Hydroxylamine as an oxygen nucleophile: substitution of sulfonamide by a hydroxyl group in benzothiazole-2-sulfonamides

ARTICLE *in* ORGANIC & BIOMOLECULAR CHEMISTRY · DECEMBER 2012

Impact Factor: 3.56 · DOI: 10.1039/c2ob26929e · Source: PubMed

3 AUTHORS:

Jos J A G Kamps
Radboud University Nijmegen
3 PUBLICATIONS **4** CITATIONS
SEE PROFILE

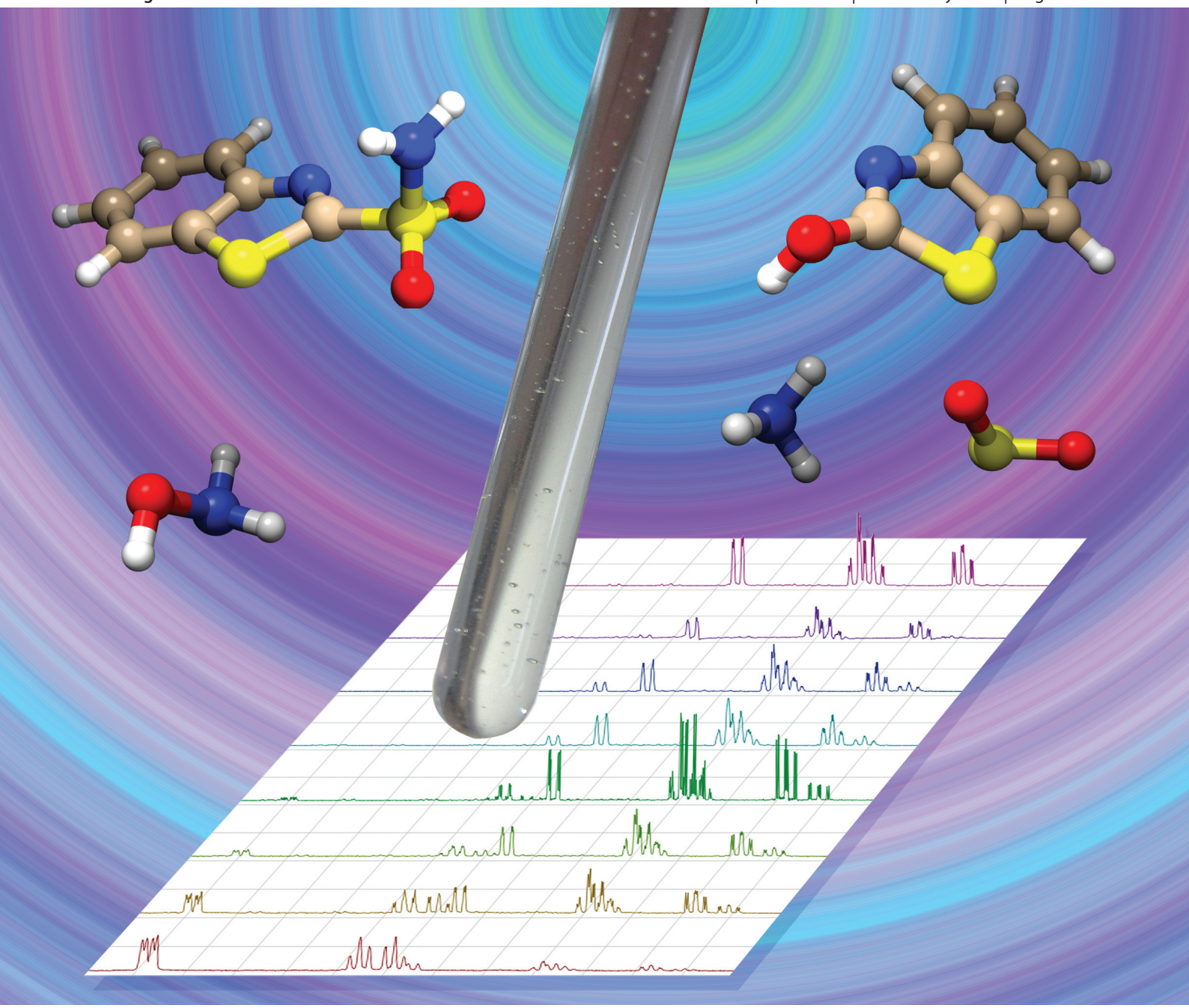
Roman Belle
Radboud University Nijmegen
4 PUBLICATIONS **7** CITATIONS
SEE PROFILE

Jasmin Mecinović
Radboud University Nijmegen
55 PUBLICATIONS **1,249** CITATIONS
SEE PROFILE

Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 11 | Number 7 | 21 February 2013 | Pages 1073–1260



ISSN 1477-0520

RSC Publishing

PAPER

Jasmin Mecinović *et al.*

Hydroxylamine as an oxygen nucleophile: substitution of sulfonamide by a hydroxyl group in benzothiazole-2-sulfonamides

Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1103

Hydroxylamine as an oxygen nucleophile: substitution of sulfonamide by a hydroxyl group in benzothiazole-2-sulfonamides†

