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Selective synthesis of 2-substituted pyridine *N*-oxides via directed *ortho*-metallation using Grignard reagents

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ABSTRACT

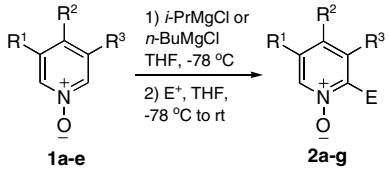
Addition of *i*-PrMgCl to pyridine *N*-oxides in THF at −78 °C generates selectively an *ortho*-metallated species, which can be trapped with various electrophiles to generate 2-substituted pyridine *N*-oxides. Furthermore, by applying a double metal-catalyzed cross-coupling, direct arylation of the pyridine *N*-oxides is achieved.

Herein, we report an efficient one-pot synthesis of 2-substituted pyridine *N*-oxides via directed *ortho*-metallation using Grignard reagents in combination with a diverse set of electrophiles. Synthesis of functionalized pyridine *N*-oxides constitutes a practical way to achieve substituted pyridines which are prominent in medicinal chemistry[1–3] and materials.[4] Transition metal-catalyzed C–H activation has proven to be efficient for the functionalization of pyridine *N*-oxides.[5–7] Although synthetically elegant, the method is limited to arylations, requires high temperatures, long reactions times, and the use of excess pyridine *N*-oxide (4 equiv, in general). The use of organolithium reagents, that is, butyllithium, for deprotonation of pyridine *N*-oxides followed by addition of an electrophile has been thoroughly studied, but so far only poor to moderate yields (14–45%) have been reported along with 2,6-disubstitution as major by-products.[8–14] The reaction between pyridine *N*-oxides and Grignard reagents has generally been reported to give rise to nucleophilic attack followed by ring-opening.[15–17] As a result, pyridine *N*-oxides were not regarded as suitable starting materials for the synthesis of substituted piperidines using Grignard reagents. Instead, another method was developed, that is, the synthesis of 2-substituted piperidines by addition of Grignard reagents to *N*-benzoyliminopyridinium ylides.[18]

Recently, we took advantage of the fact that pyridine *N*-oxides undergo rearrangement after a rapid addition of Grignard reagents at room temperature. This led to improved syntheses of both dienal oximes and 2-substituted pyridines.[19,20] However, during those studies, instead of the normal addition-rearrangement, a proton abstraction was observed when treating the *N*-oxides with alkyl Grignard reagents at −78 °C. This could potentially lead to a mild regioselective methodology for the synthesis of substituted pyridine *N*-oxides and correspondingly, to pyridines with a broad range of substituents.

Exploration of the reaction conditions was initiated by the addition of *n*-butylmagnesium chloride at −78 °C to pyridine *N*-oxide **1a** followed by quenching with deuterium oxide. A regioselective incorporation of deuterium at the 2-position was observed in more than 90% according to crude-NMR, **2a** (Table 1, entry 1). Thus, by using *n*-BuMgCl, the disubstituted by-products previously reported with *n*-BuLi were avoided. Switching the electrophile to benzaldehyde gave a significant drop in yield, and product **2b** was isolated in 45% yield (Table 1, entry 2). However, the yield was improved to

Table 1
Preparation of 2-substituted pyridine *N*-oxides



1a-e **2a-g**

Entry	*N*-Oxide	R^1	R^2	R^3	E	Product	Yield[a] (%)
1	**1a**	H	OBn	H	D	**2a**	90[b,c]
2	**1a**	H	OBn	H	PhCHOH	**2b**	45[b]
3	**1a**	H	OBn	H	PhCHOH	**2b**	65
4	**1a**	H	OBn	H	I	**2c**	67
5	**1b**	H	H	Me	PhCHOH	**2d**	61[d]
6	**1c**	H	H	OMe	PhCHOH	**2e**	86
7	**1d**	Me	H	Me	I	**2f**	92
8	**1e**	H	Ph	H	PhCHOH	**2g**	38

Conditions: (1) pyridine *N*-oxide (1 equiv), Grignard reagent (1.7 equiv) in THF at −78 °C stirred for 1 h. (2) Benzaldehyde (2.0 equiv) added at −78 °C and allowed to reach rt and stirred for another 30 min.

[a] Isolated yields.
[b] *n*-BuMgCl used for deprotonation.
[c] Yield determined by crude-NMR.
[d] Isolated as an isomeric mixture of 2,3- and 3,6-substituted *N*-oxides in a 1:1.5 ratio.

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65% by exchanging *n*-BuMgCl with *iso*-propylmagnesium chloride (*i*-PrMgCl) (entry 3, Table 1). Results for the deprotonation of substituted pyridine *N*-oxides **1a–e** using 1.7 equiv of *i*-PrMgCl followed by quenching with benzaldehyde or iodine (entries 3–8) are summarized in Table 1.

