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Regio- and Stereoselective Alkylation of Pyridine-*N*-oxides: Synthesis of Substituted Piperidines and Pyridines

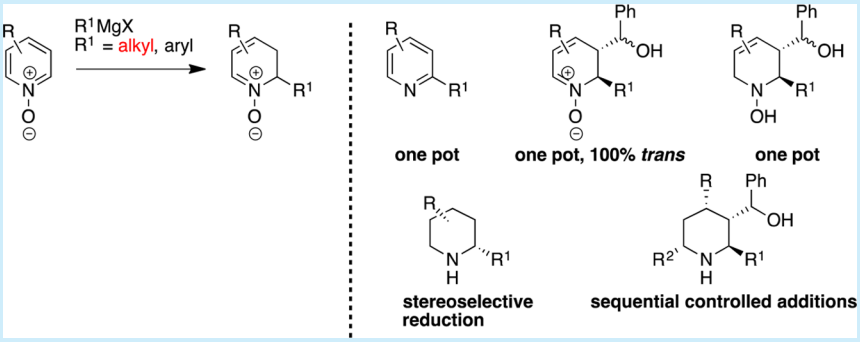
Deepak Kumar Barange,[†] Magnus T. Johnson,[‡] Andrew G. Cairns,[†] Roger Olsson,*[,§] and Fredrik Almqvist*[,†]

[†]Department of Chemistry, Umeå University, 90187 Umeå, Sweden

[‡]Centre for Analysis and Synthesis, Lund University, 22100 Lund, Sweden

[§]Chemical Biology & Therapeutic Unit, Department of Experimental Medical Science, Lund University, 22100 Lund, Sweden

Supporting Information



ABSTRACT: Regio- and stereoselective addition of alkyl Grignard reagents to pyridine-*N*-oxides gave C2-alkylated *N*-hydroxy-1,2,5,6-tetrahydropyridines and *trans*-2,3-disubstituted *N*-hydroxy-1,2,5,6-tetrahydropyridines in good to excellent yields. These intermediates were aromatized or alternatively reduced in one-pot methodologies for efficient syntheses of alkylpyridines or piperidines, respectively. These reactions have a broad substrate scope and short reaction times.

Piperidines and pyridines are recurring motifs in natural products and drugs, and they show a range of biological properties.[1,2] Despite the prevalence of these privileged structures, the synthesis of alkylpyridines[4] and alkyl-substituted piperidines remains challenging (Scheme 1).[3] Many approaches use directing or blocking groups to achieve stereoselectivity, resulting in longer routes, or utilize expensive reagents, which can limit the substrate scope.[5] Nucleophilic addition to activated pyridines represents an efficient alternative approach.[3] However, substrate synthesis is required, and the regioselectivity can be problematic.[3a,5a] We herein report a one-pot strategy utilizing regioselective alkyl Grignard additions to cheap, readily available pyridine-*N*-oxides. The diastereoselectivity resulting from successive Grignard addition is leveraged to generate C2-alkylated *N*-hydroxy-1,2,5,6-tetrahydropyridines, *trans*-2,3-disubstituted analogues, and the corresponding piperidines in a stereo- and regioselective manner.

Our previous research accessed aryl-substituted heterocycles using aryl Grignard reagents,[6,7] but analogous alkylation resulted in poorer yields. Other researchers have demonstrated nitro- and halo-directed pyridine-*N*-oxide alkylation,[8a,b] arylation of related scaffolds,[8c,d] different metal systems,[8d,e] and nitro substitution.[8f] However, alkylation of simple pyridine-*N*-oxides remains challenging. We have screened sp^3 Grignard reagents to investigate how these differ from sp^2 examples.

Gratifyingly, in this more extensive test we were able to alkylate efficiently. These room-temperature additions were followed by aromatization to access 2-alkyl, 2,6-disubstituted, and 2,3,5-trisubstituted pyridines in good yields from readily accessible pyridine-*N*-oxides (Scheme 2).

