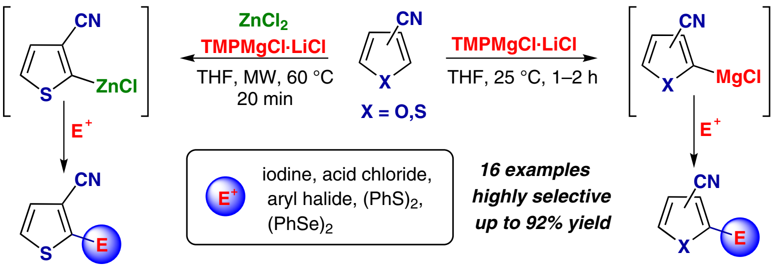
Directed Functionalization of Cyano-Substituted Furans and Thiophenes with TMPMgCl·LiCl

Fernanda M. dos Santos[a]
João H. C. Batista[a]
Ricardo Vessecchi[b]
Giuliano C. Clososki*[a,b]

[a] Núcleo de Pesquisa em Produtos Naturais e Sintéticos, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Av. do Café s / n, 14.040-903, Ribeirão Preto – SP, Brazil
gclososki@fcfrp.usp.br
[b] Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes 3900, 14040-901, Ribeirão Preto – SP, Brazil

Dedicated to Prof. João L. Callegari Lopes in the occasion of his 70th birthday



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Abstract A number of novel difunctionalized furans and thiophenes has been prepared by the reaction of the cyano-substituted substrates with TMPMgCl·LiCl followed by the reaction with electrophiles. The crucial metalation step takes place under mild conditions allowing the isolation of desired derivatives in reasonable to good yields.

Key words organomagnesium reagents, *ortho* metalation, density functional theory, furan, thiophene, nitrile

Nitriles are important organic compounds with applications in pharmaceuticals, agrochemicals, dyes, and electronic materials.[1] They are also versatile building blocks in organic synthesis since the nitrile function can be converted into various functional groups such as carboxylic acids, aldehydes, ketones, amines, and amides.[2] Moreover, nitriles are relevant precursors for nitrogen-containing heterocycles such as 2-oxazolines, thiazoles, tetrazoles, and imidazoles.[3]

Due to the prominent electron-withdrawing effect and coordination properties of the cyano group the direct *ortho* metalation using lithium amides such as LDA or LiTMP (TMP = 2,2,6,6-tetramethylpiperamidyl) is an important synthetic strategy in regioselective functionalization of aromatic and heteroaromatic nitriles.[4] In addition, a range of bases for regio- and chemoselective deprotonation have already been applied to functionalize these compounds.[5]

In recent years, mixed lithium–magnesium reagents have been successfully used for the functionalization of aromatic and heteroaromatics compounds.[6] Especially, TMPMgCl·LiCl and TMP$_2$Mg·2LiCl have proven to be highly active and soluble bases allowing smooth metalations of various substrates with an excellent functional-group compatibility.[5h–i,7,8] Following our interest in the functionalization of aromatic and heterocyclic compounds using organometallic reagents, herein we have investigated the functionalization of cyano-substituted furans and thiophenes using the base TMPMgCl·LiCl.

We initiated our work by performing a computational thermochemistry study on substrates **1a**–**d** (Figure 1). The use of computational chemistry for calculating pK_a values is nowadays an important tool to guide the experimental planning.[9] Moreover, this strategy may be used to evaluate the CH-acidity influence on the regioselectivity of metalations in aromatic and heterocyclic substrates.[10]