Jos J. A. G. Kamps, Roman Belle and Jasmin Mecinović*

Received 1st October 2012,
Accepted 26th November 2012

DOI: 10.1039/c2ob26929e

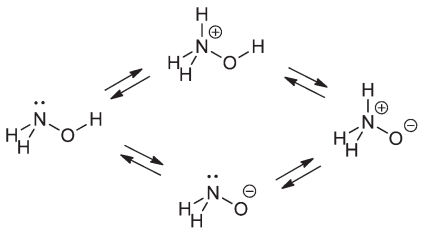
www.rsc.org/obc

Benzothiazole-2-sulfonamides react with an excess of hydroxylamine in aqueous solutions to form 2-hydroxybenzothiazole, sulfur dioxide, and the corresponding amine. Mechanistic studies that employ a combination of structure–reactivity relationships, oxygen labeling experiments, and (in)direct detection of intermediates and products reveal that the reaction proceeds *via* oxygen attack, and that oxygen incorporated in the 2-hydroxybenzothiazole product derives from hydroxylamine. The reaction, which is performed under mild conditions, can be used as a deprotection method for cleavage of benzothiazole-2-sulfonyl-protected amino acids.

Introduction

Hydroxylamine is an ambident α-effect nucleophile[1] that exists in aqueous solutions as a mixture of four species: neutral (NH_2–OH), zwitterionic (NH_3^+–O^-), protonated (NH_3^+–OH), and deprotonated (NH_2–O^-) (Scheme 1).[2] A combination of structure–reactivity studies that examined the leaving abilities of the alkoxy group from ethers, and the free energy for the ionization of hydroxylamine employing the linear free energy relationship (LFER) demonstrated that the zwitterionic form of hydroxylamine represents about 20% of all the hydroxylamine in the aqueous solution at neutral pH.[2]

Hydroxylamine usually reacts with electrophiles through its nitrogen atom. The most widely used reaction in organic chemistry employing hydroxylamine is the reaction between aldehydes or ketones and hydroxylamine to form oximes. In addition, hydroxylamines react with α,β-unsaturated esters to form Michael adducts exclusively *via* the *N*-attack,[3] and with α-ketoacids to form amide bonds under mild reaction conditions.[4] Reactions in which hydroxylamine reacts with electrophiles *via* oxygen attack are rare. For instance, recent studies by Kirby, Nome and co-workers illustrated that hydroxylamines react with phosphate esters *via* *O*-attack to form *O*-phosphorylated intermediates that are further hydrolysed in the presence of an excess of hydroxylamine.[5–7] Another reaction investigated in detail, employing the kinetic isotope effect, is the formation of *O*-acylhydroxylamine from *p*-nitrophenylacetate.[8–10] Herein, we describe that hydroxylamine reacts with benzothiazole-2-sulfonamides in aqueous media in which hydroxylamine acts as an oxygen nucleophile.



Scheme 1 Equilibria of hydroxylamine in aqueous solutions.[2]

Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands.
E-mail: j.mecinovic@science.ru.nl

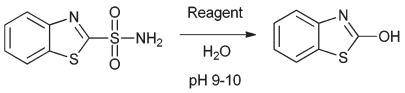
† Electronic supplementary information (ESI) available: Additional experimental information, including synthetic procedures, labeling experiments, NMR spectra and LC-MS analyses. See DOI: 10.1039/c2ob26929e

Results and discussion

During the evaluation of arylsulfonamides as ligands for binding to carbonic anhydrase[11] and CS_2 hydrolase,[12] we observed that an excess of hydroxylamine in buffered water solutions caused an apparent degradation/reaction of benzothiazole-2-sulfonamides.

Initially, we investigated the reaction between benzothiazole-2-sulfonamide (BTA) and hydroxylamine. BTA is converted to 2-hydroxybenzothiazole in the presence of 50 equiv. of hydroxylamine in water at pH 9 in 100% yield after 3 hours at room temperature (Table 1, entry 1, and Fig. 1). The progress of the reaction was monitored by real-time ^{1}H NMR spectroscopy (Fig. 1). The formation of 2-hydroxybenzothizole was confirmed by doping experiments in which the authentic

Table 1 Screening of $HONH_2$ derivatives[a]



Entry	Reagent (equiv.)	Time (h)	Conversion[b] (%)
1	$HONH_2$ (50)	3	100
2	$HONH_2$ (10)	5	100
3	$HONH_2$ (100)	1	100
4	NH_3 (665)	48	n.d.[c]
5	H_2NNH_2 (50)	48	n.d.
6	H_2O_2 (50)	48	n.d.
7	CH_3ONH_2 (50)	48	n.d.
8	H_2NOSO_3H (50)	48	n.d.
9	$HONHCH_3$ (50)	24	86[d]
10	$HON(CH_3)_2$ (50)	48	n.d.
11	$ON(CH_3)_3$ (50)	48	n.d.
12	CH_3ONHCH_3 (50)	48	n.d.
13	$H_2NCH_2CH_2OH$ (50)	48	n.d.
14	NaOCl (10)	48	n.d.
15	NaOH[e]	48	n.d.
16	NaOH[f]	48	<10

[a] Standard reaction conditions: BTA (20 mM), reagent (50 equiv., 1 M), H_2O, pH = 9–10. [b] Conversion determined by ^{1}H NMR and LC-MS. [c] n.d. = not detected. [d] A mixture of 2-hydroxybenzothiazole and *O*-(benzothiaz-2-yl)-*N*-methylhydroxylamine. [e] pH ~ 9. [f] pH ~ 12.

