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Transition-Metal-Free Amination of Pyridine-2-sulfonyl Chloride and Related *N*-Heterocycles Using Magnesium Amides

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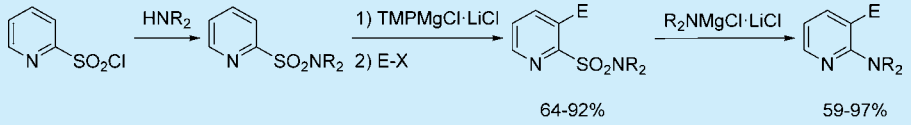
Supporting Information



ABSTRACT: A new transition-metal-free amination of pyridine-2-sulfonyl chloride and related *N*-heterocycles using magnesium amides of type $R_2NMgCl·LiCl$ is reported. Additionally, the directed *ortho*-magnesiation of pyridine-2-sulfonamides using TMPMgCl·LiCl was investigated. Reaction of the magnesium intermediates with various electrophiles and subsequent amination using magnesium amides led to a range of 2,3-functionalized pyridines. Also, cyclization reactions providing an aza-indole and an aza-carbazole were carried out.

Aminopyridines and related aminated *N*-heterocycles are important targets for the pharmaceutical industry.[1] The amination of 2-halopyridines has been extensively studied using palladium-, nickel-, copper-, or chromium-catalysis, or a transition-metal-free substitution with various amines or lithium amides.[1d,2] Most of the transition-metal-free aminations proceed at high temperatures, require long reaction times, or highly basic lithium amides.[1d,2i−l] Also, 2-halo, 2-cyano, or 2-trifluoromethylsulfonylpyridines were often used as substrates.[1d,2i,k,l] Additionally, pyridine sulfonamides have attracted attention due to their medical significance and as building blocks for the preparation of more complex pyridine derivatives.[3]

Herein, we describe a new amination procedure of chlorosulfonyl substituted *N*-heterocycles of type **1** or related sulfonamides of type **2** with magnesium amides of type **3** leading to the aminated pyridine derivatives of type **4** (Scheme 1).

Thus, pyridine-2-sulfonyl chloride (**1**) was treated with $Et_2NMgCl·LiCl$ (2.4 equiv) in THF at 0 °C and stirred for 2 h at 25 °C leading to the 2-aminated pyridine **4a** in 84% yield. This amination was extended to various magnesium amides affording the corresponding 2-aminopyridines **4b−f** under similar conditions in 73−88% yield (Scheme 1).

So far, only *ortho*-lithiation of (hetero)aryl sulfonamides and subsequent Suzuki−Miyaura cross-coupling or reaction with selected electrophiles has been reported.[4] Thus, to extend the utility of the amination method, the *ortho*-magnesiation[5] of sulfonamides of type **2** with TMPMgCl·LiCl[6] (TMP = 2,2,6,6-tetramethylpiperidyl) was investigated.

The pyridine sulfonamide **2a** was prepared from pyridine-2-sulfonyl chloride (**1**) and piperidine (3 equiv) in 81% yield. Subsequent reaction of **2a** with TMPMgCl·LiCl at 0 °C for 2 h lead to the corresponding 3-magnesiated sulfonamide of type **5** (Table 1). Quenching of this metalated species with various electrophiles such as $(BrCl_2C)_2$, I_2, or TMSCl furnished the expected products **6a−c** in 64−81% yield (entries 1−3). Arylation of the magnesium species of type **5** was achieved by transmetalation with $ZnCl_2$ and Negishi cross-coupling[7] with iodobenzene in the presence of 3 mol % $Pd(OAc)_2$ and 6 mol % SPhos,[8] which gave the sulfonamide **6d** in 82% yield (entry 4). Transmetalation of the Grignard reagent of type **5** to the corresponding copper derivative using CuCN·2LiCl[9] and subsequent reaction with allyl bromide (−20 to 25 °C, 1 h)

Scheme 1. Synthesis of 2-Aminopyridines 4a−f Starting from Pyridine-2-sulfonyl Chloride (1) Using Magnesium Amides (3)

