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Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

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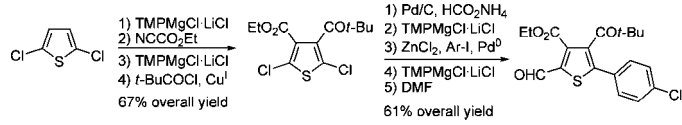
ABSTRACT



A full functionalization of all four positions of the thiophene ring was achieved. Starting from readily available 2,5-dichlorothiophene, successive magnesiations of the 3- and 4-positions using TMPMgCl·LiCl furnish, after trapping with various electrophiles, 3,4-difunctionalized dichlorothiophenes. Subsequent dechlorination and metalation or magnesium insertion into the C−Cl bond provides fully functionalized thiophenes in high yields. An application to the synthesis of a thiophene analogue of Atorvastatin (Lipitor) is reported.

The thiophene moiety is an important building block for various new materials[1] and modern drug design.[2] Five of the 100 top selling drugs in the U.S. in 2007 included a thiophene subunit.[3] Directed lithiations are known for all positions of the thiophene ring but often require low temperatures and have a low tolerance toward functional groups.[4] Magnesiations using amide bases or magnesates are compatible with some sensitive functionalities but can only be performed at the activated 2- or 5-positions.[5] Recently, we have reported directed magnesiations of aromatic and heteroaromatic substrates using the new mixed Mg/Li-amide TMPMgCl·LiCl (**1**; TMP = 2,2,6,6-tetramethylpiperidyl).[6] Herein we report that by using this reagent, it is possible to fully functionalize the thiophene ring starting from commercially available 2,5-dichlorothiophene (**2**). Thus, the thiophene **2** can be successively metalated at both the 3- and 4-position using TMPMgCl·LiCl (**1**) and leads, after quenching with electrophiles, to substituted thiophenes of type **5**. The chlorine atoms at the 2- and 5-positions are excellent directing groups for the metalations at the 3- and 4-positions. After reductive cleavage of the C−Cl bonds, the intermediate **6** is then regioselectively deprotonated at the 2- and then the 5-position again using TMPMgCl·LiCl (**1**), leading to fully functionalized thiophenes of type **7** (Scheme 1).

Thus, the reaction of 2,5-dichlorothiophene (**2**) with TMPMgCl·LiCl (**1**; 1.1 equiv, 25 °C, 30 min) leads to the corresponding 3-magnesiated thiophene **3**, which can be trapped with $PhSO_2SMe$ giving the thiomethylated compound **4a** in 92% yield. The subsequent deprotonation of **4a** using TMPMgCl·LiCl (**1**) also proceeds smoothly (−10 °C, 30

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(2) (a) Swanston, J. Thiophenes. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2006. (b) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723. For recent examples see: (c) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Iaconinoto, M. A.; Preti, D.; Shryock, J. C.; Moorman, A. R.; Vincentzi, F.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2008**, *51*, 5875. (d) Aurelio, L.; Figler, H.; Flynn, B. L.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2008**, *16*, 1319.

(3) Plavix®, Cymbalta®, Zyprexa®, Spiriva® and Evista®: Lamb, E. *Pharm. Times* **2008**, (May), 20.

(4) (a) Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362. (b) Doat, E. G.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1149.

(5) (a) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442. (b) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron* **2005**, *61*, 4779.

(6) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (d) Clososki, G.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (e) Rohbogner, C. J.; Clososki, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503.

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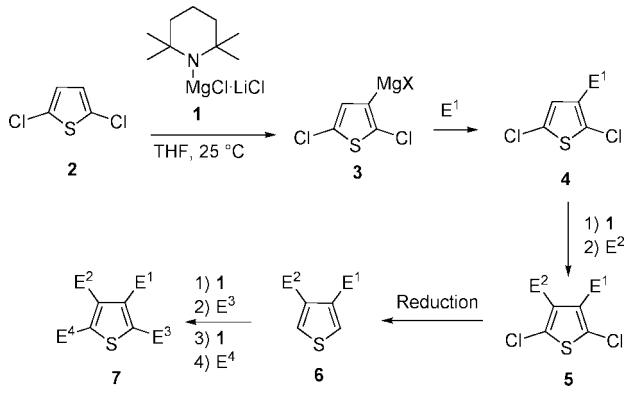
Scheme 1. Reaction Sequence Starting from 2,5-Dichlorothiophene (**2**) for the Synthesis of Fully Functionalized Thiophenes of Type **7**

