The First Synthesis of 2,2′:5′,2″-Terthiazole

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Abstract: 2,2′:5′,2″-Terthiazole, a previously unknown terthiazole isomer, was prepared by copper-mediated oxidative coupling of 2-lithiothiazole. The yield was improved in the presence of equimolar 2,2′-bithiazole. The 5,5″-positions were cleanly lithiated by lithium diisopropylamide, which demonstrates its potential in the extension of π-systems.

Key words: thiazole, copper, coupling, lithiation, oligomer

Molecules containing two or more thiazole (1,3-thiazole) rings play important roles in both biochemistry[2] and material science.[3] Although there are 28 potential isomers of the parent terthiazoles, only three isomers have been prepared to date: 4,2′:5′,4″-terthiazole (**1**), 4,2′:4′,5″-terthiazole (**2**), and 5,2′:5′,5″-terthiazole (**3**).[4] These three compounds (Figure 1) were synthesized by Stille coupling of trimethylstannylthiazoles and dibromothiazoles. Surprisingly, 2,2′:5′,2″-terthiazole (**4**), which is considered to be one of the most conventional structures among the terthiazoles, is still an unknown compound. According to the literature, an attempt to synthesize **4** via Stille coupling of 2,5-dibromothiazole with 2-tributylstannylthiazole failed.[5] Recently, synthesis of halogenated bithiazole derivatives by Suzuki–Miyaura coupling has been reported.[6] Synthesis of **4** by this method, however, is highly impractical because of the lack of availability of the required 2-thiazoleboronic acid.[5,6] In the course of our studies concerning thiazole extended π-systems,[7] we discovered a simple synthesis of **4** by copper-mediated oxidative coupling of lithiothiazoles. We here report the first synthesis of **4**.

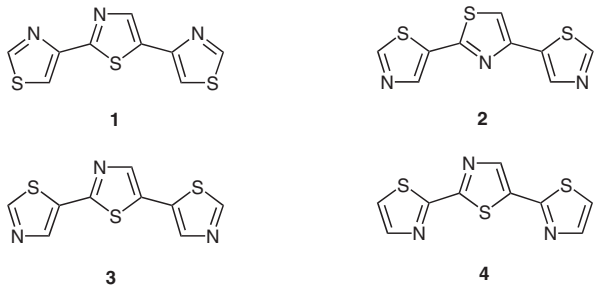

Figure 1 Known terthiazoles **1**–**3** and 2,2′:5′,2″-terthiazole (**4**)

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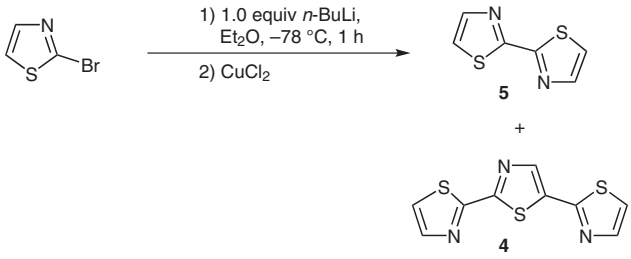
There have been a number of reports on the synthesis of 2,2′-bithiazole via coupling reactions of thiazole derivatives, for example, Ullman coupling,[8] nickel- or palladium-mediated homocoupling of 2-bromothiazole,[9] and Stille coupling of 2-stannylthiazole and 2-bromothiazole.[4] Although copper-mediated oxidative coupling of thienyllithiums has often been used for the synthesis of bithiophene derivatives,[10] there have been no reports on the use of this method for the synthesis of the parent 2,2′-bithiazole.[11] We therefore examined the coupling reaction of 2-lithiothiazole with $CuCl_2$ (Scheme 1).



