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Sulfur Heterocycles

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Synthesis of Dibenzothiophenes and Related Classes of Heterocycles by Using Functionalized Dithiocarbamates**

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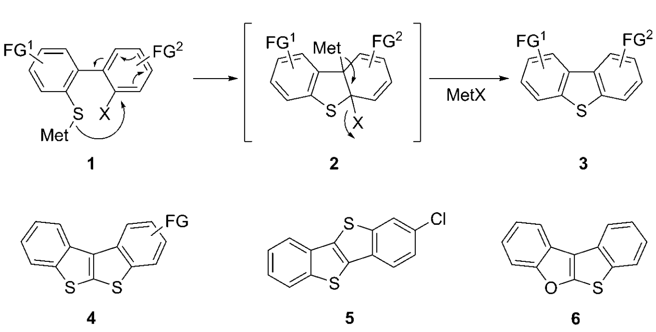
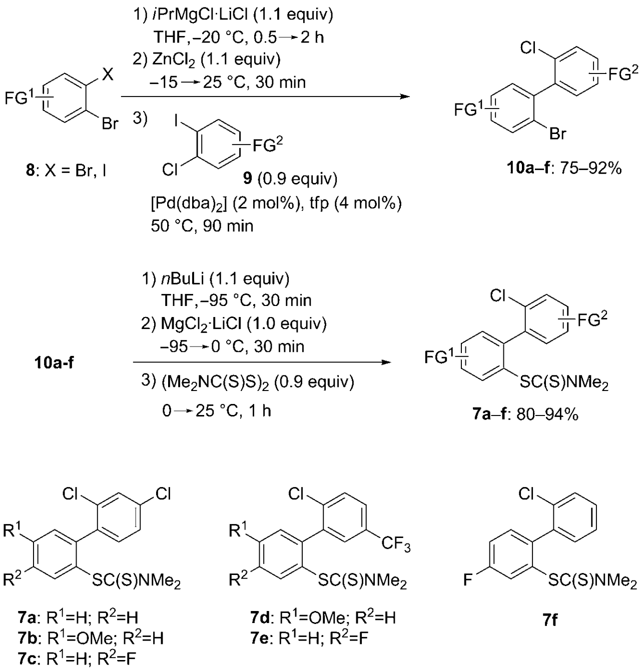
Dibenzothiophenes, benzo[*b*]thiophenes, and benzo[*c*]thiophenes have found numerous applications as dyes, pharmaceuticals, agrochemicals, or as building blocks for the synthesis of conducting polymers.[1,2] Several straightforward strategies for the synthesis of such S heterocycles have been reported.[3] Palladium-catalyzed ring closures leading to S heterocycles are especially difficult, but were realized recently, despite the deactivating effect of sulfur on transition-metal catalysts.[4,5] To avoid this poisoning of the transition-metal catalysts by thiols and thiolates, we have envisioned a ring-closure procedure involving main-group benzothiolates such as **1** as precursors, which will provide an intermediate such as **2** by an addition/elimination reaction.[6] The elimination of Met-X should result in various dibenzothiophenes of type **3** (Scheme 1).



Scheme 1. Preparation of S heterocycles by an addition/elimination reaction. FG = functional group, Met = K, X = Br, Cl.

Herein we report the successful synthesis of various classes of S heterocycles of types **3** and **4**[7] as well as [1]benzothieno[3,2-*b*][1]benzothiophene **5**[8] and the previously unknown [1]benzothieno[2,3-*b*][1]benzofuran **6** (Scheme 1), starting from readily available biaryls of type **7**. A Br/Mg or I/Mg exchange on the aryl bromides or iodides **8** was first carried out with *i*PrMgCl·LiCl[9] (−20 °C, 0.5–2 h) and then transmetalated with $ZnCl_2$. A subsequent Negishi cross-coupling reaction[10–12] ([Pd(dba)$_2$] (2 mol %; dba = *trans,trans*-dibenzylideneacetone), tri-2-furylphosphine (tfp; 4 mol %, 50 °C, 1.5 h)) with functionalized 1-chloro-2-iodobenzene derivatives **9** then afforded the polysubstituted biphenyls **10** in 75–92 % yield. Br/Li exchange proved to be superior (*n*BuLi (1.1 equiv), −95 °C, 30 min) as these biphenyls did not undergo complete Br/Mg exchange because of steric hindrance. After transmetalation with the THF-soluble magnesium complex $MgCl_2$·LiCl,[13,14] the resulting aryl magnesium species were treated with tetramethylthiuram disulfide $(Me_2NC(S)S)_2$ (0.9 equiv, 0 °C to 25 °C, 1 h)[15] to provide the biphenyl dithiocarbamates **7a–f** in yields of 80–94 % (Scheme 2).