When iodine was used as the electrophile in the reaction with *ortho*-metallated pyridine *N*-oxide **1a**, a similar yield as for the reaction with benzaldehyde (**2b**, 65%) was observed, and **2c** was isolated in 67% yield (Table 1, entry 4). Thereafter, the unsymmetric 3-picoline *N*-oxide **1b** was deprotonated and allowed to react with benzaldehyde. This yielded a 1:1.5 mixture of 2- and 6-substituted isomers **2d,** respectively, in a 61% isolated yield (Table 1, entry 5). However, by switching the methyl group to a methoxy group as in **1c**, with potential directing properties, a better result was obtained, and the 2,3-substituted pyridine *N*-oxide **2e** was isolated in 86% yield as the sole product (Table 1, entry 6). The symmetric 3,5-dimethyl-substituted *N*-oxide (**1d**) was deprotonated and reacted with iodine yielding the tri-substituted pyridine *N*-oxide **2f** in an excellent isolated yield of 92% (Table 1, entry 7). A selective monohalogenation was observed which stands in strong contrast to the reaction performed using alkyllithium, which is reported to give mainly dihalogenated products.[10] The 4-phenyl substituted pyridine *N*-oxide **1e** showed a different reactivity when treated with *i*-PrMgCl at −78 °C followed by trapping with benzaldehyde. The major product was the result of direct nucleophilic attack followed by an oxidation to yield 2-isopropyl-4-phenyl substituted pyridine *N*-oxide in 56% yield and the expected product **2g** was obtained in 38% yield (Table 1, entry 8).

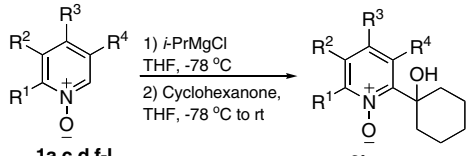
To further investigate the potential of the method and to make it more practical, we wanted to reduce the number of equivalents of the Grignard reagent. In addition, a sterically more demanding electrophile other than benzaldehyde was studied. Therefore, various pyridine *N*-oxides were reacted with 1.2 equiv of *i*-PrMgCl, followed by in situ trapping with cyclohexanone, which in addition to being more sterically hindered has acidic α-protons (Table 2). By using cyclohexanone as an electrophile, it was also possible to compare the alkylmagnesium reaction with butyllithium more directly.[10]

Regioselective 2-substitution of pyridine *N*-oxide **1f** was achieved with cyclohexanone to yield 38% of product **2h** (Table 2, entry 1), which is an improvement compared to the previously isolated 7% yield using *n*-BuLi.[10] Analogously **2i** and **2j** were isolated in improved yields of 32% and 36%, respectively (Table 2, entries 2 and 3). In comparison, using alkyllithiums, the yields were 0% and 21%, respectively, and resulted in alkylation on the methyl groups.[10] Furthermore, the corresponding 3,5-dimethyl pyridine *N*-oxide **1d** gave rise to the hydroxy-cyclohexyl substituted *N*-oxide **2k** in 81% yield (Table 2, entry 4). Pyridine *N*-oxides **1i** and **1k**, with 2-methoxy- and 2-chloro substituents, respectively, gave rise to a complex reaction mixture when reacted in the same manner (Table 2, entries 5 and 8). However, when 4-methoxy- and 4-chloro-substituted *N*-oxides **1j** and **1l** were used, the desired products **2n** and **2p** were isolated in 22% and 20% yields, respectively (Table 2, entries 7 and 9). The 3-methoxy pyridine *N*-oxide **1c** and 4-benzyloxy *N*-oxide **1a** underwent the desired deprotonation in good to excellent yields, and the tertiary alcohol-substituted pyridine *N*-oxides **2m** and **2q** were isolated in 90% and 62% yields, respectively, after the addition of cyclohexanone. High yields were obtained when 3-methoxy-substituted pyridine *N*-oxide **1c** was deprotonated and trapped with various electrophiles. To further prove the robustness of the reaction, another three electrophiles were trapped with intermediate **3** (Scheme 1).

Incorporation of substituents such as piperidinone moieties is of great interest due to their known potency in biological systems.[21–25] The direct trapping of intermediate **3** using Boc-protected piperidinone resulted in an excellent 93% isolated yield of **2r** (Scheme 1). Moreover, the introduction of halogens on heterocycles is of significant importance because of their versatility as synthetic intermediates, for example, in cross-couplings such as Heck,[26,27] Suzuki[28] or Stille.[29,30] Indeed, the addition of iodine to intermediate **3** yielded the corresponding 2-iodopyridine *N*-oxide **2s** in 96% yield (Scheme 1). Finally, by trapping intermediate **3** with phenylisocyanate, the amide substituted pyridine *N*-oxide **2t** was obtained in 81% yield. Bearing in mind the large amount of commercially available ketones, aldehydes and isocyanates, these results indicate a great potential to synthesize libraries of pyridine *N*-oxides with diverse substituents and properties (Scheme 1).

