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Regio- and Chemoselective Synthesis of Fully Substituted Thiophenes

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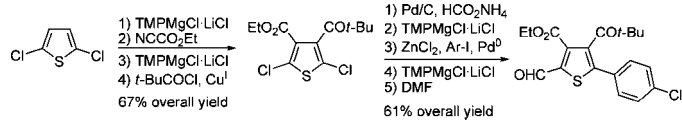
ABSTRACT



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.

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(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.

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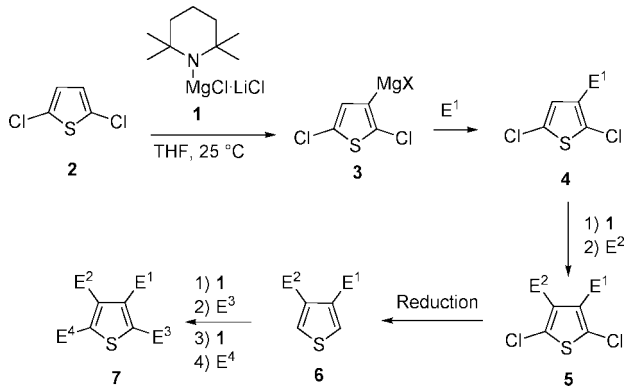
Scheme 1. Reaction Sequence Starting from 2,5-Dichlorothiophene (**2**) for the Synthesis of Fully Functionalized Thiophenes of Type **7**



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-

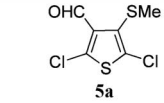
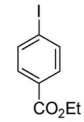
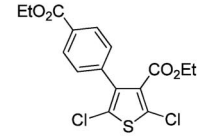
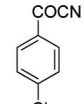
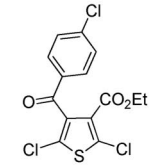
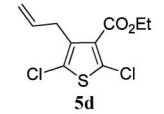
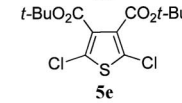
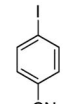
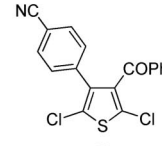
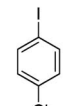
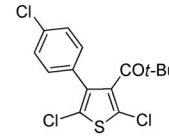
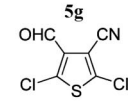
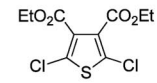
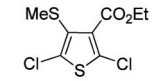
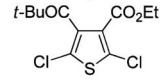
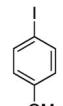
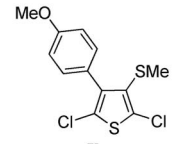
(7) All compounds are depicted in Supporting Information, and their preparation is fully described.

(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.

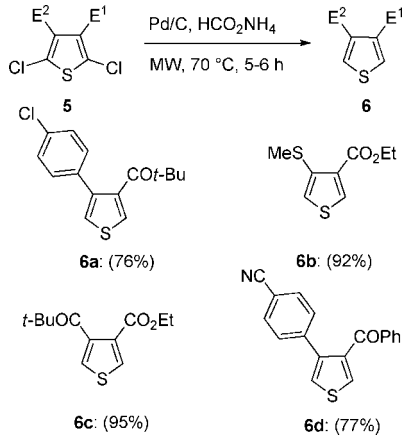
(10) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

