

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

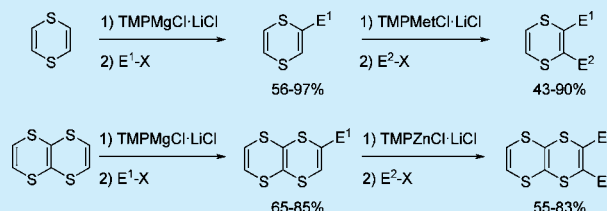
Alicia Castelló-Micó,[†] Julia Nafe,[†] Kosuke Higashida,[†] Konstantin Karaghiosoff,[†] Marc Gingras,[‡] and Paul Knochel^{*,†}

[†]Department Chemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377 München, Germany

[‡]CNRS, Aix-Marseille Université, CINAM UMR 7325, 163 Avenue de Luminy, 13288 Marseille, France

S 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 chemistry¹ and materials science.² Especially, 1,4-dithiins of type **1** (Figure 1) have attracted

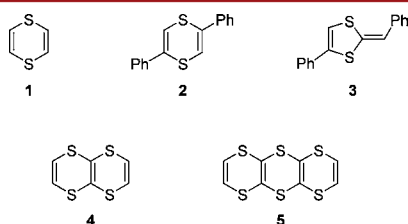
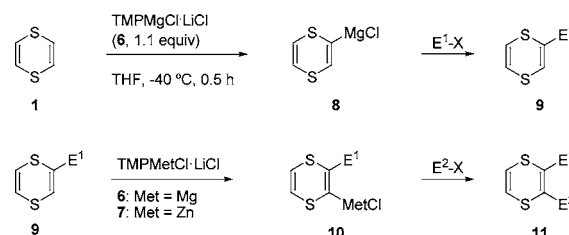


Figure 1. 1,4-Dithiin derivatives and condensed analogues.

attention because of their unique electronic and conducting properties³ 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 $-110\text{ }^{\circ}\text{C}$.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**).

We have found that the metalation of **1** with **6** produces the magnesiated 1,4-dithiin **8** at $-40\text{ }^{\circ}\text{C}$ 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 ($\text{E}^1\text{-X}$) 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 electrophiles produces a range of 2,3-disubstituted 1,4-dithiins **11**. Thus, the magnesiated 1,4-dithiin **8** was readily halogenated using iodine, tetrachlorodibromomethane, 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

Received: November 28, 2016

Published: December 30, 2016

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 ₆ H ₅ SO ₂ Cl	9c : R = Cl, 56%
4	TsCN	9d : R = CN, 60%
5	Me ₂ N=CH ₂ OCOCF ₃	9e : R = CH ₂ NMe ₂ , 58%
6	PhCHO	9f : R = CHO ^b , 97%
7	NCCO ₂ Et	9g : R = OEt, 89%
8	PhCOCl	9h : R = Ph, 78% ^b
9		9i : R = cPr, 65% ^b
10		9j : 73% ^b
11		9k : 94% ^c
12	(PhSO ₂) ₂ S	9l : 75%

^aYield of isolated, analytically pure product. ^bObtained after transmetalation with ZnCl₂ (1.2 equiv, -40 °C, 15 min) and CuCN·2LiCl (1.2 equiv, -40 °C, 15 min). ^cObtained after transmetalation with ZnCl₂ (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) sulfide¹³ produced the pentathio derivative **9l** in 75% yield (entry 12).

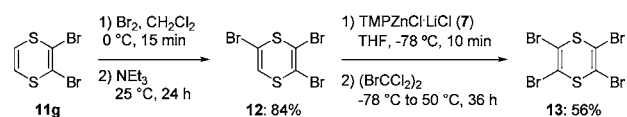
Subsequent metalation of 1,4-dithiin derivatives of type **9** was achieved using either TMPMgCl·LiCl (**6**) or TMPZnCl·LiCl (**7**). In the case of less sensitive substituents E¹, magnesiation with **6** was readily performed at -78 °C (in only 0.5 h). In the same way, 1,4-dithiins **9e–g** were magnesiated with **6** (1.05–1.1 equiv) and quenched with standard electrophiles (I₂, C₂Cl₆, NCCO₂Et, and Tietze's reagent¹²), 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 °C¹⁴ 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 (BrCCl₂)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 ₂ N=CH ₂ OCOCF ₃	11a : E ² = CH ₂ NMe ₂ , 64% ^b
2	9e	C ₂ Cl ₆	11b : E ² = Cl, 43% ^b
3	9g	I ₂	11c : E ² = I, 62% ^b
4	9g	NCCO ₂ Et	11d : E ² = CO ₂ Et, 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

