ORGANIC LETTERS

2007
Vol. 9, No. 7
1335−1337

# Synthesis of 2-Substituted Pyridines via a Regiospecific Alkylation, Alkynylation, and Arylation of Pyridine *N*-Oxides

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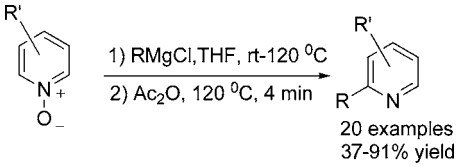
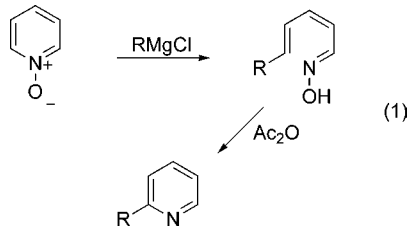
**Received January 24, 2007**

## ABSTRACT




**Sequential addition of Grignard reagents to pyridine *N*-oxides in THF at room temperature followed by treatment with acetic anhydride at 120 °C afforded 2-substituted pyridines in good to high yields. Furthermore, by exchanging acetic anhydride for DMF in the second step, 2-substituted pyridine *N*-oxides were obtained, as intermediates suitable for addition of a second Grignard reagent for the synthesis of 2,6-disubstituted pyridines.**

Herein, we report on the transition-metal free regiospecific synthesis of 2-substituted alkyl, alkynyl, and arylpyridines, a class of compounds prominent in medicinal chemistry and materials.[1] Sequential addition of Grignard reagents to pyridine *N*-oxides followed by treatment of the resulting 2,4-dienal oximes[2] with acetic anhydride affords a range of 2-substituted pyridines in good to high yields (eq 1). In 1965, Kato reported the reaction of pyridine *N*-oxides with phenylmagnesium bromide as the sole reagent, giving 2-phenylpyridine in 43% yield via a 1,2-dihydropyridine intermediate.[2b] The 4-methyl-2-phenylpyridine was reported in 23% yield. Interested in the stereospecificity, Kellogg revisited the reaction and found it to proceed via a ring-opened 2,4-dienal oxime intermediate; however, the subsequent 2-arylpyridines formed were reported in yields below 24%.[2c]




(1)

The addition of organometallic reagents to acyl- and alkyl-activated pyridines has been developed into an expedient method for the synthesis of substituted pyridines. However, the formation of isomeric mixtures of 2- and 4-substituted products has limited the application of this methodology. Although some selective additions to the 4-position have been achieved,[3] additions to the 2-positions have only been synthetically useful when the 4-position is blocked.[4] Recently, Fagnou and co-workers published the Pd-catalyzed direct arylation of pyridine *N*-oxides followed by a Pd-catalyzed reduction reaction with ammonium formate yield-

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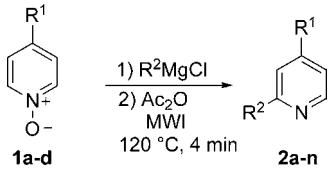
10.1021/ol070184n CCC: $37.00 
**Published on Web 03/01/2007**

ing 2-arylpyridines in good to high yields (64−86%) based on the arylbromide; however, 4 equiv of the pyridine *N*-oxide was used in the reaction.[5] The availability of the pyridine *N*-oxide could be the limiting starting material, even though there is a wealth of commercially available pyridine *N*-oxides.

In our previous report on the synthesis of 2,4-dienal oximes, the fast addition of the Grignard reagents to the pyridine *N*-oxide THF solution was identified to be key for achieving high yields of the dienal oxime.[2a] A range of alkyl, aryl, and alkynyl Grignard reagents were added to pyridine *N*-oxides in THF. After consumption of the pyridine *N*-oxide, a liquid−liquid extractive workup followed by dissolving the residue in $Ac_2O$ and further heating under microwave conditions (120 °C, 4 min) afforded 2-substituted pyridines in good to high yields (37−86%, Table 1).[6] The unsubstituted

