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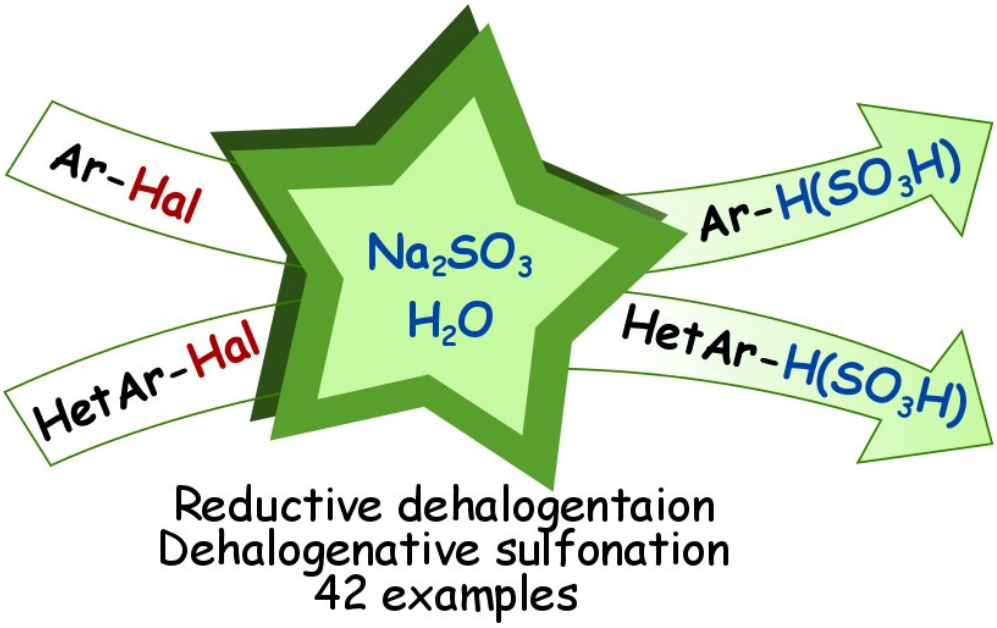

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Reductive dehalogenation and dehalogenative sulfonation of phenols and heteroaromatics with sodium sulfite in an aqueous medium

Monika Tomanová, Lukáš Jedinák and Petr Cankař *

Prototropic tautomerism was used as a tool for the reductive dehalogenation of (hetero)aryl bromides and iodides, or dehalogenative sulfonation of (hetero)aryl chlorides and fluorides, using sodium sulfite as the sole reagent in an aqueous medium. The protocol does not require a metal or phase transfer catalyst and avoids using organic solvent as the reaction medium. This method is especially suitable for substrates that readily tautomerize (such as 2- or 4-halogenated aminophenols, and 4-halogenated resorcinols), for which dehalogenation or sulfonation proceed under mild reaction conditions (≤60 °C). As sodium sulfite is an inexpensive, safe, and environmentally less hazardous reagent, this method has at least three potential applications: (i) In the deprotection of halogens as protecting groups, using sodium sulfite as a reducing agent; (ii) in the sulfonation of aromatic halides under mild reaction conditions avoiding hazardous and corrosive reagents/solvents; and (iii) in the transformation of toxic halogenated aromatics into less harmful compounds.

Introduction

Aromatic carbon–halogen bonds are common functionalities often utilized to increase the complexity of organic molecules, especially in combination with cross-coupling chemistry. The dehalogenation of aromatic halides is equally important and deserving of research attention.[1] This transformation allows halogens to be used as protecting groups at certain positions of an aromatic ring and persistent organic pollutants containing carbon–halogen bonds to be converted into less environmentally harmful compounds.[2,3] Established methods to remove halogens from aromatic rings rely on environmentally harmful transition metal catalysts,[4] radical tin chemistry,[5] or moisture-sensitive reductants.[6] Alternative methods have been developed to comply with the criteria of green chemistry, but still require special synthetic reagents or the use of organic solvents as a reaction medium.[7–10]

