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Reaction of pyridine *N*-oxides with Grignard reagents: a stereodefined synthesis of substituted dienal oximes

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Abstract—Rapid addition of Grignard reagents to pyridine *N*-oxides under mild conditions gave stereodefined dienal oximes in good to excellent yields. This reaction provides an efficient access to substituted olefins with defined stereochemistry that are potentially of interest as bioactives themselves or as versatile synthetic intermediates.

Pyridine *N*-oxides are potential starting materials for the synthesis of a multitude of target molecules.[1–3] While the addition of organometallic reagents to acyl or alkyl activated pyridines have been developed into an expedient method for the synthesis of substituted piperidines,[4–8] the analogous nucleophilic addition to pyridine *N*-oxides has been scarcely reported.[9–14] Focusing on the structural elucidation of the products from the reaction of aryl Grignard reagents with pyridine *N*-oxide **1**, Kellog et al. reported on the formation of dienal oximes **2** (10–48% yields).[12] The low yields obtained probably hampered further exploration of the reaction. Provided that the yields could be improved, dienal oximes **2** with the inherent stereodefined unsaturated system appeared to us to be attractive intermediates for further transformations. Thus, depending on the substitution pattern present in pyridine *N*-oxide **1** and the synthetic transformations used, a diverse set of compounds would be obtainable within a few steps. Furthermore, the wealth of commercially available substituted pyridine *N*-oxides **1** in combination with their easy synthesis[15–17] make them attractive as starting materials. Herein we report on the development of a synthetic methodology that generates dienal oximes **2** in high yields by the regiospecific addition of Grignard reagents to pyridine *N*-oxides **1**. These key intermediates were transformed into a diverse range of compounds, for example, substituted aliphatic amines **4** and enaminones **7**.

Initial studies show that organozinc reagents in combination with copper cyanide used in the synthesis of 4-substituted piperidines via addition to *N*-acyl pyridinium salts,[7] or the use of organolithium reagents, resulted in either no reaction or complex reaction mixtures when reacted with pyridine *N*-oxides. However, an earlier publication by Kellog et al. reported low yields using Grignard reagents.[12] Also in our hands slow addition of the Grignard reagent (PhMgCl in THF) at temperatures ranging from −50 °C to room temperature gave a moderate isolated yield of dienal oxime **2** (<40%) confirming Kellog's results. However, by rapidly adding the phenylmagnesium chloride to pyridine *N*-oxide **1a** dissolved in THF at room temperature, a clean transformation was observed, and after stirring the reaction mixture for an additional 30–60 min the reaction was quenched and dienal oxime **2a** was isolated in 85% yield (Table 1). The reaction was monitored via NMR experiments and it was shown that the transformation to the desired dienal oxime did not occur until water was added to the reaction mixture (see Fig. 1, Supplementary data).

The conditions developed for the addition of phenylmagnesium chloride were used in the addition of methylmagnesium chloride and *iso*-propylmagnesium chloride to pyridine *N*-oxides **1a** and **1b**. Unfortunately, this time, a complex reaction mixture was formed and

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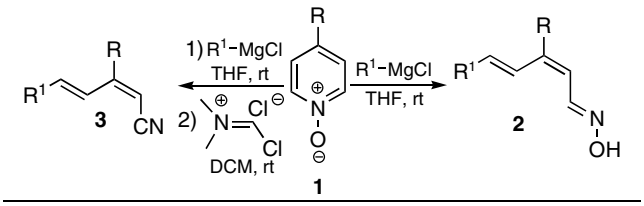
Table 1. Investigation of the formation of dienal oximes **2** derived from pyridine *N*-oxide **1** and a mild in situ transformation to conjugated nitriles **3**

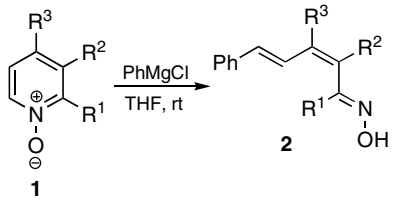


Entry	1	R	R^1	Oxime **2** (yield)[a]	Nitrile **3** (yield, %)[a]
1	**1a**	H	Ph	**2a** (85%)	**3a** (74)[b]
2	**1a**	H	$CH(Me)_2$	**2b** (trace)	**3b** (49)
3	**1b**	Ph	Me	**2c** (trace)	**3c** (64)

[a] Isolated yields calculated from pyridine *N*-oxide **1**.
[b] Obtained as an isomeric mixture of *cis–trans* and *trans–trans* dienenitrile in a 20:3 ratio, respectively, according to NMR spectroscopy.

only traces of the desired dienal oximes were observed (Table 1). However, the corresponding nitriles **3a–c** were accessible in 74%, 49% and 64% isolated yields, respectively, via a mild in situ transformation of the oxime functionality using the Vilsmeier–Haack salt[18] (Table 1). This showed that in addition to aryl Grignards the reaction worked with alkyl Grignard reagents as well. The dienal oximes are probably formed initially and the low yields of isolated alkyl substituted dienal oximes instead were attributed to the lower stability of alkyl substituted dienal oximes compared to aryl substituted dienal oximes.

