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Regioselective difunctionalization of pyridines *via* 3,4-pyridynes†

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A new regioselective 3,4-difunctionalization of 3-chloropyridines via 3,4-pyridyne intermediates is reported. Regioselective lithiation of 3-chloro-2-ethoxypyridine and a related 2-thio-derivative followed by treatment with aryl- and alkylmagnesium halides as well as magnesium thiolates at $-78\,^{\circ}\text{C}$ produced 3,4-pyridynes during heating to 75 $^{\circ}\text{C}$. Regioselective addition of the Grignard moiety in position 4 followed by an electrophilic quench in position 3 led to various 2,3,4-trisubstituted pyridines. This method was adapted into a continuous flow set-up. As an application, we have prepared a key intermediate for (\pm) -paroxetine.

Introduction

Pyridines are important heterocycles present in numerous biologically relevant molecules.¹ As a consequence, many synthetic methods have been developed for the functionalization of such N-heterocycles.² Especially, the regioselective metalation of pyridines has been broadly used.³ Also, highly unsaturated intermediates such as pyridynes (analogs of arynes⁴,⁵) offer a unique possibility of adjacent regioselective double functionalization.⁶

However, pyridyne chemistry is relatively unexplored. The generation of pyridynes often requires elaborated precursors and their further reactions with nucleophiles were of limited scope and complicated by a lack of regioselectivity. Garg showed, that the introduction of a substituent in position 2 significantly improved the regioselectivity of the nucleophilic addition using the aryne distortion model. However, the starting material preparation was lengthy and the reactivity of such 3,4-pyridynes was limited to cycloadditions and aminations. To overcome some of the previously described drawbacks, we have chosen, according to Hegarty, to use readily prepared 3-chloro-2-ethoxypyridine (1) as a precursor of 3,4-pyridyne, achieving an effective synthesis of highly decorated pyridines.

Thus, the regioselective lithiation of the pyridine ${\bf 1}$ with n-BuLi will afford the 4-lithiated pyridine ${\bf 2}$. Transmetalation with an

organomagnesium halide RMgBr·LiCl of type 3 will produce mixed diorganomagnesiums of type 4. At elevated temperatures, an elimination should proceed leading to the 3,4-pyridyne 5. After the regioselective addition of RMgX (RMgBr·LiCl or RMgCl), affording magnesiated pyridines of type 6, quenching with various electrophiles (E–X) should produce the desired polyfunctional pyridines of type 7 (Scheme 1).

Results and discussion

Herein, we report the successful outcome of this synthetic approach. In preliminary experiments, we have treated **1** with *n*-BuLi in THF at -78 °C and found that a fully regioselective lithiation towards **2** was achieved within 2 h. Addition of 4-anisylmagnesium bromide (AnMgBr·LiCl, **3a**) at -78 °C, which was prepared by the reaction of 4-anisyl bromide with magnesium turnings in the presence of LiCl,¹¹ led tentatively to the mixed diorganomagnesium reagent **4**. The optimum for the

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Scheme 1 General reaction sequence towards difunctionalized pyridines of type 7 starting from 3-chloro-2-ethoxypyridine (1) *via* the 3,4-pyridyne intermediate 5.

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elimination of 4 providing the corresponding pyridyne occurred at 75 °C in a sealed tube with 1 h reaction time. 12 Also, the use of 2 equivalents of 4-anisylmagnesium bromide (An-MgBr) was required to achieve a high yield.13 The regioselectivity of the organomagnesium addition to the pyridyne intermediate was explained by a coordinating effect of the ethoxy group at position C2. Therefore, the stabilized 3-magnesiated species 6 gave regioselectively the pure 4-arylated pyridine 7a (64% yield) after quenching the reaction mixture with sat. aq. NH₄Cl. This procedure was quite general and a range of arylmagnesium bromides added regioselectively at position 4. After aqueous workup, the 4-arylated pyridines 7b-g were obtained in 41-61% yield.14 Additionally, the use of alkylmagnesium halides (5.0 equiv.) provided the desired pyridines 7h-i, bearing an alkyl substituent at position 4, in 56-58% yield (Scheme 2). The missing material was a result of the unstability of the pyridine intermediate which may oligomerize or polymerize.¹⁵

With these optimized conditions, we have trapped the newly generated pyridylmagnesium halides of type 6 with various electrophiles leading to 3,4-difunctionalized pyridines of type 7 (Scheme 3).