Scheme 2. Preparation of the starting dithiocarbamates **7**.

This synthesis was also extended to the preparation of benzothiophenes **11a–d** and benzofurans **12a/b**. Thus, 3-bromobenzothiophene (**13a**) was magnesiated with *i*PrMgCl·LiCl[9] (1.1 equiv, −15 °C, 24 h) to the corresponding magnesium derivative. Subsequent transmetalation with $ZnCl_2$ and a Negishi cross-coupling reaction[10–12] with 1-bromo-2-iodobenzene derivatives **14** ([Pd(dba)$_2$] (2 mol %), tfp (4 mol %), 50 °C, 1.5 h) then resulted in the formation of the 3-arylated benzothiophenes **15a–d** (63–75 % yield;

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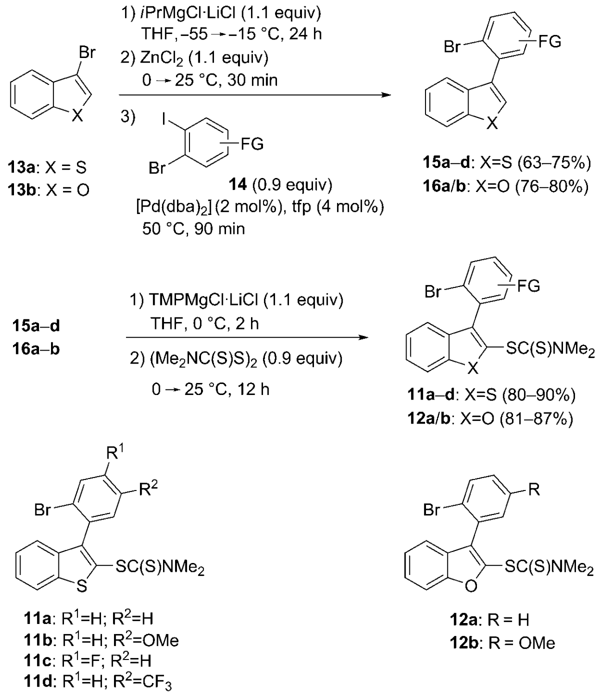
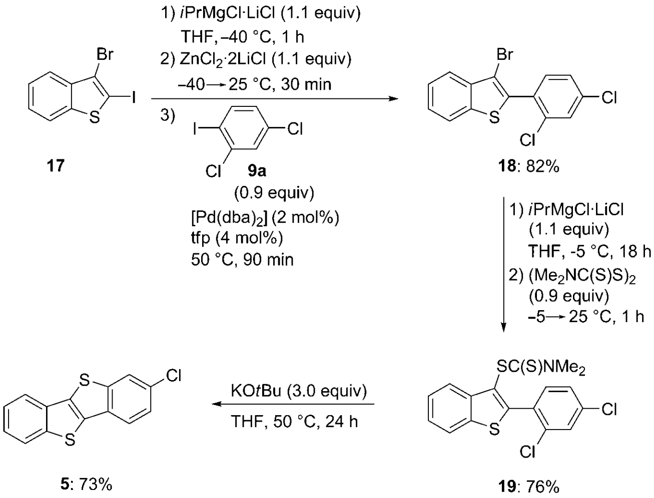


Scheme 3. Preparation of starting dithiocarbamates **11** and **12**. TMP = 2,2,6,6-tetramethylpiperidyl.