Scheme 1

Table 1 Synthesis of 2,2′-Bithiazole (**5**) and Terthiazole **4** via $CuCl_2$-Mediated Oxidative Coupling[a]

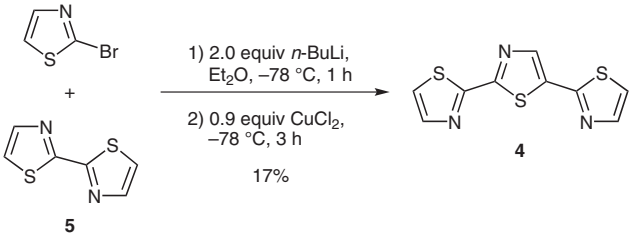
Entry	$CuCl_2$ (equiv)	Temp (°C)[b]	Time (h)[b]	Yield (%)[c]	
				5	**4**
1	1.1	25	15	3	0
2	1.1	0	6	5	0
3	1.1	–78	6	39	3
4	2.0	–78	3	46	2
5	1.0	–78	3	42	3
6	0.9	–78	3	52	4
7	0.9[d]	–78	3	46	5

[a] Reaction details are described in the experimental section.
[b] After addition of $CuCl_2$.
[c] Isolated yield.
[d] $CuCl_2$ was added in two portions with 1 h interval.

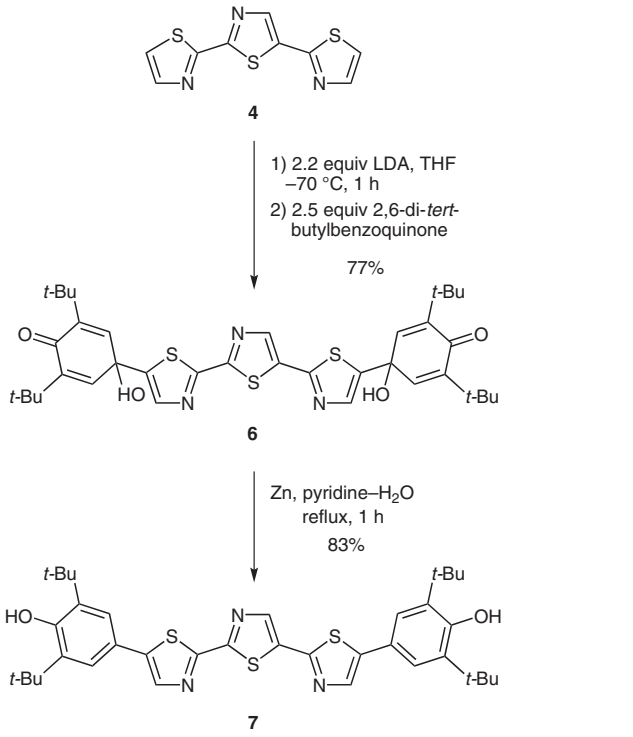
The results are summarized in Table 1. It was found that the reaction temperature after addition of $CuCl_2$ was a key factor in obtaining coupling products. When the reaction was carried out at 0 °C or room temperature, similar to the synthesis of 2,2′-bithiophene, 2,2′-bithiazole (**5**) was obtained in only 3–5% yield (entries 1 and 2). However,

when the reaction was carried out at –78 °C, compound **5** was obtained in moderate yield, and the formation of terthiazole **4** was observed (entry 3). Excess $CuCl_2$ did not affect the yield of **5** (entry 4), but a slightly reduced amount of $CuCl_2$ improved the yields of **5** (entry 6).

It was remarkable that terthiazole **4** was prepared, even at such low yield. To confirm the reproducibility of this reaction, we examined the reaction under the same conditions of entry 6 for six times, and we always obtained **4** in 2–4% yield. The mechanism of formation of **4** is unclear, but 5-lithio-2,2′-bithiazole is most likely generated in situ, probably caused by the incompleteness of the reaction of 2-lithiothiazole with $CuCl_2$. We thus added $CuCl_2$ in two portions with a one-hour interval, the yield of **4** did not increase so much (entry 7). Furthermore, we examined the coupling reaction in the presence of equimolar 2,2′-bithiazole **5** to generate 5-lithio-2,2′-bithiazole under these reaction conditions. As expected, the yield of **4** increased to 17% (Scheme 2).[12]