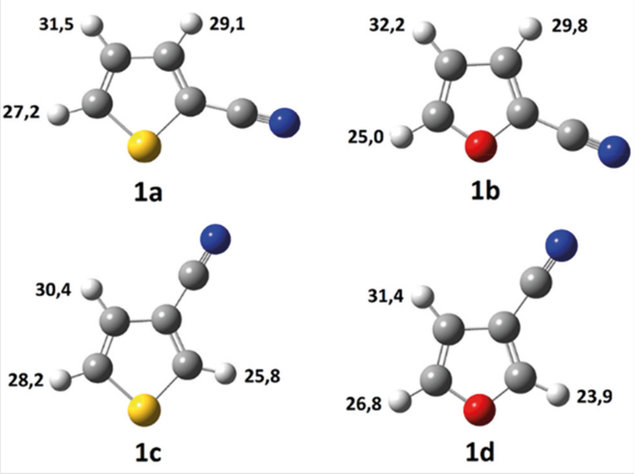
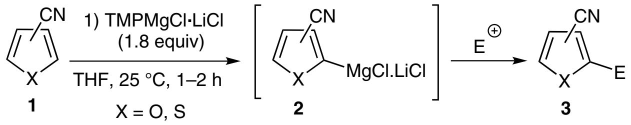


Figure 1 pK_a values of cyano-substituted furans **1a**–**d** (in unities of pK_a) for hydrogen atoms, calculated at B3LYP/6-311++G(d,p) model using THF as solvent system and furan as reference compound

The pK_a values in THF for compounds **1a**–**d** were obtained using the B3LYP/6-311++G(d,p) model[11] employing Gaussian 03 suit program.[12] Isodesmic reactions were performed to describe the reactivity of C–H bonds using furan as standard molecule. The Gibbs energy of solvation values were computed using Continuum Solvation Model (PCM model)[13] and used to estimate the pK_a values, as suggested in early studies[10] (details of computational calculations can be found in the Supporting Information). When using THF, most acidic hydrogen atoms of 2-cyano-substituted furan and thiophene are located at C-5 positions (pK_a = 27.2 and 25, respectively). In the case of the 3-cyano-substituted substrates, positions C-2 have the most acidic hydrogens (pK_a = 25.8 and 23.9 respectively).

After the computational study we examined the metalation of 2-cyano-substituted furan **1a** and thiophene **1b** with TMPMgCl·LiCl. Thus, after a screening of reaction conditions the full metalation of these substrates was achieved within two hours using 1.8 equivalents of the base at room temperature. Subsequent trapping with iodine allowed the isolation of the expected 5-iodofuran-2-carbonitrile (**3a**) and 5-iodo-2-cyanothiophene (**3b**) in 60% and 88% yields, respectively (Table 1, entries 1 and 2). In addition, under the same reaction conditions the metalation of 3-cyano-substituted substrate **1c** exclusively occured at the most acidic position. After iodolysis step, the corresponding iodide derivative **3c** was obtained in 90% yield[14] (Table 1, entry 3).

Table 1 Metalation of Substrates **1a–c** with TMPMgCl·LiCl Followed by the Reaction with Electrophiles



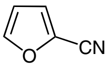
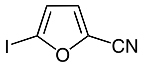
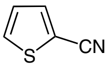
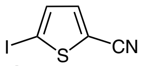
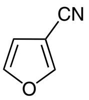
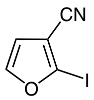
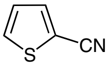
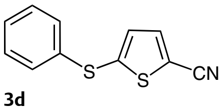
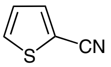
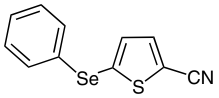
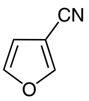
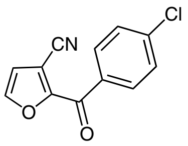
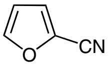
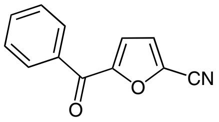
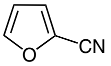
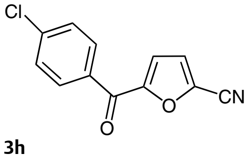
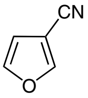
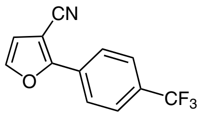
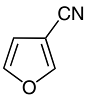
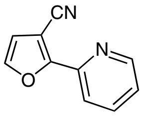
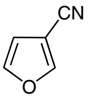
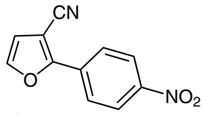
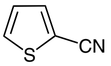
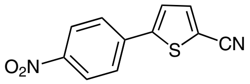
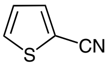
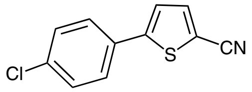
Entry	Substrate	Electrophile	Product	Yield (%)[a]
1	 **1a**	I_2	 **3a**	60
2	 **1b**	I_2	 **3b**	88
3	 **1c**	I_2	 **3c**	90
4	 **1b**	PhSSPh	 **3d**	68
5	 **1b**	PhSeSePh	 **3e**	76
6[b]	 **1c**	PhCOCl	 **3f**	85
7[b]	 **1a**	PhCOCl	 **3g**	54

