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Selective Metalations of 1,4-Dithiins and Condensed Analogues Using TMP-Magnesium and -Zinc Bases

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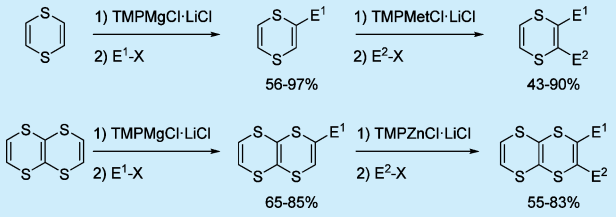
Supporting Information

ABSTRACT: TMPMgCl·LiCl and TMPZnCl·LiCl allow facile magnesiation and zincation, respectively, of the 1,4-dithiin scaffold, producing polyfunctionalized 1,4-dithiins. A subsequent metalation of these S-heterocycles can also be achieved with the same TMP bases, leading to 2,3-disubstituted-1,4-dithiins. The Mg- and Zn-TMP bases allow as well the successful metalation of 1,4,5,8-tetrathianaphthalene and 1,4,5,6,9,10-hexathiaanthracene.



Sulfur heterocycles are important building blocks for applications in medicinal chemistry[1] and materials science.[2] Especially, 1,4-dithiins of type **1** (Figure 1) have attracted attention because of their unique electronic and conducting properties[3] as well as their use for the preparation of other sulfur heterocycles.[4] Structural studies of 1,4-dithiin derivatives have also been the subject of several publications, as to whether 1,4-dithiins are flat and to understand the electronic delocalization.[5] Nevertheless, the preparation of functionalized 1,4-dithiins remains a challenge since the metalation of these scaffolds has been scarcely studied. The reaction of **1** with *n*BuLi leads to ring opening unless this lithiation is performed at −110 °C.[6] Also, the treatment of **2** with *t*BuOK gives a skeleton rearrangement affording 1,4-dithiafulvenes (**3**) due to the harsh reaction conditions.[7] We recently reported a set of kinetically highly active bases such as TMPMgCl·LiCl (**6**)[8] and TMPZnCl·LiCl (**7**)[9] for the magnesiation and zincation, respectively, of various heterocyclic scaffolds.[10] Herein we report that these mild bases allow smooth metalation of the 1,4-dithiin skeleton, enabling the preparation of mono-, di-, tri-, or tetrasubstituted dithiins. Thereafter we will also show the functionalization via magnesiation or zincation of the condensed 1,4,5,8-tetrathianaphthalene (TTN, **4**)[11] and the new 1,4,5,6,9,10-hexathiaanthracene (HTA, **5**).

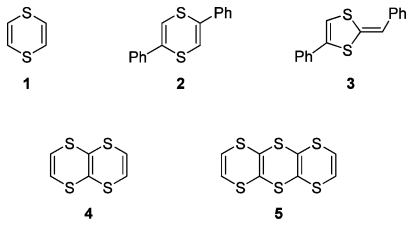
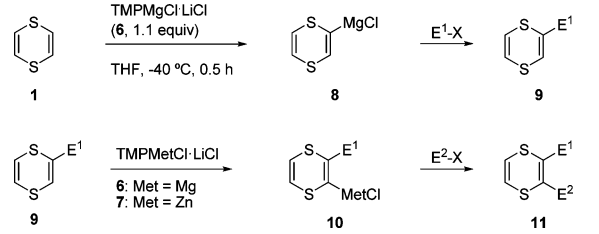


Figure 1. 1,4-Dithiin derivatives and condensed analogues.

We have found that the metalation of **1** with **6** produces the magnesiated 1,4-dithiin **8** at −40 °C within 0.5 h (Scheme 1).