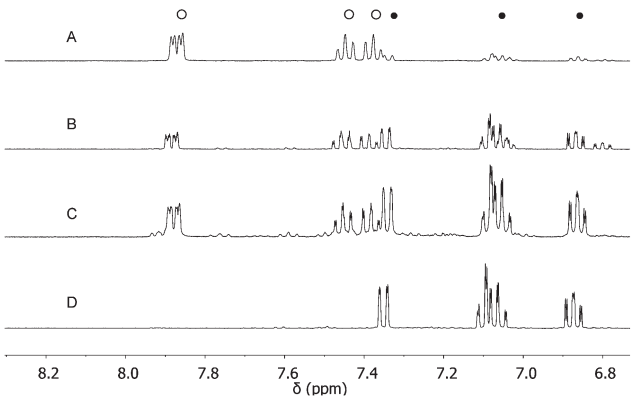
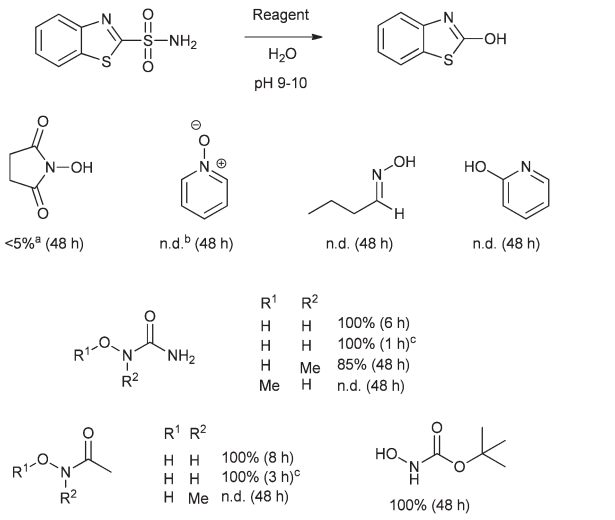


Fig. 1 The progress of the hydroxylamine-mediated substitution of a sulfonamide group from benzothiazole-2-sulfonamide (BTA) monitored by ^{1}H NMR. BTA in the presence of 50 equiv. of hydroxylamine at 25 °C after (A) 10 minutes; (B) 30 minutes; (C) 1 hour; (D) 3 hours. ○ represents BTA and ● represents 2-hydroxybenzothiazole.

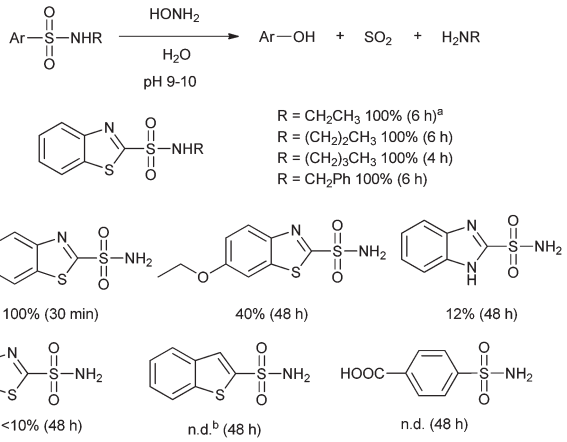
sample of 2-hydroxybenzothiazole was added into the reaction mixture after the completion of the reaction: no new signal appeared in the ^{1}H NMR spectrum. LC-MS analysis of the reaction product also provided evidence of the formation of 2-hydroxybenzothiazole (retention time 13.94 minutes, $M + H^+ = 152.16$). The completion times in the presence of 10 equiv. and 100 equiv. of hydroxylamine were 5 h and 1 h, respectively (Table 1, entries 2–3). The lack of solubility of BTA at pH 6–8 restricted us from checking the progress of the reaction at pH values close to neutral. In addition, due to the explosive potential of hydroxylamine, reactions at higher temperatures were not pursued.

