Practical One Pot Synthesis of 2-Alkyl-substituted Benzothiazoles from Bis-(2-nitrophenyl)-disulfides.

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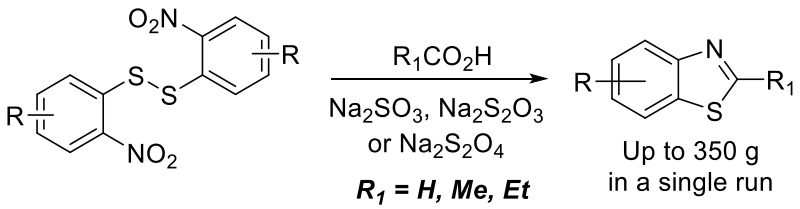
Abstract

2-Methyl benzothiazoles are widely used as key precursor for dyes, photosensitizers and fluorescent markers. Therefore, they are demanded in multigram and even kilogram amounts. Hereby, we propose a scalable single-step procedure for production of 2-alkylsubstituted benzothiazoles from corresponding bis-(2-nitrophenyl)-disulfides. Substrates containing various substituents including carboxylic and ester groups were introduced into reaction. Different sodium salts were tested as reducing agents, extensive optimization was performed. The products were obtained in the amounts of up to 350 g in a single run.



Introduction

The development of viable synthetic route, even for construction of relatively simple molecules, that meets requirements of scalability, repeatability and cost reduction pushes chemical creativity to discover new synthetic approaches, methodologies, and reaction conditions. Sometimes scope and limitations of the innovations found in such applied projects are not clear, and therefore further innovation implementation becomes limited. This tendency is observed when the efficient chemical route was developed not in academy but in industry or CRO: it happens due to the lack of time, motivation or intellectual property issues. Working many years in CRO we observed it rather frequently. The inspiration of this current paper was Idorsia publication in OPRD directed on optimization of the chemical route to sole compound, 2-methylbenzothiazole-6-carbonitrile as valuable building block for its drug discovery program [1]. After reading of the paper we decided to publish "our story" about another 2-methylbenzothiazole: 2-methyl-5-(methylthio)benzothiazole **1a**. In contrast to Idorsia the compound was important for us in terms of cyanine dyes design and synthesis like patented infrared sensitizing dye **2** (See Figure 1) [2]. In general, cyanine dyes containing benzothiazole system are known since 1887[3]. They are used[4] as photosensitizers for DSSC (dye-sensitized organic solar cells)[5] and photography[6], recording media[7], transfer dye sensors[8], fluorescent probes[9]. In all these cases a substituted 2-

methylbenzothiazoles are key intermediates, but some of them still hardly accessible. Thus abovementioned 2-methyl-5-(methylthio)benzothiazole **1a** still has limited accessibility in a large scale. Importance of the compound is indirectly proved by the paper published in 1997 year directed to the synthesis of this exact compound [10]. We tried to use this published approach on scale but unsuccessful. To the best of our knowledge, no later papers describing the synthesis of benzothiazole **1a** were published, therefore we decided to elaborate own protocol for it. Taking into account demand of the 2-alkylbenzothiazoles in multigram and even kilogram scale as building blocks for cyanine dyes synthesis and medicinal chemistry, we considered not only chemical, but also financial and ecological issues.

