# Catalyst-Free Regioselective C-3 Nitrosation of Imidazopyridines with *tert*-Butyl Nitrite under Neutral Conditions

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Received: 05.08.2015 Accepted after revision: 25.09.2015 Published online: 30.10.2015 DOI: 10.1055/s-0035-1560508; Art ID: ss-2015-h0466-op

**Abstract** We have successfully developed a novel and efficient catalyst-free method for the synthesis of 3-nitroso-substituted imidazopyridines, from readily available imidazo[1,2-*a*]pyridines and *tert*-butyl nitrite, in good to excellent yields. Importantly, the use of transition-metal catalysts, stoichiometric amounts of acids, and toxic or potentially dangerous oxidants is avoided. This easy and practical method complements nitrosation reactions by expanding the scope and practicality, and should attract much attention in synthetic and pharmaceutical chemistry.

**Key words** metal-free, C–H functionalization, nitrosation, imidazopyridines, heterocycles

Imidazoheterocycle motifs are extensively found in the subunits of a variety of bioactive compounds,<sup>1</sup> and they are also widely used as privileged structures in pharmaceutical compounds.<sup>2</sup> It is worth noting that imidazo[1,2-a]pyridine derivatives possess many excellent biological activities, including antitumor,<sup>3</sup> antibacterial,<sup>4</sup> anti-inflammatory,<sup>5</sup> antiviral,<sup>6</sup> antimicrobial,<sup>7</sup> and antipyretic<sup>8</sup> action. Importantly, the imidazo 1,2-a pyridine skeleton is the core structure in many commercially available drugs, such as zolpidem (to treat insomnia),<sup>2,9</sup> zolimidine (to treat peptic ulcers),<sup>10</sup> olprinone (to treat heart failure),<sup>11</sup> and minodronic acid (to treat osteoporosis)<sup>12</sup> (Figure 1). Consequently, many efficient and useful methods for the synthesis of imidazo[1,2apyridine derivatives have been developed.<sup>13</sup> Exploring new methods for the C-3 functionalization of imidazo[1,2*a*]pyridines has attracted considerable attention, but, unfortunately, successful examples remain limited.<sup>14</sup> In 2012, Cao and Jiang published an efficient procedure for the C-3 arylation of substituted imidazo[1,2-a]pyridines by coppercatalyzed C-H bond activation.14k In 2014, Cao et al. demonstrated a novel copper-catalyzed C-3 formylation of imidazo[1,2-*a*]pyridines with dimethyl sulfoxide by using dioxygen as the oxidant.14f In 2014, Adimurthy and coworkers communicated an elegant N-chlorosuccinimidepromoted regioselective sulfenylation of imidazo[1,2*a*]pyridines with thiophenols under mild conditions.<sup>14a</sup> In 2015, Hiebel's group reported an iodine-catalyzed regioselective sulfenylation of imidazoheterocycles in polyethylene glycol 400 (PEG 400).<sup>14b</sup> In 2015, Atmakur and co-workers reported a highly efficient iodine-dimethyl sulfoxide promoted oxidative cross-coupling of imidazo[1,2-*a*]pyridines with methyl ketones under mild conditions.<sup>14g</sup> Very recently, Li et al. described an efficient regioselective hydrazination of imidazo[1,2-a]pyridines with diethyl azodicarboxylate in neutral media under metal-free conditions.<sup>14h</sup> However, it still remains a challenging, but desirable task to develop more efficient and practical methods to C-3 functionalize the useful imidazo [1,2-a] pyridines.



