

# Facile One-Pot Direct Arylation and Alkylation of Nitropyridine *N*-Oxides with Grignard Reagents

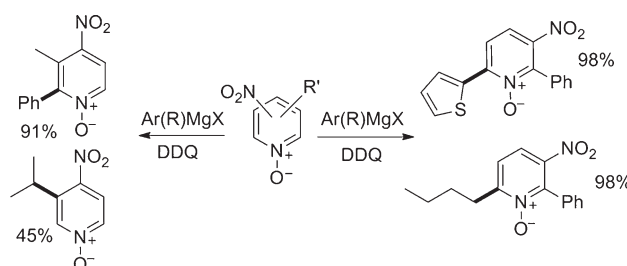
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## ABSTRACT



Facile arylation and alkylation of nitropyridine *N*-oxides were developed through the reactions of Grignard reagents with nitropyridine *N*-oxides. For the same 4-nitropyridine *N*-oxide, arylation occurred at the 2- (or 6-) position, whereas alkylation occurred at the 3-position in an adjustably site-selective manner. The cooperative action of the two groups was discovered in the reactions of 3-nitropyridine *N*-oxides. This protocol can find wide applications in building various pyridine compounds as illustrated in total syntheses of Emoxipin and Caerulomycin A and E.

The nitro group is of great importance in the activation of organic molecules.<sup>1</sup> However, use of organometallic reagents such as organolithium and Grignard reagents in the presence of a nitro group has been significantly limited in organic synthesis. This was primarily due to rapid reactions between the nitro group and related organometallic reagents.<sup>2</sup> Preparation of *o*-nitro-substituted aryl lithium or aryl magnesium compounds was only carried out at very low temperatures,<sup>3</sup> and the generation of *m*- or *p*-nitro-substituted aryl lithium was only achieved in a

microflow system.<sup>4</sup> Meanwhile, the reaction between nitroarenes and organometallic reagents is complex and strongly depends upon the carbanionic moiety in the organometallic species.<sup>2a,b,5</sup> For example, the reaction between nitroarene and alkyl magnesium halide afforded ring-alkylated nitro compounds through 1,4- and/or 1,6-conjugate addition,<sup>5</sup> whereas the reaction between a nitroarene and an aromatic magnesium halide resulted in diarylamine as a result of 1,2-addition to the nitro group.<sup>2f,h</sup> Overall, development of selective and synthetically applicable reactions of Grignard reagents in the presence of a nitro group is highly desirable.

Substituted pyridine *N*-oxides<sup>6</sup> are widely presented in natural products and biologically active compounds, and they are also used as catalysts in asymmetric reactions.<sup>7</sup> Additionally, they are also important intermediates for the syntheses of substituted pyridines as part of motifs in natural products, biologically active compounds, and

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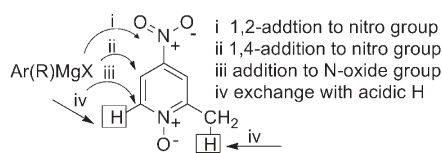
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**Scheme 1.** Possible Reactions of Grignard Reagent with 4-Nitro-2-picoline *N*-Oxide



material science.<sup>8</sup> It is of high interest to develop synthetic methodologies for the facile pyridine *N*-oxide intermediate preparations. Recently, direct arylation of pyridine *N*-oxides via transition-metal-catalyzed C–H activation has been reported.<sup>9</sup> This method was only limited to arylation and requires harsh reaction conditions, extended reaction times, and excess pyridine *N*-oxide as well as expensive transition-metal catalysts. Alternatively, an efficient and transition-metal-free arylation and alkylation of pyridine *N*-oxides was achieved through the reactions of Grignard reagents with pyridine *N*-oxides.<sup>10,11</sup> Although nitropyridine *N*-oxides constitute a significant class of heterocyclic *N*-oxides,<sup>6</sup> the reactions of Grignard reagents with nitropyridine *N*-oxides have not yet been reported to date. It is expected that these reactions are challenging because at least four possible reactions could take place (in Scheme 1).

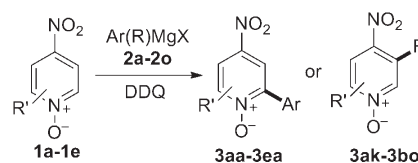
We herein report a robust direct arylation and alkylation of nitropyridine *N*-oxides, which is a one-pot transition-metal-free reaction of a Grignard reagent with nitropyridine *N*-oxides. We expect that this protocol will significantly extend the scope of the reactions of Grignard reagents in the presence of a nitro group as well as the arylation or alkylation of pyridine *N*-oxides.

