Heterocycle Synthesis

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Synthesis of Functionalized Benzo[*b*]thiophenes by the Intramolecular Copper-Catalyzed Carbomagnesiation of Alkynyl(aryl)thioethers**

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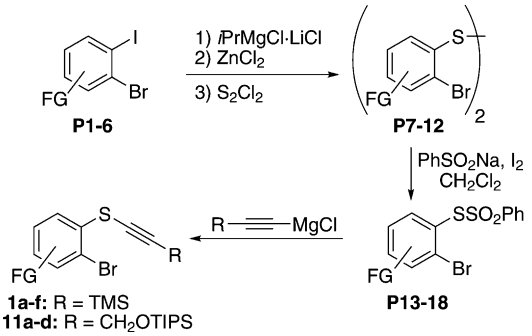
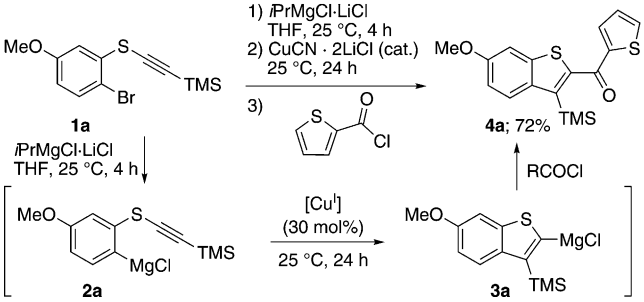
The synthesis of novel functionalized heterocycles is an important topic in synthetic organic chemistry.[1] Several methodologies for the construction of indoles, benzofurans, benzothiophenes, and other fused-ring compounds by cyclization reactions have been reported.[2] These ring-closing procedures include metalative cyclizations,[2b,3] gold-catalyzed reactions,[2a,4] copper-promoted halocyclizations,[5] and palladium-mediated iodocyclizations.[2d,6,7]

Among these heterocyclic scaffolds, benzo[*b*]thiophenes[8] are of particular interest, as they are often found in biologically active molecules such as raloxifene[9] and potential drug candidates[10] and are also widespread in material chemistry.[11] Recently, Larock and co-workers applied a Pd-catalyzed iodocyclization for the elaboration of oligomeric benzo[*b*]thiophenes.[12] Also, a novel tandem reaction consisting of an intramolecular S-vinylation and a subsequent intermolecular C–C bond formation has been reported by Lautens and co-workers.[13] Since *ortho*-alkynyl benzenethiols are not accessible by Sonogashira coupling,[14] we envisioned a metalative cyclization involving alkynyl(aryl)thioethers, which are readily available in three straightforward steps starting from the corresponding 1,2-bromoiodoarenes (Scheme 1).[15]



Scheme 1. Preparation of alkynyl(aryl)thioethers of types **1** and **11**. FG = functional group, TMS = trimethylsilyl, TIPS = triisopropylsilyl.

Herein, we report a mild and general method for the preparation of functionalized benzo[*b*]thiophenes and benzo[*b*]thieno[2,3-*d*]thiophenes by means of an intramolecular catalytic carbocupration[16,17] reaction starting from alkynyl(aryl)thioethers. The treatment of the thioether **1a** with *i*PrMgCl·LiCl[18] provided the corresponding magnesium reagent **2a** (25 °C, 4 h, > 95 % conversion; Scheme 2). In the



Scheme 2. Preparation of benzo[*b*]thiophenes by a copper-catalyzed carbomagnesiation of alkynyl(aryl)thioethers of type **1**.

presence of a catalytic amount of CuCN·2 LiCl[19] (30 mol %) a smooth cyclization occurred (25 °C, 24 h)[20] producing the magnesiated compound **3a**. A subsequent acylation reaction with thiophene-2-carbonyl chloride (0.9 equiv) afforded the polyfunctional benzothiophene **4a** in 72 % yield. Similarly, the reaction with 4-chlorobenzoyl chloride provided the acylated benzothiophene **4b** in 80 % yield (Table 1, entry 1). Various functionalized alkynyl(aryl)thioethers (**1b–e**) bearing a protected hydroxy group (**1b**) or a chloro (**1c**), cyano (**1d**), or ester substituent (**1e**) underwent cyclization under similar conditions. The intermediate Mg reagents were either acylated or allylated providing diverse polyfunctional benzothiophenes (**4b–j**) in 71–91 % yield (Table 1, entries 2–9).

In the case of the cyano-substituted thioether (**1d**), the Br/Mg exchange with *i*PrMgCl·LiCl was performed at 0 °C (1 h). For the more sensitive ester-substituted thioether (**1e**), this exchange was carried out at −25 °C (1 h). As the cyclization at this temperature is very slow and since higher temperatures (> 0 °C) lead to side reactions, stoichiometric amounts of CuCN·2 LiCl were used in this case. In fact, with microwave irradiation (50 °C, max. 100 W) the ring-closing reaction reached completion within 1 h (Table 1, entries 8 and 9). The *tert*-buyl ester is preferred, since for methyl and ethyl esters a competitive addition of *i*PrMgCl·LiCl onto the ester moiety was observed.