In palladium-catalysed cross-coupling chemistry, the undesired dehalogenation of NH-unprotected halogenated pyrazoles has been observed and attributed to base-mediated tautomerism.[11] This finding led to the question of whether halogen atoms can be removed from a broader range of (hetero)aromatic substrates based on a mechanism involving prototropic tautomerism. Some literature precedence exists for tautomerism-driven deiodination and, in a few cases, debromination of phenols, anilines, and imidazoles.[12] For instance, Engman mimicked the enzymatic reduction of *ortho*-iodophenols using sodium hydrogen telluride.[12a] In another inspiring report, Ramachandraiah reduced *para*-Br/I-phenol and α-Br/I-naphthol in a sulfite–bisulfate medium.[12b,13] Despite having only five literature examples, three of which afford only moderate yields, this method is among the greenest approaches to reducing carbon–halogen bonds in aromatic compounds. Owing to the limited number of truly green dehalogenations methods, we sought to develop a protocol that would enable the reduction of carbon–halogen bonds using environmentally less hazardous reagents in an aqueous medium.

Results and discussion

We initially screened the reduction of 4-bromophenol **1** to phenol **2** using various sulfur-based reducing agents (NaSEt, $Na_2S_2O_3$, Na_2S, and Na_2SO_3) alone or in a combination with additives (NaI, NaOAc, K_2CO_3, KOH, and $KHSO_4$). The results are summarized in Table 1. The experiments were conducted in a microwave reactor at 130 °C.[14] Sodium sulfite gave the best result among the tested reducing agents (entries 1–4), leading to quantitative conversion of 4-bromophenol **1** to phenol **2** without any detectable side products. The various additives, including $KHSO_4$, had negative (entries 5–7) or insignificant

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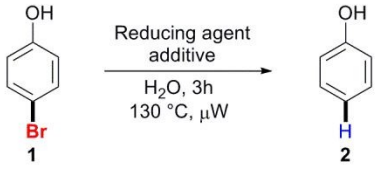
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the reaction conditions



1 2

Entry	Red. agent	Additive	**2** (%)[a]
1	NaSEt	none	7
2	$Na_2S_2O_3$	none	15
3	Na_2S	none	34
4	Na_2SO_3	none	>98
5	Na_2SO_3	K_2CO_3	77
6	Na_2SO_3	KOH	20
7	Na_2SO_3	$KHSO_4$	78
8	Na_2SO_3	KOAc	97
9	Na_2SO_3	NaI	94

Phenol **1** (0.5 mmol) was treated with a reducing angent (and additive) in water (2.5 mL) at 130 °C (μW irradiation, 150W) for 3h.[a] Yield determined by a quantitative HPLC.

effects (entry 8 and 9) on the reaction outcome. With optimized conditions in hand using sodium sulfite (entry 4), the scope and limitations were investigated using various halogenated aromatic (Table 2) and heteroaromatic compounds (Table 3). However, as the substrates showed different reactivity, the conditions were changed for each substrate individually (amount of sodium sulfite, reaction temperature, and reaction time). Generally, reactions requiring temperatures of ≥100 °C were performed under microwave irradiation, while conductive or no heating was applied for lower reaction temperatures.[15]