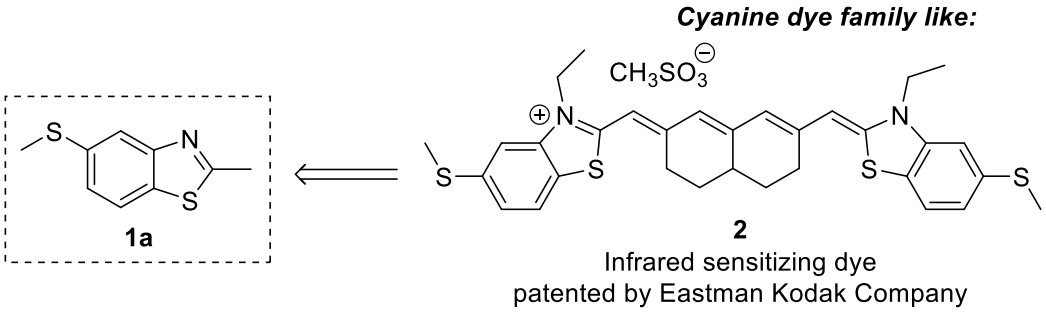
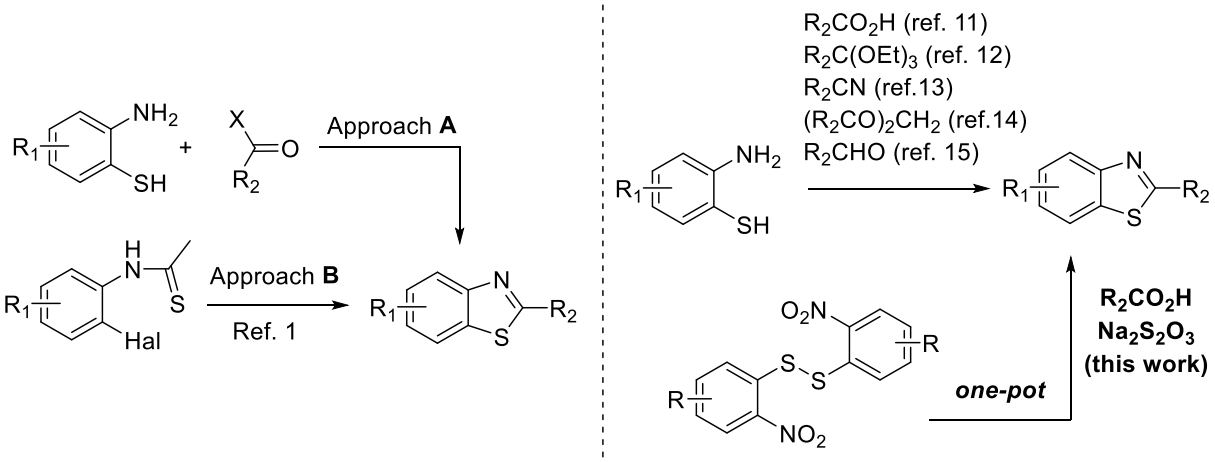


Figure 1. Initial compound of interes.

Generally there are two main approaches for synthesis of benzothiazole core: (**A**) starting from 2-aminothiophenol (also its precursor or synthetic equivalent can be used) and carboxylic acid[11] (or its synthetic equivalent like ortho ester[12], nitrile[13], β-diketone[14], aldehyde[15] etc.). The other approach (**B**) uses intramolecular cyclization of *ortho*-substituted N-arylthioamides (or their precursors/synthetic equivalents)[16]. The approach **B** usually needed TM-catalysis [1] therefore from ecological issues the approach **A** is more preferable but uses easily oxidizable 2-aminothiophenols. The main goal of this work is finding proper and reproducible conditions for the *in situ* generation of the corresponding 2-aminothiophenols form easy available commercial precursors for the further one-pot cyclization into target 2-alkylbenzothiazoles.



Scheme 1. Synthesis of 2-alkylsubstituted benzothiazoles.

Results and discussion

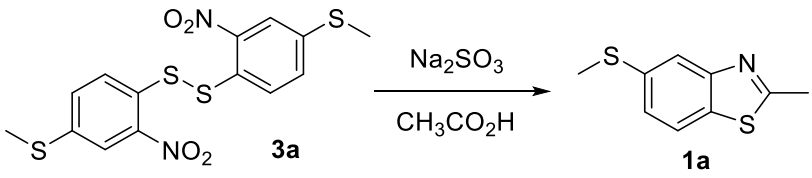
We started our investigation from optimization of target 2-methyl-5-(methylthio)-benzothiazole (**1a**) synthesis. As a starting compound the commercially available and shelf stable disulfide **3a**