The TMS-substituted benzothiophenes of type **4** were readily converted to the desilylated compounds of type **5**

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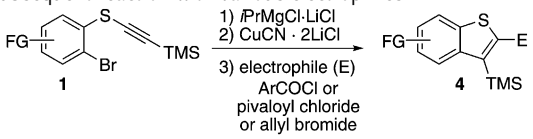
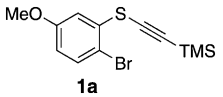
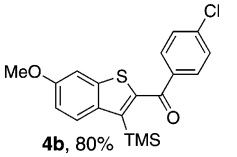
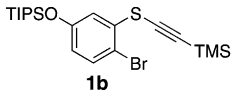
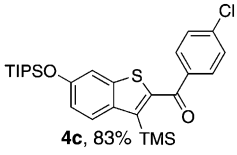
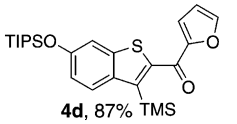
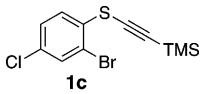
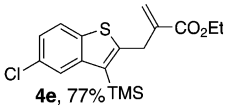
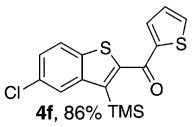
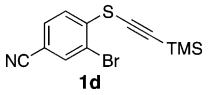
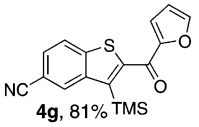
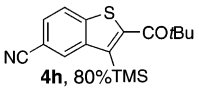
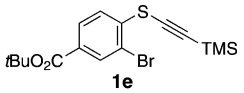
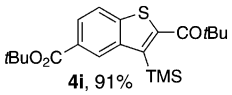
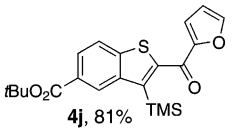
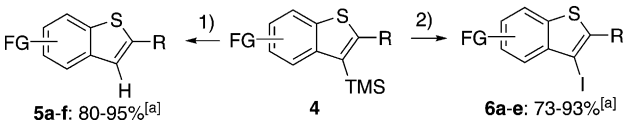
Table 1: Functionalized benzothiophenes of type **4** obtained by the copper-catalyzed carbomagnesiation of alkynyl(aryl)thioethers of type **1** and subsequent reaction with various electrophiles[a]

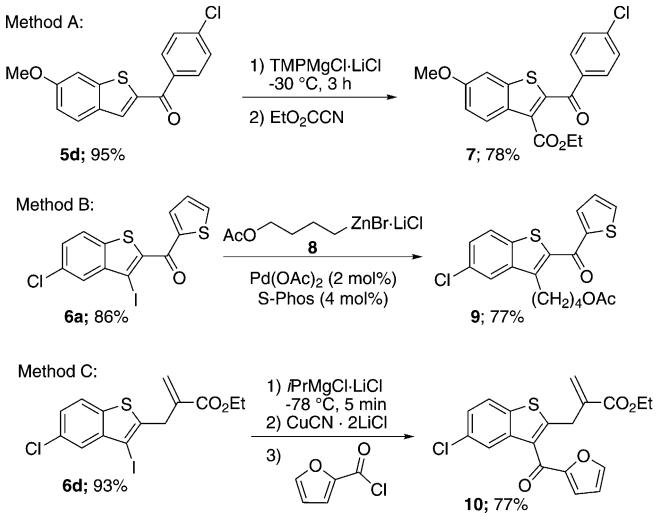


Entry	Substrate[b]	Product, yield [c]
1	 **1a**	 **4b**, 80%
2	 **1b**	 **4c**, 83%
3	**1b**	 **4d**, 87%
4	 **1c**	 **4e**, 77%
5	**1c**	 **4f**, 86%
6	 **1d**	 **4g**, 81%
7	**1d**	 **4h**, 80%
8	 **1e**	 **4i**, 91%
9	**1e**	 **4j**, 81%

[a] 0.9 equiv of electrophile was used. [b] See the Supporting Information for the reaction conditions. [c] Yield of isolated, analytically pure product based on the amount of electrophile used.



Scheme 3. Transformations of TMS-substituted benzo[*b*]thiophenes of type **4**. 1) Bu_4NF, THF, 25 °C, 1 h; 2) ICl, CH_2Cl_2, 0 °C, 5 min. [a] All compounds of types **5** and **6** are described in the Supporting Information.