Scheme 2



Scheme 3

Compound **4** is a pale yellow powder possessing both air and thermal stability. Terthiazole **4** is more soluble in common organic solvents than 2,2′:5′,2″-terthiophene. Lithiation and functionalization of **4** was examined for its utility in extending π-systems. Treatment of **4** with 2.2 equivalents of lithium diisopropylamide, followed by reaction with 2,6-di-*tert*-butylbenzoquinone, afforded bisquinol **6** in 77% yield (Scheme 3). Successive reduction of **6** with Zn and pyridine–water[13] gave bisphenol **7** in 83% yield. Compound **7** is an important synthetic intermediate in the relation of our recent studies on extended quinines incorporated with a thiazole[7] and bithiazole rings.[14]

In conclusion, we prepared 2,2′:5′:2″-terthiazole (**4**), a previously unknown terthiazole isomer, by $CuCl_2$-mediated oxidative coupling of a lithiated mixture of thiazole and 2,2′-bithiazole. Although the yield is low, this method is quite simple compared to Stille coupling or Suzuki–Miyaura coupling reactions reported for known terthiazole derivatives. Due to its facile lithiation and functionalization, compound **4** will be a good building block for new extended π-systems containing terthiazole skeletons.

$CuCl_2$-Mediated Oxidative Coupling of 2-Lithiothiazole: Synthesis of 2,2′-Bithiazole 5 and 2,2′:5′:2″-Terthiazole (4)

To a solution of 2-bromothiazole (3.0 mL, 33 mmol) in anhyd Et_2O (70 mL) was added dropwise a 1.5 M solution of *n*-BuLi in hexane (23 mL, 34 mmol) at –78 °C for 1 h, anhyd $CuCl_2$ (4.0 g, 30 mmol) was added in one portion. The mixture was stirred at –78°C for 3 h, then filtered through a Celite pad to remove inorganic materials (eluent: CH_2Cl_2). The filtrate was evaporated and the residue was purified by SiO_2 (80 g) column chromatography. From the first fraction eluted with 10% EtOAc–hexane, 2,2′-bithiazole **5** was obtained as a pale yellow powder (1.3 g, 52%), and from the second fraction eluted with 20% EtOAc–hexane, 2,2′:5′,2″-terthiazole (**4**) was obtained as a yellow powder (87 mg, 4%).

2,2′-Bithiazole (5)

Pale yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 3.1 Hz, 2 H), 7.44 (d, *J* = 3.1 Hz, 2 H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 161.66, 143.90, 120.92.

2,2′:5′,2″-Terthiazole (4)

Yellow crystals (benzene–hexane); mp 146–147 °C. MS (EI): *m/z* = 251 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 7.93 (d, *J* = 3.1 Hz, 1 H), 7.86 (d, *J* = 3.3 Hz, 1 H), 7.49 (d, *J* = 3.1 Hz, 1 H), 7.37 (d, *J* = 3.3 Hz, 1 H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 162.21, 161.03, 157.99, 144.26, 143.94, 142.00, 134.56, 121.62, 119.48. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 389 (sh, 4.15), 365 (4.41), 351 (sh, 4.35) nm. IR (KBr): ν = 3103 (m), 1538 (w), 1504 (w), 1469 (m), 1374 (m), 1314 (w), 1271 (w), 1242 (m), 1150 (m), 1051 (w), 929 (m), 866 (m), 740 (m), 631 (m), 611 (m), 473 (w) cm^{-1}. Anal. Calcd for $C_9H_5N_3S_3$: C, 43.01; H, 2.00; N, 16.71. Found: C, 43.33; H, 1.92; N, 16.62.