was chosen. Our starting point was the known procedure [10] that prescribes to reduce disulfide **3a** with zinc powder in Ac_2O/AcOH system. However, as was mentioned above, the described method has the disadvantages of the reaction. Heterogeneous reaction mixture requires vigorous stirring, zinc powder should be carefully added portionwise to avoid too intensive evolution of hydrogen, large amount of contaminated zinc acetate forms as a by-product and another reasons made the effective scale up of the reaction is rather difficult even impossible. Therefore, we decided to find another proper reductant instead of zinc for the *in situ* generation of the corresponding intermediate 2-aminothiophenol in acetic acid for the further addition of the condensing reagents for the benzothiazole ring assembling.

During the search of the appropriate reductant for the nitro group [17] we draw our attention to sodium dithionite $Na_2S_2O_4$. This compound since 1993 is recognized as effective single electron transfer reductant for nitroarenes [18], was used in similar sequence *in situ* reduction – cyclization [19, 20] and able to reduce the disulfide bond [21]. The mixing of disulfide **3a** with 10-fold excess of $Na_2S_2O_4$ in boiling acetic acid unexpectedly (because no water scavengers or acid-activating agents were in the reaction mixture) leads to the formation of the desired compound **1a** in more than 80% yield with unexpected impurity - 5-(methylthio)benzothiazole with proton in 2d position instead methyl group. The explanation of the impurity comes from the knowledge that technical sodium dithionite contains an admixture of sodium formate[22]. Moreover, earlier was showed that $Na_2S_2O_4$ decomposed in acidic water under aerobic conditions with generation of SO_2 [19]. Therefore, we decided to switch the $Na_2S_2O_4$ reductant to SO_2 surrogate like Na_2SO_3. The nitro group reduction by sulfites were known since 1944[23], but was not so popular as $Na_2S_2O_4$ ones. However, in 2014 appears the report in which one pot nitro reduction – acylation was achieved by boiling of the nitroarene with Na_2SO_3 in acetic acid [24]. The reproducibility of this published protocol using disulfide **3a** as starting material also lead us to the desired product **1a** but without 5-(methylthio)benzothiazole impurity. Thinking of reaction performance in semi-industrial scale, we tried different reagent ratios. To avoid wasting, we determined the minimal amount of sodium sulfite and acetic acid that still leads to maximal yield. The reaction was monitored by GCMS.

First, using an enormous excess of acetic acid (**3a**/acetic acid molar ratio 1/30), we conducted the reaction with different amounts of sodium sulfite. A larger excess of Na_2SO_3 led to a better yield until the **3a**/sulfite molar ratio reached 1:8. Further addition of sodium sulfite have not made any improvement. Using the optimal substrate/sulfite ratio, we gradually reduced substrate/AcOH molar ratio to 1:17.5. Further reduction of the ratio led to worse yields (Table 1, isolated yields are given). The isolation procedure was design by avoiding resources consuming chromatography. The reaction mixture was diluted with water, extracted with $CHCl_3$. Organic phase was dried, evaporated and the crude product was purified by distillation under reduced pressure affording pure product in 89% yield. The reaction was successfully scaled up with optimal reagent ratio. Up to 350 g of **1a** was obtained in a single run.

Table 1. Optimization of reagent ratio for 2-methyl-5-(methylthio)-benzothiazole (1a) synthesis.

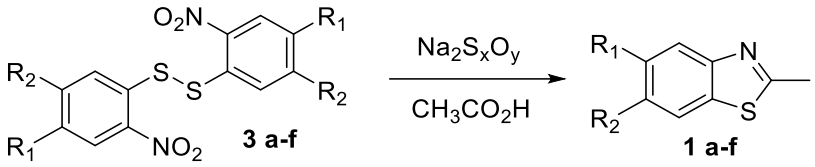


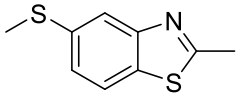
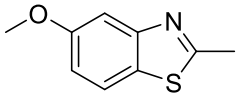
№	ν(**3a**): ν(Na_2SO_3): ν(AcOH)	Yield, %
1	1:5:30	34
2	1:6:30	57
3	1:7:30	79
4	**1:8:30**	**89**
5	1:9:30	89
6	1:10:30	89