We then examined the reactivity of other simple hydroxylamine analogues and derivatives. Ammonia, hydrazine, or hydrogen peroxide did not react with BTA under standard reaction conditions (Table 1, entries 4–6). To investigate whether hydroxylamine reacts with BTA *via* its oxygen or nitrogen atom, we tested both *O*- and *N*-substituted hydroxylamines as potential reagents for the substitution reaction (Table 1, entries 7–12). *O*-Methylhydroxylamine and hydroxylamine-*O*-sulfate did not convert BTA to any observable product (2-hydroxybenzothiazole or potential 2-aminobenzothiazole), implying that the unsubstituted oxygen atom is essential for the reactivity. *N*-Methylhydroxylamine, however, reacted with BTA, although more slowly than hydroxylamine, to form *O*-(benzothiaz-2-yl)-*N*-methylhydroxylamine and 2-hydroxybenzothiazole. In contrast, *N*,*N*-dimethylhydroxylamine and trimethylammonium oxide did not yield any product in the presence of BTA. Because the reaction of BTA and hydroxylamine occurs in slightly basic conditions, we performed control experiments under the same conditions in the absence of hydroxylamine (Table 1, entries 15–16): no product was observed by ^{1}H NMR at pH 9 and traces of the product at pH 12. Taken together, these experiments suggest that an unsubstituted oxygen of hydroxylamine is required for an efficient reaction with BTA, hence proposing the mechanism that likely involves an initial nucleophilic attack of the hydroxyl group.

We were then interested in knowing whether other *N*-substituted hydroxylamine analogues that possess a free OH group also exhibit reactivity towards BTA (Scheme 2). Butyloxime, pyridine-*N*-oxide, and 2-hydroxypyridine were inert towards BTA. Interestingly, hydroxyurea showed a comparable reactivity to hydroxylamine, quantitatively producing 2-hydroxybenzothiazole in 6 hours at room temperature (also in 1 hour at 70 °C). *N*-Methylhydroxyureas possessed a significant decrease in reactivity whereas *O*-methylhydroxyurea was found to be inactive. Acetohydroxamic acid reacted with BTA in 8 hours under

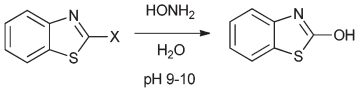


Scheme 2 Analogues of $HONH_2$ used in the standard substitution reaction. (a) Conversion determined by ^{1}H NMR and LC-MS; (b) n.d. = not detected; (c) at 70 °C.



Scheme 3 The scope of the reaction. (a) Conversion determined by ^{1}H NMR and LC-MS; (b) n.d. = not detected.

Table 2 The effect of the leaving group



Entry	Substrate	Time	Conversion[a] (%)
1	SO_3Na	48 h	12
2	SOMe	30 min	100
3	SO_2Me	30 min	100
4	COOH	48 h	n.d.[b]
5	COOMe	48 h	n.d.
6	$CONH_2$	48 h	n.d.
7	F	48 h	100
8	Cl	48 h	100
9	NH_2	48 h	n.d.
10	SMe	48 h	n.d.

[a] Conversion determined by ^{1}H NMR and LC-MS. [b] n.d. = not detected.

standard conditions (3 hours at 70 °C), while *N*-methylacetohydroxamic acid and *N*-hydroxysuccinimide produced only traces of 2-hydroxybenzothiazole. Boc-protected hydroxylamine was observed to be less reactive than hydroxylamine; the conversion was completed in 48 hours. Collectively, these results are in agreement with those employing substituted hydroxylamines (Table 1), demonstrating that there has to be an NH group adjacent to the free OH group in hydroxylamine in order to achieve an enhanced reactivity of the reagent.

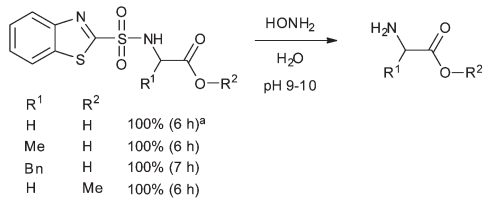
The scope of the reaction in the presence of hydroxylamine was then investigated. Modifications of the heteroaromatic group as well as of the sulfonamide functionality of BTA were considered (Scheme 3). Readily available *N*-alkyl BTAs[13] were quantitatively converted to 2-hydroxybenzothiazole within 6 hours under standard reaction conditions. Importantly, unlike BTA, which only contains exchangeable hydrogens on the amino side chain (*i.e.* NH_2), reaction between *N*-alkylated-BTA derivatives and hydroxylamine provided evidence that alkylamine is the product of the reaction. Real time ^{1}H NMR analysis clearly showed the disappearance of the alkyl signals from the starting material, and the appearance of new signals that correspond to the alkylamine product (doping/enhancement experiments ultimately proved their existence, see ESI†).

Thiazole-2-sulfonamide in the presence of 50 equiv. of hydroxylamine afforded only traces of 2-hydroxythiazole (<10%). The observed difference in the reactivity between thiazole-2-sulfonamide and benzothiazole-2-sulfonamide can be explained by the fact that the benzothiazole ring retains the aromatic character upon nucleophilic attack by hydroxylamine, whereas the thiazole ring becomes dearomatic. The reaction between 6-ethoxy-BTA and hydroxylamine took longer than that with BTA (40% conversion in 48 hours), whereas 5-chloro-BTA quantitatively reacted with hydroxylamine in only 30 minutes. These results indicate that the electrophilic character of the C-2 position of BTA is perturbed in the presence of electron-donating or electron-withdrawing groups, hence, decreasing or increasing the rate of conversion relative to BTA. Interestingly, benzimidazole-2-sulfonamide was found to be a very poor substrate for the reaction with hydroxylamine, yielding only 12% of 2-hydroxybenzimidazole. The observed limited reactivity of benzimidazole-2-sulfonamide relative to benzothiazole-2-sulfonamide can be rationalized by a substantial decrease in the electrophilic character of C-2 (nitrogen's electrons in 2p orbital overlap better than sulfur's electrons in 3p orbitals with carbon's 2p orbital). Benzothiophene-2-sulfonamide, notably, did not react with hydroxylamine under standard conditions. Similarly, 4-carboxybenzenesulfonamide was found to be inactive in the reaction with hydroxylamine. Overall, these results indicate that the substrate requires highly electrophilic C-2 and the nitrogen atom on the *ortho* position to the sulfonamide group for the reaction to proceed.

