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An improved procedure for the preparation of β-thiohydroximates for glucosinolate synthesis

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ABSTRACT

A novel and simple method is described for the synthesis of β-thiohydroximates from oximes and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose, which are key intermediates in the synthesis of glucosinolates. The procedure involves the in situ formation of an oximyl chloride from the oxime, using inexpensive bleach, which is then reacted directly under basic conditions with the thioglucopyranose.

Glucosinolates **1** are a group of sulfur-containing secondary metabolites[1] that are found in all members of the *Cruciferae*, including the Brassica vegetables such as Brussels sprouts, broccoli and oilseed rape. They have the general structure shown in Figure 1, with a β-D-glucopyranose unit attached to an *O*-sulfated anomeric *Z*-thiohydroximate function and a variable side chain, R. The side chains are biosynthesized[2] from one of three amino acids; methionine, phenylalanine or tryptophan. Further modifications to the side chain, such as elongation, hydroxylation and oxidation, mean that over 120 different naturally occurring glucosinolates have now been identified.[3]

Evidence from epidemiological and animal studies has linked the consumption of broccoli and other cruciferous vegetables with a lowered risk of cancers, in particular those of the gastrointestinal and respiratory tracts.[2,4–6] These observed anti-cancer effects have been attributed to the high content of glucosinolates in the vegetables. However the active species actually appear to be the breakdown products which arise from enzyme-catalysed hydrolysis of glucosinolates during food preparation, cooking, chewing and digestion, mediated by the compartmentalised plant enzyme myrosinase.[1,7] A wide range of degradation products are produced from this reaction, including isothiocyanates, nitriles, epithioalkanes, oxazolidine-2-thiones and thiocyanates, with biological activities including anti-cancer effects.[2,7]

Hence there is considerable interest in glucosinolates and their synthesis. Pure synthetic glucosinolates are required for biological studies, isotopically-labelled glucosinolates for metabolic studies,[8] and as analytical standards[9] and novel glucosinolate analogues for the study of their enzymatic hydrolysis.[10]

The synthesis of glucosinolates has recently been reviewed comprehensively by Rollin and Tatibouët,[10] and commonly utilises an aldehyde to provide the side-chain fragment (Scheme 1). The

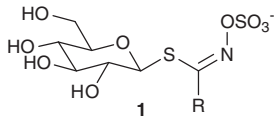
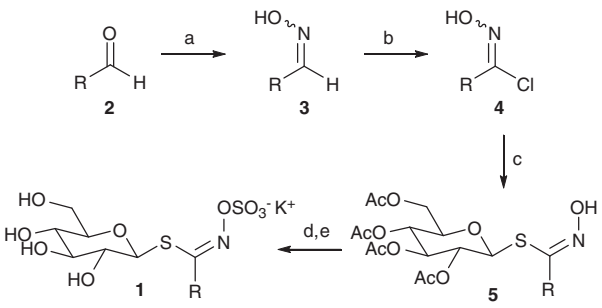


Figure 1. Generalised glucosinolate structure.



Scheme 1. General glucosinolate synthesis: Reagents: (a) $NH_2OH{\cdot}HCl$, EtOH; (b) Cl_2 or NCS; (c) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose, Et_3N, THF; (d) (i) pyridine·SO_3 complex, CH_2Cl_2, (ii) aq 2 M $KHCO_3$; (e) KOMe, MeOH.

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aldehyde is converted in two steps into the oximyl chloride **4**. The key step, first developed by Benn in the 1960s,[11] is thought to involve in situ generation of a nitrile oxide from **4** under basic conditions, which reacts with a 1,3-addition reaction with a protected β-D-thioglucopyranose to give the *Z*-thiohydroximate **5**, stereospecifically. Stereoelectronic effects operating during 1,3-addition of nucelophiles to nitrile oxides are thought to be the reason for the stereospecificity.[12] The final two steps are then sulfonation of the N-hydroxy group using pyridine·SO_3 complex and deprotection of the sugar with potassium in methanol.

Over the years this process has been updated and modified, mainly in the method by which the nitrile oxide is obtained.[10] Herein, we report a novel, simple and high yielding procedure for this key step in glucosinolate synthesis.

The nitrile oxides required for glucosinolate synthesis are unstable species that are usually generated via the facile elimination of HCl from an oximyl chloride under basic conditions. Traditionally, oximyl chlorides are prepared from oximes by reaction with chlorine gas or *N*-chlorosuccinimide (NCS) and then isolated, but are usually used without purification, for coupling to the thioglucose (Scheme 1). These reactions are not usually very high yielding The use of bleach has been described as a convenient reagent for the formation of nitrile oxides,[13] but this has not been exploited in glucosinolate synthesis.

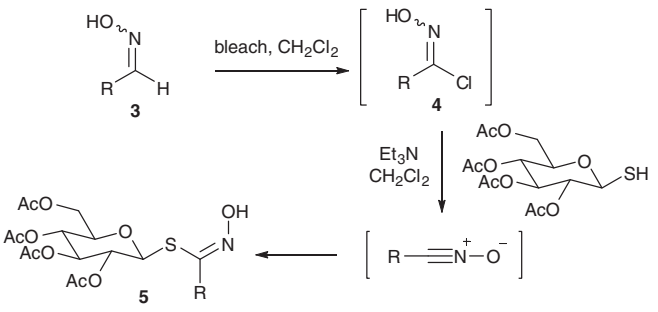
Our group has now developed a simple, novel and convenient method for the formation of thiohydroximate bonds in glucosinolates, which generates the intermediate oximyl chlorides in situ, using inexpensive, common laboratory bleach and provides higher yields than previous methods over a range of substrates.