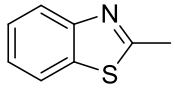
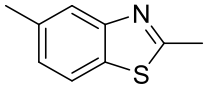
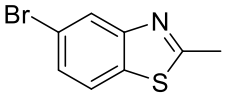
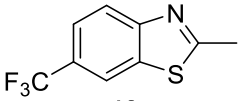
№	ν(**3a**): ν(Na_2SO_3): ν(AcOH)	Yield,%
7	1:8:22.5	89
8	1:8:20	89
9	**1:8:17.5**	**89**
10	1:8:15	83
11	1:8:12.5	70
12	1:8:10	57
13	1:8:5	23

Having the optimized procedure in hand, we tested in the reaction substrates **3 b-e** analogous to **3a** but bearing another groups instead SMe. Conversion was monitored by GCMS. However, products **1 b-d** were isolated in low yields (15-23%) and no product **1e** was formed. Therefore, we replaced Na_2SO_3 with sodium metabisulphite $Na_2S_2O_5$, sodium dithionite $Na_2S_2O_4$ and sodium thiosulphate pentahydrate $Na_2S_2O_3·5H_2O$ (in acidic media the salts disproportionate to give SO_2). No reaction was observed with sodium metabisulphite. In a case of technical $Na_2S_2O_4$ using the corresponding 2H-benzothiazoles, as in a seminal case, was observed as byproducts. The level of impurity was 2-5% (GCMS of the reaction mixture for synthesis of **1b** is given as an example in SI, pages S9-S10). The procedure works well only with pure, in house prepared sodium dithionite, but economically in house preparation of high pure $Na_2S_2O_4$ were unreasonable. By contrast, the reaction with technical sodium thiosulphate proceeded neatly, the products formed in 81-90% yield. The results are summarized on **Table 2**. It should be noted that in the protocol technical grade starting materials can be used, corresponding *o*-nitrothiophenol or any mixture of *o*-nitrothiophenol and disulfide can be introduced into reaction instead of pure disulfide. The isolation procedure was similar to the **1a** and purifications were made by distillation. Therefore, cost price of the synthesis is substantially lower. In addition, we obtained CF_3-substituted 2-methylbenzothiazole **1f** as a precursor for synthesis of various organofluorine conjugated systems. For instance, **1f** based rhodacyanine dye was tested for antileishmanial properties.[25]

Table 2. Bis-(2-nitrophenyl)-disulfides scope and sulfur-based reductant comparison.

