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Water-Promoted Chlorination of 2-Mercaptobenzothiazoles

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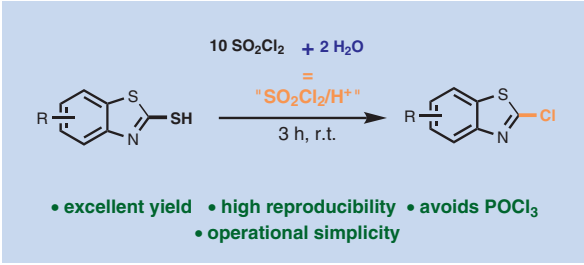

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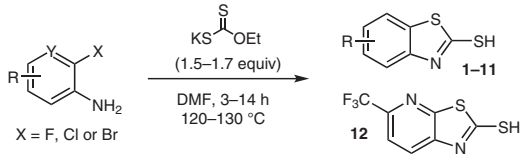
Abstract Substituted benzothiazoles play an important role in medicinal chemistry due to their pharmacological properties. Their 2-substituted derivatives are often prepared from 2-chlorobenzothiazoles, which in turn can be synthesized from the 2-mercapto precursor using sulfuryl chloride. In practice, this seemingly straightforward and widely used reaction can be impeded by poor reproducibility and low reaction yields. In this communication, we report that the simple addition of water to the reaction leads to remarkable improvements in reaction efficiency. We attribute this effect to the formation of acid through partial hydrolysis of sulfuryl chloride. This hypothesis is supported by the observation that improved yields were also obtained in the presence of some anhydrous acidic additives. The simple combination of sulfuryl chloride and water reproducibly provides excellent yields for a range of chlorinated products.

Key words benzothiazoles, sulfuryl chloride, chlorination, acid-catalyzed, water-promoted

Functionalized benzothiazoles are ubiquitous in drug discovery owing to their interesting biological and pharmacological properties.[1] We recently became interested in the preparation of 2-chlorobenzothiazoles as common and versatile intermediates *en route* to more complex benzothiazole derivatives. The preparation of chlorinated heterocycles through dehydration of their oxo-precursors using phosphoryl chloride is a useful and well-established method on lab scale.[2] However, due to the risk associated with the use of phosphoryl chloride in large-scale applications, we needed to identify a suitable replacement.[3] After a survey of methods in the literature, we decided to investigate a procedure[4] initially developed by researchers at Bayer: 2-haloanilines are converted into 2-mercaptobenzothiazoles, followed by chlorination in the presence of sulfuryl chloride.

Following this literature precedent,[4] we prepared a series of 2-mercaptobenzothiazoles in 73–90% yield through condensation of 2-haloanilines and potassium *O*-ethyl carbonodithioate (Scheme 1).

When we first carried out the subsequent chlorination reaction in the lab we made two observations: (1) The reaction usually did not proceed to completion, and full conversion could not be achieved by prolonging the reaction time, refluxing the reaction mixture or by the addition of co-solvents. (2) The reproducibility of the reaction outcomes was poor and results varied widely with the quality of the reagents. When anhydrous starting materials were used, the reaction was sluggish (~50% conversion, 3 h). But surprisingly, when we subjected a wet batch of thiol **4** to the reaction it was cleanly and efficiently converted into the corresponding chloride. This observation prompted us to further investigate the role of water in this reaction (Table 1).

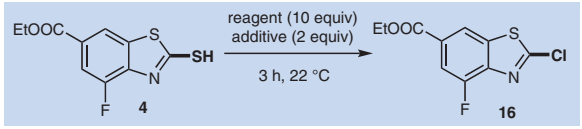


	Yield	R =		Yield	R =		Yield	R =
1	n/a[a]	H	**5**	82%	6-Me	**9**	80%	6-Br
2	81%	6-COOEt	**6**	n/a[a]	6-MeO	**10**	86%	7-F
3	82%	6-CN	**7**	74%	6-MeO	**11**	81%	6-F
4	90%	4-F-6-COOEt	**8**	87%	7-Cl	**12**	73%	

Scheme 1 Preparation of mercaptobenzothiazoles. [a] Compound obtained from a commercial source

