Heterocycles

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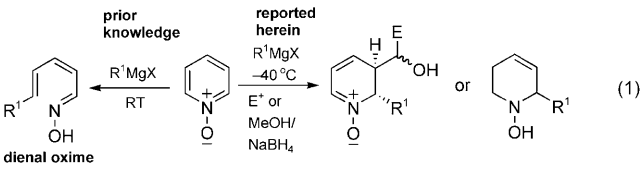
The Regio- and Stereoselective Synthesis of *trans*-2,3-Dihydropyridine *N*-oxides and Piperidines**

Hans Andersson, Magnus Gustafsson, Dan Boström, Roger Olsson, and Fredrik Almqvist**

The addition of Grignard reagents to pyridine *N*-oxides has in general been reported to give ring-opened dienal oximes in low yields [Eq. (1)].[1] As a consequence, pyridine *N*-oxides have not been considered as suitable building blocks for the

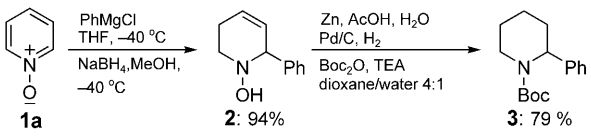


(1)

synthesis of substituted piperidines.[2] In our venture to utilize inexpensive and readily available pyridine *N*-oxides, we recently reported the formation of dienal oximes for the synthesis of substituted pyridines.[3] However, since multi-substituted piperidines are prominent in bioactive molecules and their stereoselective synthesis remains a challenge, our main focus was directed toward this class of compounds.[4] Although extensive research using a variety of pyridinium salts and nucelophiles without blocking undesired electrophilic sites (e.g., the 4-position) have been performed, these reactions generally result in the formation of regioisomeric mixtures. To achieve complete regioselectivity, *N*-iminopyridinium ylides were used to circumvent the ring-opened reactions of pyridine *N*-oxides.[2] Moreover, these reactions have a limitation; that is, establishing more than one stereogenic center at the time, especially in the stereoselective synthesis of vicinal *trans* isomers demands a multistep synthesis.[5]

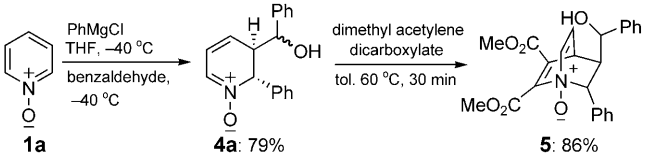
Herein we report on the discovery of a complete regio- and stereoselective synthesis of *trans*-2,3-substituted piperidines originating from the addition of Grignard reagents to pyridine *N*-oxides and the subsequent addition of an electrophile. The unique intermediate, *trans*-2,3-dihydropyridine *N*-oxide, is a stable and versatile diene for use in additional transformations. We also present the synthesis of 2-substituted piperidines from pyridine *N*-oxides. Neither of these synthetic methods encounters the earlier reported problem of the ring-opening of the pyridine *N*-oxide to give dienal oximes [Eq. (1)].

During our work on improving the yields and scope of the dienal oxime synthesis, an NMR study revealed that the ring-opening to the dienal oxime occurred during the quench of the reaction using water at ambient temperature.[3b] Therefore, instead of warming up the reaction mixture to room temperature, MeOD was added together with a reducing agent ($NaBH_4$) at −40 °C. This protocol resulted in the complete regioselective transformation to the expected 5-deuterated 2-phenyl tetrahydropyridine *N*-oxide derivative in a quantitative yield. The sequence was repeated using methanol and **2** was isolated in 94% yield (Scheme 1). A subsequent one-pot reduction and protection of **2** gave the *N*-Boc-2-phenylpiperidine **3** in 79% yield upon isolation.



Scheme 1. Synthesis of 2-phenylpiperidine from pyridine *N*-oxide. TEA = triethylamine, Boc = *tert*-butoxycarbonyl.