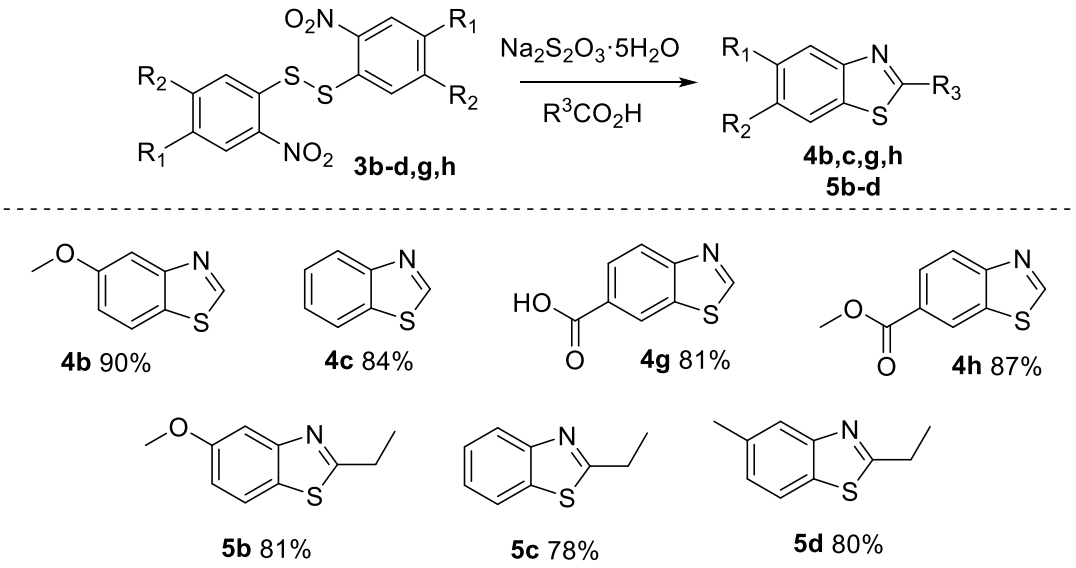


Entry	Product	Yields,[a] %			
		Na_2SO_3[b]	$Na_2S_2O_5$	$Na_2S_2O_4$[b]	$Na_2S_2O_3·5H_2O$[b]
1	 **1a**	89	–	86	87
2	 **1b**	17	–	89	90

3	 **1c**	15	–	82	81
4	 **1d**	23	–	88	89
5	 **1e**	–	–	87	86
6	 **1f**	n.d.	–	89	n.d

[a]Preparative yield was referred. [b] ν(**3**): ν(Na_2SO_3): ν(AcOH) = 1:8:17.5.

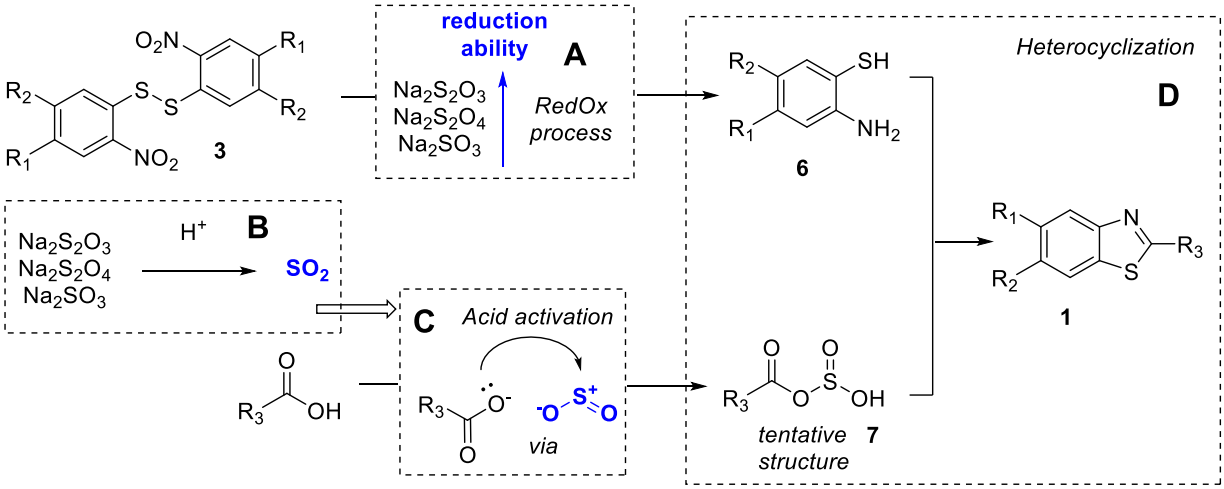
Finally, the scope of the reaction was expanded towards other aliphatic acids e.g. formic and propionic acids. Disulfides **3 b-d** were introduced to the reaction with formic and propionic acids to produce corresponding 2H-benzothiazoles **4 b,c** and 2-ethylbenzothiazoles **5 b-d**(Scheme 2). Additionally, we used aromatic acid **3g** and ester **3h** in order to illustrate primary functional group tolerance towards the reaction conditions. Benzothiazoles **4g** and **4h** were successfully obtained in a high preparative yields.



Scheme 2. Scope of the reaction.