We then investigated whether other functionalities positioned at C-2 of the benzothiazole ring allow the substitution reaction (Table 2). Sodium benzothiazole-2-sulfonate afforded 2-hydroxybenzothiazole in poor yield, whereas sulfone and sulfoxide quantitatively reacted with hydroxylamine to form 2-hydroxybenzothiazole in 30 minutes (Table 2, entries 1–3). Other electron-withdrawing groups, such as carboxylic acid, ester, and amide, surprisingly, did not furnish any detectable product (Table 2, entries 4–6). 2-Fluorobenzothiazole and 2-chlorobenzothiazole both reacted with hydroxylamine, but the reaction proceeded at a much slower rate compared to BTA (Table 2, entries 7–8).

The benzothiazole-2-sulfonyl (Bts) group is a known *N*-protecting group in organic chemistry. Current deprotection methods, which have been used for the removal of the Bts group from *N*-protected amino acids, include 50% H_3PO_2,[14] Zn/HOAc–EtOH,[14] Al–Hg/ether–water,[14] thiophenol/base,[15,16] and 4-methoxythiophenol/DIEA.[17] Using our method, cleavage of the Bts-protected glycine, alanine or phenylalanine in the presence of 50 equiv. of hydroxylamine afforded unprotected amino acids in quantitative yield in 6 hours (Scheme 4, for the real-time NMR analyses see ESI†).

To investigate the mechanism of the hydroxylamine-mediated substitution of the sulfonamide group in BTA by a hydroxyl group, we performed labeling experiments. The



R^1	R^2	
H	H	100% (6 h)[a]
Me	H	100% (6 h)
Bn	H	100% (7 h)
H	Me	100% (6 h)

Scheme 4 Deprotection of amino acids. (a) Conversion determined by ^{1}H NMR.

oxygen atom in 2-hydroxybenzothiazole product could be incorporated from hydroxylamine or from water. We performed reactions in H_2O and $H_2{}^{18}O$ and analyzed products by LC-MS (Fig. 2). LC-MS analyses revealed that the product in *both* cases has the same molecular mass (*m*/*z* 152.16), demonstrating that there is no incorporation (<5%) of oxygen in the product from water. When *O*-labeled $H^{18}ONH_2$ (~65% ^{18}O) was used for the cleavage reaction, about 65% of 2-hydroxybenzothiazole product had incorporated the heavy oxygen atom (Fig. 2). These data suggest that the oxygen atom in the product derives from hydroxylamine, and *not* from water. Also, these experiments provided evidence about the intermediate of the cleavage reaction (see ESI†). In agreement with labeling experiments, hydroxylamine quantitatively reacts with BTA to afford 2-hydroxybenzothiazole under argon, as well as in the dark, suggesting that there is no dioxygen-mediated mechanism or photochemical pathway involved in the cleavage. ^{1}H NMR and LC-MS analyses provided evidence that products of the hydroxylamine-mediated reaction of benzothiazole-2-sulfonamides are 2-hydroxybenzothiazole and alkylamine.

Using new fuchsine, a colorimetric reagent for the detection of sulfur dioxide,[18,19] we additionally proved that sulfur dioxide is the remaining product of the reaction (see ESI†). To test the possibility that the conversion of hydroxylamine results in the formation of diimide (HN═NH) intermediate, as previously reported for the reaction between phosphate esters and hydroxylamine,[7] we performed the reaction under standard conditions, but in the presence of 2 equiv. of fumarate. Careful ^{1}H NMR analysis showed that fumarate is converted to succinate, therefore indicating that diimide is an intermediate of the reaction. Control experiments using base only (without hydroxylamine) or hydroxyurea instead of hydroxylamine illustrated that diimide is only formed when hydroxylamine is used as a reagent (Fig. 3).

