Synthetic Methods

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# *The ortho* and *meta* Magnesiation of Functionalized Anilines and Amino-Substituted Pyridines and Pyrazines at Room Temperature**

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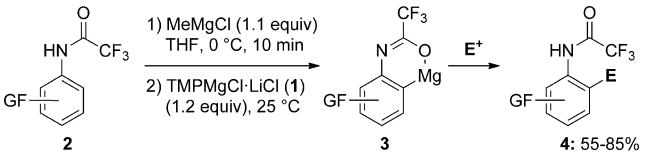
The directed lithiation[1] of anilines or aminopyridines is an important method[2] for preparing functionalized amino-substituted arenes and N-heterocycles. These scaffolds may have pharmaceutical applications as antiviral agents[3] or antibiotics.[4] Although directed *ortho* lithiations give access to various aminated aromatics, the use of strong lithium bases such as *n*BuLi or *t*BuLi is incompatible with standard carbonyl functionalities, such as an ester or a nitrile, as well as with sensitive heterocyclic moieties. Generally the amino group was protected with a pivaloyl, a *tert*-butoxycarbonyl, or a trifluoroacetyl group leading to substrates of type ArNH-COR, which, after treatment with two equivalents of base, afforded an *ortho*-lithiated bimetallic intermediate.[5] Low temperatures were usually required for these lithiations.[6] Also, the directed lithiation of trifluoroacetamides led to extensive side products.[7] Recently, we have shown that aryl magnesium reagents are readily prepared by metalation with TMPMgCl·LiCl (**1**; TMP = 2,2,6,6-tetramethylpiperidyl)[8] and that this magnesiation is compatible with sensitive functional groups.[9] However, the magnesiation of anilines proved to be sluggish and inefficient with most directing groups. After extensive experimentation, we found that trifluoroacetamides of type **2** are readily deprotonated with MeMgCl (1.1 equiv) and ring-metalated at room temperature with TMPMgCl·LiCl (**1**; 1.2 equiv), leading to dimagnesiated intermediates of type **3**, which were efficiently trapped with a range of electrophiles (**E**) to provide substituted anilides of type **4** (Scheme 1).




***Scheme 1.*** The *ortho* magnesiation of trifluoroacetamides (**3**) and reaction with electrophiles (**E**), leading to amides of type **4**.

The trifluoroacetamides of type **2** are readily obtained from the corresponding anilines in high yields and are easy-to-handle crystalline solids.[10] Thus, the treatment of the dichloroaniline derivative **2a** (1.0 equiv) with MeMgCl (1.1 equiv, THF, 0 °C, 10 min) followed by the addition of TMPMgCl·LiCl (**1**; 1.2 equiv, 25 °C, 4 h) led to the expected *ortho*-magnesiated intermediate of type **3**, which was quenched with various electrophiles such as iodine (Table 1, entry 1), ethyl 2-(bromomethyl)acrylate[11] (entry 2), or $(BrCl_2C)_2$ (entry 3) to afford the functionalized aniline derivatives **4a–c** in 68–72 % yield. A further *ortho* metalation of **4c** was realized using the same procedure with a metalation time of 4 h at 25 °C. After iodolysis, the tetrahalogenated anilide **4d** was obtained in 69 % yield (entry 4). This double *ortho,ortho′* functionalization allows a versatile preparation of pentasubstituted aniline derivatives. Thus, the quenching of the bis(magnesiated) derivative of **2a** with $MeSSO_2Me$ produced the thioether **4e** in 76 % yield. Applying the same metalation sequence (THF, 25 °C, 4 h) furnished a bis(magnesium) intermediate, which after transmetalation with CuCN·2 LiCl[12] (1.1 equiv) and acylation with 4-chlorobenzoyl chloride (−20 to 25 °C, 3 h) afforded, after work-up (aq. sat. $NH_4Cl$), directly the unprotected aniline **4f** in 81 % yield (Scheme 2).