The superposition of all the obtained experimental results allow us to preliminary proposed the mechanistic explanation of the reaction. Generally whole process could be divided into 4 parts (Scheme 3). **Part A:** reduction of bis-(2-nitrophenyl)-disulfides **3** into intermediate 2-aminothiophenols **6**. **Part B:** generation of SO_2 from reductant in acidic media. **Part C:** activation of acid by SO_2. **Part D:** heterocyclization of 2-aminothiophenols with activated acid derivative into final benzothiazoles derivative. The indirect prove of the **part A** is difference with effectivity of Na_2SO_3 in comparison with $Na_2S_2O_4$ and $Na_2S_2O_3$. The analysis of Volt-Equivalent Diagram (VED), sometimes known as Frost Diagrams (FDs) for sulphur species in acidic media clearly

showed that more "strong" reductant is more effective in the reaction [26]. The importance of **part B**, responsible for the in situ SO_2 generation in reaction mixture is proved by fact of inactivity of $Na_2S_2O_5$, which is could by SO_2 surrogate in water-free conditions. The next **part C** is responsible for the acid activation. The possibility of the acetic acid – sulphur dioxide 1 : 1 adduct formation was experimentally proved in 1944 [27] by the structure of the complex still remain tentative. In 2010 the theoretical investigation of the formic acid – sulphur dioxide system proposed the structure of covalent adducts as formic sulfurous anhydride (**7**, R_3 = H) [28]. These types of adducts are more electrophilic in comparison with free acid. Moreover, SO_2-promted activation of amide bond formation was showed earlier in close *in situ* nitro reduction – acylation using Na_2SO_3 – acetic acid system [26]. However, all these scheme is rather speculative and needed additional deep experimental investigation, which are out of the scope of this practical synthetic work.



Scheme 3. Possible reaction mechanism.

Conclusion

We proposed a simple, cheap, scalable and ecologically friendly method for synthesis of 2H-benzothiazoles and 2-alkylsubstituted benzothiazoles from corresponding bis-(2-nitrophenyl)-disulfides. A simple one-step procedure was developed and require cheap, stable and relatively non-toxic starting materials. Available technical grade starting materials were used, the products formed in high yields (78-90%) and were purified by distillation. Up to 350 g of a product was obtained in a single run. Substrates containing various substituents including carboxylic and ester groups were successfully modified.

Experimental

Materials and methods

Reagents and solvents were purchased from commercial suppliers (Sigma Aldrich, Apollo Scientific, Fisher, Acros Organic, Alfa Aesar) and used without further purification.

^{1}H and ^{13}C NMR sprectra were recorded on Varian Gemini 2000. Chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS). LCMS spectra were registered on an instrument Agilent 1100 LCMSD SL (electrospray ionization (ESI)). GCMS spectra were recorded on an

instrument Agilent GC7820A / MSD5977B (electron impact ionization (EI), ionization energy – 70 eV). Conversion was measures on the GCMS instrument (column: HP-5ms UI, 30 m×0.25 mm, 0,25 μm; carrier gas: helium 1 mL/min; temperature program: injector – 250°C, oven – 50°C for 1 min, then heating to 300°C with ramp rate 20°C/min, then 300°C for 5 min, MSD line – 280°C, MSD source – 230°C, MSD quadrupole – 150°C; injection parameters: coefficient of resolution 200:1, injection volume 0,5 μL; mass range – 35-550, ionization energy – 70 eV).

Synthetic procedures and compound characterization

2-Methyl-5-(methylthio)benzo[d]thiazole (1a)