Two equivalents[5] of water were either premixed with sulfuryl chloride for 10 minutes before addition of the substrate or water was added to the reaction mixture last. Interestingly, both procedures led to the same efficient con-

Table 1 Effects of Additives on the Conversion



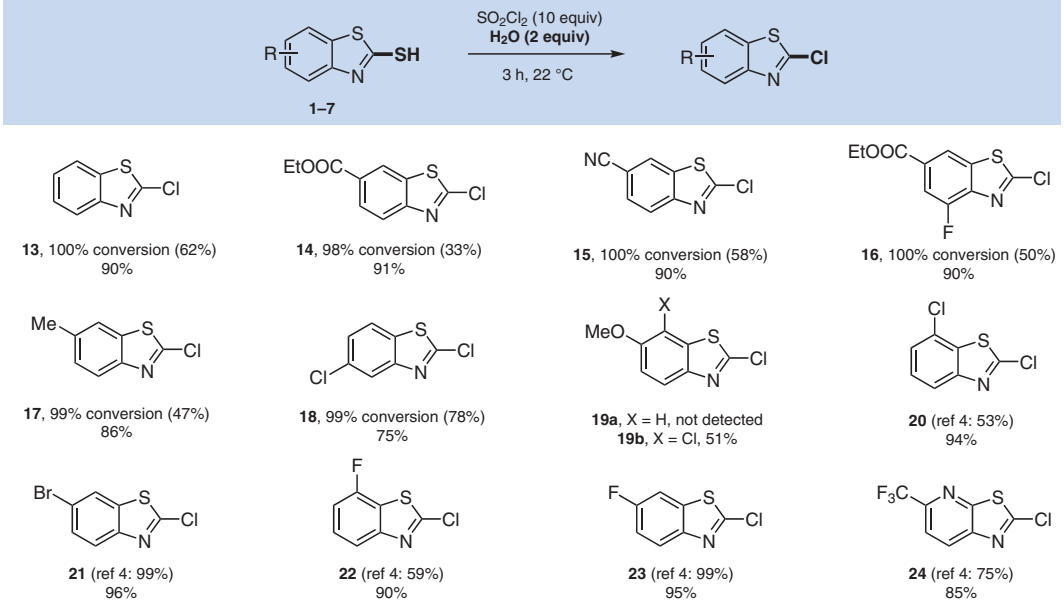
Entry	Reagent	Additive (2 equiv)	Yield[a]
1	SO_2Cl_2	–	50%[b]
2	SO_2Cl_2	H_2O (premixed)	90%
3	SO_2Cl_2	H_2O (added last)	90%
4	SO_2Cl_2	$ClSO_3H$	84%
5	SO_2Cl_2	$MeSO_3H$	79%
6	SO_2Cl_2	H_2SO_4	68%
7	SO_2Cl_2	AcOH	82%
8	$ClSO_3H$	–	n.c.[c]
9	$ClSO_3H$	H_2O (premixed)	n.c.[c]
10	SO_2Cl_2	HCl/EtOAc	46%[b]
11	SO_2Cl_2	$HCl{\cdot}NEt_3$	36%[b]
12	SO_2Cl_2	NBu_4Cl	45%[b]

[a] Yield of isolated product.
[b] Conversion by HPLC; typically, no starting material remained. The mass balance after quenching with MeOH is methylsulfinate.
[c] n.c. = no conversion.

version of starting material into product (Table 1, entries 2 and 3). We hypothesized that acid, generated through hydrolysis of sulfuryl chloride, might act as a promoter for the desired reaction. We went on to add a variety of concentrated acids to the reaction mixture, and indeed found considerably improved reaction yields compared to pure sulfuryl chloride (Table 1, entries 4–7). Interestingly, the reaction yield does not correlate with the acid strength: the very strong acids chlorosulfonic acid and methanesulfonic acid gave yields of 84% and 79%, respectively, but the much weaker acetic acid promoted the reaction with equal efficiency (82%). On the other hand, sulfuric acid gave a lower yield of 68%, accompanied by the formation of benzothiazole-2-sulfonic acid and the desulfurized benzothiazole as side products. HCl/EtOAc did not promote the reaction (see below).