The addition of other electrophiles to the reaction intermediate was studied. Surprisingly, the addition of benzaldehyde resulted in a complete regio- and stereoselective *trans*-2,3 addition, giving the novel heterocyclic diene system **4a** instead of the expected 2,5-derivative (Scheme 2).[6,7] Since **4a** and its formation is unprecedented in the literature, the structure was unambiguously determined; to support the structure of **4a** as determined by NMR spectroscopy, **4a** was reacted with dimethyl acetylenedicarboxylate in a Diels–Alder reaction to give an 86% yield of the



Scheme 2. Synthesis of *trans*-2,3-dihydropyridine *N*-oxide and subsequent Diels–Alder reaction.

[*] Dr. M. Gustafsson, Prof. R. Olsson
Acadia Pharmaceuticals AB
Per Albin Hanssons väg 35, 20512 Malmö (Sweden)
Fax: (+46) 40-601-3401
E-mail: roger@acadia-pharm.com
H. Andersson, Prof. F. Almqvist
Department of Chemistry, Umeå University
Petrus lestadius väg, 90187 Umeå (Sweden)
Fax: (+46) 90-786-7566
E-mail: fredrik.almqvist@chem.umu.se
Dr. D. Boström
Department of Applied Physics and Electronics
Umeå University, 90187 Umeå (Sweden)

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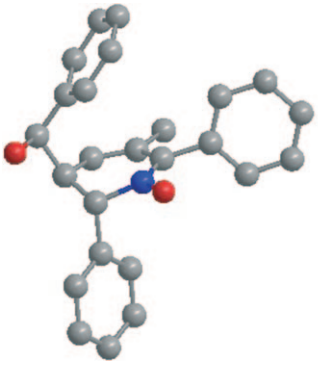
azabicyclic compound **5** upon isolation (Scheme 2). Additionally, a crystal structure of the substituted *trans*-2,3-dihydro-pyridine *N*-oxide **4i** (Figure 1) was obtained.[8] The *trans*-2,3 selectivity in the reaction was concluded from both the NMR spectroscopy and the crystal structure. The corresponding *cis* isomer was not observed in the crude reaction mixtures when analyzed by using NMR spectroscopy.



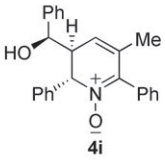
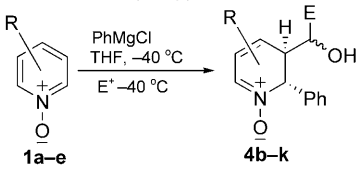
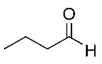
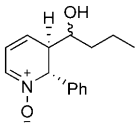
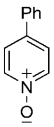
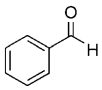
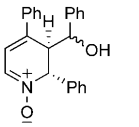
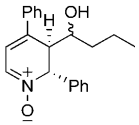
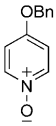
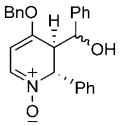
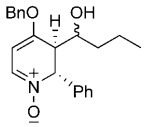
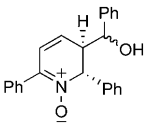
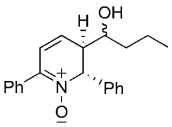
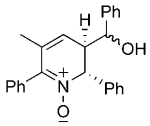
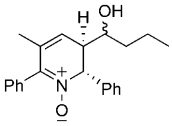
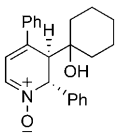