As previously described, we treated 1 with *n*-BuLi followed by addition of AnMgBr (3a, An = 4-MeO- C_6H_4). Heating to 75 °C in a sealed tube for 1 h led to the pyridyne formation. Regioselective addition of 3a afforded the 3-pyridylmagnesium species 6a. Addition of TMSCl (2.5 equiv., 25 °C, 12 h) gave the 3,4difunctionalized pyridine 7aa in an overall yield of 53% (0.5 mmol scale, Scheme 3). A scale-up to 5 mmol provided a similar yield (54%). Thiolation with S-methyl methanesulfonothioate and bromination with (CCl2Br)2 led to the thioether 7ab in 43% yield and the 3-halogenated pyridine 7ac in 57% yield. A further derivatization of the previously prepared trisubstituted pyridines (7ac) was made. This pyridine was treated with POCl3 and DMF leading to the trisubstituted 2chloropyridine 8 in 90% yield. Ouenching the pyridylmagnesium bromide 6a with both, electron-rich and electron-poor heterocyclic aldehydes afforded the benzylic alcohols 7ad and 7ae in 57-60% yield. Copper(1)-catalyzed

[a] n-BuLi (1.1 equiv), 2 h, -78 °C. [b] RMgBr·LiCl (2.0 equiv), 0.5 h, -78 °C. [c] 75 °C (sealed tube), 1 h, quench with aq. sat. NH₄Cl. [d] An= $4-\text{MeO-C}_6\text{H}_4$ - [e] $3-\text{MeS-C}_6\text{H}_4\text{MgBr-LiCI}$ (2.0 equiv) [f] AlkylMgBr-LiCI (5.0 equiv)

Scheme 2 Regioselective lithiation of 3-chloro-2-ethoxypyridine (1) and subsequent transmetalation to diorganomagnesium reagents of type 4 leading to 4-arylated pyridines of type 7 via the 3,4-pyridyne 5.

[a] n-BuLi (1.1 equiv), -78 °C, 2 h. [b] RMgBr·LiCl (2.0 equiv), -78 °C, 30 min. [c] 75 °C (sealed tube), 1 h. [d] The regioselectivity was determined by crystal structure analyses, see Supporting Information [e] POCl₃ (3.0 equiv), DMF, 0 °C, 1h, then 100 °C (sealed tube), 4 h. [f] CuCN 2LiCl (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h [g] CuCN 2LiCl (2.0 equiv), 0 °C, 10 min, then acyl chloride (2.5 equiv), 25 °C, 12 h. [h] ZnCl₂ (2.0 equiv), 0 °C, 10 min, then a mixture of aryl halide (2.5 equiv), Pd(OAc)₂ (5 mol%) and SPhos (10 mol%), 25 °C, 12 h. [i] ZnCl₂ (1.0 equiv), 0 °C, 10 min, then N-hydroxylamino benzoates (2.0 equiv) and Cu(OTf)2 (10 mol%), 0 °C to 25 °C, 12 h. [j] AlkylMgBr LiCl (5.0 equiv). [k] CuCN 2LiCl (5.0 equiv), 0 °C, 10 min, then acyl chloride (5.5 equiv), 25 °C, 12 h.

Scheme 3 Regioselective difunctionalization of 3-chloro-2-ethoxypyridine (1) towards the pyridines 7aa-7ia via the 3,4-pyridyne 5.

allylation gave the pyridine 7af in 56% yield. Additionally, copper(1)-mediated acylation with 4-chlorobenzoyl chloride led to the biaryl ketone 7ag in 58% yield. Negishi cross-coupling17 of the magnesium species 6a, after transmetalation with ZnCl₂. with ethyl 3-bromobenzoate in the presence of 5 mol% Pd(OAc)₂ and 10 mol% SPhos18 led to the 3,4-bis-arylated pyridine 7ah in 56% yield. A Cu-catalyzed electrophilic amination with Nhydroxylamino benzoates afforded the 3-aminated pyridines 7ai and 7aj in 47-54% yield.19

Next, cross-coupling reactions of 4-(3-(trimethylsilyl)phenyl)-3-pyridylmagnesium bromide (6b) led to the highly functionalized pyridines 7ba and 7bb in 53-55% isolated yield. Using the 3-pyridylmagnesium compound 6c gave the thiols 7ca and 7cb in 49-52% yield by quenching with either (CCl₂Br)₂ or DMF.14 A cross-coupling of 6d with 4-iodobenzotrifluoride gave

the expected trisubstituted pyridine 7da in 53% yield. Iodolysis of 3-magnesiated pyridine 6e gave the iodinated pyridine 7ea in 50% yield.

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Finally, the 4-alkylated pyridylmagnesium species **6h** and **6i** were further functionalized either by acylation affording the ketone **7ha** in 55% yield or quench with benzaldehyde leading to the alcohol **7ia** in 49% overall yield.

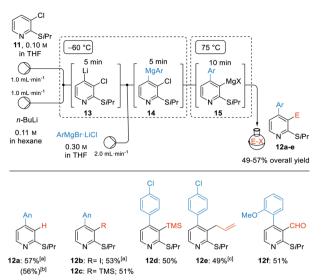
In order to extend the scope of these difunctionalizations, we investigated the use of magnesium thiolates. These nucleophiles proved to be excellent reaction partners and the treatment of the lithiated pyridine 2 with RSMgX·LiCl²0 gave regioselectively, after heating to 75 °C for 1 h in a sealed tube, 4-thiolated pyridines such as 10a-b in 69–72% yield (Scheme 4). Further quenching of the intermediate 9a with various electrophiles such as TMSCl, DMF, benzaldehyde and benzophenone gave the 2,3,4-trifunctionalized pyridines 10aa-ad in 50–71% yield. Additionally, the treatment of 9a with ethyl 2-formylbenzoate produced the phthalide 10ae in 71% yield. Further, a palladium-catalyzed cross-coupling on the sterically demanding substrate 9b gave, after 3,4-pyridyne formation, the pyridine 10ba in 67% isolated yield.

