2,3-Functionalization of furans, benzofurans and thiophenes *via* magnesiation and sulfoxide–magnesium exchange†

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The use of TMPMgCl·LiCl and *i*PrMgCl·LiCl allows a sequential 2,3-difunctionalization of various 2-arylsulfinyl furans, thiophenes and benzofurans. Subsequent use of the same reagents permits a selective full functionalization of all 4 positions of the furan and thiophene scaffolds.

Substituted furans, benzofurans and thiophenes are important heterocycles that are found in a wide variety of natural compounds and pharmaceutical molecules.[1] They are also building blocks for the elaboration of organic materials.[2] Derivatization of such heterocycles in position 2 by metalation is well established.[3] However, the functionalization of position 3 by directed metalation is much less explored. Recently, we have shown that the sulfoxide group, which has excellent metalation-directing abilities,[4] undergoes also a smooth sulfoxide–magnesium exchange on a variety of aromatic substrates, providing that a *para*-methoxyphenyl group was attached to the sulfur center.[5] Therefore, sulfoxides such as $ArSOC_6H_4OMe$, when treated with *i*PrMgCl·LiCl afford only the magnesium reagent ArMgCl and *p*-$MeOC_6H_4SO$*i*Pr.[5]

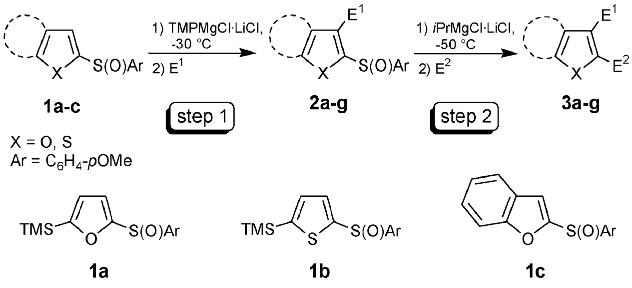
Herein, we report an efficient functionalization of positions 2 and 3 of various 5-membered heterocycles using a sulfoxide–magnesium exchange. Thus, the magnesiation of heteroaryl sulfoxides such as **1a–c** with TMPMgCl·LiCl[6] gave after quenching with an electrophile (E^1) products of type **2**. A sulfoxide–magnesium exchange triggered by *i*PrMgCl·LiCl[7] affords an intermediate magnesium reagent, which after quenching with a second electrophile (E^2), yields 2,3-disubstituted heterocycles of type **3** (Scheme 1).

The required starting 2-arylsulfinyl-heterocycles (**1a–c**) are readily available by the lithiation of benzofuran, 5-TMS-substituted thiophene and furan[8] with BuLi (0 °C, 2 h) followed by the addition of *p*-$MeOC_6H_4SOCl$[9] (1.3 equiv., −78 °C to rt, 1 h) in 47–85% yield.

Thus, the sulfoxide (**1a**) was deprotonated at position 3 with TMPMgCl·LiCl (1.1 equiv.) at −40 °C within 20 min. After transmetalation to the corresponding zinc reagent (using $ZnCl_2$ in THF) a Pd-catalyzed cross-coupling[10] ($Pd(PPh_3)_4$, 2 mol%) with ethyl 4-iodobenzoate gave the expected sulfoxide (**2a**) in 77% yield. The subsequent reaction of **2a** with *i*PrMgCl·LiCl (1.1 equiv.) in 2-methyltetrahydrofuran[11] at −50 °C for 2 h, followed by a Negishi cross-coupling ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h) with 4-chloro-iodobenzene, furnished the 2,3-difunctionalized furan **3a** in 68% yield (Table 1, entry 1). In another two step sequence, the sulfoxide (**1a**) was *ortho*-metalated and trapped with I_2. The resulting 3-iodofuran derivative then underwent a Negishi[12] cross-coupling with phenylethynylzinc chloride leading to the product **2b** in 69% yield.[13] A sulfoxide–magnesium exchange at −50 °C for 15 min, followed by a transmetalation using $ZnCl_2$ in THF and a Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h) with ethyl 4-iodobenzoate gave the desired product **3b** in 68% yield (entry 2).