Scheme 1. Synthesis of Mono- and Disubstituted 1,4-Dithiin Derivatives Using TMP Bases



Subsequent quenching of **8** with various electrophiles (E^1−X) leads to monosubstituted 1,4-dithiins of type **9**. Further functionalization of **9** can be achieved either with **6** or **7** depending on the nature of the substituent E^1, leading to the regioselectively metalated 2,3-disubstituted 1,4-dithiins **10**. Quenching with various eletrophiles produces a range of 2,3-disubstituted 1,4-dithiins **11**. Thus, the magnesiated 1,4-dithiin **8** was readily halogenated using iodine, tetrachlorodibromoethane, or benzenesulfonyl chloride to afford 2-halo-1,4-dithiins **9a**−**c** in 56−78% yield (Table 1, entries 1−3). Cyanation, aminomethylation with Tietze's reagent,[12] and the reaction with PhCHO were readily achieved, giving the corresponding adducts **9d**−**f** in 58−97% yield (entries 4−6). Acylation of **8** with $NCCO_2Et$, benzoyl chloride, and cyclopropylcarbonyl chloride provided the corresponding carbonyl-substituted 1,4-dithiins **9g**−**i** in 65−89% yield (entries 7−9). Copper-catalyzed allylation and Pd-catalyzed arylation furnished the coupling products **9j** and **9k**, respectively, in 73−94% yield (entries 10

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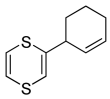
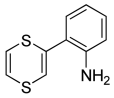
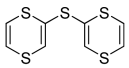
Table 1. Preparation of 2-Substituted 1,4-Dithiins of Type 9 by Magnesiation of 1,4-Dithiin (1) with TMPMgCl·LiCl (6)

entry	electrophile	product of type 9[a]
		
1	I_2	**9a**: R = I, 75%
2	$(BrCCl_2)_2$	**9b**: R = Br, 78%
3	$C_6H_5SO_2Cl$	**9c**: R = Cl, 56%
4	TsCN	**9d**: R = CN, 60%
5	$Me_2N{=}CH_2OCOCF_3$	**9e** R = CH_2NMe_2, 58%
6	PhCHO	**9f**: R = CHOHPh, 97%
		
7	$NCCO_2Et$	**9g**: R = OEt, 89%
8	PhCOCl	**9h**: R = Ph, 78%[b]
9		**9i**: R = *c*Pr, 65%[b]
10		 **9j**: 73%[b]
11		 **9k**: 94%[c]
12	$(PhSO_2)_2S$	 **9l**: 75%

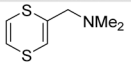
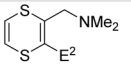
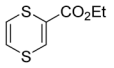
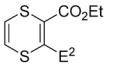
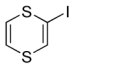
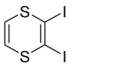
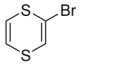
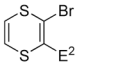
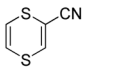
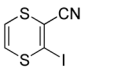
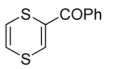
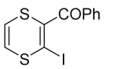
[a]Yield of isolated, analytically pure product. [b]Obtained after transmetalation with $ZnCl_2$ (1.2 equiv, −40 °C, 15 min) and CuCN·2LiCl (1.2 equiv, −40 °C, 15 min). [c]Obtained after transmetalation with $ZnCl_2$ (1.2 equiv, −40 °C, 15 min) using 3 mol % $Pd(dba)_2$ and 6 mol % P(2-furyl)$_3$.

and 11). Finally, the reaction of **8** with bis(phenylsulfonyl) sulfide[13] produced the pentathio derivative **9l** in 75% yield (entry 12).

Subsequent metalation of 1,4-dithiin derivatives of type **9** was achieved using either TMPMgCl·LiCl (**6**) or TMPZnCl·LiCl (**7**). In the case of less sensitive substituents E^1, magnesiation with **6** was readily performed at −78 °C (in only 0.5 h). In the same way, 1,4-diithins **9e−g** were magnesiated with **6** (1.05−1.1 equiv) and quenched with standard electrophiles (I_2, C_2Cl_6, $NCCO_2Et$, and Tietze's reagent[12]), leading to 2,3-disubstituted 1,4-dithiins **11a−d** in 43−90% yield (Table 2, entries 1−4). Similarly, the more sensitive 1,4-dithiins **9a**, **9b**, **9d**, and **9h** were zincated with **7** between −40 and 0 °C[14] and quenched with halogenated electrophiles, leading to 2,3-disubstituted 1,4-dithiins **11e−i** in 50−86% yield (entries 5−9). A third metalation was achieved on 2,3,5-tribromo-1,4-dithiin (**12**), previously obtained by bromination of **11g** (84% yield, Scheme 2), as treatment of **12** with **7** at −78 °C for 10 min furnished the corresponding zinc reagent, which provided tetrabromo-1,4-dithiin **13** after bromination with $(BrCCl_2)_2$ in 56% yield.