Halogenated aromatics **1** and **3–26** were subjected to the reaction with sodium sulfite in water, as shown in Table 2. 4-Bromophenol **1** was reduced at 130 °C, affording phenol **2** in 88% isolated yield (entry 1). 4-Iodophenol **3** was deiodinated at a slightly lower temperature (100 °C) to give phenol **2** in 91% yield (entry 2).[16] 2-Bromophenol **4** gave an identical yield to 4-bromophenol **1** using the same reaction temperature and time (entry 3). 2,4,6-Tribromophenol **5** required a slightly prolonged reaction time for the complete reduction of all three C–Br bonds (entry 4). Compound **6**, bearing one *ortho*-methyl substituent with respect to the bromine substituent, showed a similar reactivity to 4-bromophenol **1** (entry 5), while phenol **7**, bearing two *ortho*-methyl substituents with respect to the bromine substituent, showed increased reactivity, and was, therefore, reduced at a lower temperature (100 °C, entry 6). In contrast, two *ortho*-substituted methyl groups with respect to the phenolic hydroxyl group slightly decreased the reactivity, resulting in a longer reaction time (entry 7). The reduction of isopropyl analogue **9** to propofol **30** was completely inhibited (entry 8). The carboxyl group of phenol **10** had no effect on the reactivity (entry 9) and was presumably deprotonated under the reaction conditions, which would hinder the electron-withdrawing effect. Sodium sulfite was successfully applied to the debromination of toxic and widely used fire retardant tetrabromobisphenol A **11**[3f] with all four C–Br bonds reduced to C–H bonds, affording bisphenol **32** in 80% yield (entry 10).

Brominated thiophenol **12**, aniline **13**, and anilide **14** did not react (entries 11–13), presumably owing to a lower tendency to undergo prototropic tautomerization under the reaction conditions. Furthermore, no reaction was observed for *O*-methylated iodophenol **15** (entry 14).

The debromination of naphthol **16** was complicated by the formation of bis-, tris-, and tetra-naphthol impurities, with product **37** isolated in a lower yield (60%, entry 15). Both iodine atoms in the phenolic part of L-thyroxine **17** were reduced regioselectively, with iodides in the phenylether portion remaining untouched to afford compound **38** in 92% yield (entry 16).

Aminophenols **18** and **19** underwent facile debromination in high yields, even at 60 °C (entries 17 and 18). Remarkably, 4-bromoresorcinol **20** afforded resorcinol **40** in 96% yield at room temperature (entry 19). Unexpectedly, 4-chlororesorcinol **21** did not produce resorcinol **40**, but afforded a mixture of sulfonic acids **41** and **42**. The ratio of **41** and **42** was dependent on the reaction temperature, with sulfonic acid **41** preferred at 130 °C (entry 20, **41**/**42** = 89:11), while the ratio dropped to 59:41 at room temperature (entry 21). Sulfonic acid **41** was selectively obtained upon treatment of 4-fluororesorcinol **22** with Na_2SO_3 at room temperature after 14 days (entry 22). However, at 130 °C, isomeric sulfonic acid **42** was the major product (entry 23, **41**/**42** = 11:89). Two *meta*-oriented hydroxyl groups with respect to the bromine substituent (5-bromoresorcinol **23**, entry 24), or 1,4-OH substituted hydroquinone **24** (entry 25),[3e] led to the unexpected formation of sulfonic acids **42** and **43**, respectively. Finally, derivatives of natural polyphenols **25**[17] and **26**[18] were smoothly debrominated under mild conditions, yielding quercetin **44** (entry 26) and resveratrol **45** (entry 27), respectively.

Halogenated heteroaromatics **46–59** were subjected to the reaction with sodium sulfite in water, as shown in Table 3. Pyrazoles **46–49** were dehalogenated in yields exceeding 90% (entries 1–4). As expected, iodopyrazoles were more reactive than bromopyrazoles, requiring lower temperatures or shorter reaction times. No reaction was observed for *N*-methylated iodopyrazole **50** (entry 5). Both possible regioisomers of monobrominated imidazole **51** (C4–Br) and **52** (C2–Br) were reduced to imidazole **63** (entries 6 and 7). The reduction of imidazole C2–Br proceeded at a lower temperature compared with imidazole C4–Br. This difference in reactivity was utilized in the selective reduction of 2,4-dibromo-1*H*-imidazole **53**, which afforded 4-bromo-1*H*-imidazole **51** (entry 8). Brominated benzimidazole **54** gave the expected product of C–Br reduction (**64**) in 92% yield. Scaling up the experiment (~1 g of **54**), and applying either microwave or conductive heating