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**Table 1.** Reactions of 4-Nitropyridine *N*-Oxides with Grignard Reagents<sup>a</sup>



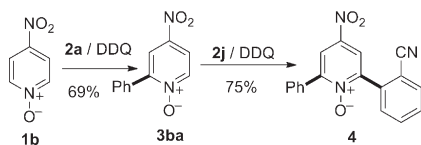
entry	R' (1)	Ar (R)	product <sup>b</sup>	yield <sup>c</sup>
1	2-Me(1a)	Ph	3aa (6-)	92%
2	1a	4-MeC <sub>6</sub> H <sub>4</sub>	3ab (6-)	85%
3	1a	3-MeC <sub>6</sub> H <sub>4</sub>	3ac (6-)	82%
4	1a	2-MeC <sub>6</sub> H <sub>4</sub>	3ad (6-)	78%
5	1a	2,4,6-(Me) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	3ae (6-)	76%
6	1a	naphthalen-1-yl	3af (6-)	79%
7	1a	thiophen-2-yl	3ag (6-)	69%
8	1a	pyridin-3-yl	3ah (6-)	70%
9	1a	2-MeOOC <sub>6</sub> H <sub>4</sub>	3ai (6-)	69%
10	H(1b)	Ph	3ba (2-)	69% <sup>d</sup>
11	1b	pyridin-3-yl	3bh (2-)	64% <sup>d</sup>
12	3-Me(1c)	Ph	3ca (2-)	91%
13	1c	2-CNC <sub>6</sub> H <sub>4</sub>	3cj (2-)	74%
14	1d <sup>e</sup>	4-MeC <sub>6</sub> H <sub>4</sub>	3db (6-)	80%
15	1d	thiophen-2-yl	3dg (6-)	90%
16	1e <sup>f</sup>	Ph	3ea (2-)	78%
17	1a	Me	3ak (3-)	47%
18	1a	Et	3am (3-)	32%
19	1b	<i>i</i> -Pr	3bn (3-)	45%
20	1b	cyclohexyl	3bo (3-)	35%

<sup>a</sup>4-Nitropyridine *N*-oxide was treated with Grignard reagent (1.2 equiv) in THF at –60 °C. After the addition reaction was completed (1–2 h), DDQ (1.2 equiv) was added. The mixture was allowed to come to room temperature and stirred for 4–6 h. <sup>b</sup>The arylated or alkylated position in product is given in parentheses. <sup>c</sup>Yield of isolated product. <sup>d</sup>About 10% diarylated product was isolated. <sup>e</sup>2-Diisopropylcarbamoylpyridine *N*-oxide. <sup>f</sup>4-Nitroquinoline *N*-oxide.

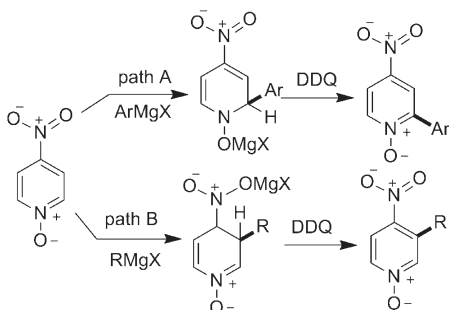
In a preliminary experiment, a complex mixture was obtained when 4-nitro-2-picoline *N*-oxide (1a) was treated with phenylmagnesium bromide (2a) at –20 °C. However, at lowered reaction temperature, 6-phenyl-4-nitro-2-picoline (3aa) was mainly obtained, in yields of 27% and 51% at –40 or –60 °C respectively. The result suggested that the addition of phenylmagnesium bromide to the *N*-oxide group could take place predominantly at a low temperature. Various oxidants (KMnO<sub>4</sub>, FeCl<sub>3</sub>, Cu(NO<sub>3</sub>)<sub>2</sub>, DDQ, and air) were then screened to oxidize the adduct dihydropyridine *N*-oxide<sup>10d</sup> into corresponding pyridine *N*-oxide *in situ*. The best result was obtained when DDQ was used, where 3aa was isolated in a 92% yield (Table 1 entry 1). This simple, transition-metal-free and highly

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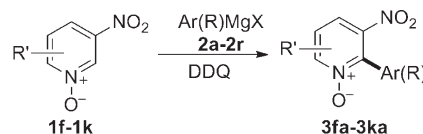
(11) For the alkylation or arylation of acyl- and alkyl-activated pyridines through the addition of organometallic reagents, see: Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863.