The thiophene **1b** undergoes the same two step reaction sequence allowing to prepare 2,3-disubstituted thiophenes. Thus, deprotonation of **1b** and trapping with *S*(4-chlorophenyl)-benzene thiosulfonate[14] led to the thioether **2c** in 78% yield. This thiophene **2c** underwent smooth exchange reaction with *i*PrMgCl·LiCl (1.1 equiv., −50 °C, 1 h), furnishing the pyridine derivative **3c** in 67% yield after transmetalation with $ZnCl_2$ and Pd-catalyzed cross-coupling with 5-bromonicotinic acid ethyl ester (entry 3). In another reaction sequence, thiophene **1b** was *ortho*-metalated with TMPMgCl·LiCl, transmetalated with $ZnCl_2$ and reacted with 4-iodobenzonitrile and 3-iodo-anisole ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h), yielding thienyl sulfoxides **2d** and **2e** in 87–89% yield. The two thiophenes **2d** and **2e** were submitted to a sulfoxide–magnesium exchange, which gave the desired secondary alcohol **3d** and the aryl-disubstituted thiophene **3e** by respective quenching of the intermediate magnesium compound with 3,4-dichloro-benzaldehyde, or cross-coupling with 4-iodobenzonitrile ((i) $ZnCl_2$; (ii) $Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h) in 83–85% yield (entries 4 and 5).

Also, benzofuran underwent *ortho*-magnesiation with TMPMgCl·LiCl (1.1 equiv., −50 °C, 45 min) and led after quenching with *S*(4-chlorophenyl)benzene thiosulfonate or after a Negishi cross-coupling with 1-fluoro-4-iodobenzene ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h) to the benzofurans **2f** and **2g** in 80–88% yield. Again, a sulfoxide–magnesium exchange with *i*PrMgCl·LiCl (1.1 equiv., −50 °C, 5 min) and coupling



Scheme 1 2,3-Difunctionalization of 5-membered heterocycles.

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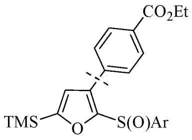
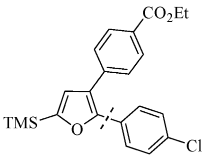
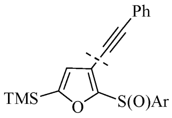
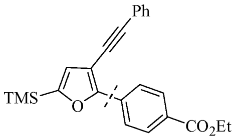
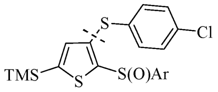
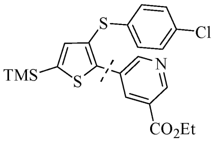
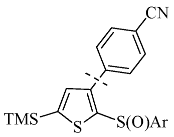
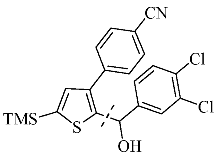
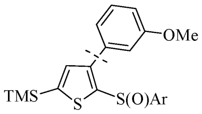
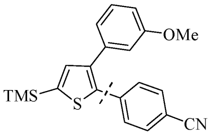
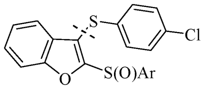
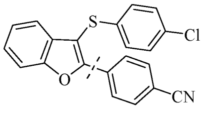
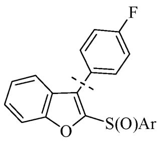
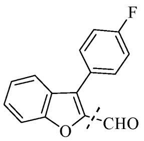
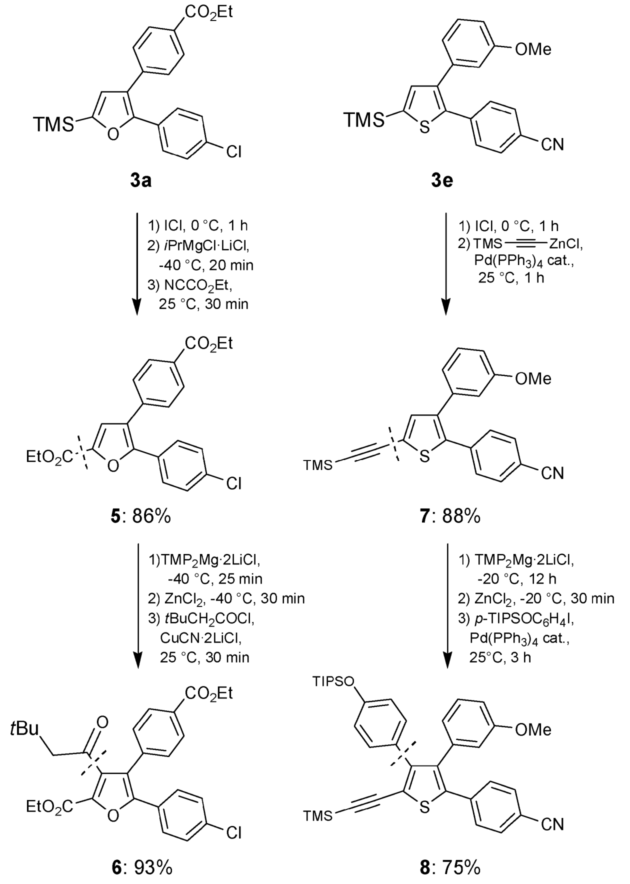
Table 1 2,3-Difunctionalized furans, thiophenes and benzofurans

