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Substitution of the Nitro Group with Grignard Reagents: Facile Arylation and Alkenylation of Pyridine *N*-Oxides

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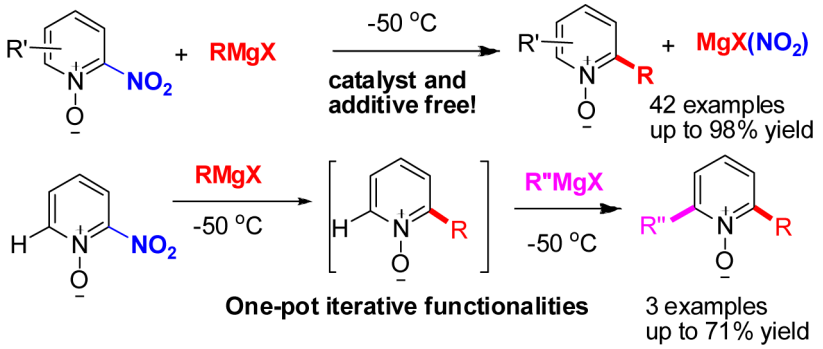
ABSTRACT



The unprecedented substitution of a nitro group with aryl or alkenyl groups of Grignard reagents affords 2-aryl or alkenylpyridine *N*-oxides in modest to high yields with high chemoselectivity. This protocol allows a simple and clean synthesis of various 2-substituted pyridine *N*-oxides and the corresponding pyridine derivatives. Furthermore, straightforward one-pot iterative functionality of pyridine *N*-oxides could also be achieved simply by successive applications of two Grignard reagents.

Substituted pyridines occur ubiquitously in natural products, biologically active compounds, and functional materials.[1] However, the functionalization of pyridine rings, for example, by halogenation or nitration, is usually difficult due to the overall low reactivity of pyridine toward electrophilic aromatic substitution. Due to the limitations of pyridine, pyridine *N*-oxides often serve as important alternatives for the syntheses of substituted pyridines.[2] Pyridine *N*-oxides are also important structural motifs in natural products[3] and biologically active compounds[4] and have found wide use as catalysts in asymmetric reactions.[5] Consequently, efforts have been devoted to the development of efficient methods for the arylation, alkenylation, and alkylation of pyridine *N*-oxides. Among known methods, transition-metal-catalyzed direct arylation via C−H activation represents one of the major strategies.[6,7] Herein we report an efficient transition-metal-free arylation and alkenylation of nitropyridine *N*-oxides based on a novel substitution of the nitro group with Grignard reagents.

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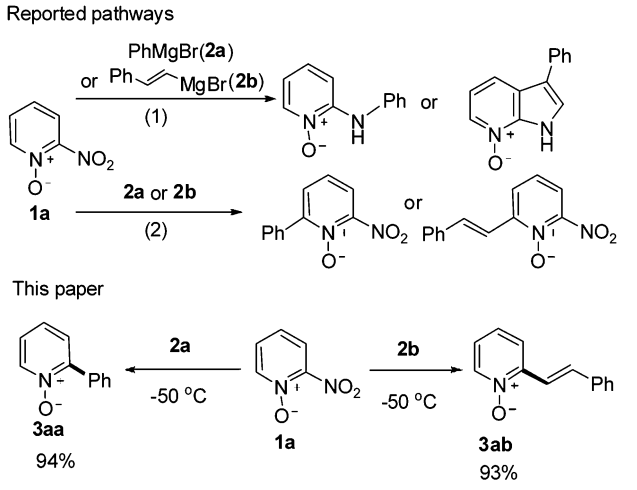
Scheme 1. Substitution of a Nitro Group Compared with the Reported Pathways in the Reactions of **1a** with **2a** or **2b**



In two preliminary experiments, we treated 2-nitropyridine *N*-oxide (**1a**) with phenylmagnesium bromide (**2a**) and (*E*)-styrylmagnesium bromide (**2b**). Two pathways are expected based on previous reports (Scheme 1): (1) the magnesium species adds to the nitro group to give 2-(phenylamino)pyridine *N*-oxide[8] or an indole compound;[9] (2) the magnesium species adds to the N→O group to lead to 6-Ph- or styryl-2-nitropyridine *N*-oxide.[10,11] However, these expected products were not observed from our reactions. Instead, arylated and alkenylated products formed by replacing the nitro group were obtained in yields of 94 and 93%, respectively (**3aa** and **3ab** in Scheme 1). To the best of our knowledge, our discovery represents the first example of the displacement of the nitro group by aryl or alkenyl groups of Grignard reagents.[12] The reaction, which does not require any transition metals and produces inorganic magnesium salts as the sole byproducts, represents a very simple, clean, and highly efficient protocol for arylation and alkenylation of pyridine *N*-oxides. It was thus further explored with the results being summarized in Table 1.