The hydrolysis reaction of sulfuryl chloride with substoichiometric amounts of water is likely to produce chlorosulfonic acid as the major product. However, this compound was ruled out as the active chlorinating agent (Table 1, entries 8 and 9). We also wondered if the concentration of chloride ions in the reaction mixture had an influence on its success. Neither the addition of tetrabutylammonium chloride nor of dry HCl in ethyl acetate (Table 1, entries 10 and 12) promoted the reaction compared to pure sulfuryl chloride (50%, entry 1). The addition of triethylamine hydrochloride even led to a diminished yield of 36% (by HPLC) (Table 1, entry 11).

As shown in Scheme 2, addition of water to the reaction reliably improved the conversion into chlorobenzothiazoles **13**–**23** and 2-chlorothiazolopyridine **24**. The products were obtained in excellent yields (86–96%) for electron-deficient or moderately electron-rich substrates. In some cases, the improvement of reaction efficiency was quite remarkable: e.g., 86% vs 47% for **17**, and even 91% vs 33% in the case of **14**.

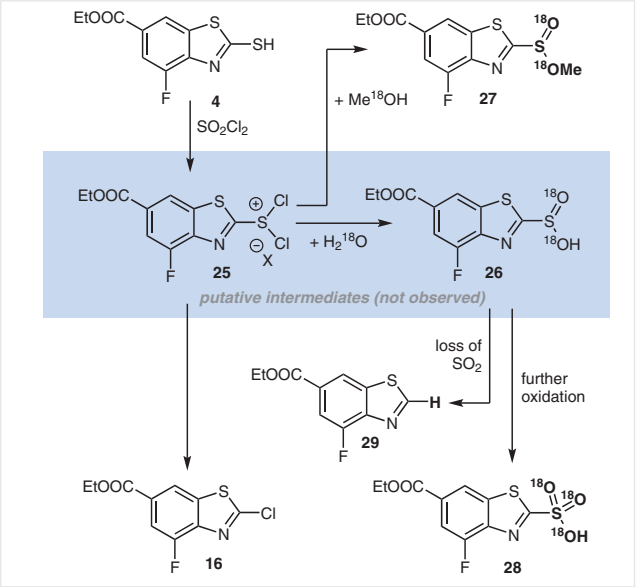


Scheme 2 Scope of the water-promoted chlorination. Values in brackets represent conversions (HPLC) in the absence of water

Compounds **19** (**a** and **b**) illustrate the limitation of this method: The electron-rich starting material **7** was fully consumed, but over-chlorination of the benzene core led to the formation of **19b**, while **19a** could not be detected. However, it must be mentioned that in the presence of water the reaction proceeded in a much cleaner fashion thus allowing the isolation of **19b**, while in the absence of water, only an intractable mixture of decomposition products was obtained.

Compared to the water-free chlorination reported in the literature,[4] our modified method delivers high yields with excellent consistency. Compounds **20**–**24** are a testament to the high reliability of the procedure: While near quantitative yields for compounds **21** (96% vs 99%[4]) and **23** (95% vs 99%[4]) could be reproduced, excellent results were also obtained for compounds **20** (94% vs 53%[4]) and **22** (90% vs 59%[4]), which performed poorly under water-free conditions.

We next set out to identify some of the intermediates and by-products of the reaction to gain an understanding of the underlying mechanism (Scheme 3). Quenching of the anhydrous reaction mixture with a large excess of methanol or ethanol yielded the corresponding methyl- or ethylsulfinate, along with the chlorinated product and traces of starting material.



Scheme 3 Observed and putative intermediates and by-products

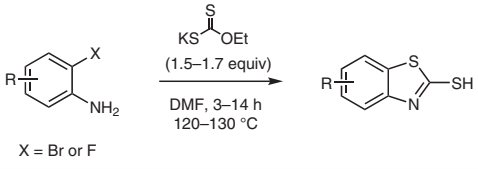
When we repeated this experiment using ^{18}O-methanol, the fully isotopically labelled sulfinate **27** was formed as the major product. When the reaction was quenched using $H_2{}^{18}O$, the fully labelled sulfonic acid **28** was detected by LC-MS. In some cases, e.g., when methanesulfonic acid was used as an additive (see the Supporting Information), significant amounts of desulfurized compound **29** were found.