Foregoing the aromatization step, alkyl Grignard addition to pyridine-*N*-oxides gave C2-alkylated *N*-hydroxy-1,2,5,6-tetrahydropyridines, allowing the efficient synthesis of 2-alkylpiperidines and *trans*-2,3-dihydropiperidines. Addition of *n*-propyl Grignard to pyridine-*N*-oxide and subsequent reduction with $NaBH_4$ gave 2-alkylated product **4a** in a moderate yield (Scheme 3). This improved to 60−70% when long-chain or cyclic Grignard reagents **4b−d** were used and further to 84% when benzylmagnesium choride was used to give the alkylated product **4e**.

The presence of a C4-phenyl substituent improved the isolated yield of the alkylation products. Short-chain alkyl Grignards afforded moderate yields, with allyl and vinyl Grignards comparable (**4n** and **4o**). Significant improvement was observed when longer chains were used, affording products **4k−m** in good yields. This trend suggests that the chain length, rather than electronic factors, determined the isolated yield.

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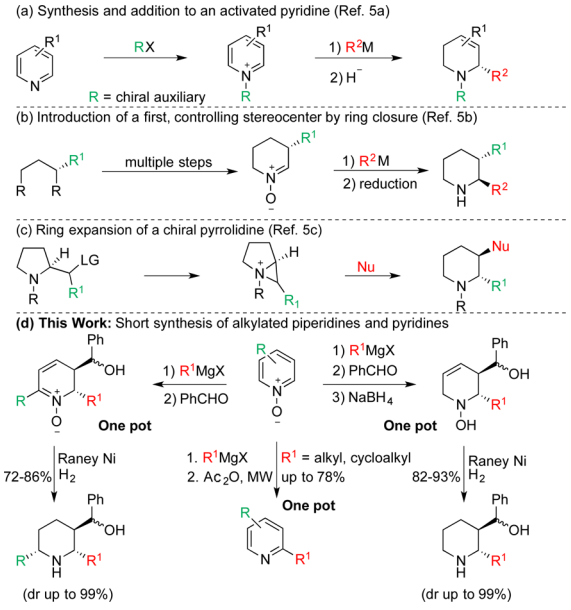
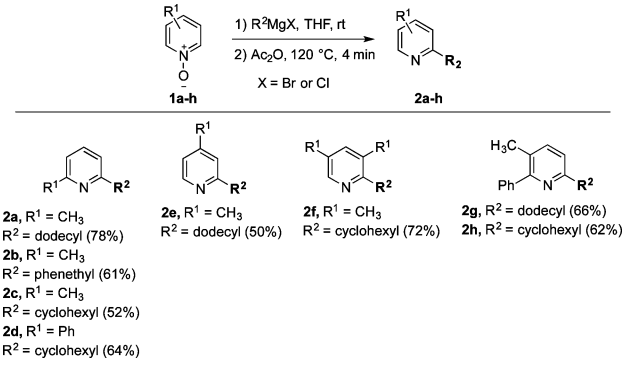
Scheme 1. Stereoselective Synthesis of Alkyl Piperidines

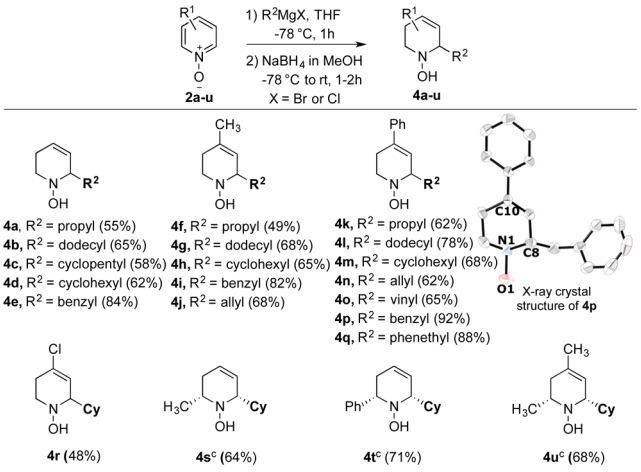


Scheme 2. Synthesis of 2-Alkylpyridine Derivatives[a,b]



[a]Isolated yields of products are shown. [b]The reactions were performed on a 1.0 mmol scale.