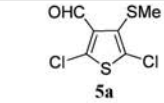
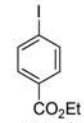
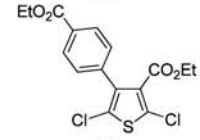
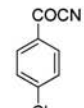
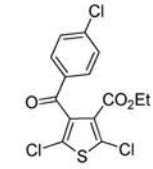
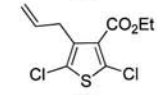
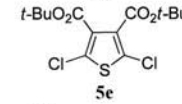
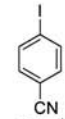
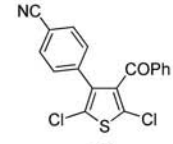
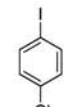
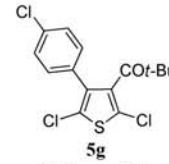
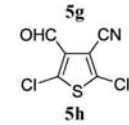
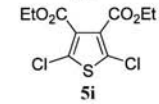
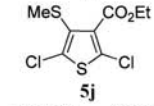
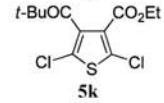
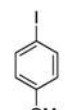
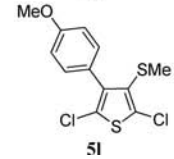


min), and the resulting magnesiated intermediate is reacted with DMF, yielding the aldehyde **5a** in 95% yield (Table 1, entry 1).

Treatment of the magnesiated intermediate **3** with ethyl cyanoformate yields the ester **4b**[7] in 76% yield. A subsequent deprotonation of **4b**[7] proceeds smoothly (−30 °C, 30 min), and the expected products **5b**−**d** are isolated in 76−95% yield after a Pd-catalyzed cross-coupling[8] reaction, a reaction with an acid cyanide,[9] or a Cu(I)-catalyzed allylation[10] (entries 2−4). Similarly, the 3-magnesiated thiophene **3** reacts directly with Boc_2O affording the ester **4e**[7] in 82% yield. Subsequent metalation and again trapping with Boc_2O furnishes the diester **5e** in 79% yield (entry 5). Ketones are sensitive functional groups and often react with polar organometallics. However, the Cu(I)-catalyzed[10] quenching of the 3-thienylmagnesium reagent **3** with acid chlorides affords the ketones **4f**[7] and **4g**.[7] These ketones readily undergo metalation using **1** (−78 to −50 °C, 30 to 45 min), and after Negishi cross-coupling[8] reactions with 4-iodobenzonitrile or 4-chloroiodobenzene, the arylated products **5f** and **5g** are obtained in 77−84% yield (entries 6 and 7). Similarly, a cyano-function is tolerated as well. Thus, the treatment of the magnesium reagent **3** with TsCN furnishes the nitrile **4h**[7] in 73% yield. After a subsequent metalation of **4h**[7] (−30 °C, 15 min) and trapping of the resulting magnesium reagent with DMF, the functionalized aldehyde **5h** is obtained in 86% yield (entry 8).

The synthesis of 3,4-substituted chlorothiophenes of type **5** is also possible using the crude intermediate products of type **4**. Thus, the reaction of the magnesium compound **3** with ethyl cyanoformate gives the corresponding 3-substi-

Table 1. Synthesis of 3,4-Disubstituted Thiophenes of Type **5**

entry	E^1 (yield)[a]	E^2 (yield)[a]	product
1	$PhSO_2SMe$ (92%)	DMF (95%)	 **5a**
2	$NCCO_2Et$ (76%)	 (95%)[b]	 **5b**
3	$NCCO_2Et$ (76%)	 (76%)	 **5c**
4	$NCCO_2Et$ (76%)	allyl bromide (85%)[c]	 **5d**
5	Boc_2O (82%)	Boc_2O (79%)	 **5e**
6	PhCOCl (78%)[c]	 (84%)[b]	 **5f**
7	*t*-BuCOCl (75%)[c]	 (77%)[b]	 **5g**
8	TsCN (73%)	DMF (86%)	 **5h**
9	$NCCO_2Et$	$NCCO_2Et$ (87%[d])	 **5i**
10	$NCCO_2Et$	$PhSO_2SMe$ (73%[d])	 **5j**
11	$NCCO_2Et$	*t*-BuCOCl (67%[d,c])	 **5k**
12	$PhSO_2SMe$	 (84%[d,b])	 **5l**