Table 1 (continued)

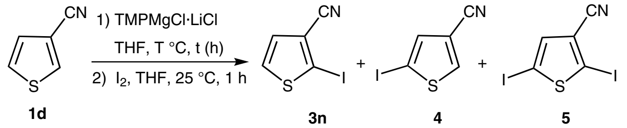
Entry	Substrate	Electrophile	Product	Yield (%)[a]
8[b]	 **1a**	4-ClC_6H_4COCl	 **3h**	63
9[c]	 **1c**	4-$BrC_6H_4CF_3$	 **3i**	92
10[c]	 **1c**	2-BrPy	 **3j**	75
11[c]	 **1c**	4-$IC_6H_4NO_2$	 **3k**	48
12[c]	 **1b**	4-$IC_6H_4NO_2$	 **3l**	60
13[c]	 **1b**	4-ClC_6H_4I	 **3m**	65

[a] Isolated yield of analytical pure compound.
[b] $Pd(PPh_3)_4$ (5 mol%) was used as catalyst after a transmetalation with $ZnCl_2$.
[c] Obtained by palladium-catalyzed cross-coupling using $Pd(dba)_2$ (2 mol%) and (*o*-furyl)$_3$P (4 mol%).

After establishing the optimal reaction conditions for the metalation of substrates **1a**–**c** we investigated the reaction of the corresponding organometallic intermediates with different electrophiles (Table 1). Metalation of **1c** with TMPMgCl·LiCl followed by reactions with diphenyldisulfide or diphenyldisselenide afforded the corresponding organochalcogen derivatives **3d** and **3e** in 68% and 76% yields, respectively (Table 1, entries 4 and 5). Moreover, after the metalation step with TMPMgCl·LiCl, the corresponding organomagnesium intermediates of type **2** were transmetalated with $ZnCl_2$ and subsequently reacted with a benzoyl chloride (1.6 equiv) in the presence of palladium catalyst[15] to provide the expected ketones **3f**–**h** in yields ranging from 54–85% (Table 1, entries 6–8). Palladium-catalyzed coupling reactions are one of the most important reactions for the functionalization of aromatics and heterocycles substrates.[16] Following transmetalation of the organomagnesium intermediate from **1b** and **1c** with $ZnCl_2$, the Negishi cross-coupling reaction was performed in the presence of $Pd_2(dba)_3$ and P(2-furyl)$_3$ to produce the expected 2- or 5-arylated derivatives **3i**–**m** in yields varying from 48–92% (Table 1, entries 9–13).

Interestingly, although pK_a calculation for **1d** shows that the hydrogen at the C-2 position is about 10^3 times more acidic than the one at C-5, the synthesis of the 2-iodo-substituted derivative using the standard procedure was accompanied by the formation of the 5-substituted regioisomer **4** as well as the 2,5-diiodide derivative **5**. However, when compared to the other studied substrates, the hydrogens of **4d** are more acidic, thus the use of excess of the base may affect the selectivity of the reaction by favoring the formation of kinetic products. Therefore, aiming to develop a more selective methodology for the metalation of **1d**, we have screened different reaction conditions using iodine as electrophile, as shown in Table 2. When 1.2 equivalents of TMPMgCl·LiCl was used, the desired compound and byproducts were obtained in 76–83% and 6–13% conversion, respectively (Table 2, entries 1 and 2). As expected, increasing the amount of base favored the formation of the diiodide **5** (Table 2, entries 3–5), which was obtained in 63% conversion (58% isolated yield) when 2.2 equivalents of the base were used (Table 2, entry 5).