We hypothesize that the thiol undergoes two oxidative chlorinations to give sulfur(IV) intermediate **25**. In the presence of methanol this compound hydrolyzes to form sulfinate **27** with the incorporation of two ^{18}O-atoms. If quenched with water, sulfinic acid **26** forms through hydrolysis, which in turn rapidly undergoes either further oxidation to **28** or loss[6] of SO_2 to form **29**.

In summary, we have discovered a very simple and convenient procedure for the synthesis of 2-chlorobenzothiazoles. While electron-rich substrates can undergo further chlorination of the aromatic core under the reaction conditions, excellent yields are obtained with electron-deficient to moderately electron-rich substrates. This method offers a reliable and high-yielding alternative to phosphoryl chloride that is safer and thus scalable.

2-Mercaptobenzothiazole (**1**) and 5-chloro-2-mercaptobenzothiazole (**6**) were purchased from commercial suppliers. All reactions were carried out under nitrogen. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer using tetramethylsilane (TMS) in DMSO-d_6 as the internal standard. ^{19}F NMR spectra were recorded on a Bruker Avance III 400 MHz. spectrometer. HRMS spectra were obtained using an LC-ESI-TOF-MS instrument. **Caution!** Special care must be taken when hydrolyzing sulfuryl chloride, especially on large scale. The hydrolysis reaction is vigorous, exothermic and releases large quantities of HCl.[7]

2-Mercaptobenzothiazole Starting Materials; General Procedure



A round-bottomed flask was charged with 2-bromoaniline or 2-fluoroaniline (>3 g, 1.0 equiv) and potassium *O*-ethyl carbonodithioate (1.5–1.7 equiv). The mixture was dissolved in DMF (10 volumes) and heated to 120–130 °C until the aniline was fully consumed (3–14 h). The reaction mixture was cooled to r.t. and filtered. The filtrate was diluted with H_2O (50 volumes) and the pH was adjusted to 1–2 using aqueous 2 M HCl. The solid precipitate was collected, washed with H_2O and dried to yield the pure product.

Ethyl 2-Mercaptobenzo[*d*]thiazole-6-carboxylate (2)

Yield: 1.5 g, 6.16 mmol (81%; from X = F); brown solid; mp 289 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.33 (t, *J* = 7.09 Hz, 3 H), 4.32 (q, *J* = 7.09 Hz, 2 H), 7.38 (d, *J* = 8.56 Hz, 1 H), 7.97 (dd, *J* = 8.50, 1.65 Hz, 1 H), 8.33 (d, *J* = 1.47 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 14.65, 61.41, 112.67, 123.71, 125.99, 128.89, 130.24, 145.17, 165.54, 192.36.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}NO_2S_2$: 240.0153; found: 240.0125.

2-Mercaptobenzo[*d*]thiazole-6-carbonitrile (3)

Yield: 5.8 g, 30.0 mmol (82%; from X = F); orange solid; mp 293 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.39 (d, J = 8.31 Hz, 1 H), 7.82 (dd, J = 8.44, 1.59 Hz, 1 H), 8.22 (d, J = 1.34 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 106.78, 113.46, 119.06, 126.49, 130.72, 131.71, 144.97, 192.17.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_5N_2S_2$: 192.9894; found: 192.9874.

Ethyl 4-Fluoro-2-mercaptobenzo[*d*]thiazole-6-carboxylate (4)

Yield: 5.76 g, 21.4 mmol (90%; from X = F); off-white solid; mp 266 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.33 (t, J = 7.15 Hz, 3 H), 4.32 (q, J = 7.09 Hz, 2 H), 7.74 (dd, J = 10.88, 1.34 Hz, 1 H), 8.17 (d, J = 1.34 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 14.58, 61.79, 114.31 (d, J = 9.5 Hz), 119.73, 126.82 (d, J = 3.0 Hz), 132.57 (d, J = 2.0 Hz), 133.99, 146.65 (d, J = 124.7 Hz), 164.72 (d, J = 1.5 Hz), 193.01.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –125.50.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_9FNO_2S_2$: 258.0053; found: 258.0053.

6-Methylbenzo[*d*]thiazole-2-thiol (5)

Yield: 2.50 g, 13.6 mmol (82%; from X = Br); pale brown solid; mp 279 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3 H), 7.14–7.29 (m, 2 H), 7.40–7.57 (m, 1 H), 7.49 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 21.18, 112.58, 122.03, 128.55, 129.91, 134.28, 139.63, 189.65.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_8NS_2$: 182.0098; found: 182.0080.

