# Improved access to thiazolo[5,4-*d*]thiazole and thieno[2,3-*d*]thiazole

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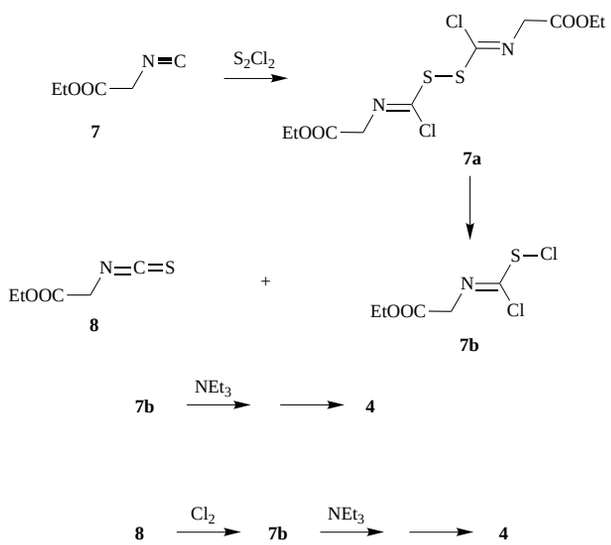
1 PERKIN

**Five-membered rings are of interest as building blocks for nonlinear optical (NLO) materials. We found easy access to the title compounds: thiazolo[5,4-*d*]thiazole 1 has been obtained in three simple steps starting with the chlorination of ethyl isothiocyanatoacetate 8, followed by dehydrohalogenation to the diethyl 2,5-dicarboxylate of 1, which yielded 1 after saponification and decarboxylation. Thieno[2,3-*d*]-thiazole 2 has been synthesized in two steps by reductive deamination of the easily available 2-aminothieno[2,3-*d*]thiazole 5.**

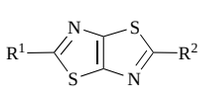
Typical NLO-phores which show high first hyperpolarizabilities, consist of an electron donor and acceptor group connected by a π-conjugated bridge. Thieno[3,2-*b*]thiophene has proved to be useful as an efficient π-electron-bridge.[1,2] It possesses a higher stability than oligoalkenes with a comparable amount of linearly conjugated double bonds, but a smaller aromatization energy and hence a higher polarizability than benzene. Compared to thiophene, the aromatization energy of thieno[3,2-*b*]thiophene is probably even smaller,[3] though possessing a more extended system of double bonds. The introduction of N-atoms in thiophene systems leads to thiazole systems, which show an enhanced hyperpolarizability when compared to benzene systems.[4] To study the influence of nitrogen atoms incorporated into thieno[3,2-*b*]thiophene, we intended to synthesize NLO-phores with thiazolo[5,4-*d*]thiazole **1** and thieno-[2,3-*d*]thiazole **2** as π-electron-bridges. Therefore, we needed a simple and inexpensive synthetic access to **1** and **2**. The overall yield of the described multi-step synthesis of **1** lies below 30%.[5] For **2** no yields have been given in the published multistep syntheses and the compound was not fully characterized on behalf of its high 'volatility'.[6,7]



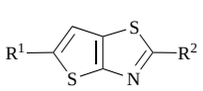

**Scheme 1**

## Results and discussion

We obtained **1** with a yield of 52% by reducing 2,5-dichlorothiazolo[5,4-*d*]thiazole **3** with zinc in acetic acid. However, the low yield of the multi-step reaction leading to **3**[8] makes this synthesis unsatisfactory. As we found, **1** could also be obtained in good yields (75%) by heating diethyl thiazolo[5,4-*d*]thiazole-2,5-dicarboxylate **4** with alkali in dry ethanol.




**1** $R^1 = R^2 = H$
**3** $R^1 = R^2 = Cl$
**4** $R^1 = R^2 = COOEt$




**2** $R^1 = R^2 = H$
**2a** $R^1 = Br$, $R^2 = H$
**2b** $R^1 = CHO$, $R^2 = H$
**2c** $R^1 = H$, $R^2 = Si(Me)_3$
**5** $R^1 = H$, $R^2 = NH_2$
**6a** $R^1 = H$, $R^2 = Br$
**6b** $R^1 = R^2 = Br$

Compound **4** (52%) has been synthesized[9] in a simple one-pot synthesis by treating ethyl isocyanoacetate **7** with dichlorodisulfane and triethylamine. The first step in the mechanism postulated by the authors is the formation of the intermediate **7a**, which decomposes to the key intermediate **7b** and ethyl isothiocyanatoacetate **8**. After reaction with triethylamine in further steps, compound **7b** leads to the diester **4** (Scheme 1).