The oximes examined were either commercially available or prepared using the appropriate aldehyde and hydroxylamine hydrochloride in good yield. These were then used as a mixture of *E*- and *Z*-isomers without further purification.

The oximes were dissolved in dichloromethane and held in a separating funnel before the addition of 3 equiv of common laboratory bleach.[14] The biphasic solution was shaken and a blue colour developed, which is due to the presence of the *C*-nitroso intermediate.[15] The organic layer was then added dropwise to a stirred solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose in dichloromethane (Scheme 2). Finally, triethylamine was added to promote formation of the nitrile oxide. The order of addition of base was critical to the coupling procedure, as it was found that thioglucose readily dimerises under basic conditions. Further optimisation led to an excess of the oxime being used to achieve the best yields.

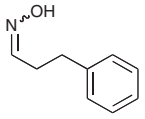
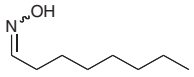
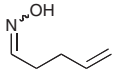
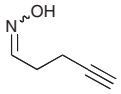
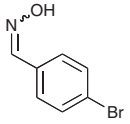
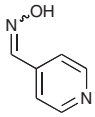
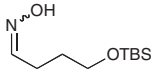
A range of substrates was employed to investigate the scope and utility of the method. The structures were based on the side chains found in naturally occurring glucosinolates, plus some extra substrates with unusual side chain functionality, and the results are summarised in Table 1.

This new procedure was observed to work simply and efficiently with all the oximes that were studied, giving improved



Scheme 2. Bleach-mediated thiohydroximate synthesis.

Table 1
Reaction conditions and results for the bleach-mediated β-thiohydroximate synthesis

Entry	Oxime	Yield (%)
1		76
2		78
3		63
4		77
5		92
6		65
7		83

yields over previous two-step methods. The first entry, which gave a 76% yield, is the precursor to the glucosinolate, gluconasturtiin, which had been made before in our laboratory in a lower yield of 61%, over two steps via the standard method involving isolation of the oximyl chloride.[16] It was similarly prepared by Gil and McLeod in 69% yield.[15] The oxime from octanal (entry 2) was previously employed to make heptyl glucosinolate, the thiohydroximate being prepared in 61% yield over two steps,[17] which is considerably lower than the 78% yield obtained herein.

Good yields were also observed with both alkenyl and alkynyl side chains (entries 3 and 4). In previous syntheses of glucosinolates with unsaturated side chains, the oximyl chlorides were prepared via nucleophilic chlorination of an alkenyl nitronate from a nitroalkane precursor, due to the perception that the presence of the alkene would prevent efficient aldoxime chlorination.[10] However, it can be seen that by using our newly developed method, but-4-enyl oxime (entry 3), gives a 63% yield, compared to only 13% from the nitroalkane in two steps.[18]

Entries 5 and 6 are aromatic oximes which would lead to novel glucosinolate structures. The final oxime (entry 7) gives a β-thiohydroximate with a TBS-protected alcohol in its side chain, which was found to be stable under the reaction conditions, and coupled in very good yield.

In summary, we have developed a new coupling method for β-thiohydroximate bond formation using inexpensive and readily available bleach as the chlorinating agent. This simplified one-step procedure is easy to carry out, is quick and gives good to excellent yields over a range of substrates. The method provides a useful improvement to the general synthetic route to glucosinolates.

Acknowledgements

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14. 3-Phenylpropanal oxime (0.20 g, 1.3 mmol) was dissolved in CH_2Cl_2 (6 ml) and shaken with bleach (Fisher Scientific, sodium hypochlorite solution, 8% available chlorine, 2.5 mL, 4.0 mmol) in a separating funnel. Once the solution had changed from colourless to blue to yellow, the organic layer was added dropwise to a solution of acetylated thioglucose (0.29 g, 0.8 mmol) in CH_2Cl_2 (4 mL). The resulting solution was then treated with Et_3N (0.4 mL, 2.7 mmol) and stirred at room temperature for 3 h. The solution was diluted with CH_2Cl_2 (5 mL) and treated with 0.5 M HCl (2 × 10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then recrystallised from MeOH to yield a white solid (0.31 g, 76%); mp 200–202 °C (Lit.[19] 198 °C); *m*/*z* 533.89 $[M+Na]^+$; ν_{max} (KBr)/cm^{-1} 3316 (NOH), 1713 (C=O), 1606 (CN); ^{1}H NMR (300 MHz, $CDCl_3$), 7.28–7.10 (5H, m, CH^{Ar}), 5.20–5.13 (1H, m, CH), 5.03–4.89 (3H, m, 3CH), 4.06 (1H, d, *J* = 11.9 Hz, $CH_2{}^{6a}$), 4.02 (1H, d, *J* = 11.9 Hz, $CH_2{}^{6b}$), 3.66–3.58 (1H, m, CH^5), 2.96–2.64 (4H, m, $2CH_2{}^{7,8}$), 1.99 (3H, s, CH_3), 1.96 (3H, s, CH_3), 1.94 (3H, s, CH_3), 1.85 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 170.8, 169.9, 169.8 (C=O), 152.2 (C=N), 140.9 (C^{Ar}) 129.1, 128.7, 126.9 (5 × CH^{Ar}), 80.3 (CH^1), 76.5 (CH^5), 74.1 (CH^3), 70.5 (CH^2), 68.4 (CH^4), 62.6 ($CH_2{}^6$), 34.8 ($CH_2{}^7$), 33.5 ($CH_2{}^8$), 21.0–20.9 (4 × OC(O)CH_3).
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