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

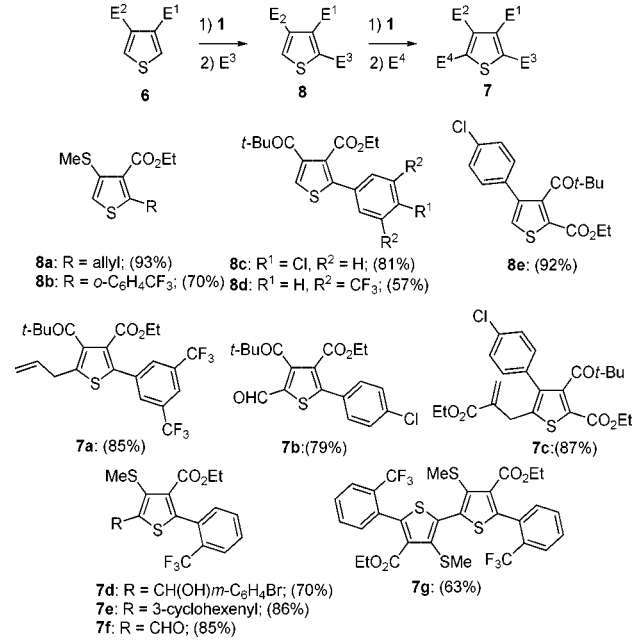
entry	E^1 (yield)[a]	E^2 (yield)[a]	product
1	$PhSO_2SMe$ (92%)	DMF (95%)	 **5a**
2	$NCCO_2Et$ (76%)	 (CO_2Et) (95%)[b]	 **5b**
3	$NCCO_2Et$ (76%)	 (COCN, Cl) (76%)	 **5c**
4	$NCCO_2Et$ (76%)	allyl bromide (85%)[c]	 **5d**
5	Boc_2O (82%)	Boc_2O (79%)	 **5e**
6	PhCOCl (78%)[c]	 (CN) (84%)[b]	 **5f**
7	*t*-BuCOCl (75%)[c]	 (Cl) (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	$PhSO_2SMe$	 (OMe) (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.

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).

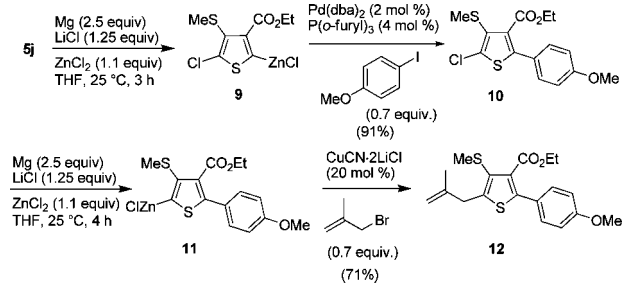
A further deprotonation of the dechlorinated thiophenes of type **6** is achieved with complete regioselectivity. When treating the thiophene **6b** and **6c** with TMPMgCl·LiCl (**1**; 1.1 equiv, −40 to −30 °C, 30−60 min), the ester moiety is acting as a directing group[13] and magnesation occurs regioselectively 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**

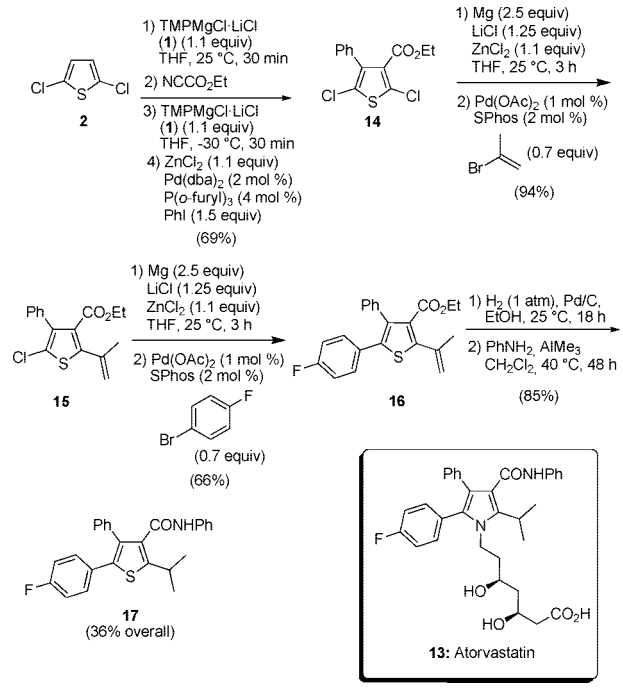


arylated product **10** in 91% yield. Repeated treatment of **10** with Mg turnings, LiCl, and $ZnCl_2$ (25 °C, 4 h) affords the zinc compound **11**, and following an allylation reaction catalyzed by CuCN·2LiCl (20 mol %),[10] the fully functionalized thiophene **12** is isolated 71% yield (Scheme 4).

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.

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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.