Scheme 3. Regiospecific C2-Alkylation of Pyridine-*N*-oxides via Grignard Addition[a,b]

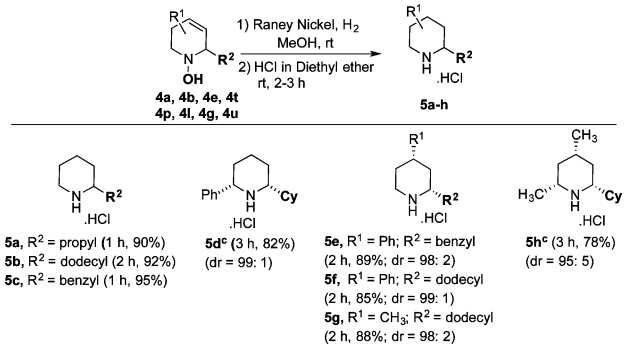


[a]Isolated yields of products are shown. [b]The reactions were performed on a 0.5 mmol scale. [c]The *cis* diastereomer was confirmed by NMR spectroscopy.

Benzyl and phenethyl Grignard reagents worked especially well, giving yields of 92% and 88% for **4p** and **4q**, respectively, while addition to 4-chloropyridine-*N*-oxide also gave 2-alkylated product **4r**. The structure of **4p** was confirmed by X-ray crystallography.[12] The moderate yields observed for **4a**, **4f**, and **4k** likely result from isolation losses due to the low molecular weight of the analogues. The *ortho*-substituted 2-phenylpyridine-*N*-oxides or 2-methylpyridine-*N*-oxides reacted well with cyclohexyl Grignard to afford products **4s**–**u** in good yields with diastereoselectivities of 99:1 *cis*:*trans*, as confirmed by NMR spectroscopy (see the Supporting Information).

The *N*-hydroxy-1,2,5,6-tetrahydropyridine derivatives were reduced with Raney nickel to give substituted piperidines in excellent yields regardless of the substitution pattern (**5a**–**g**) (Scheme 4). The facial preference of the heterogeneous catalyst

Scheme 4. Reduction of *N*-Hydroxy-1,2,5,6-tetrahydropyridines to Substituted Piperidines[a,b]



[a]Isolated yields of products are shown. [b]The reactions were performed on a 0.5 mmol scale. [c]The *cis* diastereomer was confirmed by NMR spectroscopy (see the Supporting Information).

was controlled by the steric influence of the existing stereocenters, allowing substituted alkenes to be reduced selectively to the all-*cis* products in good yields (**5f** and **5h**). The route allows the efficient synthesis of racemic coniine **5a**, a toxic alkaloid found in hemlock (*Conium maculactum*).[9]

To investigate the scope and generality of the protocol, we introduced substituents at C2, C3, and C6 of pyridine-*N*-oxide. These di- and trisubstituted piperidines often display interesting biological properties.[10] Initial C2-alkylation of pyridine-*N*-oxide followed by electrophilic trapping of the reactive intermediate gave 2,3-disubstituted *N*-hydroxy-1,2,5,6-tetrahydropyridines. Using *n*-propylmagnesium chloride and benzaldehyde as an electrophile gave **7a** in 86% yield with 91:9 diastereoselectivity (Scheme 5). However, only one C2/C3 configuration was observed, later confirmed as *trans* by X-ray crystal analysis of **7p**, and the diastereomeric mixture arose solely from the secondary alcohol.[13]

Primary dodecylmagnesium chloride and secondary cyclohexylmagnesium chloride nucleophiles gave good yields of **7b** and **7c** (Scheme 5). Larger Grignard reagents did not give higher yields in these examples; the opposite pattern was observed (propyl > cyclohexyl > dodecyl), as evidenced by comparison of **7a**–**c** and **7g**–**j**. This is likely due to steric inhibition of electrophilic trapping. **7a** was isolated in higher yield than was previously observed for the C2-alkylation (**2a**), suggesting that this earlier result represented isolation difficulties. Phenethylmagnesium bromide gave **7j** in high yield (81%), while methyl and chloro substituents at C4 gave