Similarly, the bis(trifluoromethyl) trifluoroacetamide **2b** was metalated under these optimized conditions (25 °C, 4 h), leading, after bromination, to the *ortho*-bromoanilide (**4g**) in 74 % yield. Further magnesiation of **4g** with MeMgCl and TMPMgCl·LiCl (**1**; 1.2 equiv, 25 °C, 4 h) followed, after transmetalation with $ZnCl_2$ (1.2 equiv, 0 °C, 10 min), by a Negishi cross-coupling[13] (3 % $[Pd(dba)_2]$, 5 % P(*o*-furyl)$_3$,[14] 50 °C, 3 h) provided the biphenyl **4h** in 78 % yield (Scheme 2). The use of a magnesium base (**1**) instead of a strong lithium base[15] allows the presence of a cyano group in the starting trifluoroacetamide. Thus, the magnesiation of the benzonitrile **2c** (25 °C, 2 h) with our base system gave access to a room temperature stable magnesium intermediate, which after Negishi cross-coupling[13] (25 °C, 3 h), led to the biphenyl **4i** in 65 % yield (Table 1, entry 5). Similarly, the aminonitrile **2d** was magnesiated (25 °C, 3 h) and trapped with various electrophiles, affording the expected products **4j–l** in 72–85 % yield (entries 6–8). The metalation of trifluoroacetamides bearing less-electron-withdrawing substituents such as the chloro derivative **2e** was best performed using the combination of MeMgCl (1.1 equiv, 0 °C, 10 min) and $TMP_2Mg{\cdot}2\,LiCl$[16] (**5;** 1.2 equiv, 25 °C, 5 h). Cross-coupling or allylation of the intermediate magnesium reagent furnished the desired products **4m,n** in 65 % yield (entries 9 and 10). Similarly, the chlorotrifluoromethyl trifluoroacetamide **2f** was best magnesiated with this last base combination

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***Table 1:*** Products of type **4** obtained by direct magnesiation of trifluoroacetamides of type **2** followed by the reaction with electrophiles.

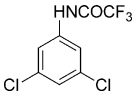
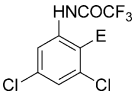
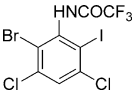
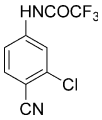
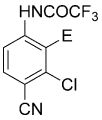
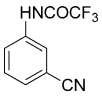
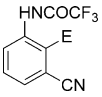
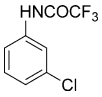
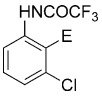
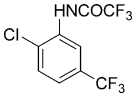
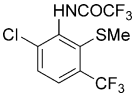
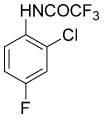
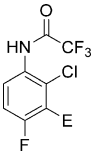
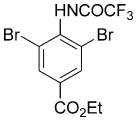
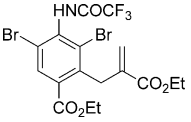
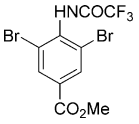
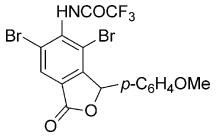
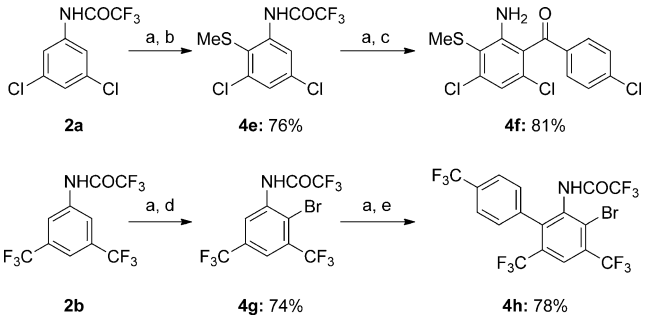
| Entry | Substrate, *T* [°C], *t* [h] | Electrophile | Product, yield [%][a] |
|---|---|---|---|
| |  | |  |
| 1 | **2a**, 25, 4 | $I_2$ | **4a**: E = I, 72 |
| 2 | **2a**, 25, 4 |  | **4b**: E = $CH_2C(=CH_2)CO_2Et$, 70[d] |
| 3 | **2a**, 25, 4 | $(BrCl_2C)_2$ | **4c**: E = Br, 68 |
| | | |  |
| 4 | **4c**, 25, 4 | $I_2$ | **4d**: E = I, 69 |
| |  | |  |
| 5 | **2c**, 25, 2 | *p*-$IC_6H_4CO_2Et$ | **4i**: *p*-$C_6H_4CO_2Et$, 65[e] |
| |  | |  |
| 6 | **2d**, 25, 3[b] | 3-bromocyclohexene | **4j**: E = 2-cyclohexenyl, 72[d] |
| 7 | **2d**, 25, 3[b] | *p*-$IC_6H_4OMe$ | **4k**: E = *p*-$C_6H_4OMe$, 75[e] |
| 8 | **2d**, 25, 3[b] | $(BrCl_2C)_2$ | **4l**: E = Br, 85 |
| |  | |  |
| 9 | **2e**, 25, 5[c] | *p*-$IC_6H_4Me$ | **4m:** E = *p*-$C_6H_4Me$, 65[e] |
| 10 | **2e**, 25, 5[c] | $BrCH_2CH{=}CH_2$ | **4n:** E = $CH_2CH{=}CH_2$, 65[d] |
| |  | |  |
| 11 | **2f**, 25, 8[c] | $MeSSO_2Me$ | **4o**, 75 |
| |  | |  |
| 12 | **2g**, 5, 3 | $(BrCl_2C)_2$ | **4p**: E = Br, 78 |
| 13 | **2g**, 5, 3 | 3-bromocyclohexene | **4q**: E = 2-cyclohexenyl, 65[d] |
| |  | |  |
| 14 | **2h**, 25, 4 |  | **4r**, 75[d] |