Entry Electrophiles E^1, E^2	Product of type **2** (step 1) Yield [%]^a	Product of type **3** (step 2) Yield [%]^a
1 p-$\mathrm{EtO_2C}$-$\mathrm{C_6H_4I}$, p-Cl-$\mathrm{C_6H_4I}$	 **2a:** 77%^{b}	 **3a:** 68%^{b}
2 (i) $\mathrm{I_2}$ (ii) $\mathrm{C_6H_5CCZnCl}$, p-$\mathrm{EtO_2C}$-$\mathrm{C_6H_4I}$	 **2b**: 69%	 **3b:** 68%^{b}
3 p-Cl-$\mathrm{C_6H_4S}$-$\mathrm{SO_2C_6H_5}$, 5-bromonicotinic acid ethyl ester	 **2c:** 78%	 **3c:** 67%^{b}
4 p-NC-$\mathrm{C_6H_4I}$, 3,4-di-Cl-$\mathrm{C_6H_3CHO}$	 **2d:** 89%^{b}	 **3d:** 83%
5 m-MeO-$\mathrm{C_6H_4I}$, p-NC-$\mathrm{C_6H_4I}$	 **2e:** 87%^{b}	 **3e:** 85%^{b}
6 p-Cl-$\mathrm{C_6H_4S}$-$\mathrm{SO_2C_6H_5}$, p-NC-$\mathrm{C_6H_4I}$	 **2f:** 88%	 **3f:** 84%^{b}
7 p-F-$\mathrm{C_6H_4I}$, DMF	 **2g:** 80%^{b}	 **3g:** 91%

[a] Yield of analytically pure product. [b] A transmetalation using zinc chloride (1.0 M in THF) was performed; Ar = $\mathrm{C_6H_4}$-pOMe.



Scheme 2 Synthesis of fully functionalized furan **6** and thiophene **8**.

with 4-iodobenzonitrile ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h) or a trapping with DMF afforded the 2,3-disubstituted benzofurans **3f** and **3g** in 84–91% yield (entries 6 and 7).

These 2,3-difunctionalized heterocycles could readily be converted into tetra-substituted systems in a straightforward manner. Thus, the 2-silylated furan (**3a**) was converted to the corresponding 2-iodofuran (ICl, 1.5 equiv., 0 °C, 1 h, 79%).[15] A subsequent I–Mg exchange with *i*PrMgCl·LiCl[7] (1.1 equiv., −40 °C, 20 min) gave the expected organomagnesium intermediate which was reacted with ethyl cyanoformate leading to the furan (**5**) in 86% yield. A further metalation at position 4 of this furan with $TMP_2Mg{\cdot}2LiCl$[16] (1.35 equiv., −40 °C, 25 min) and consecutive copper(I)-mediated acylation with 3,3-dimethylbutyryl chloride led to the tetra-substituted furan (**6**) in 93% yield. This full functionalization of the furan ring was realized in 5 steps and 42% overall yield (Scheme 2).

The thiophene scaffold could be tetra-functionalized in a similar manner. First, the trimethylsilyl group of **3e** was converted with ICl (1.5 equiv., 0 °C, 1 h) to the corresponding 2-iodothiophene which was used in the next step without further purification. Then, cross-coupling with trimethylsilylethynylzinc chloride ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 1 h), led to the tri-substituted product (**7**) in 88% yield. Finally, thiophene (**7**) was treated with $TMP_2Mg{\cdot}2LiCl$ (1.5 equiv., −20 °C, 12 h) and submitted to a Negishi cross-coupling ($Pd(PPh_3)_4$, 2 mol%, 25 °C, 3 h) with (4-iodo-phenoxy)-triisopropylsilane,[17] furnishing the fully functionalized thiophene (**8**) in 75% yield. The tetra-substitution of the thiophene system was therefore carried out in 4 steps and 49% overall yield (Scheme 2).

In summary, we have developed an efficient two-step sequence allowing a 2,3-difunctionalization of 5-membered heterocycles using the chameleon chemical behavior of the sulfoxide moiety (ArSO).[5] This versatile functional group acts as a metalation directing group in the presence of TMPMgCl·LiCl, but also as a leaving group after the reaction with *i*PrMgCl·LiCl, generating a new Grignard reagent. A further use of *i*PrMgCl·LiCl and $TMP_2Mg{\cdot}2LiCl$ allows the full substitution of the two remaining positions of these heterocycles. Further extensions of the sulfoxide group for preparing relevant polyfunctional heterocyclic scaffolds are currently being studied in our laboratories.

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