With one equivalent of elemental chlorine, alkyl- or aryl-isothiocyanates give alkyl- or aryl-*S*-chlorocarbamoyl chlorides.[10] As we found, the *S*-chlorocarbamoyl chloride **7b** can be easily obtained by treating a solution of **8** with one equivalent of chlorine. It is possible but not necessary to isolate **7b**. Treatment of the solution of **7b** in dichloromethane with dry triethylamine furnished the diester **4** in 49% yield.

Following the method of Marcaccini *et al.*,[9] the maximum yield of **4** related to **7** amounts to 25%. The higher yield (49%, related to the commercially available **8**) and the ease of the synthesis are the advantages of our approach for the synthesis of the unsubstituted **1**.

Regarding the unsubstituted thieno[2,3-*d*]thiazole **2**, there are two multi-step syntheses described in the literature, but no yields are given and the product could not be distilled and fully characterized due to its high 'volatility' and instability under standard conditions.[6,7] We could obtain pure **2** by treating 2-aminothieno[2,3-*d*]thiazole **5**[6] with *tert*-butyl nitrite and copper(II) bromide and reducing the resulting mixture of 2-bromothieno[2,3-*d*]thiazole **6a** and 2,5-dibromothieno[2,3-*d*]-thiazole **6b** with zinc–acetic acid in an overall yield of 39%. Compound **2** is indeed a volatile oil but this did not prevent the purification by distillation and its complete characterization. Furthermore, it proved to be stable for several days even when stored under air at room temperature. Compound **2** showed the expected reactivity: electrophilic substitution, like bromination with *N*-bromosuccinimide or Vilsmeier formylation, proceeds at the 5-position of the thiophene-ring. Metallation with *n*-butyllithium takes place at the 2-position. This could be shown by

reaction of the lithium-salt of **2** with trimethylchlorosilane, which gave **2c**. The nonlinear optical properties of chromophores bearing the π-electron-bridges **1** and **2** will be published elsewhere.

## Experimental

Spectroscopic analyses were carried out at the Technische Universität Braunschweig, Braunschweig FRG. All the melting points were determined with a Kofler-Heiztisch microscope and are uncorrected. $^1$H and $^{13}$C experiments were performed on a Bruker AM 400 instrument with $Si(Me)_4$ as internal standard: chemical shifts in $\delta$ values are given in ppm, $J$ values are given in Hz. Mass spectra were registered on a Finnigan MAT 8430 (70 eV). Infrared spectra were recorded on a Nicolet FT-IR 320. Elemental analyses were performed on a Carlo Erba elemental analyser 1106. Solvents were dried using standard methods.

**Thiazolo[5,4-*d*]thiazole 1**

(*a*) A solution of 2,5-dichlorothiazolo[5,4-*d*]thiazole **3** (1.0 g, 4.7 mmol) and zinc powder (1.3 g, 20 mmol) in acetic acid (10 cm$^3$) was refluxed for 9 h. The reaction mixture was poured onto ice and neutralized with sodium hydrogen carbonate. After filtration, the precipitate was recrystallized from EtOH–$H_2O$ (50 : 50 v/v) and yielded **1** as colourless needles (350 mg, 52%), mp 150 °C (lit.,[5] mp 150–151 °C from aqueous EtOH); $\delta_H$(400 MHz, $CDCl_3$) 8.95 (2 H, s, H-2/5); $\delta_C$(100 MHz, $CDCl_3$) 150.8 (C-3a/6a), 155.3 (C-2/5); *m*/*z* 142 (M, 100%), 115 (22), 88 (60); (*b*) A solution of diethyl thiazolo[5,4-*d*]thiazole-2,5-dicarboxylate **4** (5.0 g, 17.5 mmol) and potassium hydroxide (2.0 g, 35.5 mmol) in dry ethanol (50 cm$^3$) was refluxed for 8 h under nitrogen. After cooling, the solvent was evaporated and the residue was recrystallized from EtOH–$H_2O$ (50 : 50 v/v). It yielded **1** as colourless needles (1.87 g, 75%), mp 150 °C (lit.,[5] mp 150–151 °C from aqueous EtOH).