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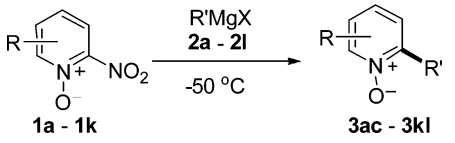
Table 1. Arylation and Alkenylation of Pyridine *N*-Oxides via the Substitution of the Nitro Group Using Grignard Reagents[a]

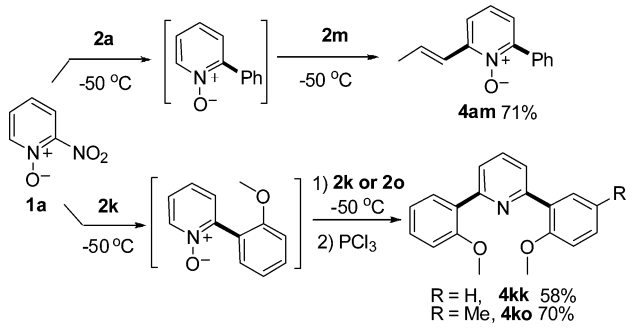


entry	**1** (R)	**2** (R′)	product	yield[b] (%)
1	**1a** (H)	**2c** (3-MeC_6H_4)	**3ac**	94
2	**1a**	**2d** (2-MeC_6H_4)	**3ad**	78
3	**1a**	**2e** (thiophen-2-yl)	**3ae**	96
4	**1a**	**2f** (cyclohexenyl)	**3af**	68
5	**1b** (6-Me)	**2a**	**3ba**	81
6	**1b**	**2b**	**3bb**	90
7	**1b**	**2g** (4-$MeOC_6H_4$)	**3bg**	85
8	**1b**	**2h** (2-NCC_6H_4)	**3bh**	63
9	**1b**	**2i** (2-$Me_2NCOC_6H_4$)	**3bi**	68
10	**1c** (4-Me)	**2j** (naphthalen-1-yl)	**3cj**	89
11	**1c**	**2k** (2-$MeOC_6H_4$)	**3ck**	84
12	**1c**	**2l** (CH_2=CH)	**3cl**	70
13	**1d** (3-Me)	**2a**	**3da**	88
14	**1d**	**2b**	**3db**	83
15	**1d**	**2d**	**3dd**	98
16	**1d**	**2e**	**3de**	98
17	**1d**	**2j**	**3dj**	98
18	**1d**	**2h** (2-NCC_6H_4)	**3dh**	77
19	**1d**	**2m** [(*E*)-prop-1-enyl]	**3dm**	78
20	**1e** (5-Me)	**2b**	**3eb**	67
21	**1e**	**2l**	**3el**	68
22	**1e**	**2n** (4-MeC_6H_4)	**3en**	72
23	**1f** (4-COOH)	**2e**	**3fe**	85[c]
24	**1f**	**2k**	**3fk**	88[c]
25	**1f**	**2l**	**3fl**	79[c]
26	**1g** (4-COOMe)	**2a**	**3ga**	88
27	**1g**	**2k**	**3gk**	93
28	**1g**	**2l**	**3gl**	85
29	**1h** (5-COOH)	**2g**	**3hg**	79[c]
30	**1i** (5-COOMe)	**2a**	**3ia**	87
31	**1i**	**2e**	**3ie**	81
32	**1j** (5-MeO-6-Cl)	**2b**	**3jb**	98
33	**1j**	**2e**	**3je**	86
34	**1j**	**2f**	**3jf**	98
35	**1j**	**2g**	**3jg**	91
36	**1j**	**2m**	**3jm**	92
37	**1j**	**2n**	**3jn**	98
38	**1k** (5-MeO-6-Br)	**2e**	**3ke**	83
39	**1k**	**2g**	**3kg**	77
40	**1k**	**2l**	**3kl**	68

[a] Reactions were carried out at −50 °C by adding 1.2 equiv of Grignard reagents to a solution of 2-nitropyridine *N*-oxides in THF. [b] Yields of isolated products after flash chromatography. [c] 2.1 equiv of Grignard reagents was used.