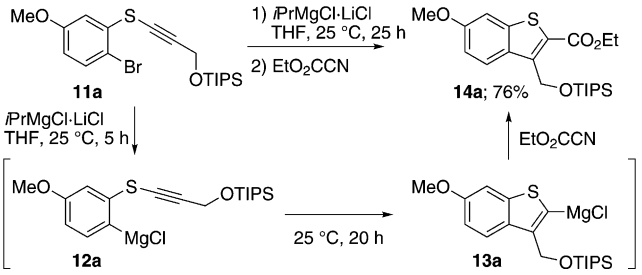


Scheme 4. Further functionalization of the benzo[*b*]thiophenes of types **5** and **6**.

(Bu_4NF (1.5 equiv), THF, 25 °C, 1 h) or to 3-iodobenzothiophenes of type **6** (ICl (1.1 equiv), CH_2Cl_2, 0 °C, 5 min)[21] (Scheme 3). Heterocycles **5** and **6** are valuable intermediates and can be further functionalized by three general types of reactions: a direct magnesiation (method A), a Negishi cross-coupling reaction (method B), or an I/Mg-exchange reaction (method C, Scheme 4).

Thus, the metalation of benzothiophene **5e** with TMPMgCl·LiCl[22] (−30 °C, 3 h, TMP = 2,2,6,6-tetramethylpiperidyl) followed by a reaction with ethyl cyanoformate afforded the 2,3-disubstituted benzothiophene **7** in 78 % yield (method A, Scheme 4). Here, the carbonyl group acts as a directing group[23] and the metalation occurs regioselectively on position 3 of the benzo[*b*]thiophene ring. Alternatively, the heterocyclic iodide **6a** underwent a Pd-catalyzed[24] Negishi cross-coupling reaction[25] with 4-acetoxybutylzinc bromide[26] **8** (25 °C, 1 h) to provide the polyfunctional benzothiophene **9** in 77 % yield (method B). The third transformation involves an I/Mg-exchange reaction on the iodide **6d** using *i*PrMgCl·LiCl (−78 °C, 5 min). After a subsequent copper(I)-catalyzed acylation reaction with 2-furoyl chloride, the benzothiophene **10** was produced in 77 % yield (method C, Scheme 4). This magnesiation by means of I/Mg exchange is complementary to the deprotonation with TMPMgCl·LiCl (method A), and is relevant when direct deprotonation is not successful because of chemo- and/or regioselectivity problems.

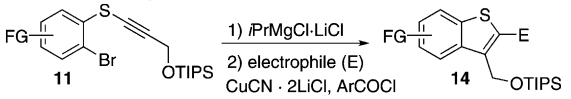
Interestingly, the activated triple bond of substrates bearing a propargylic group is more susceptible to carbometalation,[16,17] and the cyclization therefore occurs without addition of a copper catalyst. Thus, treatment of the thioether **11a** with *i*PrMgCl·LiCl (1.1 equiv, 25 °C, 5 h) provided the magnesium reagent **12,** which underwent ring closure (25 °C, 20 h) leading to the Mg intermediate **13a**. After a carboxylation with ethyl cyanoformate the benzothiophene **14a** was obtained in 76 % yield (Scheme 5).

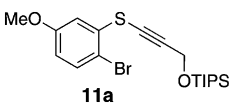
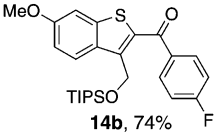
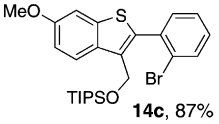
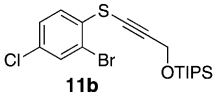
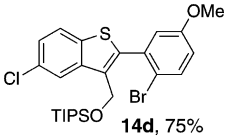
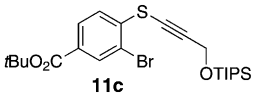
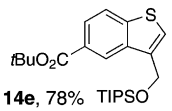


Scheme 5. Preparation of benzo[*b*]thiophenes by cyclization of protected hydroxymethyl-substituted alkynyl(aryl)thioethers.

Likewise, copper(I)-catalyzed acylation or Pd-catalyzed cross-coupling reactions afforded the derived benzothiophenes **14b–d** in 74–87% yield (Table 2, entries 1–3). The cyclization of the ester-substituted arene **11c** was carried out at lower temperatures (−5 to 0°C, 52 h) to avoid decomposition of this sensitive Mg intermediate. The ester-substituted benzothiophene **14e** was obtained in 78% yield (Table 2, entry 4).