**Diethyl thiazolo[5,4-*d*]thiazole-2,5-dicarboxylate 4**

A stirred solution (mechanical stirrer) of ethyl isothiocyanatoacetate **8** (14.5 g, 0.1 mol) in dry $CH_2Cl_2$ (100 cm$^3$) was cooled to 10 °C and chlorine gas (7.0 g, 0.1 mol, approx. 5.0 cm$^3$) was added slowly. After complete addition, the unreacted chlorine was removed by introduction of a stream of nitrogen. Dry triethylamine (20.2 g, 0.2 mol, 28 cm$^3$) was added dropwise below −50 °C. The mixture was stirred while raising the temperature slowly to 10 °C, and then filtered. Evaporation of the filtrate left a residue, which was stirred together with a little EtOH to give pure **4** as colourless needles (14.0 g, 49%), mp 140 °C (lit.,[9] 140–141 °C from EtOH); $\nu_{max}$(KBr)/cm$^{-1}$ 1737, 1447 and 1000 (lit.,[9] 1735, 1450 and 1005); *m*/*z* 286 (M, 70%), 241 (24), 214 (100) [lit.,[9] 286 (64), 241 (18), 214 (100)].

**Procedure for the Sandmeyer-analogous reaction of 2-aminothieno[2,3-*d*]thiazole 5**

A solution of **5** (7.9 g, 50 mmol) in dry acetonitrile (200 cm$^3$) was treated dropwise under nitrogen with a solution of copper(II) bromide (7.0 g, 31 mmol) and *tert*-butyl nitrite (7.9 g, 75 mmol) in dry acetonitrile (100 cm$^3$) at 65 °C. Ten minutes after the gas evolution has ceased, the reaction mixture was cooled down to room temperature, diluted with hydrochloric acid (6 M, 200 cm$^3$) and extracted with diethyl ether (3 × 100 cm$^3$). The combined organic layers were washed with hydrochloric acid (6 M, 200 cm$^3$), dried over sodium sulfate and evaporated. The residue was placed on a silica gel column and eluted with a mixture of cyclohexane–$CH_2Cl_2$ (50 : 50 v/v). Two main fractions were collected, which gave the bromo derivatives **6a** and **6b** after evaporation of the solvent and sublimation.

**2-Bromothieno[2,3-*d*]thiazole 6a.** This compound was obtained as colourless microcrystals (2.85 g, 25%), mp 44 °C (sublimation) (Found: C, 27.28; H, 0.86; N, 6.26. Calc. for $C_5H_2BrNS_2$: C, 27.29; H, 0.92; N, 6.36%); $\delta_H$(400 MHz, $CDCl_3$) 7.17 (1 H, d, $J_{6,5}$ 5.6, H-6), 7.45 (1 H, d, $J_{5,6}$ 5.6, H-5); *m*/*z* 221, 219 (M, 100/98%), 140 (60).

**2,5-Dibromothieno[2,3-*d*]thiazole 6b.** This compound was obtained as colourless microcrystals (3.75 g, 24%), mp 110 °C (sublimation) (Found: C, 20.20; H, 0.43; N, 4.55; S, 21.29. Calc. for $C_5HBr_2NS_2$: C, 20.09; H, 0.34; N, 4.68; S, 21.44%); $\delta_H$(400 MHz, $CDCl_3$) 7.14 (1 H, s, H-6); *m*/*z* 301, 299, 297 (M, 44, 100, 40%), 220, 218 (22/20).

**Thieno[2,3-*d*]thiazole 2.** A mixture of **6a** (2.85 g, 13 mmol), **6b** (3.75 g, 12.3 mmol) and zinc powder (3.3 g, 50 mmol) in acetic acid (30 cm$^3$) was refluxed for 8 h. After cooling, the reaction mixture was poured on ice and neutralized by addition of sodium hydrogen carbonate. The resulting aqueous suspension was extracted with diethyl ether (3 × 100 cm$^3$). The combined organic layers were dried (sodium sulfate) and evaporated. Distillation of the residue yielded pure **2** as a pale yellow oil (2.8 g, 79%), bp 80 °C (2 mm) (Found: C, 42.77; H, 2.56; N, 10.05; S, 45.71. Calc. for $C_5H_3NS_2$: C, 42.53; H, 2.14; N, 9.92; S, 45.41%); $\delta_H$(400 MHz, $CDCl_3$) 7.18 (1 H, d, $J_{6,5}$ 5.8, H-6), 7.37 (1 H, dd, $J_{5,6}$ 5.8, $J_{5,2}$ 1.3 H-5), 8.77 (1 H, d, $J_{2,5}$ 1.3, H-2); $\delta_C$(100 MHz, $CDCl_3$) 117.3 (C-6), 127.3 (C-5), 131.7 (C-6a), 154.7 (C-2), 157.7 (C-3a); *m*/*z* 141 (M, 100%).