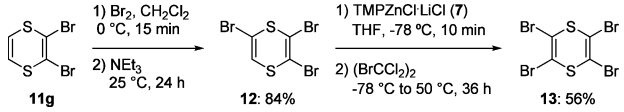
The same metalation procedure was applied to the condensed S-heterocycle TTN (**4**) using TMPMgCl·LiCl. This magnesiation proceeded at −78 °C in 10 min and produced a magnesiated TTN that reacted smoothly with typical electrophiles (by iodolysis, bromination, cyanation, thiomethylation, carbonylation, and acylation), leading to

Table 2. Preparation of Disubstituted 1,4-Dithiin-Derivatives of Type 11 by Metalation of Dithiins of Type 9 Using Mg- and Zn-TMP Bases 6 and 7

entry	substrate	electrophile	product of type 11[a]
			
1	**9e**	$Me_2N{=}CH_2OCOCF_3$	**11a**: $E^2 = CH_2NMe_2$, 64%[b]
2	**9e**	C_2Cl_6	**11b**: E^2 = Cl, 43%[b]
			
3	**9g**	I_2	**11c**: E^2 = I, 62%[b]
4	**9g**	$NCCO_2Et$	**11d**: $E^2 = CO_2Et$, 90%[b]
		I_2	
5	**9a**		**11e**: 68%[c]
			
6	**9b**	$(BrCCl_2)_2$	**11f**: E^2 = Br, 50%[c]
7	**9b**		**11g**: E^2 = Allyl, 74%[c]
		I_2	
8	**9d**		**11h**: 86%[d]
		I_2	
9	**9h**		**11i**: 78%[c]

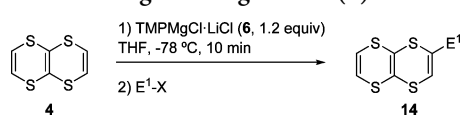
[a]Yields of isolated, analytically pure products. [b]TMPMgCl·LiCl (1.05−1.1 equiv, −78 °C, 0.5 h) was used. [c]TMPZnCl·LiCl (1.1 equiv, −40 °C, 0.5 h) was used. [d]TMPZnCl·LiCl (1.1 equiv, 0 °C, 0.5 h) was used.

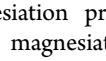
Scheme 2. Synthesis of Tribrominated 1,4-Dithiin 12 and Subsequent Metalation by TMPZnCl·LiCl (7) Leading to Tetrasubstituted Dithiin 13



monosubstituted TTNs **14a−f** in 65−89% yield (Table 3). A second metalation of the monosubstituted TTNs of type **14** was best achieved with TMPZnCl·LiCl (**7**) at −40 °C in 0.5 h,

Table 3. Preparation of Monosubstituted TTNs by Metalation of 4 Using TMPMgCl·LiCl (6)



entry	electrophile	product of type 14[a]
1	I_2	**14a**: E^1 = I, 89%
2	$(BrCCl_2)_2$	**14b**: E^1 = Br, 89%
3	TsCN	**14c**: E^1 = CN, 73%
4	$MeSO_2SMe$	**14d**: E^1 = SMe, 78%
5	$NCCO_2Et$	**14e**: $E^1 = CO_2Et$, 72%
6		**14f**: E^1 = CO*c*Pr, 65%[b]

[a]Yields of isolated, analytically pure products. [b]CuCN·2LiCl was used.

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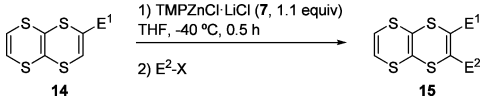
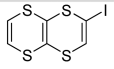
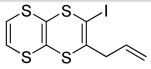
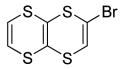
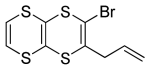
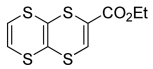
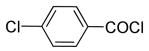
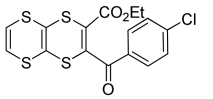
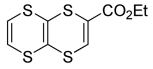
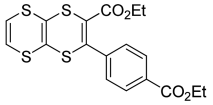
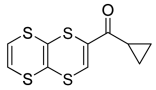
providing 3,4-disubstituted TTNs **15a–e** in 55–83% yield after quenching with allyl bromide, acyl chloride, aryl iodide (Negishi cross-coupling), or iodine (Table 4). Finally, we