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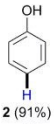
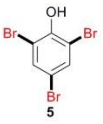
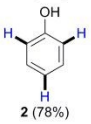
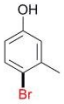
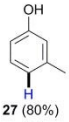
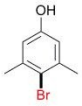
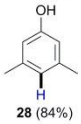
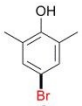
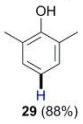
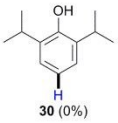
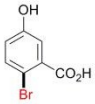
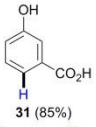
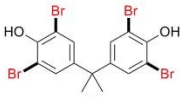
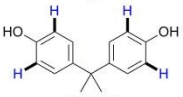
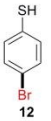
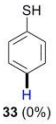
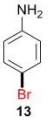
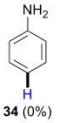
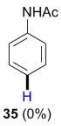
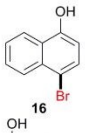
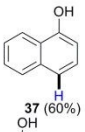
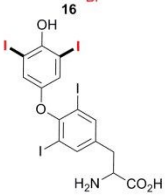
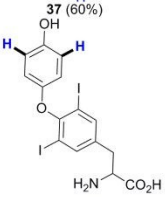
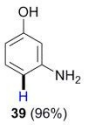
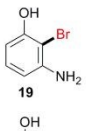
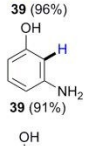
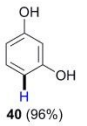
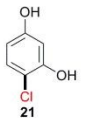
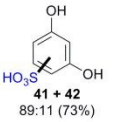
Table 2. Scope of halogenated aromatics

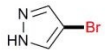
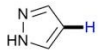
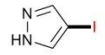
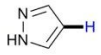
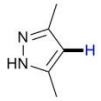
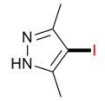
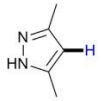
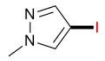
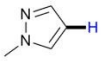
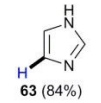
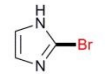
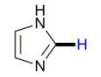
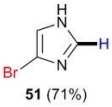
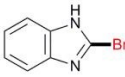
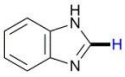
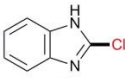
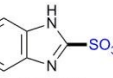
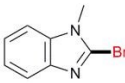
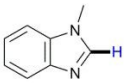
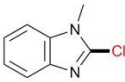
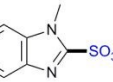
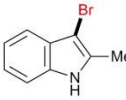
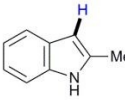
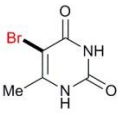
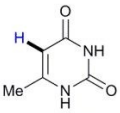
Ar-Hal $\xrightarrow{Na_2SO_3,\ H_2O,\ \mu W\ (150W)}$ Ar-H or Ar-SO_3H

Entry	Substrate	Na_2SO_3 (equiv.)	T (°C)	time (h)	Product (yield %)
1	 **1**	12	130	3	 **2** (88%)
2	 **3**	12	100	3	 **2** (91%)
3	 **4**	12	130	3	 **2** (88%)
4	 **5**	12	130	5	 **2** (78%)
5	 **6**	4	130	2	 **27** (80%)
6	 **7**	12	100	4	 **28** (84%)
7	 **8**	12	130	10	 **29** (88%)
8	 **9**	12	130	10	 **30** (0%)
9	 **10**	12	130	3	 **31** (85%)
10	 **11**	16	130	12	 **32** (80%)
11	 **12**	12	130	3	 **33** (0%)
12	 **13**	12	130	3	 **34** (0%)
13	 **14**	12	130	3	 **35** (0%)
14	 **15**	12	100	3	 **36** (0%)
15	 **16**	4	130	0.5	 **37** (60%)
16	 **17**	10	130	2	 **38** (92%)
17	 **18**	10	60[a]	18	 **39** (96%)
18	 **19**	10	60[a]	18	 **39** (91%)
19	 **20**	12	rt	18	 **40** (96%)
20	 **21**	4	130	1	 **41 + 42** 89:11 (73%)
21	**21**	12	rt	90d	**41 + 42** 59:41 (82%)
22	**22**	12	rt	14d	**41** (83%)
23	**22**	4	130	6	**41 + 42** 11:89 (91%)
24	**23**	12	130	6	**42** (66%)
25	**24**	4	130	0.5	**43** (77%)
26	**25**	10	60[a]	18	**44** (87%)
27	**26**	15	60[a]	6	**45** (90%)