The performance of multi-step organometallic reactions in a continuous flow set-up using microreactors often proved to be advantageous, allowing a much better reaction control than in batch with milder and more selective reactions conditions. Thus, we examined the arylation of 2-isopropylthio-3-chloropyridine (11) and subsequent trapping with electrophiles. In a calibration experiment in batch, we treated 11 with n-BuLi (-60 °C, 10 min) followed by the addition of AnMgBr (3a, 6.0 equiv., -60 °C, 0.5 h, then 75 °C, 1 h) leading to the desired 2,4-disubstituted pyridine 12a in 56% yield.

We transposed this reaction sequence into a continuous flow set-up as shown in Scheme 5. Mixing n-BuLi with the starting material **11** afforded the lithiated species **13** after 5 min residence time at -60 °C. Adding various arylmagnesium bromides of type 3 via a third pump gave the transient magnesium species

[a] n-BuLi (1.1 equiv), 2 h, -78 °C. [b] RSMgCl·LiCl (2.0 equiv), 0.5 h, -78 °C. [c] 75 °C (sealed tube), 1 h, quench with sat. NH₄Cl_(aq) or E-X. [d] ZnCl₂ (2.0 equiv), 0 °C, 0.5 h, then Pd(OAc)₂ (10 mol%), SPhos (20 mol%) and 4-iodoanisole (2.5 equiv), 0 °C to 25 °C. 12 h.

Scheme 4 Selective lithiation of 3-chloro-2-ethoxypyridine (1) and subsequent transmetalation towards the diorganomagnesium reagents of type 9 leading to 4-thiolated pyridines of type 10.



[a] The regioselectivity was determined by crystal structure analyses, see SI. [b] yield in batch. [c] CuCN-2LiCl (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h.

Scheme 5 Continuous flow set-up for the difunctionalization of 3-chloro-2-(isopropylthio)pyridine 11 *via* pyridyne formation and subsequent quenching of the generated 3-pyridylmagnesium reagent 15 with various electrophiles.

of type **14** which were heated to 75 °C for 10 min. This very reproducible procedure provided the stable 3-pyridylmagnesium species **15** which was directly pumped into a round bottom flask containing various electrophiles. Quenching with sat. aq. NH₄Cl gave the pyridine **12a** in 57% isolated yield. Alternatively, iodination (with I₂), silylation (with TMSCl), allylation (with allyl bromide) and formylation (with DMF) gave the expected 2,3,4-trisubstituted pyridines **12b-f** in 49–53% overall yield. For this multi-step procedure, the flow setup proved to be advantageous for its high reproducibility, good temperature control and its potential for easy scale up for eventual industrial applications.

[a] n-BuLi (1.1 equiv), -78 °C, 2 h. [b] 4-F-C₆H₄MgBr-LiCl (3.0 equiv), -78 °C, 30 min. [c] 75 °C (sealed tube), 1 h. [d] methyl cyanoformate (5.0 equiv), 0 °C to 25 °C, 12 h. [e] BnBr (neat), microwave irradiation, 120 °C, 30 h, [f] 5% Pd/C (100 mol%), 1 atm H₂, MeOH, 25 °C, 18 h.

Scheme 6 Route towards the key intermediate 18 of the synthesis of (\pm) -paroxetine (16).

Next, we applied this method for the preparation of a key intermediate of the synthesis of (\pm) -paroxetine (16).²³ Thus, starting from 3-chloro-2-ethoxypyridine (1), we have prepared the trisubstituted pyridine (7ja) on a 5 mmol scale with 53% overall yield. Treatment of 7ja with neat benzyl bromide at 120 °C for 30 h afforded the *N*-benzylated pyridone 17 in 80% yield.²⁴ Then, a selective hydrogenation of the pyridone 17 using H_2 gas and Pd/C gave the desired *trans*-substituted piperidone 18 in 50% yield (Scheme 6).²⁵

Conclusions

In conclusion, we have developed a new regioselective 3,4-difunctionalization of 3-chloropyridines *via* 2-alkoxy or 2-alkylthiol 3,4-pyridyne intermediates using as nucleophiles aryland alkylmagnesium halides as well as magnesium alkythiolates. The resulting 3-pyridylmagnesium species were quenched with various electrophiles, producing polyfunctional 2,3,4-substituted pyridines.

In addition, this methodology was converted into a convenient continuous flow set-up. As an application, we have prepared a key intermediate for the synthesis of the antidepressant (\pm) -paroxetine **16**.

Author contributions

B. H. and D. D. performed the experiments and analysed the data. P. F. and B. M. discussed the results. K. K. measured and analyzed the crystal structures. P. K. conceived the project and wrote the paper. B. H., D. D., P. F. and B. M. contributed to the editing.

Conflicts of interest

There are no conflicts to declare.

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