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Amination of 2-Pyridinesulfonic and 8-Quinolinesulfonic Acids with Magnesium Amides

Moritz Balkenhohl, Vasiliki Valsamidou, and Paul Knochel*

Abstract: The amination of 2-pyridine- and 8-quinolinesulfonic acids using magnesium amides of the type $R_2NMgCl{\cdot}LiCl$ is reported. Thus, several cyclic and acyclic amines were converted into the corresponding amides using *i*PrMgCl·LiCl, which reacted readily with sulfonic acids to produce aminopyridines and –quinolines. Various amines attractive in drug chemistry were suitable for this transformation.

Introduction

Aminated *N*-heterocycles and especially aminopyridines and –quinolines are important targets for the pharmaceutical industry.[1] Chloropyramine (**1**), for example, is an antihistaminic and the pyridine **2** is a CXCR3 Inhibitor.[2] The aminoquinoline primaquine (**3**) is commonly prescribed for the treatment of malaria,[3] and crenolanib (**4**) is currently being evaluated as a drug against various types of tumors (Figure 1).[4]

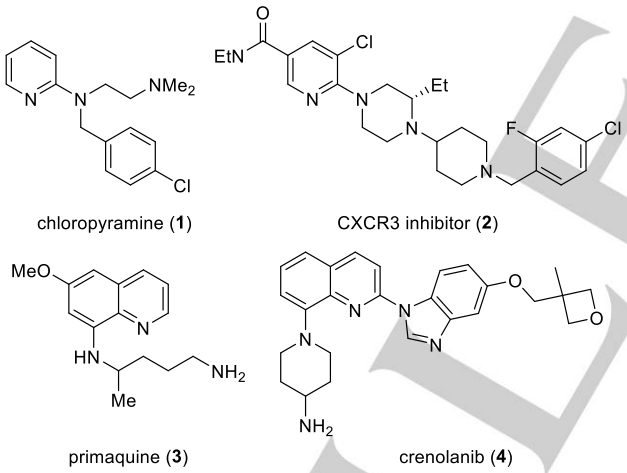

Figure 1. Various pharmaceutically active aminopyridines and –quinolines.

Thus, the development of C-N bond forming reactions is of high importance. So far, transition-metal-catalyzed methods using Ni-, Pd-, Cr-, Co-, or Cu-salts have been used for the formation of the C-N bond (Figure 2a).[5] However, transition-metals are expensive and often toxic.[6] Therefore, the development of transition-metal-free amination methods is highly desirable. So far, 2-halo, 2-mercapto and 2-cyanopyridines, pyridine-2-phosphorodiamidates, and 2-pyridyl trifluoromethanesulfonate or pyridine *N*-oxides were found to be suitable substrates for this transformation (Figure 2b).[7] However, many of these methods require high temperatures or highly basic lithium amides. Recently, transition-metal-free aminations of 2-pyridinesulfonyl chloride and related heterocycles using magnesium amides of type $R_2NMgCl{\cdot}LiCl$ have been reported (Figure 2c).[8] 2-Pyridinesulfonyl chloride, though, is a sensitive reagent which decomposes at 25 °C within several hours.[9] Albeit being commercially available, quinoline-8-sulfonyl chloride also decomposes at ambient temperature within three to five months. 2-Pyridine- or 8-quinolinesulfonic acids (**5** and **6**) are commercially available and stable reagents, which are formed upon decomposition of the corresponding sulfonyl chloride. Herein, we report the amination of 2-pyridine- and