Table 2. Investigation of the formation of dienal oximes **2** derived from picoline *N*-oxides **1c–e**



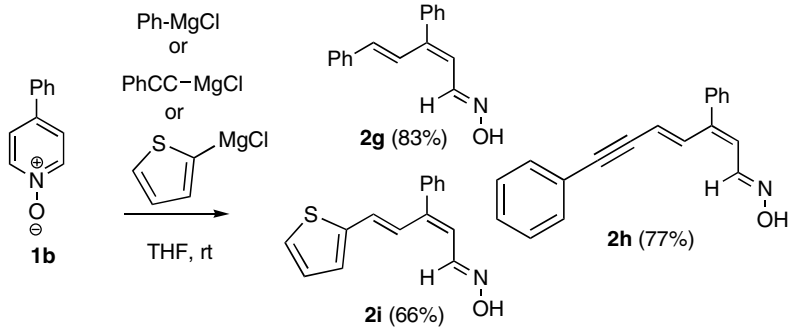
Entry	1	R^1	R^2	R^3	Oxime **2** (yield, %)[a]
1	**1c**	Me	H	H	**2d** (79)
2	**1d**	H	Me	H	**2e** (0)
3	**1e**	H	H	Me	**2f** (81)

[a] Isolated yields.

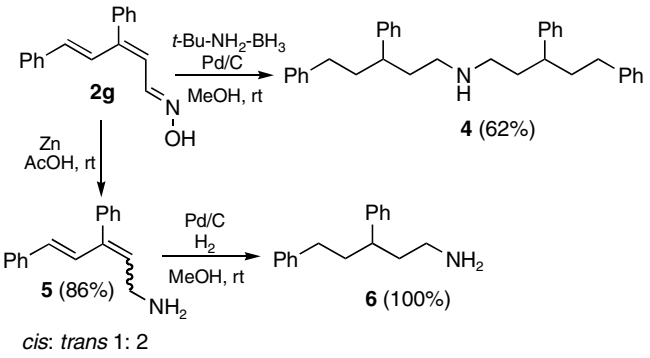
Substituted pyridine *N*-oxides, for example, the picoline *N*-oxide series **1c–e** were reacted with phenylmagnesium chloride (Table 2). High yields of dienal oximes were obtained with 2- and 4-substituted pyridine *N*-oxides and 5-substituted ketoxime **2d** and aldoxime **2f** were isolated in a 79% and 81% yields, respectively (Table 2). 2-Substituted pyridine *N*-oxides are easily obtained by the present method, via sequential addition of Grignard reagents to pyridine *N*-oxides followed by mild oxidation (air, DMF, 120 °C, 8 h).[19] Thus, substituted stereodefined dienal ketoxime are obtainable. 3-Substituted picoline *N*-oxide **1d**, on the other hand, gave no dienal oxime when reacted with phenylmagnesium chloride, instead the major isolated product was 2-phenyl-3-methyl pyridine.[19]

Phenyl, phenylethynyl- and thienylmagnesium chloride also reacted well and the phenyl and alkynyl and heteroaryl dienal oximes **2g–i** were isolated in 83%, 77% and 66% yields, respectively, when reacted with **1b** (Scheme 1). All the dienal oximes were obtained as single isomers, the stereodefined 5-substituted (1*E*,2*Z*,4*E*)-penta-2,4-dienaloxime was formed in all cases according to ^{1}H NMR analysis.[20]