Table 2 Screening of Reaction Conditions for Metalation of **1d**



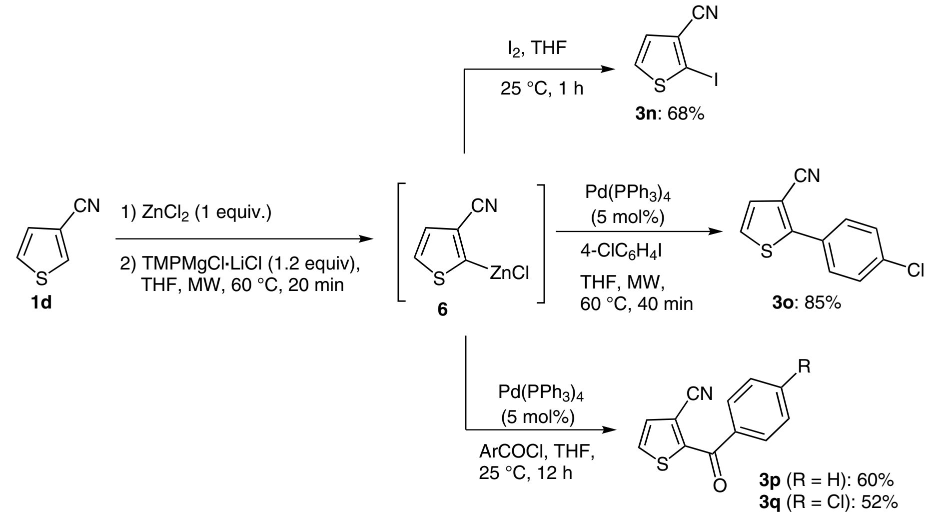
Entry	Base (equiv)	$ZnCl_2$ (equiv)	Time (h)	Temp (°C)	Conv. (%)[a] of **3n**	Conv. (%) of **4**[a]	Conv. (%)[a] of **5**
1	1.2	–	3	25	76	3	3
2	1.2	–	3	0	83	5	8
3	1.4	–	2	25	75	–	14
4	1.8	–	2	25	50	6	33
5	2.2	–	3	25	27	5	63
6[b]	1.2	1	3	25	85	6	–
7[b]	1.4	1	3	25	81	5	2
8[b,c]	1.2	1	0.3	60	92	4	–
9[b,c]	1.2	1	0.3	100	90	6	–
10[b,c]	1.2	1	0.3	140	88	6	–

[a] Determined by GC–MS analysis.
[b] A solution of $ZnCl_2$ in THF (1 mol/L) was added prior to the addition of the base.
[c] Reaction performed in a microwave reactor.

The complexation of organic substrates with $ZnCl_2$ prior to the addition of the corresponding mixed lithium–magnesium bases has already proved to be an interesting strategy for the preparation of organozinc compounds.[17] Thus, after the addition of a solution of $ZnCl_2$ in THF (1 equiv) to thiophene **1d**, subsequent addition of TMPMgCl·LiCl (1.2 and 1.4 equiv, respectively) was done dropwise. Further analysis after the reaction quench with excess of iodide indicated a more selective reaction, in which compound **3n** was obtained in 81–85% conversion (Table 2, entries 6 and 7).