6-Methoxybenzo[*d*]thiazole-2-thiol (7)

Yield: 1.0 g, 4.97 mmol (74%; from X = Br); brown solid; mp 196 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.77 (s, 3 H), 6.99 (dd, J = 8.86, 2.51 Hz, 1 H), 7.22 (d, J = 8.93 Hz, 1 H), 7.35 (d, J = 2.45 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.16, 106.39, 113.54, 115.27, 131.15, 135.66, 157.09, 188.82.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_8NOS_2$: 198.0047; found: 198.0045.

7-Chlorobenzo[*d*]thiazole-2-thiol (8)

Yield: 6.7 g, 33.0 mmol (87%; from X = F); grey solid; mp 261 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.26 (dd, J = 7.58, 1.34 Hz, 1 H), 7.35–7.49 (m, 2 H), 14.04 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 111.78, 124.18, 125.21, 128.64, 129.41, 142.72, 189.54.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_5ClNS_2$: 201.9552; found: 201.9561.

6-Bromobenzo[*d*]thiazole-2-thiol (9)

Yield: 4.0 g, 16.0 mmol (80%; from X = Br); orange solid; mp 299 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.23 (d, J = 8.68 Hz, 1 H), 7.56 (dd, J = 8.56, 1.96 Hz, 1 H), 7.98 (d, J = 1.83 Hz, 1 H), 13.89 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 114.36, 116.83, 124.64, 130.45, 131.90, 141.03, 190.53.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_5BrNS_2$: 245.9047; found: 245.9041.

7-Fluorobenzo[*d*]thiazole-2-thiol (10)

Yield: 6.2 g, 33.2 mmol (86%; from X = F); brown solid; mp 206 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.11–7.26 (m, 2 H), 7.46 (td, J = 8.25, 5.62 Hz, 1 H), 14.07 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 109.00 (d, J = 3.4 Hz), 110.21 (d, J = 18.9 Hz), 115.70 (d, J = 23.1 Hz), 129.20 (d, J = 7.5 Hz), 143.56 (d, J = 6.6 Hz), 154.38 (d, J = 244.4 Hz), 289.38.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_5FNS_2$: 185.9847; found: 185.9865.

6-Fluorobenzo[*d*]thiazole-2-thiol (11)

Yield: 5.9 g, 31.9 mmol (81%; from X = F); red-brown solid; mp 255 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.20–7.35 (m, 1 H), 7.22–7.34 (m, 1 H), 7.66 (dd, J = 8.50, 2.14 Hz, 1 H), 13.81 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 108.87 (d, J = 27.5 Hz), 113.37 (d, J = 8.9 Hz), 114.71 (d, J = 24.8 Hz), 130.75 (d, J = 11.0 Hz), 137.96, 159.11 (d, J = 241.3 Hz), 189.93.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_5FNS_2$: 185.9847; found: 185.9856.

5-(Trifluoromethyl)thiazolo[5,4-*b*]pyridine-2-thiol (12)

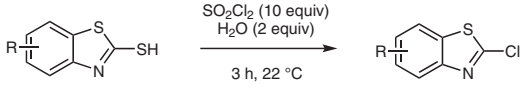
Yield: 3.5 g, 14.1 mmol (73%; from X = Cl); pale brown solid; mp 151 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.77 (d, J = 8.31 Hz, 1 H), 7.91 (d, J = 8.44 Hz, 1 H), 13.45–14.88 (m, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 120.07 (q, J = 3.0 Hz), 120.38, 122.03 (q, J = 273.73), 139.49, 142.15 (q, J = 34.7 Hz), 152.62, 190.58.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_4F_3N_2S_2$: 236.9768; found: 236.9749.