[a] Isolated yield of analytically pure product. [b] After transmetalation using $ZnCl_2$ (1.1 equiv) and a Pd-catalyzed cross-coupling reaction. [c] After transmetalation using CuCN·2LiCl (20 mol %). [d] Overall yield over two steps.

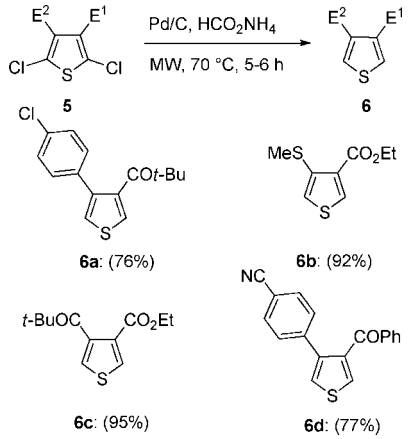
(7) All compounds are depicted in Supporting Information, and their preparation is fully described.

(8) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E *Acc. Chem. Res.* **1982**, *15*, 340. A transmetalation from Mg to Zn proved to be convenient due to the higher stability of Zn-reagents compared to the corresponding Mg-reagents.

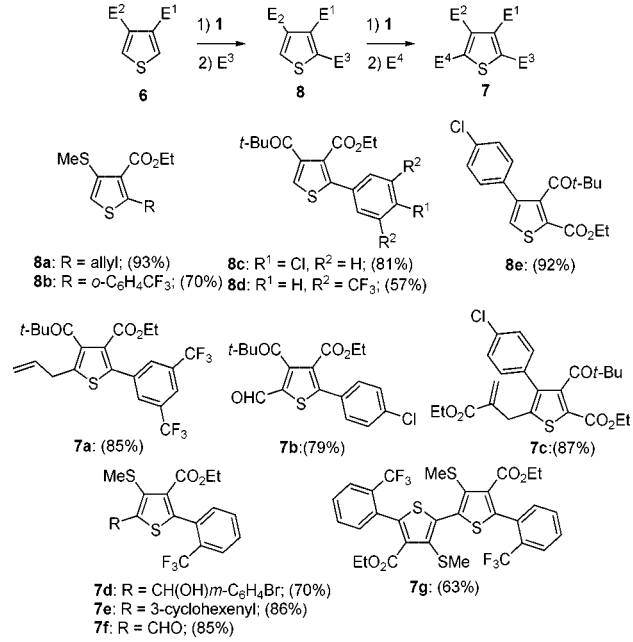
(9) Duplais, C; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiéz, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2968.

(10) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

Scheme 2. Synthesis of Thiophenes of Type **6** using Pd/C and HCO_2NH_4 under Microwave Irradiation



Scheme 3. Synthesis of Fully Substituted Thiophenes of Type **7**



tuted dichlorothiophene. After an aqueous workup, the crude mixture is again treated with TMPMgCl·LiCl (**1**; −30 °C, 30 min) and quenched with $NCCO_2Et$, yielding the diester **5i** in 87% overall yield (entry 9). Similarly, $PhSO_2SMe$ or an acid chloride can be used as a second electrophile (E^2) leading to the 3,4-substituted thiophenes **5j** and **5k** in 67−73% overall yield (entries 10 and 11). When quenching the thienylmagnesium reagent **3** with $PhSO_2SMe$, the subsequent deprotonation of the crude reaction mixture proceeds smoothly (−10 °C, 30 min), and the resulting magnesium reagent can be used in a Pd-catalyzed cross-coupling reaction[8] to give the expected product **5l** in 84% overall yield (entry 12).