**5-Bromothieno[2,3-*d*]thiazole 2a**

A concentrated solution of *N*-bromosuccinimide (700 mg, 4 mmol) in *N*,*N*-dimethylformamide was added in the dark to a stirred solution of **2** (500 mg, 3.5 mmol) in *N*,*N*-dimethylformamide (10 cm$^3$). After further stirring for 24 h, the reaction mixture was poured into water. Extraction with diethyl ether (3 × 50 cm$^3$), drying over sodium sulfate and evaporation of the solvent gave a residue, which was purified using a silica gel column. Elution of the column with $CH_2Cl_2$ gave **2a** as a yellow oil (600 mg, 77%) (Found: C, 27.39; H, 0.99; N, 6.38; S, 29.22. Calc. for $C_5HBrNS_2$: C, 27.29; H, 0.92; N, 6.36; S, 29.13%); $\delta_H$(400 MHz, $CDCl_3$) 7.30 (1 H, s, H-6), 8.85 (1 H, s, H-2); *m*/*z* 221, 219 (M, 100, 94%), 140 (44).

**Thieno[2,3-*d*]thiazole-2-carbaldehyde 2b**

A mixture of **2** (560 mg, 4 mmol), phosphorus oxychloride (920 mg, 0.56 cm$^3$) and *N*-phenyl-*N*-methylformamide (727 mg, 6 mmol, 0.71 cm$^3$) was first stirred at 0 °C for 15 min, then stirred for 2 h at 60 °C and finally stirred at room temperature overnight. The solution was then poured on ice and extracted with diethyl ether (3 × 50 cm$^3$). The ether layer was dried (sodium sulfate) and evaporated to yield a residue, which was recrystallized from EtOH to give **2b** as yellow needles (250 mg, 37%), mp 143 °C (from EtOH) (Found: C, 42.62; H, 1.70; N, 8.23; S, 37.71. Calc. for $C_6H_3NOS_2$: C, 42.59; H, 1.79; N, 8.28; S, 37.90%); $\delta_H$(400 MHz, $CDCl_3$) 7.99 (1 H, s, H-6), 9.10 (1 H, s, H-2), 10.00 (1 H, s, CHO); *m*/*z* 169 (M, 100%).

**(2-Trimethylsilyl)thieno[2,3-*d*]thiazole 2c**

To dry tetrahydrofuran (50 cm$^3$), a solution of *n*-butyllithium in hexane (9.9 cm$^3$, 1.6 M) was added at 0 °C under nitrogen. The mixture was cooled to −100 °C and treated dropwise with a concentrated solution of **2** (2.25 g, 15.9 mmol) in dry tetrahydrofuran. The temperature was allowed to rise to −80 °C. Freshly distilled trimethylchlorosilane (1.7 g, 15.7 mmol, 2 cm$^2$) was then added dropwise to the reaction mixture over a period of 10 min. After complete addition, the mixture was stirred for 20 min at −80 °C and then allowed to warm to room temperature. The solution was then hydrolyzed by addition of water (32 cm$^3$) and extracted with diethyl ether (3 × 50 cm$^3$). The organic layers were separated, dried (sodium sulfate) and evaporated. The residue was placed on a silica gel column and eluted with $CH_2Cl_2$ yielding **2c** (2.2 g, 65%) as an oil; $\delta_H$(400 MHz, $CDCl_3$) 0.45 (9 H, s, $CH_3$), 7.23 (1 H, d, $J_{6,5}$ 5.7, H-6), 7.42 (1 H, d, $J_{5,6}$ 5.7, H-5); $\delta_C$(100 MHz, $CDCl_3$) −1.1 ($CH_3$), 117.0 (C-6), 127.2 (C-6a), 127.5 (C-5), 134.8 (C-2), 178.3 (C-3a); *m*/*z* 213

(M, 66%), 198 (100) (HRMS: found: 213.0103, Calc. for $C_8H_{11}NS_2Si$: 213.0102).

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