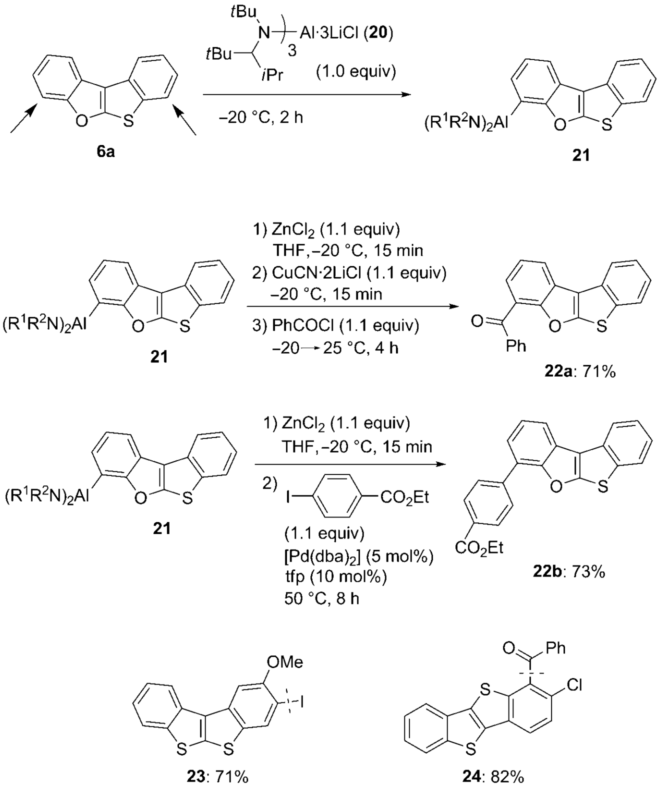


Scheme 4. Preparation of the S-heterocycle **5**.

Scheme 3). The magnesiation of compounds **15** with TMPMgCl·LiCl[16] (1.1 equiv, 0 °C, 2 h) followed by a trapping reaction with $(Me_2NC(S)S)_2$ (0.9 equiv, 0 °C to 25 °C, 12 h) afforded the desired benzothienyl dithiocarbamates **11 a–d** in 80–90 % yield. Similarly, 3-bromobenzofuran (**13 b**) was converted using the same two-step sequence into the benzofuryl dithiocarbamate (**12 a/b**; 81–87 %) via the intermediates **16 a/b** (76–80 %; Scheme 3).

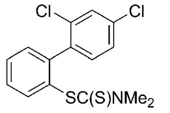
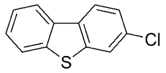
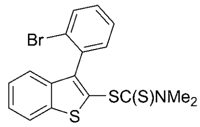
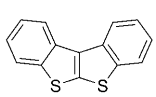
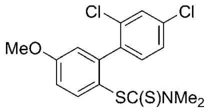
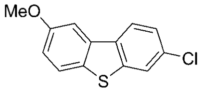
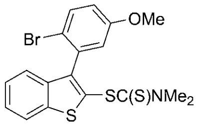
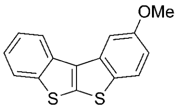
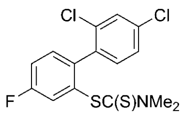
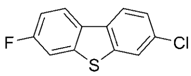
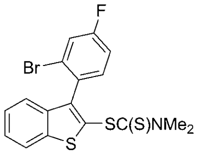
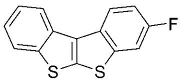
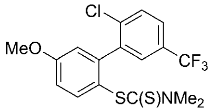
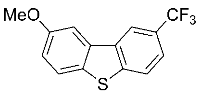
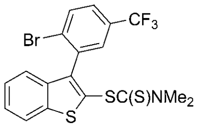
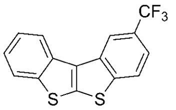
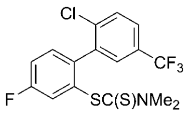
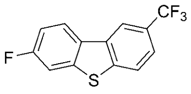
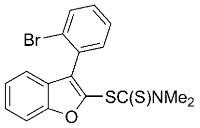
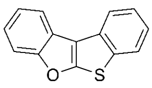
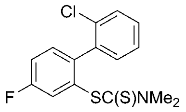
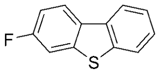
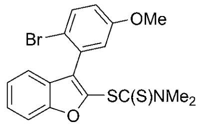
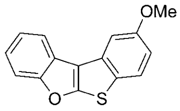
The chloro-substituted dithiocarbamates **7** were converted by treatment with *t*BuOK (3.0 equiv, THF, 50 °C) into the corresponding potassium thiolates, which undergo an addition/elimination ring closure to provide the desired functionalized dibenzothiophenes **3 a–f** in 71–96 % yield within 0.75–24 h (Table 1, entries 1–6). The rate of the cyclization depends on the substitution pattern of both aromatic rings. In general, electron-withdrawing substituents on the ring bearing the leaving group (chloride) enhance the reaction rates (entries 4 and 5). Microwave irradiation dramatically accelerates the cyclization of **7 c** and **7 f**. These substrates do not undergo ring closure under thermal conditions, but the reaction is complete after 45 minutes of microwave irradiation (90 °C). Bromo-substituted precursors such as **11 a–d** and **12 a/b** can also be used in such a ring-closure reaction. Treatment with *n*BuLi (1.05 equiv, THF, −20 °C) leads to a complete cyclization within 30 minutes at −20 °C and furnishes the tetracyclic heterocyclic products **4 a–d** in 78–90 % yield (entries 7–10) and **6 a/b** in 72 and 76 % yield, respectively (entries 11 and 12). A possible mechanism may involve a Br/Li exchange,[17] followed by a substitution reaction of the intermediate aryl lithium compound on the dithiocarbamate group to give the desired products as well as dimethylthiocarbamoyllithium $(LiC(S)NMe_2)$,[18] which may decompose under these conditions. An alternative radical mechanism cannot be excluded.[19]