Figure 1. X-ray crystal of structure **4i.**

Changing the electrophile in the reaction from benzaldehyde (**6a**) to the aliphatic butyraldehyde (**6b**) resulted in the isolation of *trans*-2,3-dihydropyridine *N*-oxide **4b** in 59% yield (Table 1, entry 1). 4-Phenylpyridine *N*-oxide (**1b**) and 4-benzyloxypyridine *N*-oxide (**1c**) were also reacted with phenylmagnesium chloride and benzaldehyde or butyraldehyde, giving high yields of the corresponding *trans*-2,3-dihydropyridine *N*-oxides **4c**–**4f** upon isolation (Table 1, entries 2–5). Almost quantitative yields of the corresponding *trans*-2,3-dihydropyridine *N*-oxides **4g** and **4h** were obtained for the reaction using 2-phenylpyridine *N*-oxide (**1d**) (Table 1, entries 6 and 7). In connection with our earlier reported synthesis of substituted pyridine *N*-oxides this reaction demonstrated the potential for the synthesis of a diverse set of multisubstituted derivatives.[3a] Depending on the starting material used, the reaction has the advantage of proceeding at −78 °C. Although a slight decrease in yields was observed, for example, **4c** and **4g** were isolated in 72% and 97% yields respectively, when a reaction temperature of −78 °C was used, as compared to 81% and 98% yields, respectively, when a reaction temperature of −40 °C was used; the steresoselectivity of the *sec*-alcohol formed in the reaction with the aldehyde increases as the reaction temperature is decreased. The diastereomeric ratio (d.r.) of **4g** changed from 92:8, at a reaction temperature of −78 °C, to 78:22 at a reaction temperature of −40 °C. The d.r. for **4c** at the reaction temperatures of −78 °C and −40 °C were greater than 98:2 and 89:11, respectively.[9] Strikingly at −78 °C only one diastereomer, having three stereogenic centers introduced in the reaction sequence, was observed for **4c**. A decrease in the reactivity was observed when using 3-methyl-2-phenylpyridine *N*-oxide (**1e**) as a starting material. The reactions were slow at −40 °C and were therefore performed at −20 °C instead.[10] Reasonable yields, 56% and 71%, of the highly substituted 2,3-dihydropyridine *N*-oxides **4i** and **4j**, respectively, were obtained (Table 1, entries 8 and 9). In addition to the aldehydes, the ketone reactivity was also investigated. Cyclohexanone was added at −40 °C to the

Table 1: Synthesis of *trans*-2,3-dihydropyridine *N*-oxides.[a,b]



Entry	*N*-oxide		E^+		Product		Yield [%][c]
1	**1a**	(R=H)	**6b**		**4b**		59
2	**1b**		**6a**		**4c**		81
3	**1b**		**6b**		**4d**		80
4	**1c**		**6a**		**4e**		86
5	**1c**		**6b**		**4f**		71
6	**1d**		**6a**		**4g**		98
7	**1d**		**6b**		**4h**		96
8	**1e**		**6a**		**4i**		56 [d]
9	**1e**		**6b**		**4j**		71 [d]
10	**1b**		**6c**		**4k**		50[e]

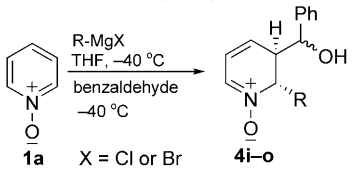
[a] Reaction conditions: *N*-oxide (1 equiv) in THF, phenylmagnesium chloride (1.2 equiv), aldehyde (1.5 equiv). [b] Diastereomeric ratio (d.r.) for all compounds given in reference [9]. [c] Yields of isolated products. [d] Reaction performed at −20 °C. [e] Reaction performed in toluene.

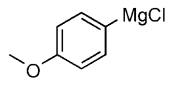
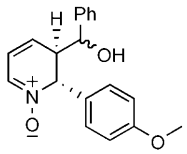
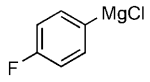
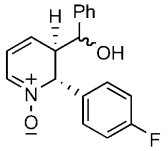
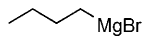
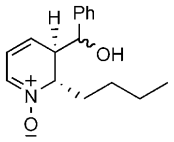
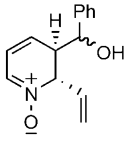
intermediate formed by reacting 4-phenylpyridine *N*-oxide with phenylmagnesium chloride. The standard conditions using THF as the solvent gave no product, therefore the less polar and noncoordinating solvent toluene was used. The rational was to get a tighter coordination of the carbonyl group to the magnesium, and thereby increase the reactivity of the ketone. Product **4k** was isolated in 50% yield, with the same complete regioselectivity and *trans* stereoselectivity as previously observed for the aldehydes. As expected, when both *ortho* positions are blocked as for 2,6-dimethyl-pyridine *N*-oxide, no addition occurs at the given conditions.