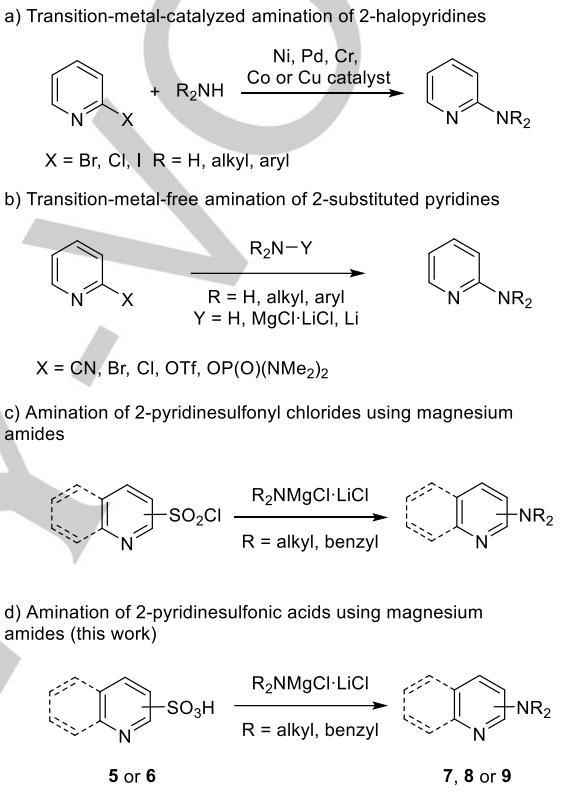

Figure 2. Various conditions for amination reactions, including the transition-metal-free amination of 2-pyridinesulfonic acids using magnesium amides.

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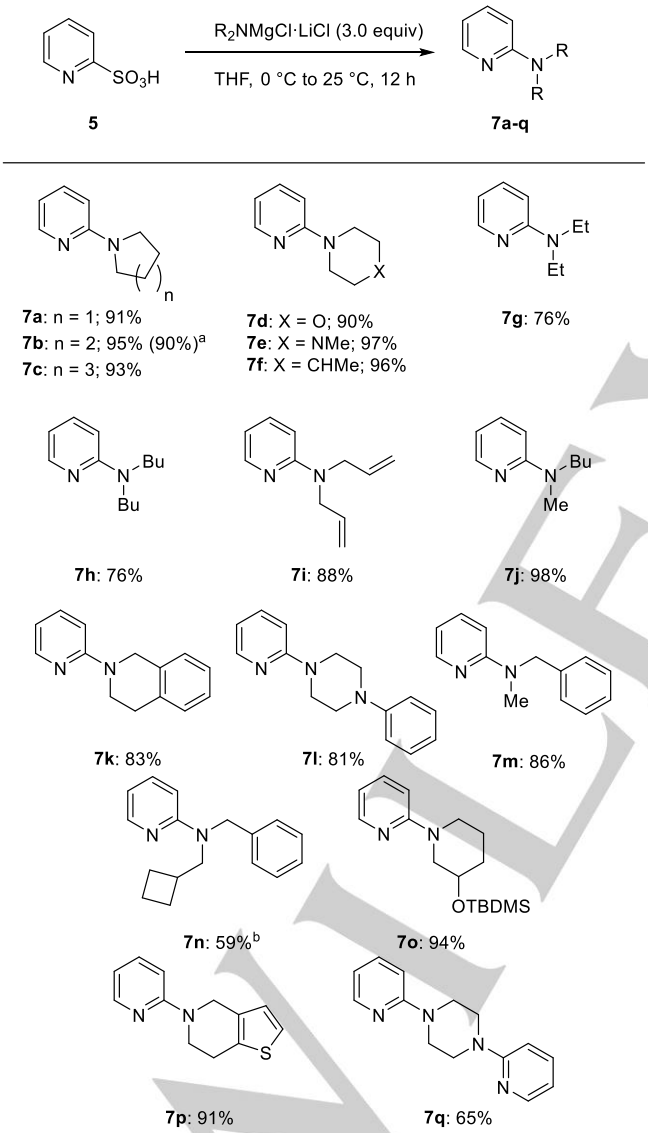
8-quinolinesulfonic acids using magnesium amides of type $R_2NMgCl{\cdot}LiCl$, leading to aminopyridines of type **7** and **8** and aminoquinolines of type **9** (Figure 2d).