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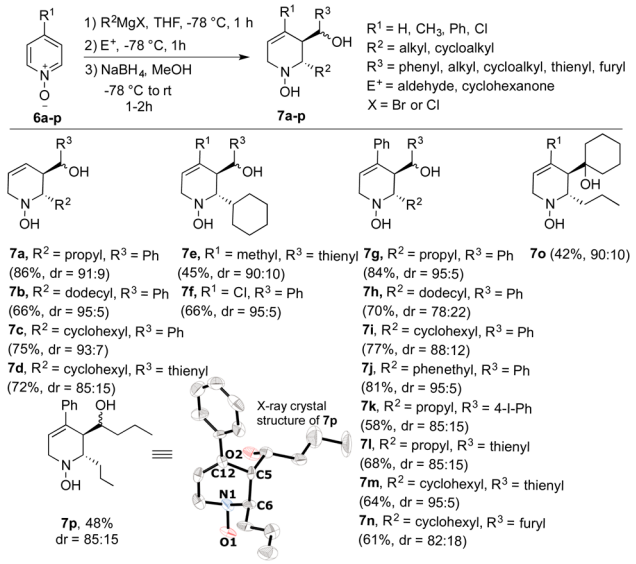
Scheme 5. Synthesis of *trans*-2,3-Di- and 2,3,4-Trisubstituted *N*-Hydroxy-1,2,5,6-tetrahydropyridines[a,b,c]

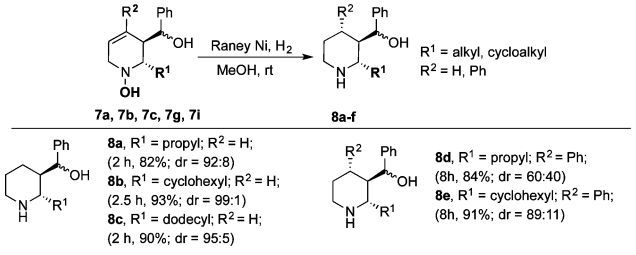


[a]The reactions were performed on a 1.0 mmol scale using Grignard reagent, $NaBH_4$ (3 equiv), and electrophile (2 equiv). [b]The diastereomeric ratios were determined by ^1H NMR analysis with reference to the secondary alcohol, and the *trans* configuration was assigned from X-ray crystallography. [c]Combined yields of two diastereomers are shown.

moderate yields of **7e** and **7f**, respectively. Thiophene-2-carboxaldehyde was used as the electrophile with only a small loss of yield. We then explored butyraldehyde and cyclohexanone as electrophiles together with *n*-propyl Grignard reagent in the 2,3-addition. Rewardingly, these gave **7n** and **7o** in 42−48% isolated yield despite the acidic α protons in the electrophiles.

The diastereoselectivities trended lower with a C4 aryl substituent but appear to be dependent on the specific combination of Grignard and electrophile. Some di- and trisubstituted *N*-hydroxy-1,2,5,6-tetrahydropyridines were reduced to the corresponding piperidines **8a−e** (Scheme 6), with

Scheme 6. Synthesis of Di- and Trisubstituted Piperidines[a,b]



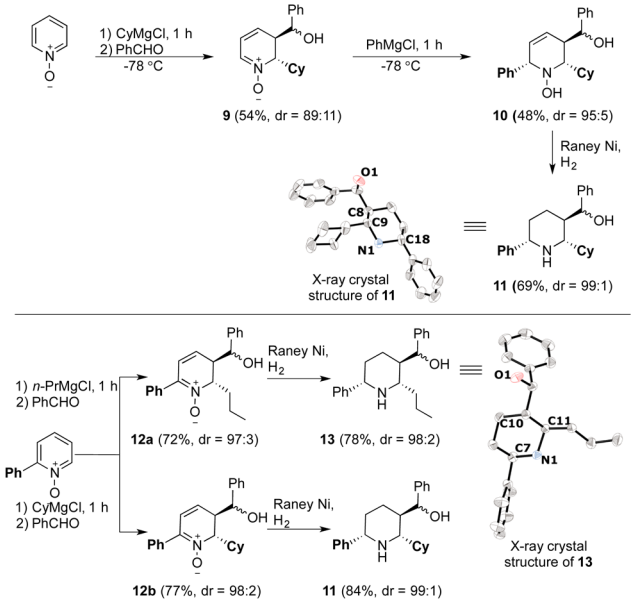
[a]Isolated yields are shown. [b]The reactions were performed on a 1.0 mmol scale.

the less hindered C4-unsubstituted piperidines **8a−c** formed faster and in better yields and diastereoselectivity. A protection−oxidation sequence can also be used to access the corresponding ketones with high diastereoselectivity (see the Supporting Information).