An isomeric structure of heterocycles of type **4**, namely the substituted [1]benzothieno[3,2-*b*][1]benzothiophene **5**, could be prepared by a slight modification of the procedure shown in Scheme 1. Thus, a selective I/Mg exchange on 3-bromo-2-iodo-benzothiophene (**17**; *i*PrMgCl·LiCl (1.1 equiv), −40 °C, 1 h) followed by a transmetalation with $ZnCl_2$ and



Scheme 5. Alumination and subsequent acylation, iodolysis, or Negishi cross-coupling reaction to give the substituted heterocyles **22 a/b**, **23**, and **24**.

Table 1: Preparation of various S heterocycles of type **3**, **4**, and **6**.

Entry	Substrate	T [°C][a]	Product[b]	Entry	Substrate	T [°C][a]	Product[b]
1	 **7a**	50 (12)[c]	 **3a**: 94%[b]	7	 **11a**	−20 (0.5)[e]	 **4a**: 80%[b]
2	 **7b**	50 (18)[c]	 **3b**: 81%[b]	8	 **11b**	−20 (0.5)[e]	 **4b**: 90%[b]
3	 **7c**	90 (0.75)[d]	 **3c**: 78%[b]	9	 **11c**	−20 (0.5)[e]	 **4c**: 83%[b]
4	 **7d**	50 (4)[c]	 **3d**: 96%[b]	10	 **11d**	−20 (0.5)[e]	 **4d**: 78%[b]
5	 **7e**	50 (4)[c]	 **3e**: 81%[b]	11	 **12a**	−20 (0.5)[e]	 **6a**: 72%[b]
6	 **7f**	90 (0.75)[d]	 **3f**: 71%[b]	12	 **12b**	−20 (0.5)[e]	 **6b**: 76%[b]

[a] The reaction times (h) for the ring-closing reaction are given in parentheses. [b] Yield of the analytically pure isolated product. [c] KO*t*Bu (3 equiv) was used for the ring closure. [d] Microwave irradiation was used. [e] *n*BuLi (1.05 equiv) was used for the ring closure.

Negishi cross-coupling with 2,4-dichloroiodobenzene (**9a**) provides the 2-arylated benzothiophene **18** in 82% yield. A Br/Mg exchange of **18** with *i*PrMgCl·LiCl (1.1 equiv, −5 °C, 18 h) and subsequent quenching with $(Me_2NC(S)S)_2$ furnishes **19** in 76% yield. This dithiocarbamate undergoes a smooth ring closure in the presence of *t*BuOK (3.0 equiv, THF, 50 °C, 18 h) to give the tetracyclic heterocycle **5** in 73% yield (Scheme 4).