[a] Conductive heating (oil bath).

Table 3 Scope of halogenated aromatics.

HetAr-Hal → (Na_2SO_3, H_2O, μW (150W)) → HetAr-H(SO_3H)

Entry	Substrate	Na_2SO_3 (equiv.)	T (°C)	t (h)	Product (yield %)
1	 **46**	8	130	5	 **60** (91%)
2	 **47**	4	130	1	 **60** (94%)
3	 **48**	4	130	1	 **61** (90%)
4	 **49**	4	100	4	 **61** (92%)
5	 **50**	4	130	1	 **62** (0%)
6	 **51**	8	130	5	 **63** (84%)
7	 **52**	4	100	1	 **63** (97%)
8	 **53**	4	100	1	 **51** (71%)
9	 **54**	4	100	3	 **64** (92%)[a]
10	 **55**	4	130	1	 **65** (94%)
11	 **56**	4	100	3	 **66** (68%)
12	 **57**	4	130	1	 **67** (61%)
13	 **58**	4	130	1	 **68** (92%)
14	 **59**	4	100	0.5	 **69** (80%)

[a] The reaction provided benzimidazole **64** (94%) at 5 mmol scale using either μW irradiation (fiber optic sensor) or oil bath.

afforded equivalent results (entry 9). Chlorinated benzimidazole **55** yielded sulfonic acid **65** instead of reduced benzimidazole **64** (entry 10). Unexpectedly, the reduction of *N*-methylated bromobenzimidazole **56** also proceeded successfully (entry 11). Furthermore, the sulfonation of chlorinated derivative **57** was successful (entry 12). Indole **58** was readily debrominated to compound **68** in 92% yield (entry 13). Finally, uracil derivative **59**, capable of lactam/lactim tautomerism, smoothly afforded debrominated product **69** (entry 14).

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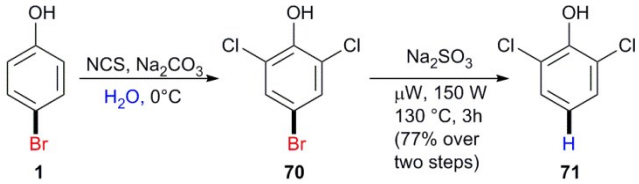
An example of a bromine substituent being used as a protecting group is shown in Scheme 1. The chlorination of 4-bromophenol **1** with *N*-chlorosuccinimide in water gave intermediate **70**, which was then reduced by Na_2SO_3. This one-pot two-step process afforded 2,6-dichlorophenol **71** in 77% yield.



Scheme 1. One-pot chlorination and debromination

Mechanistic study and proposal

In general, phenols and heterocycles bearing bromine or iodine underwent dehalogenation upon treatment with sodium sulfite (except **23** and **24**, Table 2). A mechanism explaining debromination and deiodination by Na_2SO_3 in water is shown in Scheme 2. The reaction of 4-bromoresorcinol **20** with Na_2SO_3 at 40 °C followed second-order kinetics, with both **20** and Na_2SO_3 appearing in the rate equation: $-(d[ArBr]/dt) = k_1[ArBr][Na_2SO_3]$, $k_1 = 5.65 \times 10^{-4}$ M^{-1} s^{-1}. This information, together with the observed kinetic isotopic effect ($k'_{H/D}$ = 5.09), indicated that prototropic tautomerism mediated by Na_2SO_3 was the rate-determining step. Therefore, Na_2SO_3 plays a dual role; first, mediating proton transfer from resorcinol **20** through anion **72** to give keto tautomer **73**, and second, abstracting bromine from tautomer **73** to produce resorcinol **40** (path A). The latter step was fast and irreversible, because highly reactive bromosulfonate **74** is rapidly hydrolysed to sodium bisulfate. Alternatively, thermodynamically more-stable diketo tautomer **75** is involved in the mechanism if its formation from monoketo tautomer **73** is faster than bromine abstraction from **73** (path B).