Table 4. Synthesis of Disubstituted TTN Derivatives of Type 15 Using TMPZnCl·LiCl (7)

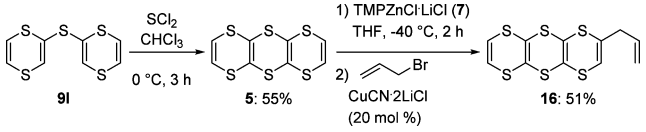


entry	substrate	electrophile	product of type 15[a]
1	 **14a**		 **15a**: 68%[b]
2	 **14b**		 **15b**: 71%[b]
3	 **14d**		 **15c**: 55%[b]
4	 **14d**	I_2	 **15d**: 74%[c]
5	 **14e**		**15e**: E^2 = I, 83%

[a]Yields of isolated, analytically pure products. [b]CuCN·2LiCl was used. [c]$Pd(dba)_2$ (6 mol %) and P(2-furyl)$_3$ (12 mol %) were used.

prepared the new hexathiaanthracene (HTA, **5**) using the previously described dithiin **9l** (Table 1, entry 9) by a condensation with SCl_2 in chloroform (0 °C, 3 h, 55% yield; Scheme 3).[15] X-ray analysis of this new condensed S-

Scheme 3. Synthesis of 1,4,5,6,9,10-Hexathiaanthracene (5) and Subsequent Functionalization by TMPZnCl·LiCl (7)



heterocycle showed that this molecule is not planar but rather that the conformation of **5** is best viewed as a fused boat system of three units linked together (Figure 2).[14,16] The mild Zn-TMP base **7** reacted with **5** to provide a zincated intermediate that was readily allylated, leading to S-heterocycle **16** in 51% yield.

The substituted 1,4-dithiins prepared above are interesting building blocks for the construction of more elaborated S-heterocycles. Consequently, the treatment of **9k** with 2-thiophenecarboxaldehyde in EtOH under microwave irradiation (130 °C, 15 min) produced tricyclic heterocycle **17** in 60% yield (Scheme 4). Moreover, 2,3-disubstituted dithiin **11c** was submitted to a Sonogashira cross-coupling leading to

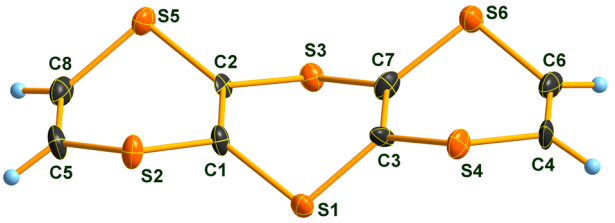
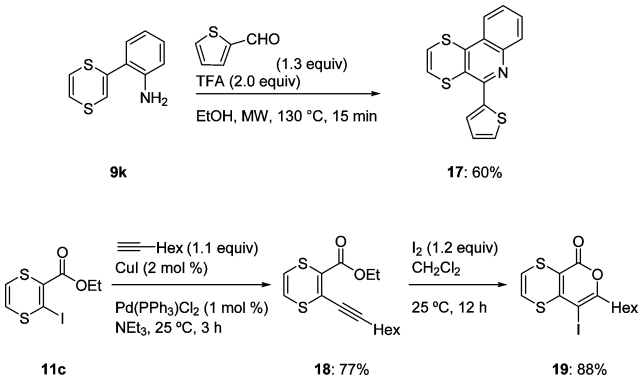


Figure 2. Crystal structure of HTA (**5**).

Scheme 4. Ring Closure of 9k and 11c Leading to S-Heterocycles



alkyne **18** in 77% yield. Treatment with iodine in CH_2Cl_2 produced the endo cyclization product **19** in 88% yield.

In summary, we have shown that TMPMgCl·LiCl (**6**) and TMPZnCl·LiCl (**7**) are excellent bases for facile metalation of the sensitive 1,4-dithiin scaffold. Interestingly, these metalation procedures can be extended to the condensed heterocycles TTN and HTA. The preparation of additional S-heterocycles via metalation of **6** or **7** is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03539.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1518627 (**5**), 1518630 (**11e**), 1518626 (**14c**), 1518629 (**14d**), and 1518628 (**9l**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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