The S heterocycles prepared can be further functionalized by a regioselective alumination by using the hindered aluminum amide **20**.[20,21] Thus, treatment of the O,S-tetracyclic compound **6a** with **20** (1.0 equiv, THF, −20 °C, 2 h) led to a regiospecific alumination at the α position to the furan unit (left arrow in Scheme 5). This result arises from a preferential complexation of the hindered aluminum base to the oxygen atom. The resulting aluminum organometallic compound **21** was acylated (1: $ZnCl_2$ (1.1 equiv); 2: CuCN·2 LiCl (1.1 equiv); 3: PhCOCl (1.1 equiv, −20 °C→25 °C, 4 h)) to provide the ketone **22a** in 71% yield. Furthermore, Negishi cross-coupling of **21** (1: $ZnCl_2$ (1.1 equiv); 2: $[Pd(dba)_2]$ (5 mol%), tfp (10 mol%), ethyl 4-iodobenzoate (1.1 equiv, 50 °C, 8 h)) led to the arylated product **22b** in 73% yield. It was possible to regiospecifically metalate the heterocycles **4b** and **5** by using the same base. The substituents present in those substrates (for example, a chloride or a methoxy group) fully direct the alumination. Trapping either with iodine (1: **20** (1.0 equiv, 0 °C, 4 h) 2: $ZnCl_2$ (1.1 equiv); 3: I_2 (1.5 equiv , −20 °C→25 °C, 0.5 h)) or acylation (1: **20** (1.0 equiv, −40 °C, 2 h) 2: $ZnCl_2$ (1.1 equiv); 3: CuCN·2 LiCl (1.1 equiv); 4: PhCOCl (1.1 equiv, −20 °C→25 °C, 4 h)) afforded the substituted heterocycles **23** and **24** in yields of 71 and 82%, respectively (Scheme 5).

In summary, we have developed a cyclization reaction that leads to various condensed S heterocycles. The precursors for the ring-closing reaction are readily prepared by a palladium-catalyzed cross-coupling method. We have also shown that the newly formed S heterocycles can be regioselectively functionalized using the hindered aluminum base **20**. Further extensions of this method for preparing material-relevant compounds are currently underway.

Experimental Section

Synthesis of **3a** (Table 1, entry 1): A dry and argon-flushed 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with a solution of **7a** (342 mg, 1.0 mmol) and KO*t*Bu (337 mg, 3.0 mmol) in dry THF (10 mL). This solution was then heated at 50 °C for 12 h. After standard work up, the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (pentane/diethyl ether; 9:1) to give **3a** (206 mg, 94 %) as a colorless solid.

Synthesis of **4a** (Table 1, entry 7): A dry and argon-flushed 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with a solution of **11a** (408 mg, 1.0 mmol) in dry THF (10 mL) and cooled to −20 °C. *n*BuLi (0.49 mL, 2.14 M in hexane, 1.05 mmol) was then added dropwise and the mixture stirred for 0.5 h. The reaction was stopped by the addition of MeOH (5 drops) and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (pentane) to give **4a** (201 mg, 84 %) as a colorless solid.

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Keywords: aluminum · amide bases · benzothiophene · cross-coupling · sulfur heterocycles

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[12] A slow addition (90 min) of the zinc reagent to the iodoarene was necessary to avoid the formation of the undesired homocoupling products. Therefore, zinc reagents were used instead of the less-stable magnesium species.

[13] CH_2Cl_2 proved to be the best solvent for $Me_2NC(S)S)_2$. Since the addition of $Me_2NC(S)S)_2$ (dissolved in CH_2Cl_2) to the lithium species resulted in the formation of undesired by-products, a transmetalation to the corresponding Mg species was preferred.

[14] Anhydrous LiCl (424 mg, 10 mmol) and Mg turnings (243 mg, 10 mmol) were placed in a Schlenk tube, followed by dry THF (10 mL). 1,2-Dichloroethane (0.79 mL, 10 mmol) was then added in one portion and THF (10 mL) was added in small portions. After 5 h, $MgCl_2 \cdot LiCl$ (0.5 M in THF) was obtained as a colorless solution.

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