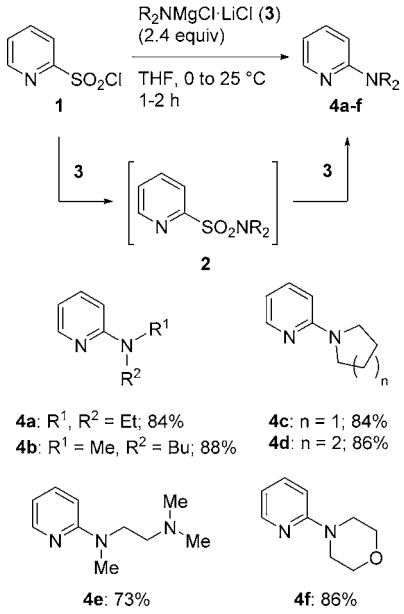


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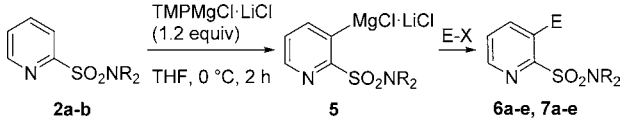
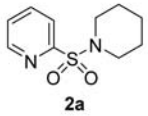
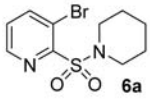
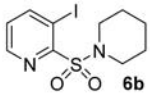
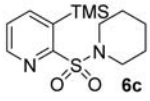
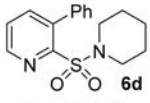
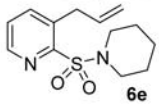
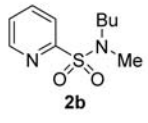
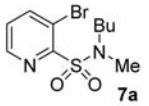
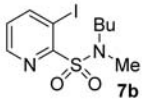
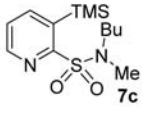
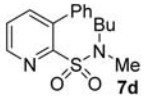
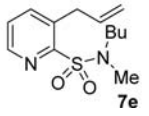
Table 1. *ortho*-Functionalization of Sulfonamides 2a and 2b Using TMPMgCl·LiCl



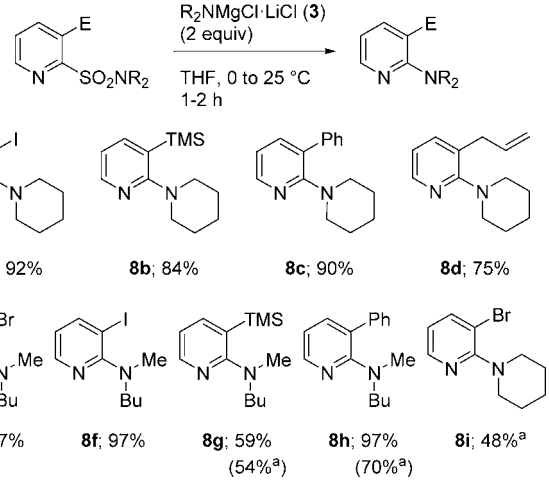
entry	reagent	electrophile	product	yield (%)[a]
1	 2a	$(BrCl_2C)_2$	 6a	74
2	2a	I_2	 6b	81
3	2a	TMSCl	 6c	64
4	2a	PhI	 6d	82[b]
5	2a		 6e	90[c]
6	 2b	$(BrCl_2C)_2$	 7a	73
7	2b	I_2	 7b	73
8	2b	TMSCl	 7c	84
9	2b	PhI	 7d	85[b]
10	2b		 7e	92[c]

[a]Isolated yield. [b]The cross-coupling was performed with 3 mol % $Pd(OAc)_2$ and 6 mol % SPhos after transmetalation with a 1 M $ZnCl_2$ solution (1.2 equiv). [c]Allylation was performed after transmetalation with a 1 M CuCN·2LiCl solution (1.2 equiv).

afforded the allylated sulfonamide **6e** in 90% yield (entry 5). Similarly, the pyridine sulfonamide **2b**, prepared from pyridine-2-sulfonyl chloride (**1**) and the acyclic amine *N*-butylmethylamine in 86% yield, was magnesiated and subsequently quenched with several electrophiles leading to the 3-substituted sulfonamides **7a**–**e** in 73–92% yield (entries 6–10). The substituted sulfonamides of type **6** and **7** were smoothly aminated with two different magnesium amides leading to the corresponding aminopyridines **8a**–**h** under standard conditions in up to 97% yield (Scheme 2).[10]