Synthesis of 4 in the Presence of 5

To a solution of 2-bromothiazole (0.1 mL, 1.0 mmol) and 2,2′-bithiazole (**5**, 168 mg, 1.0 mmol) in anhyd Et_2O (15 mL) was added dropwise a 1.5 M solution of *n*-BuLi in hexane (1.3 mL, 2.0 mmol) at –78 °C under nitrogen atmosphere. After stirring at –78 °C for 1 h, anhyd $CuCl_2$ (121 mg, 0.9 mmol) was added in one portion. The mixture was stirred at –78 °C for 3 h, then filtered through a Celite

pad to remove inorganic materials (eluent: CH_2Cl_2). The filtrate was evaporated and the residue was purified by SiO_2 (30 g) column chromatography. Bithiazole **5** (121 mg) was recovered from the first fraction (eluent: 10% EtOAc–hexane), and the terthiazole **4** (42 mg, 17%) was obtained from the second fraction (eluent: 20% EtOAc–hexane), as a pale yellow powder.

Lithiation and Functionalization of 4 – Synthesis of Bisquinol 6

To a solution of diisopropylamine (0.15 mL, 1.1 mmol) in anhyd THF (10 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (0.7 mL, 1.1 mmol) at –70 °C under nitrogen atmosphere. After stirring at 0 °C for 1 h, a solution of **4** (126 mg, 0.5 mmol) in THF (5 mL) was added dropwise at –70 °C, and the mixture were stirred at –70 °C for 1 h. 2,6-Di-*tert*-butylbenzophenone (275 mg, 1.25 mmol) in THF (5 mL) was added dropwise at –70 °C, and the mixture were stirred at 0 °C for 1.5 h. The mixture was quenched by sat. NH_4Cl solution, extracted with EtOAc (3 × 20 mL), washed with H_2O, brine, and dried with anhyd Na_2SO_4. The solution was evaporated and the residue was purified by SiO_2 (50 g) column chromatography (eluent: 5% EtOAc–benzene) to give bisquinol **6** (268 mg, 77%) as a yellow powder. This compound was used for the next reaction without further purification.

Compound 6

Yellow powder. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.72 (s, 1 H), 7.61 (s, 1 H), 6.69 (s, 2 H), 6.68 (s, 2 H), 1.72 (s, 2 H), 1.25 (s, 36 H).

Synthesis of Bisphenol 7

To a solution of **6** (268 mg, 0.4 mmol) in pyridine (8 mL) and H_2O (0.8 mL) was added zinc powder (1.01 g, 15.5 mmol), and the mixture was refluxed for 1.5 h. After cooling to r.t., the mixture was passed through a Celite pad to remove zinc powder. The filtrate was extracted with EtOAc (3 × 20 mL), washed with 1% HCl, sat. $NaHCO_3$ solution, brine, and dried with anhyd Na_2SO_4. The solution was evaporated and the residue was purified by SiO_2 (40 g) column chromatography (eluent: 10% EtOAc–hexane) to give bisphenol **7** (213 mg, 83%) as an orange powder.

Compound 7

Orange crystals (CH_2Cl_2–hexane); mp 280–281 °C. MS (EI): *m/z* = 659 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.95 (s, 1 H), 7.86 (s, 1 H), 7.44 (s, 2 H), 7.38 (s, 2 H), 5.43 (s, 1 H), 5.41 (s, 1 H), 1.50 (s, 18 H), 1.49 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.16, 158.33, 155.59, 154.94, 154.75, 143.69, 141.60, 141.55, 138.54, 138.10, 136.96, 136.93, 134.65, 124.12, 124.08, 122.13, 34.45, 30.18. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 427 (4.67), 274 (4.17) nm. IR (KBr): ν = 3615 (s), 2955 (s), 2910 (m), 2870 (m), 1433 (s), 1405(s), 1387 (s), 1302 (m), 1223 (s), 1135 (m), 1116 (m), 1050 (w), 928 (s), 902 (m), 880 (m), 853 (m), 820 (m), 769 (w), 703 (w), 608 (m) cm^{-1}. HRMS: *m/z* calcd for $C_{37}H_{45}N_3O_2S_3$: 659.2674; found: 659.2701.

References and Notes

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