1,2-bis(4-(methylthio)-2-nitrophenyl)disulfane (**3a**) (400.0 g, 0.9987 mol) was mixed with 1000 mL of acetic acid and the resulting suspension was heated to its boiling point. Sodium sulphite (969.3 g, 7.698 mol) was added portionwise for 3 hours under vigorous stirring. Then, the reaction mixture was boiled for 16 h under stirring. The reaction mixture was cooled to 90°C, 3000 mL of water was added. The reaction mixture was allowed to cool to room temperature and extracted with chloroform (2 × 3000 mL). The combined organic phases were washed with water (2 × 3000 mL). The solvent was removed under reduced pressure. The residue was mixed with diethyl ether (1500 mL) and silica gel (Kieselgel Merck 60, 200 g), the resulting mixture was stirred for 15 min, the silica gel was filtered off. The solvent was removed under reduced pressure. The residue was dried in vacuo (1.0 mm Hg) and distilled (1.0 mm Hg, fractions boiling at 108-115°C were collected) to afford the product **1a** (346.3 g, 89%) as a yellowish oil that solidifies under cooling. M. p. 41-45°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.28 (dd, J = 8.4, 1.9 Hz, 1H), 2.76 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.44, 154.19, 136.67, 132.24, 123.94, 122.59, 119.17, 20.24, 15.65. LCMS, positive mode, m/z: 196 $[M+H]^+$.

General procedure for synthesis of 2-methylbenzo[d]thiazoles 1b-f

5-Methoxy-2-methylbenzo[d]thiazole (1b). 1,2-bis(4-methoxy-2-nitrophenyl)disulfane (**3b**) (200.0 g, 0.5435 mol) was mixed with acetic acid (1500 mL), the resulting suspension was heated to its boiling point. Sodium dithionite (756.0 g, 4.348 mol) was added portionwise for 5 hours under vigorous stirring. Then, the reaction mixture was boiled for 16 h under stirring. The reaction mixture was cooled to 90°C, water (1000 mL) was added. The reaction mixture was allowed to cool to room temperature. Water (500 mL) was added and the reaction mixture was stirred until complete dissolution of sodium dithionite. The reaction mixture was extracted with chloroform (2 × 1500 mL), combined organic layers were washed with water (2 × 2000 mL). The solvent was removed under reduced pressure. The precipitate of sodium dithionite was filtered off. The

obtained substance was dried in vacuo (1.0 mm Hg) and distilled (1.0 mm Hg) to give the product **1b** (173.7 g, 0.9691 mol, 89 %) as a colourless liquid that solidifies under cooling. M. p. 38°C. Note: The procedure works well only with pure sodium dithionite. If sodium dithionite contains an admixture of sodium formate, the procedure with sodium thiosulphate can be used instead. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.01 (dd, J = 8.7, 2.5 Hz, 1H), 3.81 (s, 3H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.96, 158.37, 154.26, 126.76, 122.13, 114.04, 105.10, 55.41, 19.75. LCMS, positive mode, m/z: 180 $[M+H]^+$.

2-Methylbenzo[d]thiazole (1c). Colourless liquid, 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (dd, J = 8.0, 1.3 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.0, 1.3 Hz, 1H), 7.38 (m, 1H), 2.79 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.31, 153.42, 135.64, 126.40, 125.14, 122.37, 20.18. LCMS, positive mode, m/z: 150 $[M+H]^+$.

2,5-Dimethylbenzo[d]thiazole (1d). Yellowish solid, 88% yield. M. p. 36-40°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 7.19 (d, J = 8.1 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.30, 153.83, 135.95, 132.58, 126.57, 122.36, 121.86, 21.39, 20.19. LCMS, positive mode, m/z: 164 $[M+H]^+$.

5-Bromo-2-methylbenzo[d]thiazole (1e). Yellowish solid, 87% yield. M. p. 79°C. Ref.[29] 78-80°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.4, 1.9 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.89, 154.65, 134.89, 127.89, 124.82, 124.22, 119.23, 20.27. GCMS (m/z): 227, 229 $[M]^+$.

2-Methyl-6-(trifluoromethyl)benzo[d]thiazole (1f). White solid, 89% yield. M. p. 62°C. Ref.[30] 56-57°C. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.27 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 2.83 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.12 (s), 152.54 (s), 139.48, 126.94 (q, J = 32.1 Hz), 124.35 (q, J = 272.0 Hz), 123.41, 120.80 (q, J = 3.5 Hz), 118.66 (q, J = 4.2 Hz), 19.88. ^{19}F NMR (376 MHz, DMSO-d6) δ -60.53 (s). LCMS, positive mode, m/z: 218 $[M+H]^+$.