A one-pot procedure involving first the magnesiation of **2a** or **2b** with TMPMgCl·LiCl, then a reaction with an electrophile

Scheme 2. Desulfonylation of Sulfonamides of Type 6 and 7 To Give Aminopyridines 8a–h

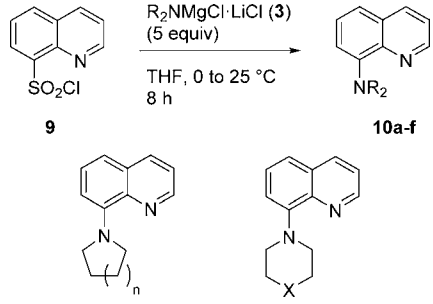


[a]*ortho*-Functionalization and desulfonylation was performed in one pot.

(such as $(BrCl_2C)_2$, TMSCl, or PhI) and subsequent amination with a magnesium amide gave the 2,3-disubstituted aminopyridines **8g**–**i** in 48–70% yield (Scheme 2).

Additionally, the amination procedure was performed with commercially available 8-quinolinesulfonyl chloride (**9**). Interestingly, the magnesium amide of type **3** prepared from pyrrolidine (5 equiv) using *i*PrMgCl·LiCl (5 equiv) reacted with **9** to afford the aminated quinoline **10a** in 99% yield. Extension to further cyclic amides led to the corresponding amination products **10b**–**f** in 36–98% yield (Scheme 3).

Scheme 3. Synthesis of 8-Aminoquinolines 10a–f Starting from 8-Quinolinesulfonyl Chloride (9)



Furthermore, the *ortho*-metalation of the quinoline scaffold was investigated. Thus, the quinoline sulfonamides **11a**–**b** were readily magnesiated using TMPMgCl·LiCl and reacted with iodine. Subsequent reactions with the piperidine magnesium amide of type **3** afforded the 2,3- and 7,8-functionalized quinolines **12a**–**b** in 52–59% yield over two steps (Scheme 4).

Also, the mechanism of this amination was briefly examined. Two mechanistic pathways can be postulated. The first mechanism involves an addition of the magnesium amide of type **3** to the pyridine core leading to the intermediate **13**, which, after elimination of R_2NSO_2MgCl, affords the aminated pyridine **4** (S_NAr; pathway A; Scheme 5). Alternatively, a

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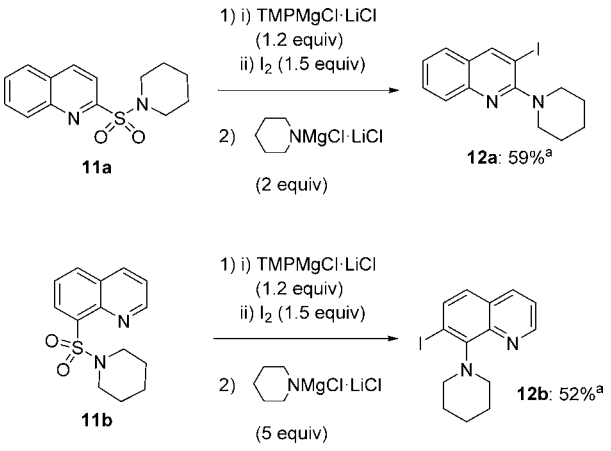
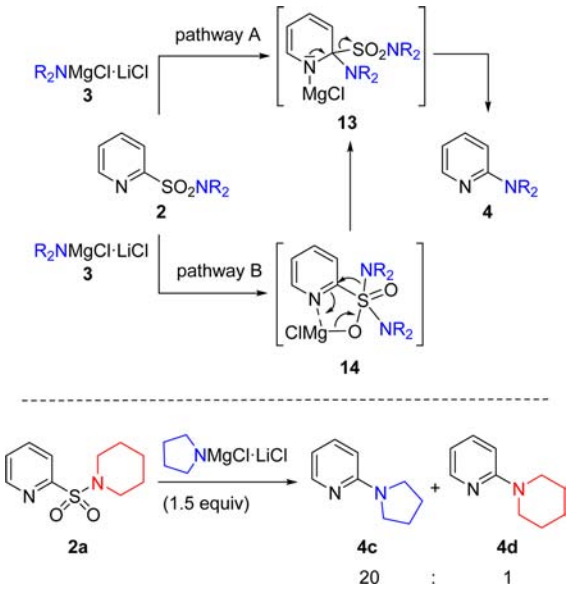
Scheme 4. *ortho*-Functionalization and Desulfonylation of Quinoline Sulfonamides 11a and 11b



[a]Yield over two steps.