Finally, in order to expand the scope to include cross-coupling reactions and, thus, gain access to 2-aryl-substituted pyridine *N*-oxides, we explored the utility of the generated metallated pyridine *N*-oxide in combination with aryl halides. These types of reactions have been described extensively in the literature, for example, the use of palladium,[31] iron,[32] as well as copper[33] in combination with Grignard reagents and different halides. Unfortunately, both iron and copper reagents, which are easier to handle and are inexpensive, only resulted in isolation of starting material in attempts to couple intermediate **4** with different aryl halides. Alternatively, as to aryl halides, the use of bench-stable diaryliod-

Table 2
ortho-Metallation followed by trapping using cyclohexanone

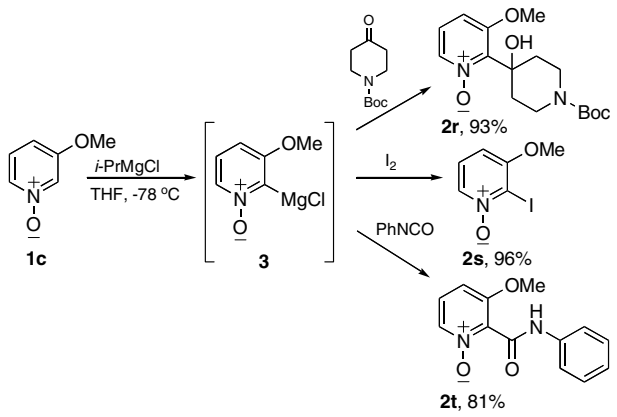


1a,c,d,f-l **2h-q**

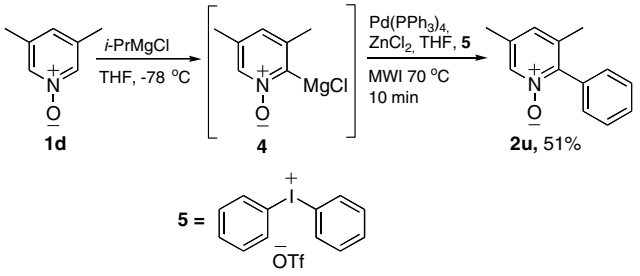
Entry	*N*-Oxide	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1	**1f**	H	H	H	H	**2h**	38
2	**1g**	Me	H	H	H	**2i**	32
3	**1h**	H	H	Me	H	**2j**	36
4	**1d**	H	Me	H	Me	**2k**	81
5	**1i**	OMe	H	H	H	**2l**	0
6	**1c**	H	H	H	OMe	**2m**	90
7	**1j**	H	H	OMe	H	**2n**	22
8	**1k**	Cl	H	H	H	**2o**	0
9	**1l**	H	H	Cl	H	**2p**	20
10	**1a**	H	H	OBn	H	**2q**	62

Conditions: (1) pyridine *N*-oxide (1 equiv), Grignard reagent (1.2 equiv) in THF at −78 °C stirred for 1 h. (2) Cyclohexanone (1.5 equiv) added at −78 °C and allowed to attain rt and stirred for another 30 min.

[a] Isolated yields.



Scheme 1.



Scheme 2.

onium salts has proven efficient for introduction of aryl substituents.[34] However, the direct coupling with Grignard reagents has not been reported, and as in the case when adding diphenyliodonium triflate directly to intermediate **4**, a complex reaction mixture was obtained. A more promising result was observed, using a double metal-catalyzed cross-coupling[35] of diphenyliodonium triflate **5** and Grignard reagent **4**. We initially attempted the palladium-assisted coupling at room temperature.[36] Unfortunately, although completely regioselective, this only gave 10% of the desired 2-phenyl-substituted product. However, by using microwave-assisted synthesis[37] for 10 min at 70 °C, which is a faster and milder method compared to that previously reported, a yield of 51% of **2u** was obtained (Scheme 2).

In conclusion, we have developed a mild method for the selective 2-substitution of pyridine *N*-oxides via a directed *ortho*-metallation. The generated intermediates could be trapped successfully with various electrophiles, ranging from aldehydes, ketones and halogens. We also demonstrated the usefulness of the metallation reagents through a direct arylation using a double metal-catalyzed cross-coupling reaction. These reactions together constitute a platform to synthesize a range of 2-substituted pyridine *N*-oxides, thus allowing for fine-tuning and optimization of their properties.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedures and compound characterization data of compounds **2a**–**u**) associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2008.09.104.

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