A proposed mechanism of hydroxylamine-mediated substitution of benzothiazole-2-sulfonamides is based on the following observations: (i) hydroxylamine and *N*-methylhydroxylamine,

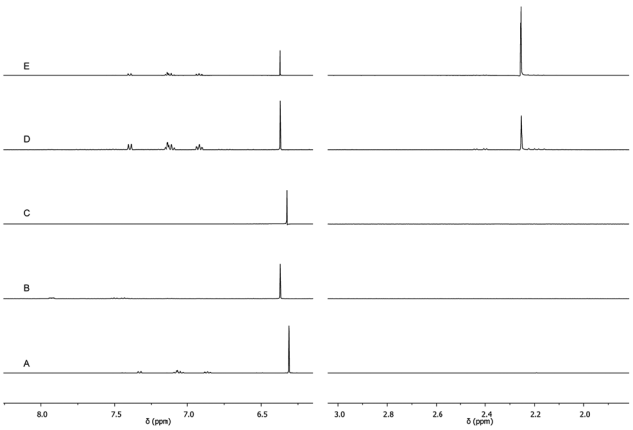


Fig. 3 Indirect detection of diimide; diimide reduces fumaric acid to succinic acid. Peaks at 6.3 ppm represent the fumaric acid protons, while peaks at 2.3 ppm represent the succinic acid protons. (A) BTA substitution reaction in the presence of fumaric acid and using hydroxyurea as a reagent; (B) BTA, base and fumaric acid; (C) hydroxylamine, base and fumaric acid; (D) BTA substitution reaction in the presence of fumaric acid using hydroxylamine as a reagent; (E) BTA substitution reaction mixture in the presence of fumaric acid, which was after completion (as in D) doped with sodium succinate.

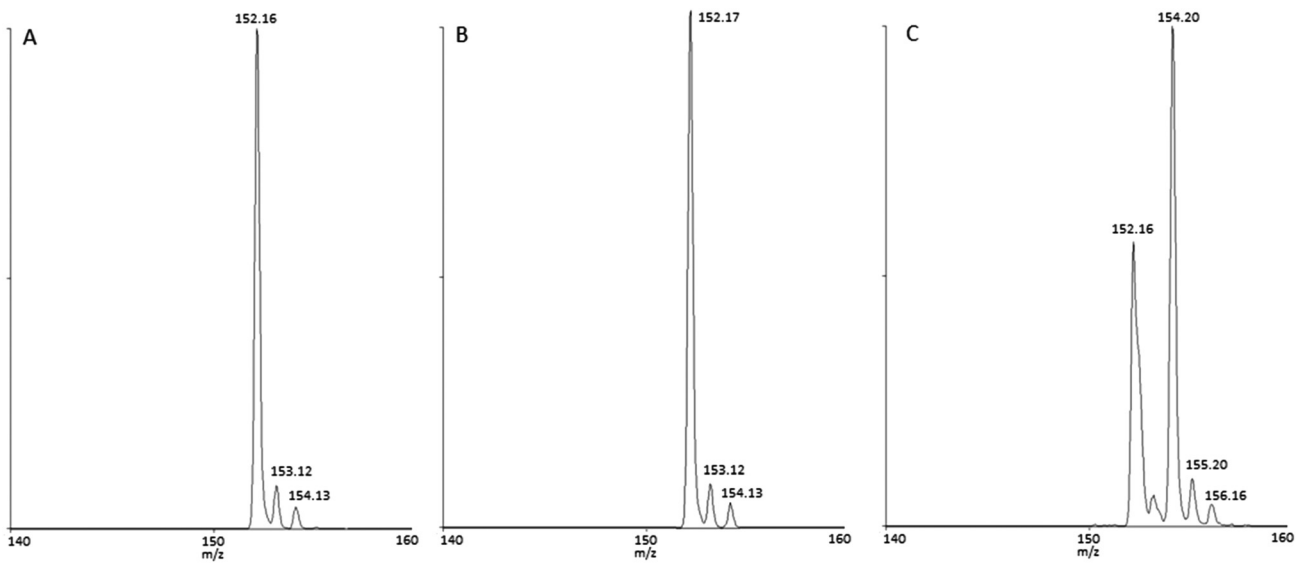
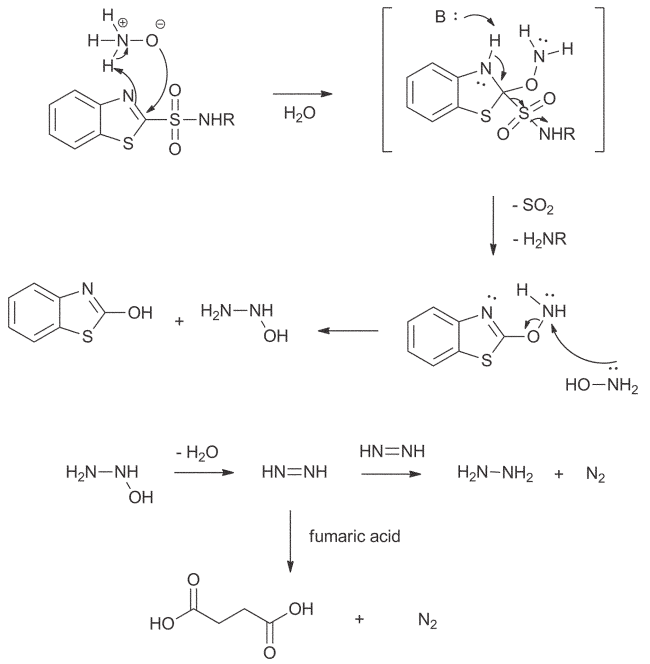


Fig. 2 LC-MS$^+$ spectra of (A) standard substitution of BTA using $HONH_2$ in $H_2{}^{16}O$; (B) standard substitution of BTA using $HONH_2$ in $H_2{}^{18}O$; (C) standard substitution of BTA using $H^{18}ONH_2$ in $H_2{}^{16}O$.