To demonstrate the scope of the transformation, we sequentially alkylated pyridine-*N*-oxide to give 2,3,6-trisubstituted piperidines. 2,3-Addition gave *N*-oxide **9**, which was treated with phenylmagnesium chloride to obtain **10** with high diastereoselectivity. Compound **10** was reduced to trisubstituted piperidine **11**, the structure of which was confirmed by X-ray crystallography.[12]

In order to rapidly access trisubstituted piperidines, we applied the alkylation−electrophilic trapping protocol to commercial 2-phenylpyridine-*N*-oxide. This sequence proceeded in good yield, and the *N*-oxide intermediates **12a** and **12b** were subsequently reduced to 2,3,6-trisubstituted piperidines **13** and **11**, respectively, with excellent diastereoselectivity (Scheme 7).

Scheme 7. Synthesis of 2,3,6-Trisubstituted Piperidines from Pyridine-*N*-oxides

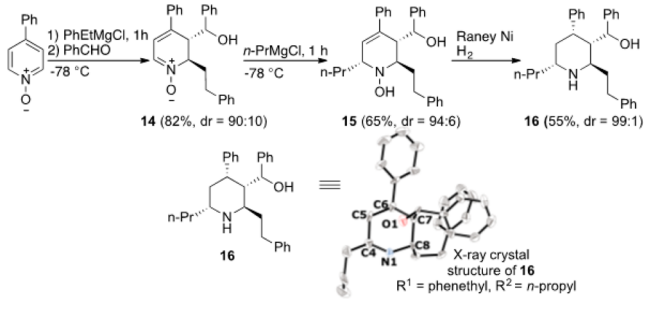


The C6-phenyl of **13** has a *cis* orientation with respect to the C2-propyl of the trisubstituted piperidine, despite the bulky C3 substituent, on the face of which the metal would approach. This may reflect a haptophilic contribution from the hydroxyl group.[11]

These complementary approaches allow both diverse analogue production and rapid, high-yielding syntheses of focused libraries and single products.

Polysubstituted piperidines are valuable, complex drug-like frameworks.[12] Our procedure was extended to allow the efficient synthesis of 2,3,4,6-tetrasubstituted piperidines (Scheme 8). The 2-alkylated *trans*-2,3-dihydropyridine-*N*-oxide **14** was synthesized in good yield and diastereoselectivity.

Scheme 8. Synthesis of Tetrasubstituted Piperidines



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Further Grignard addition to this C4-substituted substrate was highly stereoselective but gave a different stereochemical outcome to that observed in the C4-unsubstituted example, affording tetrasubstituted *N*-hydroxy-1,2,5,6-tetrahydropyridine **15**. Subsequent reduction gave piperidine **16** with excellent diastereoselectivity (99:1), as confirmed through 2D NOESY NMR spectroscopy and crystal structure analysis (see the Supporting Information).

In summary, we have demonstrated an efficient and regiospecific alkyl Grignard addition to pyridine-*N*-oxides to afford C2-alkylated *N*-hydroxy-1,2,5,6-tetrahydropyridines and *trans*-2,3-disubstituted analogues in good to excellent yields. These products were stereoselectively reduced to 2,3,4-tri- and 2,3,4,6-tetrasubstituted piperidine derivatives. We were also able to use C-alkylation of pyridine-*N*-oxides to synthesize valuable substituted pyridine derivatives from cheap and readily available pyridine-*N*-oxide starting materials in a regiospecific manner. Further investigations into the scope of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02667.

Experimental procedures and spectroscopic and X-ray crystallographic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: fredrik.almqvist@umu.se.
*E-mail: roger.olsson@med.lu.se.

ORCID

Fredrik Almqvist: 0000-0003-4646-0216

Notes

The authors declare no competing financial interest.

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(13) Crystallographic data for **2p**, **7p**, **11**, **13**, and **16** have been deposited with the Cambridge Crystallographic Data Centre as CCDC numbers 1479099, 1479111, 1479100, 479102, and 1487575, respectively. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.

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