Results and Discussion

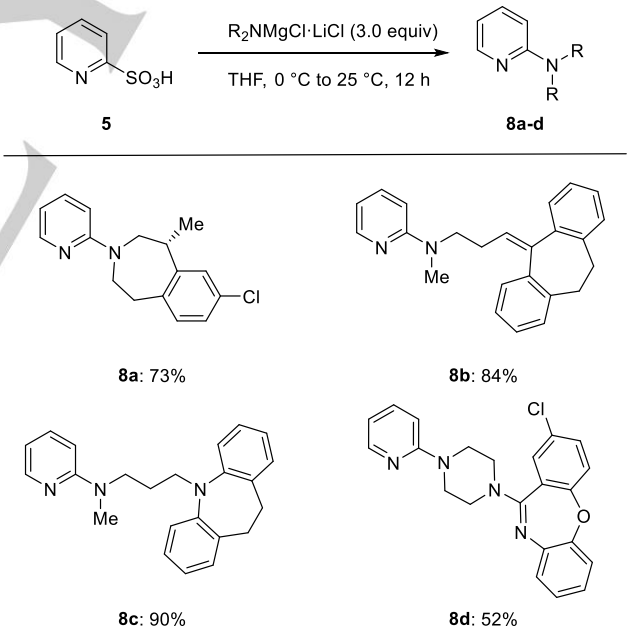
Thus, pyrrolidine (3.0 equiv) was dissolved in THF and treated with *i*PrMgCl·LiCl (3.0 equiv) at 0 °C. The resulting magnesium amide $R_2NMgCl{\cdot}LiCl$ was then added to a suspension of 2-pyridinesulfonic acid (**5**) in THF at 0 °C and stirred at 25 °C for 12 h. After workup, the aminopyridine **7a** was isolated in 91% yield (Scheme 1). Using less equivalents of magnesium amide led to a decrease in yield. Other cyclic amides derived from piperidine, azepane, morpholine, *N*-methylpiperazine, or 4-methylpiperidine gave aminopyridines **7b-f** in 90-97% yield. Additionally, the upscaling of the reaction was evaluated by preparing the aminopyridine **7b** on a 50 mmol scale in 90% yield. Symmetrical amides prepared from diethyl-, dibutyl-, or diallylamine yielded pyridines **7g-i** in 76-88% yield. The unsymmetrical amine *N*-butylmethylamine was also suitable for the amination reaction, leading to the aminopyridine **7j** in 98% yield. Other amines bearing e.g. a cyclobutane ring or a TBDMS-protected alcohol, produced the aminopyridines **7k-o** in 59-94% yield. Amines containing a heterocycle such as a pyridine or a thiophene gave the corresponding pyridines **7p**-**q** in 65-91% yield.



[a]The reaction was performed on a 50 mmol scale. [b]5.0 equiv of magnesium amide was used.

Scheme 1. Amination of 2-pyridinesulfonic acid (**5**) using magnesium amides of type $R_2NMgCl{\cdot}LiCl$ leading to aminopyridines **7a-q**.

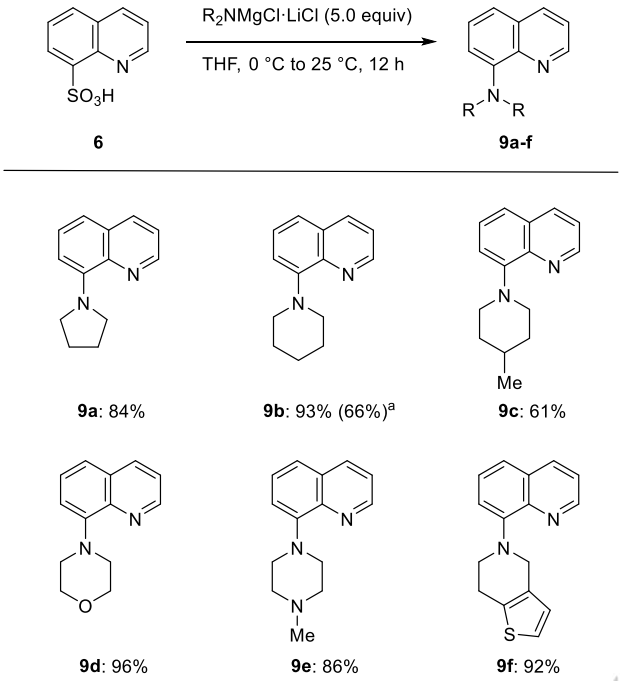
As an extension, several amines important in medicinal chemistry were employed in this amination protocol. Thus, lorcaserin hydrochloride hemihydrate was treated with an excess of *i*PrMgCl·LiCl in order to neutralize the hemihydrate and the HCl salt, which resulted in the formation of the respective magnesium amide. This amide readily reacted with 2-pyridinesulfonic acid (**5**), to give aminopyridine **8a** in 73% yield (Scheme 2). Also, the HCl salts of the amines nortriptyline and desipramine were neutralized and deprotonated using *i*PrMgCl·LiCl. The resulting amides were employed in the amination reaction, leading to pyridines **8b-c** in 84-90% yield. The antidepressant amoxapine gave the polycyclic heterocycle **8d** in 52% yield.