Scheme 5 Proposed mechanism of the substitution reaction.

unlike *O*-methylhydroxylamine, react with BTA, (ii) the reaction does not occur in the absence of hydroxylamine under basic conditions, (iii) the nitrogen atom at the *ortho* position to the sulfonamide group is likely necessary for the reaction, (iv) the oxygen atom incorporated in the product derives from hydroxylamine, and does not derive from water, and (v) diimide is an intermediate of the reaction. These observations propose a mechanism in which hydroxylamine *via* its N–O oxygen atom attacks the electrophilic C-2 atom of the substrate, and concomitantly, the *ortho* nitrogen atom of the heteroaromatic ring abstracts the proton from the zwitterionic hydroxylamine (Scheme 5). Deprotonation and donation of lone-pair electrons from the nitrogen to the five-membered ring causes the elimination of the sulfonamide group (*via* the formation of sulfur dioxide and alkylamine) and the formation of an unstable benzothiazole-*O*-hydroxylamine intermediate. The intermediate further reacts with excess of hydroxylamine to afford 2-hydroxybenzothiazole product (or its tautomeric keto form) and hydroxyhydrazine. There has been some discrepancy between experimental and computational data in the literature about the existence of hydroxyhydrazine.[20,21] Although we do not have direct evidence for the formation of hydroxyhydrazine, its potential existence is in agreement with the report by Kirby *et al.*,[7] in which hydroxyhydrazine dehydrates to form diimide. Diimide can further react with another molecule of diimide to form hydrazine and nitrogen.[22]

Conclusions

In summary, we have demonstrated that hydroxylamine mediates the conversion of benzothiazole-2-sulfonamides to 2-hydroxybenzothiazole, sulfur dioxide, and the corresponding amine *via* the mechanism in which hydroxylamine acts as an oxygen nucleophile. The reaction reported here thus represents one of the very few examples in which hydroxylamine reacts with electrophiles *via* its oxygen atom. The utility of the reaction was exemplified by the efficient cleavage of benzothiazole-2-sulfonyl-protected amino acids: hydroxylamine-mediated cleavage, thus, represents a mild and alternative method to the currently existing methods for the deprotection of the Bts group.

Experimental

Standard substitution reaction of BTA and analogues

4.3 mg (0.020 mmol, 1 equiv.) of benzothiazole-2-sulfonamide (BTA) was added to water (1 mL). To this suspension were added the reagent (1.0 mmol, 50 equiv.) and 8 μL of NaOH (50% in H_2O) to adjust the pH to 9–10. When the reaction mixture became clear and colorless after shaking, it was transferred to an NMR tube and analysed at specific time points by ^{1}H NMR and additionally by LC-MS. For ^{1}H NMR analysis, D_2O was used as a solvent, whereas H_2O was used to analyse the sample by LC-MS.

When the reagent exists as a hydrochloride salt, more equivalents of base were used to adjust the pH.

Detection of 2-hydroxybenzothiazole

A standard substitution reaction of BTA was performed using 59 μL of $HONH_2$ (1.0 mmol, 50 equiv., 50% in H_2O) as a reagent. The progress of the reaction was monitored by ^{1}H NMR. For doping/enhancement experiment, the solution was treated with 3.0 mg (0.020 mmol, 1 equiv.) of 2-hydroxybenzothiazole after the reaction was fully completed. The resulting solution was again recorded by ^{1}H NMR, which showed that no new peaks appeared.

Detection of amine

A standard substitution reaction of BTA was performed, using 0.020 mmol of *N*-alkyl substituted BTA and 59 μL of $HONH_2$ (1.0 mmol, 50% in H_2O) as a reagent. The progress of the reaction was monitored using ^{1}H NMR. For doping/enhancement, 0.020 mmol (1 equiv.) of the corresponding amine was added after the reaction was completed. This final solution was recorded by ^{1}H NMR, showing that no new peaks were formed.

Detection of SO_2

The color reagent was prepared by dissolving 24.1 mg of new fuchsine in 1 mL of EtOH. To this dark pink solution were added 58 mL of H_2O and 2.75 mL of concentrated H_2SO_4. The mixture was briefly shaken before 250 μL of 37–41% formaldehyde was added. After the brown clear solution was formed, it was left for 10 minutes before it was used to color the samples.

A standard BTA substitution reaction was performed using $HONH_2$ as a reagent. The mixture was stirred for 24 hours,

followed by ^{1}H NMR and LC-MS analyses, showing that no starting material was left in the reaction mixture. A control experiment was started at the same time using 4.3 mg (0.020 mmol, 1 equiv.) of benzothiazole-2-sulfonamide in 1 mL of D_2O and 8 μL of NaOH (50% in H_2O). A sample (50 μL) was then added to the colour reagent (950 μL) and the mixture was recorded after a few minutes by UV-Vis spectroscopy at 587 nm.