General procedure for synthesis of 2H-benzo[d]thiazoles 4b,c,g,h

Methyl benzo[d]thiazole-6-carboxylate (4h). Dimethyl 3,3'-disulfanediylbis(4-nitrobenzoate) (**3h**) (20.0 g, 47.2 mmol) was dissolved in formic acid (200 mL), the reaction mixture was heated to its boiling point. Sodium thiosulfate (93.6 g, 377.4 mmol) was added for 2 hours under vigorous stirring. The resulting suspension was boiled for 16 h under stirring. The reaction mixture was cooled to room temperature, excess of formic acid was removed under reduced pressure. The solid residue was mixed with water (200 mL) and extracted with chloroform (2 × 200 mL), the combined organic phase was washed with water (200 mL). Chloroform was removed under reduced pressure.

The residue was distilled (1.0 mm Hg) to afford the product **4h** (15.7 g, 87% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.84 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 3.91 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.34, 160.85, 156.32, 134.44, 127.18, 126.98, 125.11, 123.48, 52.82. LCMS, positive mode, m/z: 194 $[M+H]^+$.

5-Methoxybenzo[d]thiazole (4b). Colourless liquid, 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 7.11 (dd, J = 8.8, 2.3 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.52, 156.93, 154.45, 125.23, 122.64, 115.44, 105.51, 55.47. LCMS, positive mode, m/z: 166 $[M+H]^+$.

Benzo[d]thiazole (4c). Colourless liquid, 84% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.48, 153.46, 133.98, 126.60, 125.90, 123.47, 122.94. LCMS, positive mode, m/z: 136 $[M+H]^+$.

Benzo[d]thiazole-6-carboxylic acid (4g). White solid, 81% yield. M. p. 245-246°C. Ref.[31] 245-246°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (s, 1H), 9.58 (s, 1H), 8.81 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.08 (dd, J = 8.5, 1.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.01, 159.67, 155.49, 133.72, 128.42, 126.97, 124.47, 122.72. LCMS, positive mode, m/z: 180 $[M+H]^+$; negative mode, m/z: 178 $[M–H]^-$.

General procedure for synthesis of 2-ethylbenzo[d]thiazoles 5b-d

2-Ethylbenzo[d]thiazole (5c). 1,2-Bis(2-nitrophenyl)disulfane (**3c**) (30.0 g, 97.4 mmol) was added to propionic acid, the suspension was heated to its boiling point. Sodium thiosulfate (186.1 g, 750 mmol) was added portionwise for 2 hours under vigorous stirring. The suspension was boiled for 16 h under stirring. The reaction mixture was cooled to 90°C, water (200 mL) was added. The reaction mixture was allowed to cool to room temperature and extracted with chloroform (2 × 300 mL), the combined organic phase was washed with water (300 mL). The solvent was removed under reduced pressure. The residue was dried in vacuo (1.0 mm Hg) and distilled (1.0 mm Hg) to afford the product **5c** (24.8 g, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 3.12 (q, J = 7.5 Hz, 2H), 1.37 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 172.92, 152.78, 134.54, 125.93, 124.67, 122.05, 121.98, 26.93, 13.38. LCMS, positive mode, m/z: 164 $[M+H]^+$.

2-Ethyl-5-methoxybenzo[d]thiazole (5b). Yellowish oil, 81% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J = 8.7 Hz, 1H), 7.47 (s, 1H), 7.02 (d, J = 8.7 Hz, 1H), 3.82 (s, 3H), 3.08 (q,

J = 7.5 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.36, 158.32, 153.90, 126.21, 121.16, 114.12, 104.63, 55.06, 27.26, 13.23. LCMS, positive mode, m/z: 194 $[M+H]^+$.

2-ethyl-5-methylbenzo[d]thiazole (5d). Orange oil, 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.72 (s, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 3.08 (q, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.95, 153.20, 135.47, 131.48, 126.09, 122.04, 121.46, 26.95, 20.91, 13.40. LCMS, positive mode, m/z: 178 $[M+H]^+$.

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