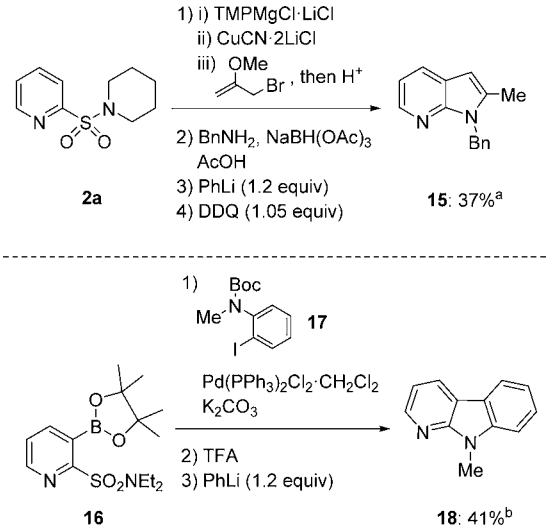
Scheme 5. Plausible Mechanisms for the Amination of Pyridines Using Magnesium Amides



second mechanism may involve the addition of $R_2NMgCl·LiCl$ (**3**) to the sulfonamide group providing intermediate **14**, which may undergo an intramolecular transfer of the amino moiety leading to intermediate **13** and finally to the aminopyridine **4** (pathway B, Scheme 5). Evidence for this second pathway was found when a pyridine-2-sulfonamide $PySO_2NR^1_2$ reacted with the magnesium amide $R^2_2NMgCl·LiCl$, which led to mixtures of $PyNR^1_2$ and $PyNR^2_2$. When, for example, sulfonamide **2a** was reacted with the pyrrolidine magnesium amide of type **3** (1.5 equiv) the ratio between amines **4c** and **4d** was 20:1 (Scheme 5).[11] Notice that the treatment of 1-naphthalenesulfonyl chloride with an excess of magnesium amide $R_2NMgCl·LiCl$ only led to the formation of the corresponding sulfonamide, and no amination product was detected, showing the importance of the heterocyclic nitrogen atom present in intermediate **14** for this amination.

Finally, the amination method was extended to cyclization reactions. Thus, pyridine sulfonamide **2a** was magnesiated with TMPMgCl·LiCl and then transmetalated with CuCN·2LiCl. Subsequent reaction with 2-methoxyallyl bromide[12] followed by acidic enol ether cleavage gave the corresponding ketone in 94% yield. Subsequent reductive amination using benzylamine, sodium triacetoxyborohydride, and acetic acid[13] afforded the desired pyridine sulfonamide in 73% yield. Deprotonation with phenyllithium (1.2 equiv) led to a lithium amide that underwent a smooth cyclization, which, after aromatization using DDQ (1.05 equiv), gave the azaindole **15** in 47% yield over two steps (Scheme 6).

Scheme 6. Synthesis of Heterocycles via Cyclization Reactions Using Phenyllithium



[a]Yield over four steps. [b]Yield over three steps.

Also, sulfonamide **16** reacted with the Boc-protected iodoaniline **17** under Suzuki–Miyaura cross-coupling conditions.[4a,14] Subsequent deprotection using TFA gave the desired pyridine sulfonamide in 49% yield over two steps. Reaction with phenyllithium led to the aza-carbazole **18** in 84% yield (Scheme 6).

In summary, we have reported a new mild transition-metal-free amination of pyridine-2-sulfonyl chloride and related *N*-heterocycles using magnesium amides. The method was applied to cyclization reactions leading to an aza-indole and an aza-carbazole. Further extensions of the method are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03703.

Full experimental details; Mechanistic insights; ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Amination of **7e** led to double-bond isomerization instead of clean formation of the desired aminated compound of type **8**.

(11) See the Supporting Information for further details.

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