***Table 1:*** (Continued)

| Entry | Substrate, *T* [°C], *t* [h] | Electrophile | Product, yield [%][a] |
|---|---|---|---|
| |  | |  |
| 15 | **2i**, 25, 4 | *p*-$MeOC_6H_4CHO$ | **4s**, 71 |

[a] Yield of isolated, analytically pure product. [b] TMPMgCl·LiCl (2.0 equiv) was used. [c] $TMP_2Mg{\cdot}2\,LiCl$ (1.2 equiv) was used. [d] 10% CuCN·2 LiCl was added. [e] Obtained by Pd-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.2 equiv) using 3% $[Pd(dba)_2]$ and 5% P(*o*-furyl)$_3$.



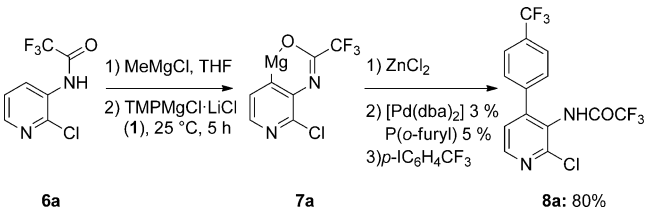

***Scheme 2.*** Double metalation of trifluoroacetamides **2a** and **2b**. Reagents and conditions: a) MeMgCl, THF (1.1 equiv, 0°C, 10 min) then TMPMgCl·LiCl (**1**; 1.2 equiv, 25°C, 4 h). b) $MeSSO_2Me$ (1.1 equiv, −20°C, 2 h). c) CuCN·2 LiCl (1.1 equiv, −20 to 25°C, 3 h) then $NH_4Cl$. d) $(BrCl_2C)_2$ (1.1 equiv, 0 to 25°C, 1 h). e) $ZnCl_2$ (1.2 equiv, 0°C, 10 min) then $[Pd(dba)_2]$ 3%, P(*o*-furyl) 5% and *p*-$IC_6H_4CF_3$ (1.1 equiv, 50°C, 3 h).