Scheme 2. Amination of 2-pyridinesulfonic acid (**5**) using magnesium amides leading to aminopyridines **8a**-**d**.

Interestingly, 8-quinolinesulfonic acid (**6**) was also a suitable reagent for the amination reaction. Thus, when the amides (5.0 equiv) derived from several amines, including 4-methylpiperidine or *N*-methylpiperazine, were employed in the amination reaction, 8-aminoquinolines **9a-f** were obtained in 61-96% yield. The

upscaling of this method was demonstrated upon the synthesis of aminoquinoline **9b** on a multi-gram scale in 66% yield (Scheme 3).



[a]The reaction was performed on a 20 mmol scale.

Scheme 3. Amination of 8-quinolinesulfonic acid (**6**) using magnesium amides, leading to aminoquinolines **9a**-**f**.

Conclusions

In summary, the amination of 2-pyridine- and 8-quinolinesulfonic acid is reported. Several amines, including pharmaceutically active substrates, were applicable to the reaction protocol, affording the respective 2-aminopyridines and 8-aminoquinolines. Finally, this amination was readily scaled-up to 50 mmol scale. Further extensions of this work are currently underway in our laboratories.

Experimental Section

***i*PrMgCl·LiCl**: Magnesium turnings (2.67 g, 110 mmol) and anhydrous LiCl (4.66 g, 100 mmol) were placed in an argon-flushed flask and THF (50 mL) was added. A solution of *i*PrCl (9.13 mL, 100 mmol) in THF (50 mL) was slowly added at 25 °C. The Grignard reagent formation begun within a few minutes. After addition, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98% of *i*PrMgCl·LiCl is obtained.[10]

Synthesis of aminopyridine **7a**: *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol, 3.0 equiv) was added to a solution of pyrrolidine (0.25 mL, 3.00 mmol, 3.0 equiv) in THF (5 mL) at 0 °C. The solution was stirred for 15 min at 0 °C and 15 min at 25 °C before being added to a suspension of 2-pyridinesulfonic acid (**5**, 159 mg, 1.00 mmol, 1.0 equiv) in THF (5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*, yielding aminopyridine **7a** (135 mg, 912 µmol, 91% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H), 7.42 (ddd, J = 8.5, 7.1, 2.0 Hz, 1H), 6.50 (ddd, J = 7.1, 5.0, 0.9 Hz, 1H), 6.35 (dt, J = 8.6, 1.0 Hz, 1H), 3.50 – 3.39 (m, 4H), 2.04 – 1.97 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 157.5, 148.3, 137.0, 111.2, 106.6, 46.8, 25.7.

Acknowledgments

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Keywords: amination • aminopyridines • magnesium • pyridine • quinoline

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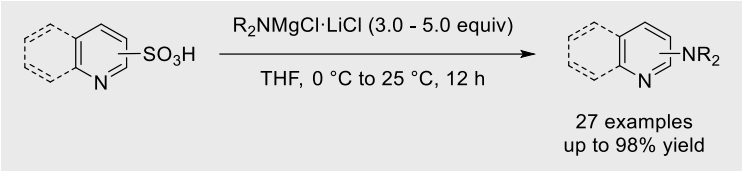

***N*-Heterocycles**

*Moritz Balkenhohl, Vasiliki Valsamidou, and Paul Knochel**

Page No. – Page No.

Amination of 2-Pyridinesulfonic and 8-Quinolinesulfonic Acids with Magnesium Amides

The amination of 2-pyridine- and 8-quinolinesulfonic acids using magnesium amides is reported. Various amides reacted with *N*-heterocyclic sulfonic acids, leading to aminopyridines and –quinolines in up to 98% yield. Various amines important in medicinal chemistry, such as the antidepressant amoxapine, were suitable for these aminations.