^{18}O-labeling experiments

To a suspension of BTA (0.43 mg, 2.0 μmol, 1 equiv.) in 100 μL of $H_2{}^{18}O$ were added 5.9 μL of $HONH_2$ (50% in H_2O, 100 μmol, 50 equiv.) and NaOH (1 μL, 50% in H_2O). Similarly, to a suspension of BTA (0.43 mg, 2.0 μmol, 1 equiv.) in $H_2{}^{16}O$ (100 μL) were added $H^{18}ONH_2$·HCl (7 mg, 100 μmol, 50 equiv.) and NaOH (2 μL, 50% in H_2O). The incorporation of oxygen atom in the intermediate and in the product was monitored by LC-MS.

Detection of diimide

To a white suspension of 4.3 mg (0.020 mmol, 1 equiv.) of benzothiazole-2-sulfonamide in 1 mL of H_2O were added 4.64 mg (0.040 mmol, 2 equiv.) of fumaric acid, 59 μL of $HONH_2$ (50% in H_2O, 1.0 mmol, 50 equiv.), and 16 μL of NaOH (50% in H_2O) to adjust the pH to 9–10. After shaking, all starting materials were dissolved. The mixture was stirred for 24 hours at room temperature. A rotary evaporator was used to remove the solvent *in vacuo*, while the water bath was not heated above 40 °C. The obtained solid was redissolved in D_2O and the solution was analysed by ^{1}H NMR spectroscopy.

Acknowledgements

Radboud University Nijmegen is gratefully acknowledged for financial support.

Notes and references

1 E. Buncel, I. H. Um and F. Terrier, in *Patai's Chemistry of Functional Groups*, John Wiley & Sons Ltd, 2009.
2 A. J. Kirby, J. E. Davies, D. J. Fox, D. R. W. Hodgson, A. E. Goeta, M. F. Lima, J. P. Priebe, J. A. Santaballa and F. Nome, *Chem. Commun.*, 2010, **46**, 1302–1304.
3 Y. Xiang, H.-J. Gi, D. Niu, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, 1997, **62**, 7430–7434.
4 I. Pusterla and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 513–516.
5 A. J. Kirby, D. W. Tondo, M. Medeiros, B. S. Souza, J. P. Priebe, M. F. Lima and F. Nome, *J. Am. Chem. Soc.*, 2009, **131**, 2023–2028.
6 A. J. Kirby, J. E. Davies, T. A. S. Brandão, P. F. Silva da, W. R. Rocha and F. Nome, *J. Am. Chem. Soc.*, 2006, **128**, 12374–12375.
7 A. J. Kirby, B. S. Souza, M. Medeiros, J. P. Priebe, A. M. Manfredi and F. Nome, *Chem. Commun.*, 2008, 4428–4429.
8 R. A. Hess, A. C. Hengge and W. W. Cleland, *J. Am. Chem. Soc.*, 1997, **119**, 6980–6983.
9 W. P. Jencks, *Biochim. Biophys. Acta*, 1958, **27**, 417–418.
10 W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1960, **82**, 1778–1786.
11 P. W. Snyder, J. Mecinović, D. T. Moustakas, S. W. Thomas III, M. Harder, E. T. Mack, M. R. Lockett, A. Héroux, W. Sherman and G. M. Whitesides, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 17889–17894.
12 M. J. Smeulders, T. R. M. Barends, A. Pol, A. Scherer, M. H. Zandvoort, A. Udvarhelyi, A. F. Khadem, A. Menzel, J. Hermans, R. L. Shoeman, H. J. C. T. Wessels, L. P. van den Heuvel, L. Russ, I. Schlichting, M. S. M. Jetten and H. J. M. Op den Camp, *Nature*, 2011, **478**, 412–416.
13 S. W. Wright and K. N. Hallström, *J. Org. Chem.*, 2006, **71**, 1080–1084.
14 E. Vedejs, S. Lin, A. Klapars and J. Wang, *J. Am. Chem. Soc.*, 1996, **118**, 9796–9797.
15 G. M. Wuts, R. L. Gu and J. M. Northuis, *Tetrahedron Lett.*, 1998, **39**, 9155.
16 E. Vedejs and C. Kongkittingam, *J. Org. Chem.*, 2000, **65**, 2309–2318.
17 H. Lee, J. H. Jeon, J. C. Lim, H. Choi, Y. Yoon and S. K. Kim, *Org. Lett.*, 2007, **9**, 3291–3293.
18 A. Steigmann, *J. Soc. Chem. Ind.*, 1942, **61**, 18–19.
19 W. M. Grant, *Anal. Chem.*, 1947, **19**, 345–346.
20 R. Lascola, R. Withnall and L. Andrews, *Inorg. Chem.*, 1988, **27**, 642–648.
21 K. Maziarz and D. W. Ball, *J. Mol. Struct. (THEOCHEM)*, 2002, **577**, 213–218.
22 D. M. Stanbury, *Inorg. Chem.*, 1991, **30**, 1293–1296.