(25°C, 8 h) providing, after treatment with $MeSSO_2Me$ (−20°C, 2 h) the thioether **4o** in 75% yield (entry 11). The high kinetic activity of TMPMgCl·LiCl (**1**) also allows the performance of *meta* magnesiation.[17] Thus, the chlorofluoroanilide **2g** was regioselectively metalated at position 3 with TMPMgCl·LiCl (**1**; 1.2 equiv, 5°C, 3 h) leading, after bromination or allylation, to the 1,2,3,4-tetrasubstituted anilides (**4p**,**q**) in 65–78% yield (entries 12 and 13). Remarkably, an ester substituent does not interfere with the metalation sequence (no addition of MeMgCl to the ester function was observed). Thus, the benzoates **2h** and **2i** were submitted to the metalation procedure (MeMgCl 1.1 equiv, 0°C, 10 min; TMPMgCl·LiCl (**1**) 1.2 equiv, 25°C, 4 h), affording the desired magnesium intermediates. Allylation with ethyl 2-(bromomethyl)acrylate[11] produced the pentasubstituted benzoate **4r** in 75% yield (entry 14), whilst the addition of *p*-anisaldehyde to the magnesiated methyl benzoate directly resulted the lactone **4s** in 71% yield (entry 15). Most of the resulting trifluoroacetamides of type **4** can be readily deprotected to the corresponding anilines of type **12** by treatment with $K_2CO_3$ (3 equiv, in 1:1 MeOH:$H_2O$, 25°C, 12 h; 80–95% yields).[18,19]

The selective metalation of functionalized aminopyridines is of special importance owing to their use as precursors with pharmaceutical relevance.[20] Our newly developed metal-

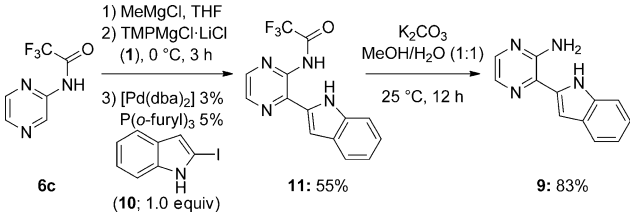
ation sequence allowed a smooth regioselective magnesiation of amino-pyridines **6a–b** and -pyrazine **6c**. Thus, the metalation of the aminopyridine derivative **6a** (MeMgCl 1.1 equiv, 0 °C, 10 min; TMPMgCl·LiCl (**1**) 1.5 equiv, 25 °C, 5 h) furnished the 4-pyridylmagnesium derivative **7a**. Its Pd-catalyzed cross-coupling under standard conditions provided the 2,3,4-trisubstituted pyridine **8a** in 80% yield (Scheme 3).




***Scheme 3.*** Metalation sequence leading to 4-magnesiated aminopyridines of type **7** and subsequent quenching with electrophiles, leading to the trisubstituted pyridine **8a**.

The magnesium reagent **7a** was also brominated ($(BrCl_2C)_2$; 0 to 25 °C, 1 h), leading to the bromopyridine **8b** in 67% yield (Table 2, entry 1). The pyridyl trifluoroacetamide **6b** was metalated in a similar fashion (25 °C, 4 h) and was allylated, arylated, and brominated as described above to provide the pyridines **8c–e** in 65–66% yield (entries 2–4). The readily available pyrazyl trifluoroacetamide **6c** was metalated under our conditions (0 °C, 3 h) and functionalized by a bromination and a cross-coupling to give the corresponding pyrazines **8f–g** in 65% yield (entries 5 and 6).

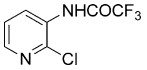
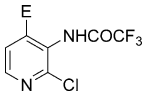
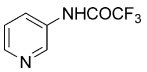
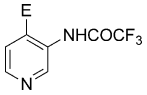
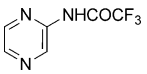
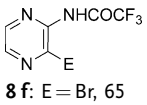
As an application, we prepared a GSK-3 and Lck protein kinase inhibitor **9**[21] using our standard metalation procedure (0 °C, 3 h). After transmetalation with $ZnCl_2$ and Pd-catalyzed cross-coupling with unprotected 2-iodoindole,[22] the pyrazine **11** was isolated in 55% yield. Deprotection with $K_2CO_3$ in MeOH/$H_2O$ (1:1) provided the kinase inhibitor **9** in 83% yield (Scheme 4).