^aYields of isolated, analytically pure products. ^bTMPMgCl·LiCl (1.05–1.1 equiv, -78 °C, 0.5 h) was used. ^cTMPZnCl·LiCl (1.1 equiv, -40 °C, 0.5 h) was used. ^dTMPZnCl·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 Tetrabrominated 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 ₂ SMe	14d : E ¹ = SMe, 78%
5	NCCO ₂ Et	14e : E ¹ = CO ₂ Et, 72%
6		14f : E ¹ = COcPr, 65% ^b

^aYields of isolated, analytically pure products. ^bCuCN·2LiCl was used.

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

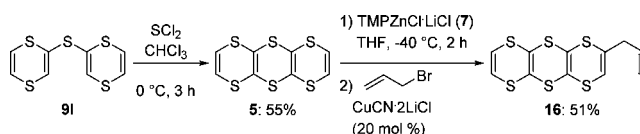
Table 4. Synthesis of Disubstituted TTN Derivatives of Type 15 Using TMPZnCl·LiCl (7)

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

^aYields of isolated, analytically pure products. ^bCuCN·2LiCl was used. ^cPd(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 SCl₂ 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

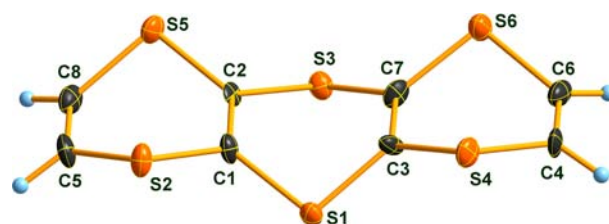
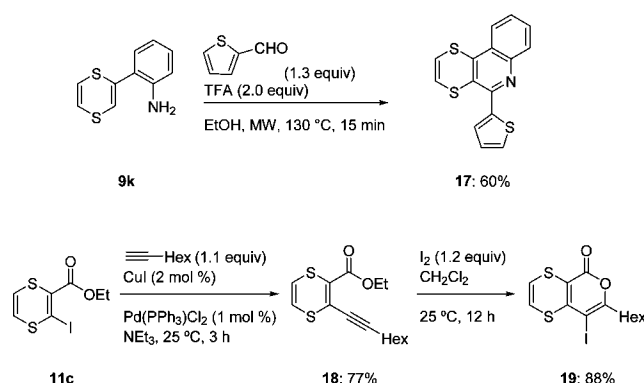


Figure 2. Crystal structure of HTA (**5**).

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



alkyne **18** in 77% yield. Treatment with iodine in CH₂Cl₂ 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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

ORCID

Paul Knochel: 0000-0001-7913-4332

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research received funding from the Deutsche Forschungsgesellschaft. We also thank BASF AG (Ludwigshafen) and Albemarle (Frankfurt) for generous gifts of chemicals.

■ REFERENCES

(1) (a) Metzner, P.; Thuillier, A. In *Sulfur Reagents in Organic Synthesis*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic