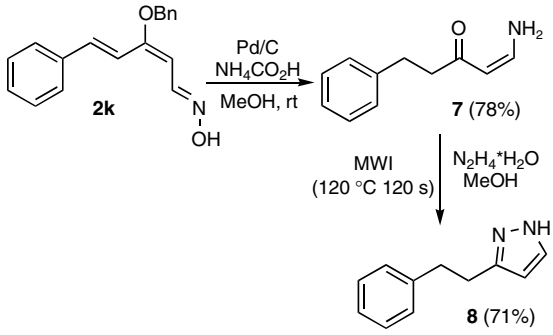
With an efficient synthetic protocol to stereodefined dienal oximes in hand we wished to perform further transformations to a diverse set of molecules. In general, we observed that dienal oximes **2** were prone to form dihydropyridines at elevated temperature. Therefore, mild transformations of the oxime functionality were desired. Encouraged by the successful formation of nitriles **3a–c** we investigated the possibility of reducing dienal oximes to the corresponding substituted saturated primary amines. The practical hydrogen transfer method (Pd/C, ammonium acetate in MeOH) used to reduce dihydropyridines to piperidines[7] did not give the primary amine **6**, instead secondary amine **4** was isolated as the major product in a 48% yield.[21] A significant improvement was seen when a combination of *t*-$BuNH_2$–BH_3 with Pd/C[22] was used giving secondary amine **4** in an isolated yield of 62% from **2g** (Scheme 2). Other methods that had been reported to selectively reduce oximes to amines were tested only to find that reagents such as $NaCNBH_3$[23] or $LiAlH_4$[24] returned the starting material while BH_3–SMe_2[25] gave a complex reaction mixture. However, Zn dust in acetic acid[26] gave a rapid and clean conversion to the unsaturated primary amine **5** (Scheme



Scheme 1. Aryl-, phenylethynyl- and thiophene-substituted dienal oximes.



Scheme 2. Reduction of dienal oximes.



Scheme 3. Synthesis of substituted enaminone **7** and pyrazole **8**.

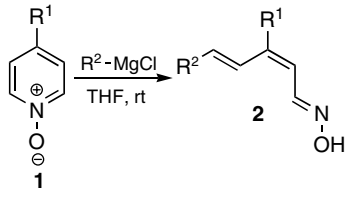
2). NMR spectroscopy showed a 2:1 mixture of *E*/*Z* isomers. This mixture was then easily converted to primary amine **6** in quantitative yield (86% from **2g**) by using Pd/C, H_2 in methanol (Scheme 2).

So far, the substituents at pyridine *N*-oxide had been either alkyl or aryl in various positions. In all cases, the Grignard reagent had selectively added to the 2-position and no addition at the 4-position had been observed. This was also the case using 4-chloro substituted *N*-oxide **1f**. Hence, the chloro substituted dienal oxime **2j** was obtained in an excellent yield of 86% and no product formed by substituting chloride was detected (Table 3). Also 4-benzyloxy substituted pyridine *N*-oxide **1g** gave the corresponding dienal oximes in high to excellent yields on reaction with aryl, heteroaryl and alkynyl Grignard reagents (Table 3, 76–95%, entries 2–5).

A selective debenzylation together with reduction of the oxime functionality would provide a novel method to generate substituted enaminones from 4-benzyloxy substituted pyridine *N*-oxides. Enaminones are versatile intermediates that combine the ambident nucleophilicity of enamines together with the ambident electrophilicity of enones. This makes enaminones very important in the synthesis of heterocycles.[27–30] Previous attempts to reduce the oximes using Pd/C and ammonium formate in methanol gave the secondary amines **4** as the major products. However, applying this method on the benzyloxy substituted intermediate **2k** gave no dimerization and instead enaminone **7** was isolated in high yield 78% (Scheme 3). To illustrate the potential of this intermediate in heterocycle synthesis, enaminone **7** was reacted with hydrazine hydrate under microwave irradiation to give pyrazole **8** in 71% yield (Scheme 3).[31]

In conclusion, we have shown that rapid addition of aryl, alkynyl and alkyl Grignard reagents to pyridine *N*-oxides can be used to synthesize substituted stereodefined olefins in high yields. The cis, trans configuration obtained is of considerable interest, (e.g., the anticarcinogenic and antioxidative effects seen with conjugated lineloic acids has been attributed to the cis, trans isomers).[32] Moreover, in a few steps, the conjugated dienal oximes can be converted into a diverse set of compounds exemplified herein by nitriles, amines, enaminones and pyrazoles. Thus, this methodology constitutes an excellent platform to design and perform diversity-oriented synthesis.

Table 3. Reaction of functionalized pyridine *N*-oxides



Entry	*N*-oxide **1**	R^1	R^2	Oxime **2** (yield, %)[a]
1	**1f**	Cl	Ph	**2j** (86)
2	**1g**	OBn	Ph	**2k** (95)
3	**1g**	OBn	Naphthyl	**2l** (83)
4	**1g**	OBn	PhCC	**2m** (78)
5	**1g**	OBn	Thiophene	**2n** (76)

[a] Isolated yields.

Acknowledgements

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Supplementary data

Detailed experimental procedures and compound characterization data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.161.

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