***Scheme 4.*** Synthesis of the GSK-3 and Lck protein kinase inhibitor (**9**) by chemoselective magnesiation and subsequent deprotection.

In summary, we have developed a practical magnesiation procedure of trifluoroacetamides of anilines, aminopyridines, and aminopyrazines that is performed mostly at room temperature, compatible with several carbonyl functionalities, and subsequent quenching with aryl, heteroaryl, and allylic halides, brominating or acylating agents affords substituted anilides with satisfactory yields. Both *ortho*,*ortho'* and *meta* positions to the $NH_2$ group can be functionalized using this method. We are currently extending this procedure to other biologically relevant heterocyclic substrates.

***Table 2:*** Products of type **8** obtained by direct magnesiation of N-hetero trifluoroacetamides followed by the reaction with electrophiles.

| Entry | Substrate, *T* [°C], *t* [h] | Electrophile | Product, yield [%][a] |
|---|---|---|---|
| |  | |  |
| 1 | **6a**, 25, 5[b] | $(BrCl_2C)_2$ | **8b:** E = Br, 67 |
| |  | |  |
| 2 | **6b**, 25, 4 | 3-bromocyclohexene | **8c**: E = 2-cyclohexenyl, 65[c] |
| 3 | **6b**, 25, 4 | *p*-$IC_6H_4CO_2Et$ | **8d**: E = *p*-$C_6H_4CO_2Et$; 66[d] |
| 4 | **6b**, 25, 4 | $(BrCl_2C)_2$ | **8e**: E = Br, 65 |
| |  | |  |
| 5 | **6c**, 0, 3 | $(BrCl_2C)_2$ | **8f**: E = Br, 65 |
| 6 | **6c**, 0, 3 | *p*-$IC_6H_4CO_2Et$ | **8g**: E = *p*-$C_6H_4CO_2Et$, 65[d] |

[a] Yield of isolated, analytically pure product. [b] TMPMgCl·LiCl (1.5 equiv) was used. [c] 10% CuCN·2 LiCl was added. [d] Obtained by Pd-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.2 equiv) using 3% $[Pd(dba)_2]$ and 5% P(*o*-furyl)$_3$.

## *Experimental Section*

Typical procedure (for **4k**): A solution of *N*-(3-cyanophenyl)-2,2,2-trifluoroacetamide (**2d**; 428 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was treated at 0 °C with MeMgCl (2.85 M in THF, 1.1 equiv) for 10 min. Then, TMPMgCl·LiCl (**1**; 1.07 M in THF, 2 equiv) was added and stirred at 25 °C for 3 h. The reaction mixture was cooled to 0 °C, and $ZnCl_2$ (1.0 M in THF, 1.2 equiv) was added and stirred for 15 min. $[Pd(dba)_2]$ (35 mg, 0.03 equiv), P(*o*-furyl)$_3$ (23 mg, 0.05 equiv), and 4-iodoanisole (514 mg, 2.2 mmol, 1.1 equiv) were added and the reaction mixture was stirred for 3 h at 25 °C. Quenching with a saturated aqueous $NH_4Cl$ solution and extracting with $CH_2Cl_2$ and EtOAc afforded, after purification by flash chromatography ($SiO_2$, *i*Hex/EtOAc = 9:1), **4k** as a white solid (480 mg, 75%).

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[19] Preparation of **12a**: $K_2CO_3$ (413 mg, 3 mmol, 3 equiv) was added to a solution of *N*-(2-chloro-3-cyclohex-2-en-1-yl-4-fluorophenyl)-2,2,2-trifluoroacetamide (**4q**) (321 mg, 1 mmol, 1 equiv) dissolved in MeOH:$H_2O$ (1:1, 4 mL) and stirred at 25 °C for 12 h. The reaction mixture was filtered and rinsed with EtOAc and dried over anhydrous $Na_2SO_4$, and purification by flash chromatography ($SiO_2$, *i*Hex/EtOAc = 95:5) afforded the aniline **12a** as a pale orange oil (214 mg, 95 %).

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