in yielding TIO **21**. We have thus

disclosed two original approaches to introduce the rare thioimidate *N*-oxide function, which is under current study in our laboratory.[17]

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(15) **Preparation of the Thiohydroximate 19**
NCS (0.88 g, 6.6 mmol) was added to a solution of aldoxime **18** (1.75 g, 6 mmol) in DMF (5 mL), and the mixture was left at r.t. for 4 h. After cooling to –78 °C, ethanethiol (1.33 mL, 18 mmol) then $Et_3N$ (2.5 mL, 18 mmol) were added dropwise. The reaction mixture was slowly allowed to reach r.t. and stirred for a further 12 h. After hydrolysis ($H_2O$, 100 mL) and extraction with $CH_2Cl_2$ (3 × 100 mL), the combined organic phases were washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and then evaporated. Purification of the residue over silica gel (PE–EtOAc, 7:3) afforded the 4-O-silylated derivative of **24** as an oil. This intermediate was dissolved in THF (20 mL) and reacted with TBAT (1.2 equiv) at r.t. for 14 h. $H_2O$ (20 mL) was then added and the mixture was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, then evaporated under reduced pressure. *S*-Ethyl 2,3-*O*-isopropylidene-L-erythronimidothioate (**19**) was isolated as a colorless solid (1.2 g, 84% yield) by silica gel flash chromatography (PE–EtOAc, 1:1). Mp 40–41 °C; $R_f$ = 0.18 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –54 (*c* 1.0, $CHCl_3$). IR (KBr): 3356, 2992, 1688, 1451, 1375, 1269, 1223, 1208, 1056, 998, 895, 859, 806, 740 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.6 Hz, $CH_3CH_2$), 1.40 and 1.53 [2 s, 6 H, $C(CH_3)_2$], 3.11 (m, 2 H, $CH_3CH_2$), 3.68 (m, 1 H, H-4b), 3.79 (m, 1 H, H-4a), 4.40 (dd, 1 H, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 4.4 Hz, H-3), 4.89 (d, 1 H, $J_{2,3}$ = 6.0 Hz, H-2), 9.40 (s, 1 H, NOH). $^{13}C$ NMR (100 MHz, $CDCl_3$) : δ = 15.1 ($CH_3CH_2$), 25.6 ($CH_3CH_2$), 25.4, 27.3 [$C(CH_3)_2$], 61.7 (C-4), 76.9 (C-2), 78.6 (C-3), 109.5 ($C(CH_3)_2$), 150.8 (C=N). MS (IS): *m/z* = 236.0 $[M + H]^+$. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_9H_{18}NO_4S$: 236.0957; found: 236.0968.
(16) **Preparation of the Thioimidate *N*-Oxide 21**
$Ph_3P$ (55 mg, 0.21 mmol) was added to a solution of DEAD (40% in toluene, 95 µL, 0.21 mmol) in THF (10 mL). After 10 min of stirring, the thiohydroximate **19** (50 mg, 0.21 mmol) was added, and the reaction mixture was kept at reflux overnight. After hydrolysis ($H_2O$, 20 mL) and extraction with $CH_2Cl_2$ (3 × 30 mL), the combined organic phases were dried over $MgSO_4$, filtered, and then evaporated. (3*S*,4*S*)-2-Ethylsulfanyl-3,4-isopropylidene-dioxy-3,4-dihydro-5*H*-pyrrole-1-oxide (**21**) was isolated as a colorless solid (45 mg, 98% yield) after silica gel flash chromatography (EtOAc). Mp 145–150 °C; $R_f$ = 0.5 (EtOAc); $[\alpha]_D^{20}$ –136.5 (*c* 1.0, MeOH). IR (neat): 1570, 1422, 1383, 1261, 1234, 1204, 1154, 1076, 1021, 864, 836, 706, 663 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, 3 H, *J* = 7.6 Hz, $CH_3CH_2$), 1.39 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.13 (q, 2 H, *J* = 7.6 Hz, $CH_3CH_2$), 4.06 (dt, 1 H, $^2J_{5b,5a}$ = 14.7 Hz, $J_{5b,4}$ = $^5J_{5b,3}$ = 1.2 Hz, H-5b), 4.13 (dd, 1 H, $^2J_{5b,5a}$ = 14.7 Hz, $J_{5a,4}$ = 5.3 Hz, H-5a), 4.90 (ddd, 1 H, $J_{4,3}$ = 6.5 Hz, $J_{4,5a}$ = 5.3 Hz, $J_{4,5b}$ = 1.4 Hz, H-4), 5.34 (d, 1 H, $J_{4,3}$ = 6.5 Hz, H-3). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 15.6 ($CH_3CH_2$), 23.4 ($CH_3CH_2$), 26.0, 27.2 [$C(CH_3)_2$], 66.4 (C-5), 73,1 (C-4), 81.7 (C-3); 112.8 [$C(CH_3)_2$], 144.0 (C-2). MS (IS): *m/z* = 218.0 $[M + H]^+$. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_9H_{16}NO_3S$: 218.0851; found: 218.0841.
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