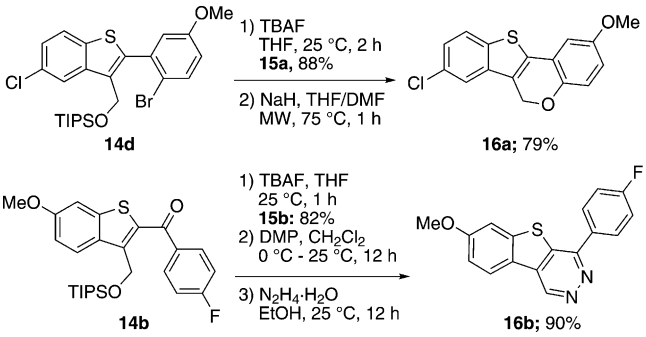
Table 2: Functionalized benzothiophenes of type **14** obtained by carbomagnesiation of alkynyl(aryl)thioethers of type **11** and subsequent reaction with electrophiles[a]



Entry	Substrate[b]	Product, yield[c]
1	 **11a**	 **14b**, 74%
2	**11a**	 **14c**, 87%
3	 **11b**	 **14d**, 75%
4	 **11c**	 **14e**, 78%

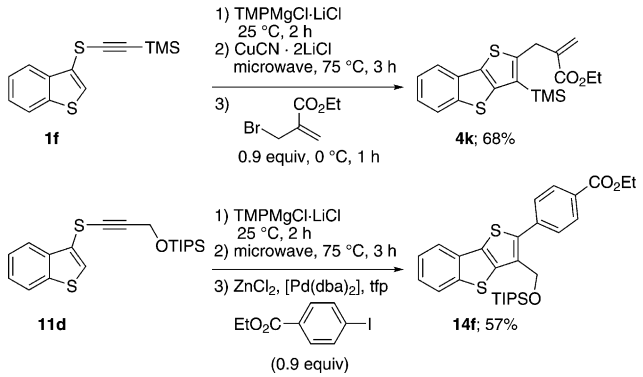
[a] 0.9 equiv of electrophile was used. [b] See the Supporting Information for the reaction conditions. [c] Yield of isolated, analytically pure product based on the amount of electrophile used. dba = dibenzylideneacetone, tfp = tri(2-furyl)phosphine.

The benzylic hydroxy group of benzothiophenes of type **14** can be further used to prepare new heterocyclic scaffolds. Desilylation of compound **14d** (Bu_4NF (1.5 equiv), THF, 25°C, 2 h, **15a**, 88%) followed by deprotonation of the free alcohol (NaH (2 equiv), THF/DMF, 25°C, 2 h) and subsequent microwave-assisted (75°C, max. 150 W, 2 h) nucleophilic aromatic substitution led to the thieno[3,2-*c*]chromene **16a** in 79% yield. Likewise, the deprotected benzylic alcohol **15b** was oxidized to the aldehyde with Dess–Martin periodinane (2 equiv, CH_2Cl_2, 0°C, 12 h) and condensation with hydrazine hydrate (3 equiv, EtOH, 25°C, 12 h) furnished the thieno[2,3-*d*]pyridazine **16b** in 90% yield (Scheme 6).



Scheme 6. Intramolecular aromatic substitution reaction leading to new heterocyclic scaffolds. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane.

The present methodology can be extended to the preparation of benzothienothiophenes. Thus, ethynylbenzothiophene **1f** was conveniently metalated with TMPMgCl·LiCl (25°C, 2 h). The ring closure is more challenging, since it involves the formation of a fused five-membered ring on an existing five-membered ring. This is much less favored than the formation of a six-membered ring. However, it was achieved using catalytic CuCN·2 LiCl (30 mol%) and microwave irradiation (75°C, max. 200 W, 3 h). A Cu^I-catalyzed allylation with ethyl (2-bromomethyl)acrylate[27] produced the benzo[*b*]thieno[3,2-*d*]thiophene **4k** in 68% yield (Scheme 7). As expected, the more activated substrate **11d** cyclized in the absence of a copper catalyst under similar conditions. After transmetalation to zinc and Pd-catalyzed cross-coupling with ethyl 4-iodobenzoate, the functionalized benzothienothiophene **14f** was obtained in 57% yield.



Scheme 7. Functionalized benzo[*b*]thieno[2,3-*d*]thiophenes obtained by carbomagnesiation and subsequent reaction with electrophiles.

In summary, we have reported a new intramolecular copper-catalyzed carbomagnesiation procedure for the preparation of magnesiated benzothiophenes starting from alkynyl(aryl)thioethers. Further reactions with various electrophiles gave access to highly functionalized benzo[2,3-*b*]thiophenes and benzo[*b*]thieno[2,3-*d*]thiophenes in excellent yields. This method tolerates a wide range of functional groups, and further modifications of the cyclization products afford highly diversified benzothiophene derivatives as well as new heterocyclic scaffolds. An extension of this methodology to other heteroarenes is currently underway in our laboratories.

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Keywords: benzo[*b*]thiophenes · carbomagnesiation · copper catalysis · cyclization · heterocycle synthesis

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