**Table 1.** Synthesis of 2-Substituted and 2,4-Disubstituted Pyridines[a]



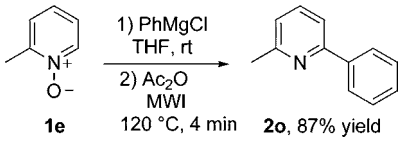

| entry | $R^1$ (*N*-oxide) | $R^2$ | product | yield[b] |
|---|---|---|---|---|
| 1 | H (**1a**) | Ph | **2a** | 63% |
| 2 | H (**1a**) | *p*-MeOPh | **2b** | 83% |
| 3 | H (**1a**) | *p*-MePh | **2c** | 83% |
| 4 | H (**1a**) | Bn | **2d** | 38% |
| 5 | Ph (**1b**) | Ph | **2e** | 86% |
| 6 | Ph (**1b**) | Ph | **2e** | 81%[c] |
| 7 | Ph (**1b**) | naphthalen-2-yl | **2f** | 75% |
| 8 | Ph (**1b**) | PhCC | **2g** | 78% |
| 9 | Ph (**1b**) | cy-propylCC | **2h** | 86% |
| 10 | Ph (**1b**) | thiophen-2-yl | **2i** | 73% |
| 11 | BnO (**1c**) | Ph | **2j** | 82% |
| 12 | BnO (**1c**) | naphthalen-2-yl | **2k** | 79% |
| 13 | BnO (**1c**) | *iso*-propyl | **2l** | 45% |
| 14 | BnO (**1c**) | Me | **2m** | 37% |
| 15 | Cl (**1d**) | Ph | **2n** | 74% |

[a] Conditions: (1) pyridine *N*-oxide (1 equiv), Grignard reagents (1.5 equiv) in THF at 25 °C. (2) $Ac_2O$, 120 °C, 4 min. [b] Isolated yields, two steps. [c] Conventional heating at 120−140 °C for 1 h.

*N*-oxide **1a**, having the potential of forming 4-addition products, yielded exclusively 2-substituted pyridines (entries 1−4, Table 1). Both the *p*-MeOPh derivative **2b** and *p*-MePh **2c** were isolated in the same high yield (83%), and the *p*-MePh **2c** result was comparable with the 86% yield reported by using direct arylation.[5] In addition to 2-arylpyridines (entries 1−7, 11, 12, and 15; Table 1), 2-alkynyl (entries 8 and 9, Table 1), heteroaryl (entry 10, Table 1), and alkyl (entries 4, 13, and 14; Table 1) were also accessible by adding the corresponding Grignard reagents to pyridine *N*-oxides (**1a**−**d**). Complete consumption of the pyridine *N*-oxide was achieved with aryl, heteroaryl, and alkynyl Grignards. However, alkyl Grignards resulted at best in only modest yields of 38%, 45%, and 37% of pyridines **2d**, **2l**, and **2m**, respectively, by increasing the amount of Grignard reagent to 2 equiv; beyond that, no improvement was seen. The starting materials, pyridine *N*-oxides, were isolated in around 40% yields. Starting out with 4-substituted pyridine *N*-oxides **1b**−**d** yielded the 2,4-disubstituted pyridines **2e**−**n** (entries 5−15, Table 1). Substituted 4-chloropyridines are predisposed for further transformations such as nucleophilic substitutions and cross-couplings. A limitation using this strategy for the synthesis of substituted pyridines is the availability of substituted 4-chloropyridines. The 74% yield achieved with 4-chloropyridine *N*-oxide (**1d**) is an improvement compared to the published 55% yield using phenoxycarbonyl-activated 4-chloropyridine (entry 15, Table 1).[7] Conventional heating in the second step and cyclizing the dienal oxime gave a comparable yield to that using microwave heating (compare entries 5 and 6, Table 1).

2-Substituted pyridine *N*-oxides have one less reactive α-site (i.e., 2- and 6-postions) that potentially could drive the reaction to give 4-substituted products. Phenylmagnesium chloride was added to 2-methyl pyridine *N*-oxide **1e**, and the 2,6-disubstituted pyridine **2o** was formed in high yield (87%). The 2,4-substituted pyridine was not observed which is the major isomer formed using acylpyridinium salts[3b] (Scheme 1). This method is an alternative to using 2-halo-

**Scheme 1.** Synthesis of 2,6-Disubstituted Pyridines




pyridines and a Pd catalyst published by Wolf (2-Br, 61% yield)[8] and Knochel (2-Cl, 96% yield).[9]

Having established that the two-step protocol worked with unsubstituted as well as with 2- and 4-substituted pyridine *N*-oxides, 3-substituted pyridine *N*-oxides were reacted using the developed conditions (Scheme 2). Interestingly, the 2,4-dienal intermediate was not formed by adding Grignard reagents to 3-substituted pyridine *N*-oxides. The corresponding 2,3-disubstituted pyridine was formed directly. Addition to the 3-methyl derivative **1f** gave the sterically more congested 2,3-disubstituted pyridine **2p** as the major product in moderate 43% yield but with excellent selectivity; the minor 2,5-disubstituted isomer was formed in trace amounts. Interestingly, although smaller Grignard reagents (e.g.,

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(6) Exothermic onset temperature ($T_0$) for pyridine *N*-oxide is 288 °C.