Chlorination Using Sulfuryl Chloride/Water; General Procedure



A mixture of the 2-mercaptobenzo[*d*]thiazole (>1 g, 1 equiv) and sulfuryl chloride (10 equiv) was stirred at 20–25 °C for 15 min. Next, H_2O (2 equiv) was added and the mixture was stirred at 20–25 °C for an additional 3 h. A sample was taken, quenched with MeCN/H_2O (2:1) and analyzed by HPLC. After completion of the reaction, the mixture was diluted with MeCN (5 volumes) and slowly quenched with H_2O (20 volumes). The product precipitated from the aqueous solution. The solid was collected and washed with H_2O. Drying under vacuum afforded the pure product. In the case of the liquid product 2-chlorobenzo[*d*]thiazole (**13**), the reaction mixture was extracted with EtOAc. The organic layer was then dried and concentrated to afford the product as an oil.

2-Chlorobenzo[*d*]thiazole (13)

Yield: 3.30 g, 19.5 mmol (90%); yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45–7.62 (m, 2 H), 7.96 (dd, J = 8.07, 0.73 Hz, 1 H), 8.09 (dd, J = 7.89, 0.92 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 122.81, 122.86, 126.49, 127.47, 136.19, 150.91, 153.23.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_7H_5ClNS: 169.9831; found: 169.9844.

Ethyl 2-Chlorobenzo[*d*]thiazole-6-carboxylate (14)

Yield: 0.65 g, 2.66 mmol (91%); off-white solid; mp 106 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.35 (t, *J* = 7.09 Hz, 3 H), 4.36 (q, *J* = 7.09 Hz, 2 H), 7.96–8.23 (m, 2 H), 8.80 (d, *J* = 0.86 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 14.64, 61.64, 122.91, 124.93, 127.65, 128.01, 136.56, 153.83, 157.43, 165.58.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9ClNO_2S$: 242.0043; found: 241.9975.

2-Chlorobenzo[*d*]thiazole-6-carbonitrile (15)

Yield: 0.40 g; 2.06 mmol (90%); off-white solid; mp 171 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (dd, *J* = 8.50, 1.65 Hz, 1 H), 8.14 (d, *J* = 8.44 Hz, 1 H), 8.70 (d, *J* = 1.47 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 108.80, 118.92, 123.87, 128.16, 130.74, 136.89, 153.39, 158.37.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_4ClN_2S$: 194.9784; found: 194.9768.

Ethyl 2-Chloro-4-fluorobenzo[*d*]thiazole-6-carboxylate (16)

Yield: 21.0 g, 80.9 mmol (90%); off-white solid; mp 185 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.35 (t, *J* = 7.09 Hz, 3 H), 4.37 (q, *J* = 7.09 Hz, 2 H), 7.84 (dd, *J* = 11.00, 1.47 Hz, 1 H), 8.64 (d, *J* = 1.22 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 14.56, 62.02, 113.30 (d, *J* = 10.1 Hz), 121.12 (d, *J* = 2.0 Hz), 128.81 (d, *J* = 3.0 Hz), 139.10 (d, *J* = 1.5 Hz), 142.38 (d, *J* = 7.0 Hz), 154.00 (d, *J* = 128.9 Hz), 158.37, 164.70 (d, *J* = 1.5 Hz).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –121.93.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8ClFNO_2S$: 259.9943; found: 259.9942.

2-Chloro-6-methylbenzo[*d*]thiazole (17)

Yield: 0.64 g, 3.30 mmol (86%); pale brown solid; mp 117 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.39–2.46 (m, 3 H), 7.36 (dd, *J* = 8.38, 1.16 Hz, 1 H), 7.79–7.92 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 21.04, 121.77, 121.94, 128.35, 135.76, 135.87, 148.47, 151.40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_8H_7ClNS: 183.9988; found: 183.9995.

2,5-Dichlorobenzo[*d*]thiazole (18)

Yield: 0.38 g, 2.48 mmol (75%); off-white solid; mp 72 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (dd, *J* = 8.68, 2.08 Hz, 1 H), 8.09 (d, *J* = 1.96 Hz, 1 H), 8.16 (d, *J* = 8.68 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 122.46, 124.46, 126.69, 132.29, 134.99, 151.65, 155.65.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_4Cl_2NS$: 203.9442; found: 203.9446.

2,7-Dichloro-6-methoxybenzo[*d*]thiazole (19b)

Monochlorination product **19a** was not detected. Instead, dichloride **19b** was obtained as the major product. The structure was confirmed by MS, ^{1}H NMR and ^{13}C NMR.