- Press: London, 1994. (b) Carmack, M. *Sulfur Rep.* **1995**, *16*, 299. (c) Senning, A. *Sulfur Rep.* **2003**, *24*, 191. (d) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39. (e) Hu, Y.; Li, C.-Y.; Wang, X.-M.; Yang, Y.-H.; Zhu, H.-L. *Chem. Rev.* **2014**, *114*, 5572.
- (2) (a) Gingras, M.; Raimundo, J.-M.; Chabre, Y. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1686. (b) Wu, W.; Liu, Y.; Zhu, D. *Chem. Soc. Rev.* **2010**, *39*, 1489. (c) Ito, H.; Watanabe, D.; Yamamoto, T.; Tsushima, N.; Muraoka, H.; Ogawa, S. *Chem. Lett.* **2013**, *42*, 646. (d) Boyd, D. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 15486.
- (3) (a) Kao, J.; Lilly, A. C. *J. Am. Chem. Soc.* **1987**, *109*, 4149. (b) Bryce, M. R.; Chesney, A.; Lay, A. K.; Batsanov, A. S.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2451. (c) Guillaumet, G.; Suzenet, F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2008; Vol. 8, pp 857–905. (d) Peintinger, M. F.; Beck, J.; Bredow, T. *Phys. Chem. Chem. Phys.* **2013**, *15*, 18702.
- (4) (a) Parham, W. E. In *Organic Sulfur Compounds*; Kharasch, N., Ed.; Pergamon Press: New York, 1961; Vol. 1, pp 248–256. (b) Kobayashi, K.; Gajurel, C. L. *Sulfur Rep.* **1986**, *7*, 123.
- (5) (a) Saebo, S.; Radom, L.; Ritchie, G. L. D. *J. Mol. Struct.: THEOCHEM* **1984**, *108*, 59. (b) Borbulevych, O. Y.; Shishkin, O. V. *J. Mol. Struct.* **1998**, *446*, 11. (c) Pelloni, S.; Faglioni, F.; Soncini, A.; Ligabue, A.; Lazzeretti, P. *Chem. Phys. Lett.* **2003**, *375*, 583. (d) Vessally, E. *Bull. Chem. Soc. Ethiop.* **2008**, *22*, 465. (e) Ilkhani, A. R.; Hermoso, W.; Bersuker, I. B. *Chem. Phys.* **2015**, *460*, 75.
- (6) (a) Schoufs, M.; Meyer, J.; Vermeer, P.; Brandsma, L. *Rec. Trav. Chim. Pays-Bas* **1977**, *96*, 259. For other selective metalations of heterocycles, see: (b) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (d) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139. (e) Pelletier, G.; Constantineau-Forget, L.; Charette, A. B. *Chem. Commun.* **2014**, *50*, 6883.
- (7) Andreu, R.; Garín, J.; Orduna, J.; Royo, J. M. *Tetrahedron Lett.* **2001**, *42*, 875.
- (8) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) García-Álvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079.
- (9) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (b) Bresser, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1914. (c) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584. (d) Unsinn, A.; Ford, M. J.; Knochel, P. *Org. Lett.* **2013**, *15*, 1128. (e) Blanc, R.; Groll, K.; Bernhardt, S.; Stockmann, P. N.; Knochel, P. *Synthesis* **2014**, *46*, 1052. (f) Shen, Z.-L.; Sommer, K.; Knochel, P. *Synthesis* **2015**, *47*, 2617.
- (10) (a) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794. (b) Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958. (c) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253. (d) Sämann, C.; Coia, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1430. (e) Dhayalan, V.; Knochel, P. *Synthesis* **2015**, *47*, 3246. (f) Klier, L.; Aranzamendi, E.; Ziegler, D.; Nickel, J.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Org. Lett.* **2016**, *18*, 1068. (g) Nafe, J.; Knochel, P. *Synthesis* **2016**, *48*, 103. (h) Benischke, A. D.; Ellwart, M.; Becker, M. R.; Knochel, P. *Synthesis* **2016**, *48*, 1101.
- (11) (a) Meline, R. L.; Elsenbaumer, R. L. *Synth. Met.* **1997**, *86*, 1845. (b) Meline, R. L.; Elsenbaumer, R. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2467.
- (12) (a) Kinast, G.; Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239. (b) Werner, V.; Ellwart, M.; Wagner, A. J.; Knochel, P. *Org. Lett.* **2015**, *17*, 2026.
- (13) (a) Dötze, M.; Klar, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *84*, 95. (b) Kerverdo, S.; Fernandez, X.; Poulain, S.; Gingras, M. *Tetrahedron Lett.* **2000**, *41*, 5841. (c) Kerverdo, S.; Gingras, M. *Tetrahedron Lett.* **2000**, *41*, 6053.
- (14) See the [Supporting Information](#).
- (15) Amosova, S. V.; Penzik, M. V.; Potapov, V. A.; Albanov, A. I. *Chem. Heterocycl. Compd.* **2013**, *48*, 1716.
- (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.