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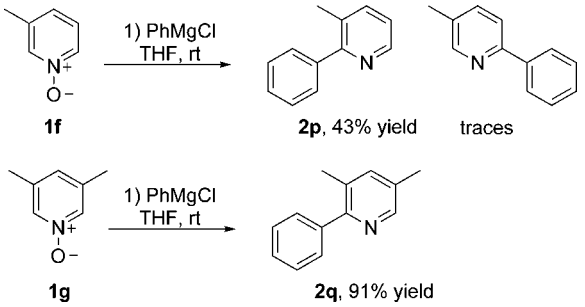
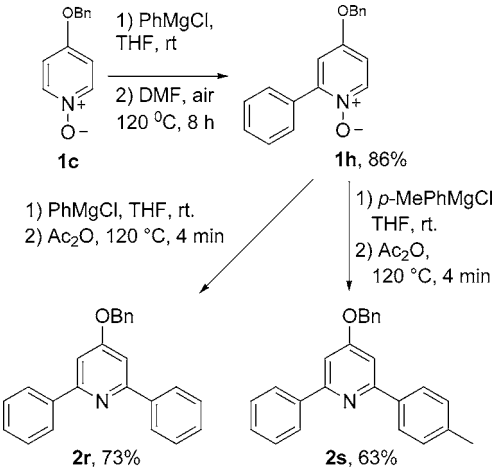
**Scheme 2.** Synthesis of 2,3-Disubstituted and 2,3,5-Trisubstituted Pyridines




ethylmagnesium chloride) when added to acyl pyridinium salts have been reported to preferentially add to the 2-position and not to the less-hindered 6-position, using the larger phenylmagnesium halides, 6-substitution predominates over 2-substitution.[10] This is a diversification from our results that gives practically only the 2-substituted product. However, more importantly, an isomeric mixture of 2-, 4-, and 6-substituted products is formed using acyl-activated pyridines. The 3,5-dimethyl-substituted pyridine *N*-oxide **1g** gave the 2,3,5-trisubstituted pyridine **2q** in excellent 91% yield.

The sequential synthesis of unsymmetrical 2,6-disubstituted pyridines from the symmetrical ones has been scarcely reported, and the few examples reported so far have mostly relied on the 2,6-dihalo pyridines.[11] Pyridine *N*-oxides are easily synthesized by a number of methods[12] which would open up for the use of 2-substituted pyridines (e.g., see Scheme 1) in the synthesis of 2,6-disubstituted pyridines. However, forming the pyridine *N*-oxide directly from the 2,4-dienal oxime formed after the first addition of the Grignard reagents would give an attractive synthesis that would be able to start from 2,6-unsubstituted pyridine *N*-oxides. Although sequential addition can be achieved with the Fagnou methodology, the use of 4 equiv of the pyridine *N*-oxide makes it less attractive. During the methodology development presented herein, it was noticed that by heating the dienal oximes the corresponding pyridine *N*-oxides were formed. Thus, the synthesis of unsymmetrical 2,6-disubstituted unsymmetrical pyridines would be straightforward. After the first Grignard addition to **1c**, the crude product was dissolved in DMF and heated to give the 2-phenyl pyridine *N*-oxide **1h** in 86% yield. A subsequent phenylmagnesium chloride addition to pyridine *N*-oxide **1h** yielded the 2,6-diphenyl-substituted pyridine **2r** in 73% yield (Scheme 3). However, addition of *p*-tolylmagnesium chloride to **1h**

**Scheme 3.** Sequential Addition to Pyridine *N*-Oxide




furnished the 2,6-unsymmetrical substituted pyridine **2s** in 63% yield.

Neither pyridine **2r** nor the corresponding *p*-tolyl-disubstituted pyridine was observed in the latter reaction. In addition to the efficient synthesis of 2,6-disubstituted pyridines, this procedure is also well suited for sequential addition of Grignard reagents with very similar structural properties, which potentially could render purification problems by the formation of the symmetrical 2,6-disubstituted pyridine.

In summary, we have developed a general, high-yielding synthesis of 2-substituted pyridines. The reaction is completely selective, exclusively forming one regioisomer, which simplifies the purification step. Alkyl, alkynyl, and aryl 2-substituted pyridines can potentially be synthesized using 2-, 3-, and 4-substituted pyridine *N*-oxides as starting materials. With the exception of 3-methyl pyridine *N*-oxide, the pyridines are formed via an intermediate 2,4-dienal oxime.

**Acknowledgment.** We thank the Swedish Natural Science Research Council and the Knut and Alice Wallenberg foundation for financial support.

**Supporting Information Available:** Synthetic procedures and the characterization of compounds **2a**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070184N

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