**Scheme 2.** Sequential Arylation of 4-Nitropyridine *N*-Oxide

efficient protocol was further explored, and the results were summarized in Table 1. It was found that 4-nitropyridine *N*-oxides could be readily arylated with various Grignard reagents, such as one that is sterically hindered (Table 1, entry 5), functionalized (entries 9 and 13), or heteroaromatic (entries 7, 8, 11, and 15). This direct arylation was also suitable to 4-nitroquinoline *N*-oxide (entry 16) and amide-containing 4-nitropyridine *N*-oxide (entries 14 and 15). In the case of 4-nitropyridine *N*-oxide (**1b**), two different aryl groups could be incorporated into the *N*-oxide with a reasonable yield after sequential reactions with Grignard reagents (Scheme 2). Interestingly, the reactions of Grignard reagents with 3-substituted 4-nitropyridine *N*-oxide (**1c**) predominantly led to a more sterically hindered 2, 3, 4-trisubstituted pyridine *N*-oxide with excellent selectivity (entries 12 and 13).<sup>10e</sup>

**Scheme 3.** Two Pathways of Reactions between 4-Nitropyridine *N*-Oxides with Grignard Reagents

It is worth noting that when 4-nitropyridine *N*-oxides were treated with alkyl Grignard reagents, alkylation took place regioselectively at the 3-position (ortho to a nitro group) (Table 1, entries 17–20). Similarly, the more sterically hindered 2,3,4-trisubstituted pyridine *N*-oxides were afforded (**3ak** and **3am**). As illustrated in Scheme 3, different addition pathways might take place here when 4-nitropyridine *N*-oxide was treated with an aromatic Grignard reagent as opposed to the alkyl Grignard reagent. The arylation occurred at the 2- or 6-position through an addition to the  $N\rightarrow O$  group mechanism,<sup>9a</sup> whereas the alkylation occurred at the 3- or 5-position through a conjugate addition to the nitro group.<sup>5a</sup> This unique addition pattern would allow for predictable regioselective arylation or alkylation. Additionally, it helps in further understanding and thus best utilizing the reactivity of the nitro group as well as the  $N\rightarrow O$  group.

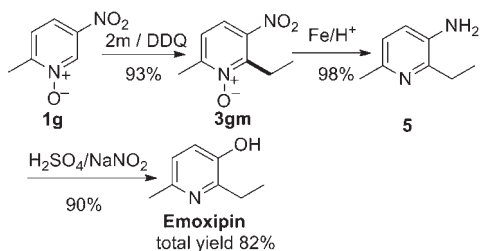
**Table 2.** Reactions of 3(5)-Nitropyridine *N*-Oxides with Grignard Reagents<sup>a</sup>

entry	R'(1)	Ar (R)	product	yield <sup>b</sup>
1	2-Me( <b>1f</b> )	Ph	<b>3fa</b>	92%
2	<b>1f</b>	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3fb</b>	89%
3	<b>1f</b>	naphthalen-1-yl	<b>3ff</b>	94%
4	<b>1f</b>	Et	<b>3fm</b>	82%
5	<b>1f</b>	<i>i</i> -Pr	<b>3fn</b>	59%
6	<b>1f</b>	cyclohexyl	<b>3fo</b>	75%
7	<b>1f</b>	<i>t</i> -Pentyl	<b>3fp</b>	37%
8	6-Me( <b>1g</b> )	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3gb</b>	98%
9	<b>1g</b>	2-MeC <sub>6</sub> H <sub>4</sub>	<b>3gd</b>	98%
10	<b>1g</b>	naphthalen-1-yl	<b>3df</b>	98%
11	<b>1g</b>	2-MeOOC <sub>6</sub> H <sub>4</sub>	<b>3gi</b>	91%
12	<b>1g</b>	Me	<b>3gk</b>	93%
13	2-Ph( <b>1h</b> )	Ph	<b>3ha</b>	95%
14	<b>1h</b>	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3hb</b>	98%
15	<b>1h</b>	naphthalen-1-yl	<b>3hf</b>	91%
16	<b>1h</b>	thiophen-2-yl	<b>3hg</b>	98%
17	<b>1h</b>	2-CNC <sub>6</sub> H <sub>4</sub>	<b>3hj</b>	91%
18	<b>1h</b>	2-MeOOC <sub>6</sub> H <sub>4</sub>	<b>3hi</b>	98%
19	<b>1h</b>	Me	<b>3hk</b>	91%
20	<b>1h</b>	Et	<b>3hm</b>	98%
21	<b>1h</b>	<i>n</i> -Bu	<b>3hr</b>	98%
22	<b>1h</b>	cyclohexyl	<b>3ho</b>	78%
23	<b>1h</b>	<i>t</i> -Bu	<b>3hs</b>	31%
24	6-Ph( <b>1i</b> )	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3ib</b>	98%
25	<b>1i</b>	<i>i</i> -Pr	<b>3in</b>	98%
26	<b>1i</b>	cyclohexyl	<b>3io</b>	88%
27	<b>1j<sup>c</sup></b>	Ph	<b>3ja</b>	80%
28	<b>1k<sup>d</sup></b>	Ph	<b>3ka</b>	78%

<sup>a</sup> Reaction conditions were same as those in Table 1. <sup>b</sup> Yield of isolated product. <sup>c</sup> 6-Chloro-3-nitropyridine *N*-oxide. <sup>d</sup> 3-Nitroquinoline *N*-oxide.