Yield: 0.30 g, 1.28 mmol (51%); brown solid; mp 92 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.97 (s, 3 H), 7.45 (d, *J* = 8.93 Hz, 1 H), 7.95 (d, *J* = 8.93 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.48, 112.38, 113.55, 122.53, 137.45, 144.79, 150.23, 153.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_6Cl_2NOS$: 233.9547; found: 233.9545.

2,7-Dichlorobenzo[*d*]thiazole (20)

Yield: 0.95 g, 4.64 mmol (94%); pale yellow solid; mp 58 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.53–7.72 (m, 2 H), 7.89–8.03 (m, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 121.92, 125.54, 126.33, 129.02, 135.75, 151.45, 153.36.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_4Cl_2NS$: 203.9442; found: 203.9438.

6-Bromo-2-chlorobenzo[*d*]thiazole (21)

Yield: 0.98 g, 3.91 mmol (96%); off-white solid; mp 108 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (dd, *J* = 8.68, 2.08 Hz, 1 H), 7.91 (d, *J* = 8.68 Hz, 1 H), 8.41 (d, *J* = 1.83 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 119.19, 124.46, 125.46, 130.68, 138.05, 149.93, 154.40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_4BrClNS$: 247.8936; found: 247.8928.

2-Chloro-7-fluorobenzo[*d*]thiazole (22)

Yield: 0.95 g, 4.86 mmol (90%); brown oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (td, *J* = 8.99, 0.61 Hz, 1 H), 7.62 (td, *J* = 8.22, 5.69 Hz, 1 H), 7.86 (d, *J* = 8.19 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 111.93 (d, *J* = 17.7 Hz), 118.96 (d, *J* = 3.6 Hz), 122.34 (d, *J* = 17.0 Hz), 128.53 (d, *J* = 7.9 Hz), 152.80 (d, *J* = 2.9 Hz), 153.25 (d, *J* = 2.3 Hz), 155.38 (d, *J* = 247.9 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_7H_4ClFNS: 187.9737; found: 187.9727.

2-Chloro-6-fluorobenzo[*d*]thiazole (23)

Yield: 0.96 g, 5.12 mmol (95%); pale yellow solid; mp 98 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45 (td, *J* = 9.08, 2.75 Hz, 1 H), 7.94–8.10 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 108.99 (d, *J* = 27.9 Hz), 115.52 (d, *J* = 24.9 Hz), 123.86 (d, *J* = 9.6 Hz), 136.93 (d, *J* = 12.2 Hz), 147.26, 152.55 (d, *J* = 3.0 Hz), 159.92 (d, *J* = 244.1 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_7H_4ClFNS:187.9737; found: 187.9747.

2-Chloro-5-(trifluoromethyl)thiazolo[5,4-*b*]pyridine (24)

Yield: 0.85 g, 3.56 mmol (85%); off-white solid; mp 102 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 8.56 Hz, 1 H), 8.68 (d, *J* = 8.44 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 119.75, 121.36 (q, J = 274.1 Hz), 131.99, 143.91 (q, J = 34.8 Hz), 146.46, 157.15, 157.96.

HRMS (ESI): mass ion not found.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591553.

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(3) Both SO_2Cl_2 and $POCl_3$ react with water in a violent, exothermic reaction with evolution of gas. However, the high density and limited miscibility of $POCl_3$ with water makes its use particularly hazardous: During the quench with water a delayed onset of the hydrolysis reaction can occur resulting in a dangerous accumulation and potential run-away of the reaction.

(4) Zhu, L.; Zhang, M.; Miao, D. *J. Heterocycl. Chem.* **2005**, *42*, 727.

(5) The addition of one, two or three equivalents of water led to the same reaction performance. After these initial experiments, we decided to use 2 equivalents of water as standard conditions.

(6) The rapid decomposition of heterocyclic sulfinic acids through loss of SO_2 under acidic conditions is well documented. See for example: Evans, R. M.; Jones, P. G.; Palmer, P. J.; Stephens, F. F. *J. Chem. Soc.* **1956**, 4106.

(7) When quenching excess reagent from a reaction containing 5 g of mercaptobenzothiazole in 25 g of sulfuryl chloride, 6 liters of gaseous by-products (mainly hydrogen chloride) were released.