Next the reactivity of different Grignard reagents was studied using pyridine *N*-oxide (**1a**) and benzaldehyde as the electrophile at −40°C. *p*-Methoxyphenyl- and *p*-fluorophenylmagnesium chloride yielded the corresponding 2,3-dihydropyridine *N*-oxides **4l** and **4m** in 72% and 76% yields, respectively, (Table 2, entries 1 and 2). The scope of the reaction was expanded to the addition of alkyl substituents. Pyridine *N*-oxide (**1a**) was reacted with *n*-butylmagnesium bromide and then benzaldehyde was added to give the 2-butyl-substituted derivative **4n** in 28% yield upon isolation (Table 2, entry 3,). This low yield was expected given our previous studies using alkyl Grignards for *ortho*-metallation of pyridine *N*-oxides.[11] Yields in the range of 28% are not optimal in preparative organic synthesis, therefore to include the potential to synthesize alkyl substituted piperidines in reasonable yields with this method, the addition of vinyl Grignard reagents were of interest. The double bond introduced would be reduced in the hydrogenation step of the dihydropyridine *N*-oxide. An increase in the yield of the 2-vinyl substituted 2,3-dihydropyridine *N*-oxide (**4o**) was obtained when compared to the yield of the reaction using *n*-butylmagnesium bromide (compare entries 4 and 3 in Table 2).

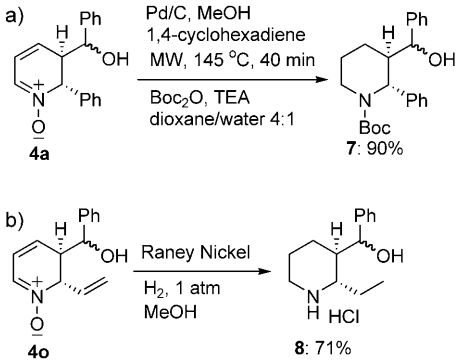
With the ability to introduce both aryl and vinyl substituents to the system in complete regioselectivity and high stereoselectivity, we set out to synthesize both 2-aryl and 2-alkyl trans-2,3-substituted piperidines. An excellent 90% yield of the *N*-Boc-piperidine **7** was obtained upon isolation after using a microwave assisted one-pot procedure with 2,3-dihydropyridine *N*-oxide **4a** (Scheme 3a).[12] The 2-alkyl-substituted analogue **8** was efficiently synthesized from 2,3-dihydropyridine *N*-oxide **4o** using Raney Nickel to yield **8** in 71% as the hydrochloride salt (Scheme 3b).[13]

Table 2: Synthesis of 2,3 *trans*-dihydropyridine *N*-oxides.[a,b]



Entry	R	Product	Yield [%][c]
1		**4l** 	72
2		**4m** 	76
3		**4n** 	28
4		**4o** 	60

[a] Reaction conditions: *N*-oxide (1 equiv) in THF, phenylmagnesium chloride (1.2 equiv), aldehyde (1.5 equiv). [b] Diastereomeric ratio (d.r.) for all compounds given in reference [9]. [c] Yields of isolated products.



Scheme 3. Reduction to piperidines.

In conclusion, we have shown that inexpensive and readily available pyridine *N*-oxides can be used with advantage for the complete regio- and stereoselective synthesis of substituted 2,3-dihydropyridine *N*-oxides and substituted piperidines. This short two-step reaction for the formation of substituted piperidines gives a unique diene as an intermediate. This intermediate is amenable to a number of reactions (e.g. Diels–Alder reactions) and has therefore its own warranted interest.

Experimental Section

General procedure exemplified by the reaction of **1a** and **6a** (Scheme 2): The pyridine *N*-oxide **1a** (100 mg, 1.05 mmol) was dissolved in THF (5 mL) and cooled using a dry-ice/acetonitrile bath for 10 min before adding PhMgCl (173 mg, 1.26 mmol) dropwise. The resulting mixture was stirred for 60 min in the cooling bath before benzaldehyde (166 mg, 1.58 mmol) was added, and then the resulting mixture was stirred for another 60 min at −40°C. Then aqueous saturated NH_4Cl was added and the resulting slurry extracted three times with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The crude reaction mixture was purified using column chromatography (CH_2Cl_2

and 3% MeOH) which after concentration from CH_2Cl_2 gave **4a** as a yellow foam (231 mg, 79%).