Next the reactions of Grignard reagents with 3-nitropyridine *N*-oxides were investigated. Unlike 4-nitropyridine *N*-oxides where the addition could take place either at the 2-/6-position via the addition directed by the  $N\rightarrow O$  group or at the 3-/5-position via the addition directed by the nitro group (Scheme 3), 3-nitropyridine *N*-oxide related additions are expected to occur at only the 2-/6-position due to the additive electronic effects between the  $N\rightarrow O$  group and nitro group. As a result both arylation and alkylation of 3-nitropyridine *N*-oxides should be straightforward, and in fact they were furnished with high yields as shown in Table 2. In addition to primary and secondary alkylation, tertiary alkyl groups could also be introduced onto the *N*-oxides (Table 2, entries 7 and 23).<sup>12</sup> The reaction of 3-nitropyridine *N*-oxide with PhMgBr gave 2-phenylated, 6-phenylated, and 2,6-diphenylated products in yields of

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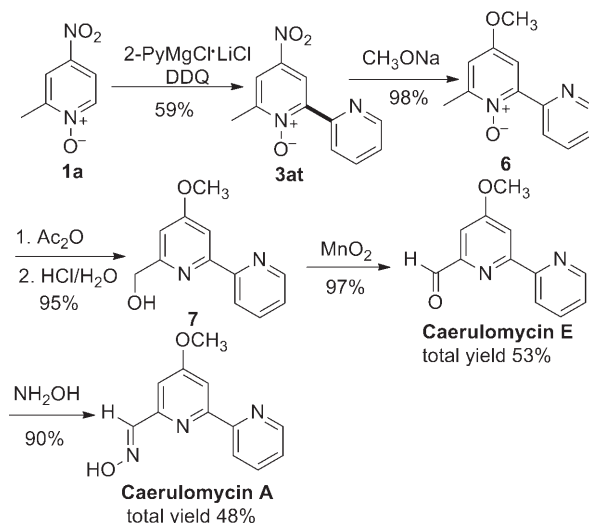
**Scheme 4.** Total Synthesis of Emoxipin

31%, 22%, and 15% respectively. One solution to address this poor selectivity had been achieved through the arylation of 6-chloro-3-nitropyridine *N*-oxide (**1j**) followed by dechlorination (Table 2, entry 27).

To our best knowledge, the procedure described herein provides the simplest method for direct arylation and alkylation of nitropyridine *N*-oxides. It also represents one of very few highly selective reactions of Grignard reagents in the presence of a nitro group. To further illustrate its synthetic potential, total syntheses of Emoxipin<sup>13</sup> and other two natural products (Caerulomycin A and E<sup>14</sup>) using this method as the key step were outlined in Schemes 4 and 5. In Scheme 4, 6-methyl-3-nitropyridine *N*-oxide (**1g**) was ethylated at the 2-position in an excellent yield using EtMgBr (**2m**). Reduction of **3gm** followed by diazotization and hydrolysis afforded Emoxipin in an overall yield of 82%. Notably, this high yield synthesis eliminated conditions of high pressure and high temperature as reported in its original preparation. In Scheme 5, starting with commercially available compound **1a**, Caerulomycin E and A were made in four and five steps respectively. The key intermediate compound **3at** was prepared via the direct arylation with 2-pyridyl Grignard reagent. According to the reported procedures<sup>14c</sup> **3at** was transformed into Caerulomycin E and A with an overall yield of 53% and 46%, respectively. Obviously the reagents used in our syntheses are readily available, and corresponding procedures were very straightforward.

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**Scheme 5.** Total Synthesis of Caerulomycin A and E

In summary, we have extended the reaction between Grignard reagents and pyridine *N*-oxides to nitropyridine *N*-oxides and developed a simple transition-metal-free one-pot direct arylation and alkylation of nitropyridine *N*-oxides. This protocol has significantly extended the scope of the reactions of Grignard reagents in the presence of a nitro group as well as the arylation or alkylation of pyridine *N*-oxides. Because nitropyridine *N*-oxides are an important class of heterocyclic *N*-oxides and can be readily transformed into other functional groups, this methodology can be potentially used to synthesize various pyridine compounds. Furthermore, the patterns of nitro and *N*→*O* groups in directing the arylation and alkylation of Grignard reagents are of great interest to help in further understanding related mechanisms and better utilizing the reactions for related synthetic applications.

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**Supporting Information Available.** Experimental procedures and <sup>1</sup>H and <sup>13</sup>CNMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.