This reaction was then tested on a series of 2-nitropyridine *N*-oxides (Table 1, **1a**–**1k**). Interestingly, 3-methyl-2-nitropyridine *N*-oxide (**1d**) underwent sterically hindered arylation and alkenylation smoothly without any competitive deprotonation or addition at the 6-position (Table 1, entries 14–19). Heteroaryl or functionalized aryl magnesium reagents such as **2e**, **2h**, or **2i** could also be used for the corresponding arylation, leading to the expected products

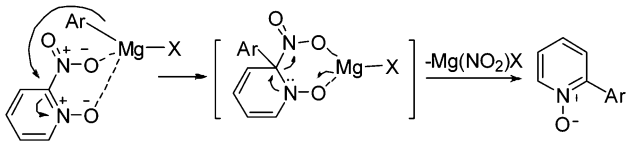
Scheme 2. One-Pot Iterative Arylation or Alkenylation of Pyridine *N*-Oxide



in 63−98% yields. This substitution reaction showed a remarkable tolerance toward different functional groups. Nitropyridine *N*-oxides bearing carboxyl groups (**1f** and **1h**) or ester groups (**1g** and **1i**) also underwent arylation or alkenylation readily. Even more interesting is that, in this case, the arylation or alkenylation with Grignard reagents still proceeded smoothly in the presence of a highly electrophilic chlorine or bromine atom at the 6-position as shown by **1j** and **1k** (Table 1, entries 32−40). These findings have demonstrated that this reaction provides a new protocol for C−C bond formation that involves conditions that are remarkably milder than those of many known transition-metal-catalyzed couplings and direct C−H functionalizations. The observed tolerance to halogens in these arylations and alkenylations also offers the opportunity for performing additional cross-couplings on the reaction products, which should allow more complicated structures to be prepared. In spite of the general applicability of this reaction, it was found that the reactions between 2-nitropyridine *N*-oxides and alkyl Grignard reagents failed to give the corresponding aklylated products. Instead, the attempted reactions only resulted in a complicated mixture of products.

To further probe the synthetic potentials of this efficient arylation and alkenylation protocol, one-pot iterative arylation or alkenylation of pyridine *N*-oxides was performed (Scheme 2). For instance, oxide **1a** was first arylated by the displacement of the nitro group, and the produced oxide was subjected to in situ arylation or alkenylation with a second Grignard reagent.[10] Therefore, straightforward one-pot iterative functionality of pyridine *N*-oxides could be achieved simply by successive applications of two Grignard reagents. As illustrated in Scheme 2, compounds **4kk** and **4ko**, which belong to a class of important tridentate ligands[13] and structural cores for pH-sensitive molecular tweezers,[14] were conveniently prepared in one pot.

Scheme 3. Possible Mechanism for the Substitution of the Nitro Group Using Grignard Reagents



We propose that this S_NAr substitution of the nitro group by Grignard reagents is promoted by the cooperative action of the NO_2 and N→O groups (Scheme 3). The Ar group is directed to the most electrophilic C2, which results in the departure of the nitro group. This rationale is supported by the fact that the same displacement does not occur when the nitro group is located at C3 or C4.[10b]

In summary, we have discovered an unprecedented substitution of the nitro group by aryl or alkenyl groups of Grignard reagents. Since 2-nitropyridine *N*-oxides can be conveniently obtained from readily available 2-aminopyridines through oxidation, this reaction provides a very simple, clean, and highly efficient protocol for the arylation and alkenylation of pyridine *N*-oxides without transition metal catalysts. In contrast to many known transition-metal-catalyzed couplings and direct C−H functionalization in which a reactive chlorine or bromine atom can seldom be tolerated, these arylations and alkenylations proceeded smoothly in the presence of a highly electrophilic C−Cl or C−Br bond. Besides, this reaction allows the one-pot, iterative arylation or alkenylation of pyridine *N*-oxides, which offers a facile synthetic method for preparing di- or polysubstituted pyridine *N*-oxides and thus the corresponding pyridine derivatives. Furthermore, it also provides a novel route for the activation of the nitro group as leaving group based on the unprecedented reactivity of nitro group toward Grignard reagents discovered by this work.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.