The stereoelectronic effects of substituents on the aromatic ring corresponded to the proposed tautomerism-driven mechanistic pathway. 3-Aminophenols **18** and **19** and 3-hydroxyphehols (resorcinols) **20**, **25**, and **26** underwent debromination at much lower temperatures than other substrates owing to the presence of a second amino or

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Scheme 2 Kinetic study and proposed mechanism.

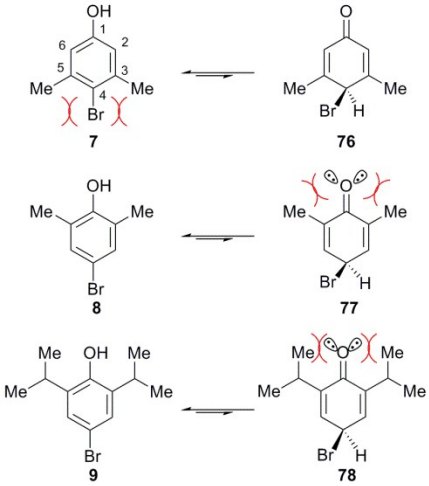
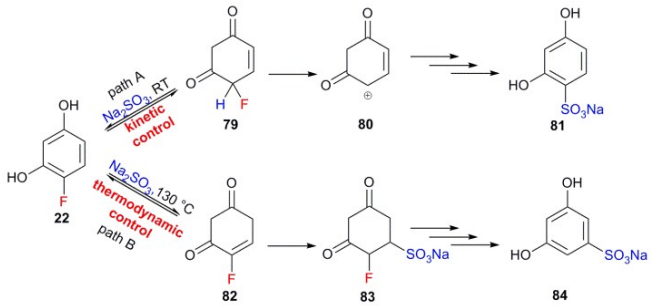


Figure 2 Steric effects on the dehalogenation.

hydroxyl functionality that effectively shifted the equilibrium toward the reactive keto tautomers. Steric hindrance around the C–Br bond of phenol **7**, caused by two *ortho*-methyl substituents, had a slightly positive effect on the reactivity, resulting in a lower reaction temperature compared with structurally related phenols. In contrast, steric hindrance around the phenolic hydroxyl groups in compounds **8** and **9** had the opposite effect (see Table 2, entries 6–8). This phenomenon can be attributed to the relative stability of the keto tautomers of compounds **7**–**9** (Figure 1). Steric hindrance around C4–Br is released when C4 adopts sp^3 hybridization, as shown in keto tautomer **76**. In contrast, keto tautomers **77** and **78** experienced increased steric hindrance around the C1–O bond compared with the corresponding enol forms **8** and **9**. This resulted in lower population of the keto tautomers and, as a consequence, the reactivity of phenols **8** and **9** being decreased or completely diminished.

Heterocycles capable of annular or lactam–lactim tautomerism underwent debromination or deiodination in a similar fashion to phenols. Unprotected NH or OH functionalities were critical for the reactivity of both heterocycles and phenols, as demonstrated by the unreactivity of *O*/*N*-methylated derivatives **15** and **50** (see entry 14 in Table 2 and entry 5 in Table 3). Therefore, the successful debromination of *N*-methylated benzimidazole **56** must have proceeded through a distinct mechanistic pathway, presumably via formation of a carbene intermediate (Table 3, entry 11). Accordingly, a carbene mechanism was also involved in the debromination of imidazoles **52** and **53** and benzimidazole **54** (see Table 3, entries 7–9).