The reductive cleavage of a carbon-chlorine bond can be achieved by various metal-catalyzed reactions.[11] We chose the method developed by Schlosser using Pd/C and ammonium formate as a reductive system.[12] However, we have observed that conventional heating leads to a sluggish reaction. For example, the reduction of the dichlorothiophene **5g** in EtOH at 80 °C using a sealed tube requires 5 days to achieve completion. However, by using microwave irradiation (100 W, 70 °C, open vessel), the reduction is complete within 5 h and the dechlorinated thiophene **6a** is isolated in 76% yield.

Remarkably, this reduction is completely selective and only reduces the carbon−chlorine bonds at the thiophene ring without affecting other aromatic C−Cl bonds (see Scheme 2, compound **6a**). The same procedure is used for the chlorothiophenes **5f**, **5j**, and **5k** (5−6 h, 100 W, 70 °C, open vessel) furnishing the dechlorinated products **6b**−**d** in 77−95% yield (Scheme 2).

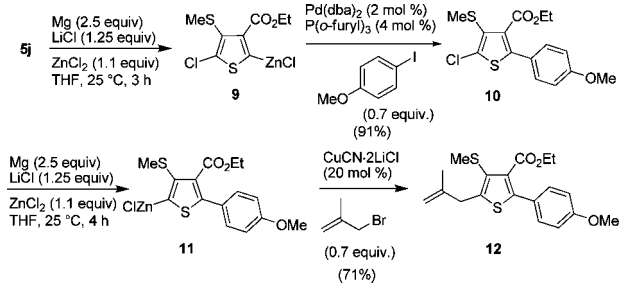
A further deprotonation of the dechlorinated thiophenes of type **6** is achieved with complete regioselectivity. When treating the thiophene **6b** and **6c** with TMPMgCl·LiCl (**1**; 1.1 equiv, −40 to −30 °C, 30−60 min), the ester moiety is acting as a directing group[13] and magnesation occurs regioselectively next to this ester group. Cu(I)-catalyzed allylation[10] or Pd-catalyzed cross-coupling reactions[8] afford the expected products **8a**−**8d** in 57−93% yield. Similarly, a ketone can also play the role of an efficient directing group, and the product **8e** is isolated in 92% yield after deprotonation of **6a** and quenching with $NCCO_2Et$.

The remaining 5-position can be metalated as well between −50 and −20 °C with TMPMgCl·LiCl (**1**; 1.1 equiv, 30−45 min). The resulting magnesiated intermediates are trapped with aldehydes and DMF or can be used in allylations[10] or cross-coupling reactions[8] furnishing the fully substituted thiophene derivatives **7a**−**7f** in 70−87% yield. Moreover, the magnesiated thiophene derived from thiophene **8b** can be subjected to a transition-metal-free homocoupling reaction using chloranil,[14] and the highly functionalized dithiophene **7g** is obtained in 63% yield (Scheme 3).

Recently, we have reported a LiCl-mediated magnesium insertion into aryl chlorides and bromides under mild and convenient conditions.[15]By using this method, the dichlorothiophenes of type **5** can also be magnesiated directly at the 2- and 5-positions. Thus, the addition of the dichlorothiophene **5j** to Mg turnings (2.5 equiv), LiCl (1.25 equiv), and $ZnCl_2$ (1.1 equiv) in THF regioselectively gives the zincated intermediate **9** (25 °C, 3 h), which can be arylated in a Pd-catalyzed reaction with 4-iodoanisole leading to the

(11) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.
(12) (a) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116. (b) Bobbio, C.; Rausis, T.; Schlosser, M. *Chem. Eur. J.* **2005**, *11*, 1903.
(13) (a) Macklin, T.; Snieckus, V. In *Handbook of C−H Transformations*; Dyker G., Ed.; Wiley-VCH: Weinheim, 2005; p 106. (b) Hartung, C. G.; Snieckus V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; p 330.
(14) Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5010.
(15) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.