It has also been shown that organozinc reagents have a good thermal stability and can be prepared from mixed lithium–zinc reagents using high temperatures in a microwave reactor.[18] Therefore, we envisioned that the precomplexation of the substrate with $ZnCl_2$ could allow the metalation with TMPMgCl·LiCl to be performed under microwave irradiation. Thus, after the screening of specific temperatures, the optimal metalation reaction was found to be at 60 °C within 20 minutes (Table 2, entry 8). Interestingly, the use of this procedure has prevented the formation of diiodide **5** and gave the desired iodide **3n** in 68% isolated yield. Moreover, reaction of the organozinc intermediate **6** with acid chlorides or an aryl halide in the presence of palladium(0) catalyst allowed the isolation of the 2-functionalized derivatives **3o**–**q** in yields varying from 52–85% (Scheme 1).[19]

In summary, we have described the directed functionalization of a series of cyano-substituted furans and thiophenes using the mixed lithium–magnesium amide TMPMgCl·LiCl. The metalation step occurs under mild conditions, and the reaction of the corresponding organometallic intermediates enables the preparation of novel difunctionalized furans and thiophenes in moderate to good yields. In the case of thiophene-3-carbonitrile, the best regioselectivity was obtained when the metalation was performed in a microwave reactor in the presence of zinc chloride. The scope of these methodologies and their applicability to-



Scheme 1 Metalation of substrate **1d** with TMPMgCl·LiCl in the presence of $ZnCl_2$ followed by the reaction with electrophiles

wards the synthesis of biologically active molecules are currently being investigated in our laboratories.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560586.

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(14) **Synthesis of 3c**
In a flame-dried flask flushed with nitrogen, substrate **1c** (93 mg, 1 mmol) was dissolved in THF (1.5 mL). TMPMgCl·LiCl (1.0 M in THF, 1.8 mL, 1.8 mmol) was added dropwise at 25 °C, and the mixture was stirred for 2 h. After that, a solution of iodine (507.6 mg, 2 mmol) in THF (2 mL) was added dropwise at 0 °C, and the reaction was stirred for 1 h at 25 °C. The reaction mixture was quenched with sat. aq $NaHSO_3$ solution (5 mL), extracted with EtOAc (3 × 15 mL), and dried over anhydrous $MgSO_4$. After the filtration, solvent was evaporated in vacuo. Purification by flash-chromatography column (hexane–EtOAc, 95:5) furnished the product **3c** as a yellow solid (197 mg, 90%); mp 67–69 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.0 Hz, 1 H), 6.60 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 113.7, 113.2, 108.3, 100.2. IR (KBr): 3425, 3143, 2233, 1485, 1344, 1160, 1018, 877, 747, 629 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 219 (43) [M^+], 190 (7), 127 (29), 64 (100). ESI-HRMS: *m/z* calcd for C_5H_3INO $[M + H]^+$: 219.9259; found: 219.9258.

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(19) **Synthesis of 3o**
In a flame-dried vial flushed with nitrogen, substrate **1d** (109 mg, 1 mmol) was dissolved in THF (1.5 mL), and a solution of $ZnCl_2$ (1.0 M in THF, 1 mL, 1 mmol) was added. The mixture was stirred for 10 min at 25 °C then TMPMgCl·LiCl (1.0 M in THF, 1.2 mL, 1.2 mmol) was added dropwise, and the mixture was heated for 20 min at 60 °C in a microwave reactor. After that, $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (0.5 mL) and 1-chloro-4-iodobenzene (330 mg, 1.4 mmol) in THF (0.5 mL) were added to the reaction mixture which was then heated for 40 min at 60 °C in the microwave reactor. The mixture was then cooled to 25 °C, quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 15 mL), and dried over anhydrous $MgSO_4$. After the filtration, solvent was evaporated in vacuo. Purification by flash-chromatography column (hexanes–EtOAc, 95:5) furnished the product **3o** as a white solid (186 mg, 85%); mp 83–85 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 2 H), 7.45 (m, 2 H), 7.35 (d, *J* = 5.3 Hz, 1 H), 7.29 (d, *J* = 5.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 135.9, 130.5, 129.8, 129.5, 129.0, 125.8, 115.64, 106.50. MS (EI, 70 eV): *m/z* (%) = 219 (100) [M^+], 184 (43), 140 (41), 113 (7), 92 (6), 75 (8), 58 (12), 45 (12). ESI-HRMS: *m/z* calcd for $C_{11}H_7ClNSNa$ $[M + Na]^+$: 241.9807; found: 241.9800.