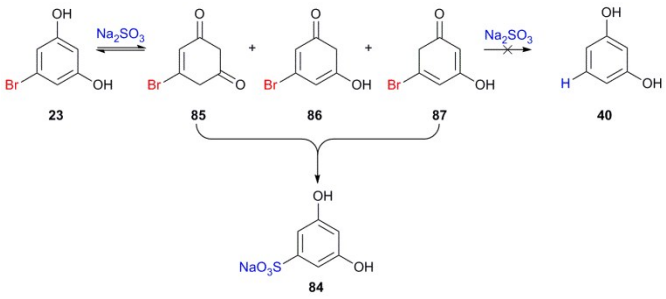
In contrast to (hetero)aryl bromides and iodides, chlorides and fluorides afforded sulfonic acids instead of dehalogenated products. The dehalogenative formation of sulfonic acids is rationalized in Scheme 3, as exemplified by 4-fluororesorcinol **22** (see Table 2, entries 22 and 23). At room temperature, sodium sulfite mediates the formation of kinetic 4H-tautomer **79**, which subsequently participates in a S_N1-like reaction (via cation **80**) with the sulfite anion, leading to sulfonate **81** (path A). At 130 °C, the reaction sequence most likely proceeds through thermodynamic 2H-tautomer **82** (path B). The 1,4-conjugate addition of sodium sulfite to thermodynamic 2H-tautomer **82** gives adduct **83**, which then affords sulfonate **84** after HF elimination. The dechlorinative sulfonation of 4-chlororesorcinol **21** (Table 2, entries 20 and 21) was assumed to occur via the 4H-tautomer, because the steric demand and lower electronegativity of the chlorine atom did not favour analogous tautomerism to the 2H-tautomer at a higher temperature (Scheme 3). Consequently, the rate of the S_N1-like reaction of **21** was accelerated at 130 °C to afford predominantly sulfonic acid **41**, while less-favourable sulfonic acid **42** (Table 2, entry 20) was likely to form via a competitive addition–elimination mechanism through a kinetic or thermodynamic tautomer. This competitive mechanism was comparable to the S_N1-like reaction at room temperature, but with only the kinetic tautomer involved (Table 2, entry 21). In contrast, the sulfonation of chlorinated benzimidazole **55** and its *N*-methyl analogue **57** occurred via S_NAr (Table 3, entries 10 and 12).



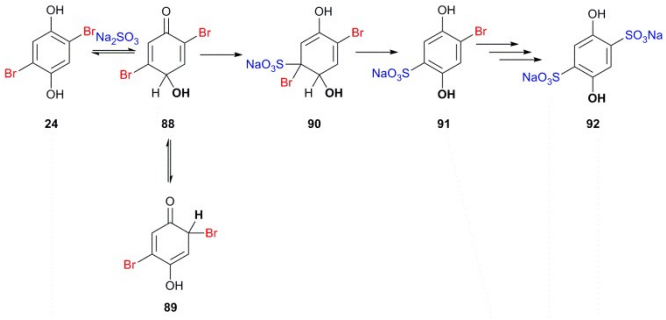
Scheme 3 Defluorinative sulfonation of 4-fluororesorcinol **22**.

There were two exceptions in which the addition–elimination mechanism accounted for the unexpected sulfonation of bromophenols (see Table 2, entries 24 and 25). First, none of the tautomers of 5-bromoresorcinol **23** (**85**–**87**) allowed bromine abstraction by Na_2SO_3 from the sp^3-hybridized carbon atom, which explained why the conjugated nucleophilic addition of sulfite was favoured over C–Br reduction to C–H (Scheme 4). Second, the reaction of sodium sulfite with hydroquinone **24** most likely proceeded through 4H-tautomer

88 rather than 2H-tautomer **89** (Scheme 5). As bromine abstraction from the sp^2-hybridized carbon atom of tautomer **88** was unfavourable, 1,4-addition led to adduct **90**. Attempts to isolate intermediate **91** failed, because it underwent a further addition–elimination sequence with the sulfite to yield disulfonate **92**.