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[6] Reaction also performed in 10 mmol scale which gave 2 grams of **4a** (72% yield).

[7] A. T. Ondrus, M. F. Pasutto, E. E. Knaus, *Can. J. Chem.* **1978**, *56*, 1913–1918.

[8] Nonius KappaCCD diffractometer ($Mo_{K\alpha}$ radiation $\lambda = 0.71073$ Å; $T = 150(2)(1)$ K). Data collection: COLLECT (Nonius (1999). COLLECT. Nonius BV, Delft, The Netherlands.); cell refinement: SCALEPACK ("Macromolecular Crystallography, Part A": Z. Otwinowski, W. Minor, *Methods in Enzymology*, *Vol. 276* (Eds.: C. W. Carter, Jr., R. M. Sweet), Academic Press, New York, **1997**, pp. 307–326); data reduction: DENZO ("Macromolecular Crystallography, Part A": Z. Otwinowski, W. Minor, *Methods in Enzymology*, *Vol. 276* (Eds.: C. W. Carter, Jr., R. M. Sweet), Academic Press, New York, **1997**, pp. 307–326) and SCALEPACK; program(s) used to solve structure: SHELXS97 (G. M. Sheldrick, SHELXS97 and SHELXL97, University of Göttingen, Germany, **1997**); All non-hydrogen atoms were refined anisotropically and hydrogen atoms by a riding model by full-matrix least-squares on F^2. Program(s) used to refine structure: SHELXL97 (G. M. Sheldrick, SHELXS97 and SHELXL97. University of Göttingen, Germany, **1997**); **4i**: $C_{25}H_{23}NO_3$, $M_r = 385.46$, colorless crystal ($0.36 \times 0.19 \times 0.10$ mm), triclinic, $P\bar{1}$; $a = 12.6060(2)$, $b = 12.7430(2)$, $c = 13.5770(2)$ Å, $\alpha = 80.5110(8)$, $\beta = 88.3720(8)$, $\lambda = 68.2780(8)°$, $V = 1997.13(5)$ Å^3; $Z = 4$, $\mu = 0.084$ mm^{-1}, $\rho_{calc} = 1.282$ g cm^{-3}; 17373 measured reflections ($2\theta_{max} = 55°$), 9141 unique reflections ($R_{int} = 0.026$), 7480 reflections with $I > 2\sigma$, 524 parameters, largest max./min. in the final difference Fourier synthesis 1.102 e Å^3/−0.367 e Å^3; $R_1 = 0.0663$ ($I > 2\sigma(I)$), wR_2 (all data) = 0.2154. CCDC 715909 (**4i**) and 715910 (**4e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] The diasteremeric ratio (d.r.) values were determined by NMR analysis of the crude reaction mixtures. The relative configuration was determined by the crystal structure of **4i** and **4e** and NMR analysis of the crystals, which proved to be the major isomer. Compounds assigned based upon comparison to **4i** and **4e** and reported as major/minor: **4a** 83:17, **4b** 82:12, **4c** 89:11, **4d** 89:11, **4e** 88:12, **4f** 72:28, **4g** 78:22, **4h** 90:10, **4i** 50:50, **4j** 60:40, **4l** 81:19 , **4m** 79:21 , **4n** 81:19, **4o** 81:19.

[10] A series of temperature experiments at −78, −40, −20, and 0 °C proved that −20 °C was the upper temperature limit. At temperatures above −20 °C a substantial amount of dienal oxime was observed.

[11] H. Andersson, M. Gustafsson, R. Olsson, F. Almqvist, *Tetrahedron Lett.* **2008**, *49*, 6901–6903.

[12] J. F. Quinn, D. A. Razzano, K. C. Golden, B. T. Gregg, *Tetrahedron Lett.* **2008**, *49*, 6137–6140.

[13] Compounds **3** and **7** were also accessible using Raney Nickel in 93 and 88% yields, respectively.