Scheme 4. Magnesium Insertion into Dichlorothiophenes of Type **5**

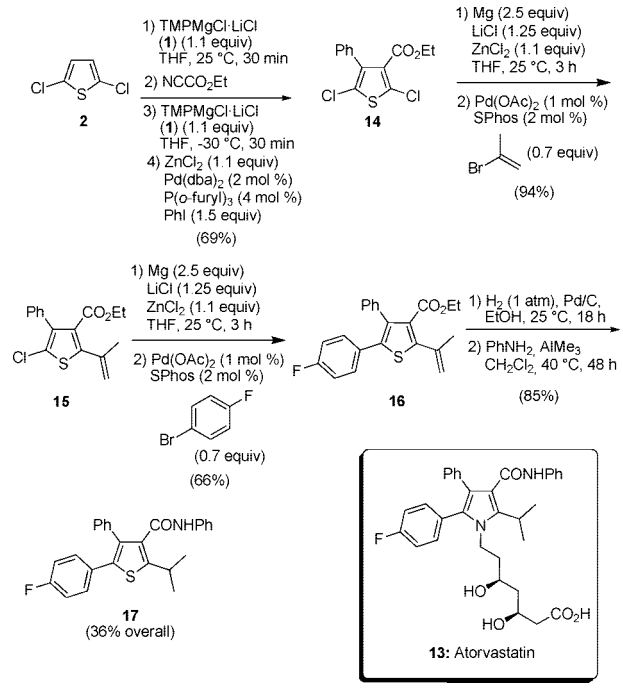


arylated product **10** in 91% yield. Repeated treatment of **10** with Mg turnings, LiCl, and $ZnCl_2$ (25 °C, 4 h) affords the zinc compound **11**, and following an allylation reaction catalyzed by CuCN·2LiCl (20 mol %),[10] the fully functionalized thiophene **12** is isolated 71% yield (Scheme 4).

As an application, we have prepared a thiophene analogue of Atorvastatin (**13**; Lipitor, HMG-CoA reductase inhibitor, anticholesterol agent) starting from 2,5-dichlorothiophene (**2**).[16] Using the procedure described above, selective deprotonations and successive quenching with ethyl cyanoformate and iodobenzene in a Negishi cross-coupling reaction furnishes the 3,4-disubstituted dichlorothiophene **14** in 69% yield. Regioselective magnesium insertion in the presence of LiCl and $ZnCl_2$ (25 °C, 3 h) and subsequent Pd-catalyzed cross-coupling with 2-bromopropene (using $Pd(OAc)_2$ and SPhos[17] as a catalytic system) affords the alkene **15** in 94% yield. The Mg-insertion into the remaining C−Cl bond of **15** proceeds smoothly (25 °C, 3 h). A Negishi cross-coupling reaction with 4-bromofluorobenzene then yields the arylated product **16** in 66% yield. After hydrogenation of the double-bond and amide formation using Weinreb's method[18] ($PhNH_2$, $AlMe_3$), the thiophene analogue **17** of Atorvastatin (**13**) is obtained in 85% yield (36% overall yield, Scheme 5).

In summary, we have reported a complete functionalization of all positions of the thiophene ring starting from readily

Scheme 5. Application to the Synthesis of a Thiophene-Based Atorvastatin (Lipitor) Derivative



available 2,5-dichlorothiophene (**2**) using the powerful base TMPMgCl·LiCl (**1**).[19] This method is tolerating important functional groups, such as ketones, esters or nitriles. Extensions of this reaction to other heterocyclic systems is currently underway in our laboratories.

Acknowledgment. We thank the European Research Council (ERC), the Deutsche Forschungsgemeinschaft (DFG), SFB 749, and the Fonds der Chemischen Industrie for financial support. We thank W. C. Heraeus GmbH (Hanau), Chemetall GmbH (Frankfurt), BASF AG (Ludwigshafen), and Evonik Industries AG (Hanau) for the generous gift of chemicals.

Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802513Q

(16) Similar structures have been reported as steroid nuclear receptor modulators and protein kinase inhibitors: (a) Flatt. B.; Gu, X. H.; Martin, R.; Mohan, R.; Murphy, B.; Nyman, M.; Stevens, W. C.; Wang, T. L.; Bannen, L. C. Patent WO 2007024744, 2007. (b) Brenchley, G.; Charrier, J.-D.; Durrant, S.; Knetgel, R; Ramaya, S. Patent WO 2007139816, 2007.

(17) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 468.

(18) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.

(19) TMPMgCl·LiCl (**1**) is available from Chemetall (Frankfurt) and Aldrich.