Scheme 4 Debrominative sulfonation of 5-bromoresorcinol **23**.



Scheme 5 Debrominative sulfonation of hydroquinone **24**.

Conclusions

Sodium sulfite has been demonstrated as an inexpensive, safe, and environmentally less hazardous reagent for the reductive dehalogenation or dehalogenative sulfonation of (hetero)aryl halides in an aqueous medium. The reactivity of (hetero)arylhalides is directly proportional to their tendency to tautomerize. A kinetic study showed that sodium sulfite played a key role in the formation of a reactive tautomer (rate-determining step), which subsequently participated in distinct pathways to yield either dehalogenated or sulfonated products. The outcome of a reaction was influenced by the nature of the halogen atoms (Br and I afford dehalogenation, while F and Cl afford sulfonation) and the structure of the reactive tautomer. Sulfonation occurred regardless of the halogen atom if a reactive tautomer possessed a halogen atom bonded to an sp^2-hybridized carbon. Outside of tautomerism-driven dehalogenation/sulfonation, imidazoles and benzimidazoles bearing Br/Cl substituents at the C-2 position underwent debromination via formation of a carbene intermediate or dechlorinative sulfonation via S_NAr.

The potential of this method has been demonstrated in the synthesis of 2,6-dichlorophenol **71**, which was efficiently prepared from phenol **1** in a two-step procedure employing chlorination with *N*-chlorosuccinimide and debromination with sodium sulfite in an aqueous medium. This one-pot reaction demonstrated that bromine can be used as a temporary protecting group and sodium sulfite as a deprotecting agent. Furthermore, the method allowed the transformation of halogenated pollutants into less harmful compounds, as shown in the reductive debromination of toxic fire retardant tetrabromobisphenol A **11** and debrominative sulfonation of 2,5-dibromohydroquinone **24**, an unintended disinfectant byproduct displaying embryotoxic properties.

Despite reductive dehalogenation based on prototropic tautomerism having already been suggested for several biologically relevant phenols or imidazoles, this study demonstrated the more comprehensive reactivity of sodium sulfite with variously halogenated and structurally diverse (hetero)aromatics. Prototropic tautomerism was found to be essential for reactivity with sulfite (for most substrates) and was the rate-determining factor from a kinetics perspective.

Experimental

General protocol for the dehalogenation of (hetero)aromatics

A 10-mL reaction vessel equipped with a magnetic stir bar was charged with aryl halide (0.5 mmol), anhydrous sodium sulfite (amount specified for each compound), and demineralized water (2.5 mL). Under conventional heating, the mixture was stirred at ambient temperature or in a preheated oil bath in a closed vessel for a specified time. Under microwave irradiation, the vessel containing reaction mixture was sealed, premixed for 1 min with rapid stirring in a CEM Discover SP microwave synthesizer, and then irradiated at a maximum power of 150 W with simultaneous cooling using compressed air (24 psi). When the desired temperature was reached (ramping time, ~1 min), the power was automatically adjusted to maintain the set reaction temperature for a specified time. Finally, the vessel was cooled to approximately 40 °C with compressed air (cooling time, ~1 min). The workup procedures for individual compounds are described in the supporting information. Generally, hydrodehalogenated products were obtained in sufficient purity after liquid–liquid extraction, with no chromatographic purification required. Sulfonated products were obtained after acidification with hydrochloric acid.

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Conflicts of interest

There are no conflicts to declare.

Acknowledgements

M.T. and L.J. contributed equally. This work was supported by the Operational Programme Enterprise and Innovations for Competitiveness (grant CZ.01.1.02/0.0/0.0/15_019/0004431) and the internal Palacky University IGA grants (IGA_PrF_2018_29 and IGA_LF_2018_32).

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