Figure 1 Popular drugs containing the imidazopyridine motif

Nitroso compounds have been widely used as important synthetic intermediates in organic transformations, such as ene reactions,<sup>15</sup> nitroso aldol reactions,<sup>16</sup> and cycloadditions.<sup>17</sup> Additionally, there are some biologically active aromatic nitroso compounds with proven special activity against HIV-1 infectivity.<sup>18</sup> As a consequence, the introduction of a nitroso group into an organic skeleton is an attractive synthetic goal. Unfortunately, synthetic methods for the construction of nitroso compounds are rather limited.<sup>19</sup> Classical methods for the synthesis of nitroso compounds mainly focus on the oxidation of anilines to the corresponding nitrosoarenes.<sup>20</sup> Despite the various advantages of these methods, wider application is limited by factors such as the use of excess oxidants in these reactions and the formation of undesired byproducts such as azo and azoxy compounds. Some other methods have been developed for the nitrosation of organomercury,<sup>21</sup> thallium,<sup>22</sup> silicon,<sup>23</sup> and electronrich arenes<sup>24</sup> in the presence of nitrosyl chloride. Also, direct nitrosation of imidazopyridines by using sodium nitrite-acetic acid has been a well-known and popular method for the synthesis of 3-nitrosoimidazopyridines.<sup>25</sup> Nevertheless, these methods generally have some drawbacks, such as the use of noncommercially available arylmetallics or acid-oxidative conditions. In 2012. Molander and coworkers reported a mild and selective method for the ipsonitrosation of organotrifluoroborates in the presence of nitrosonium tetrafluoroborate.<sup>26</sup> However, it is still highly desirable to discover new methods to prepare nitroso compounds that utilize inexpensive nitroso reagents and proceed under non- or low-oxidative neutral conditions.

There have been several reports recently on the use of *tert*-butyl nitrite as an excellent nitro source (NO<sub>2</sub>), such as in nitro-carbocyclization of activated alkenes,<sup>27</sup> direct C–H nitration of arenes,<sup>28</sup> nitration of quinoline *N*-oxides,<sup>29</sup> nitration of arylboronic acids,<sup>30</sup> nitration of phenols,<sup>31</sup> and nitration/cyclization of 1,7-enynes.<sup>32</sup> Nevertheless, to the best of our knowledge, reports on the use of *tert*-butyl nitrite as the nitroso source (NO) have been rare. In 2014, Jiao and coworkers reported an efficient tetrabutylammonium bromide catalyzed (10 mol%) dehydrogenative N-incorporation of simple imines, with *tert*-butyl nitrite as the nitroso source, leading to quinoxaline *N*-oxides.<sup>33</sup> Herein, we report a novel and direct, catalyst-free nitrosation of imidazopyridines under neutral conditions, with simple and readily available *tert*-butyl nitrite as the nitroso source.

As shown in Table 1, we started our studies by exploring the reaction between 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with *tert*-butyl nitrite (**2**) to optimize the reaction conditions. Initially, several transition-metal salts, such as palladium(II) acetate, palladium(II) chloride, copper(II) acetate, and iron(II) chloride (10 mol% catalytic amount relative to **1a**) were tested in *N*,*N*-dimethylformamide at 90 °C under an air atmosphere, but no obviously different activity was observed (entries 1–4). To our delight, the desired nitrosated imidazopyridine (**3a**) was obtained in 75% yield in the absence of a catalyst (entry 5). These results confirm that a catalyst-free nitrosation coupling reaction is possible. Additionally, different solvents were examined, showing that acetonitrile was superior to the others (entries 5–10). Different reaction temperatures were also surveyed (entries 10-13), and the best result was obtained when the reaction was conducted at 80 °C (entry 11).

Table 1 Optimization of the Reaction Conditions<sup>a</sup>



Entry	Catalyst	Solvent	Temp	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	DMF	90	71
2	PdCl <sub>2</sub>	DMF	90	66
3	Cu(OAc) <sub>2</sub>	DMF	90	72
4	FeCl <sub>2</sub>	DMF	90	72
5	none	DMF	90	75
6	none	DMSO	90	71
7	none	H <sub>2</sub> O	90	44
8	none	1,4-dioxane	90	70
9	none	DCE	90	78
10	none	MeCN	90	81
11	none	MeCN	80	81
12	none	MeCN	70	74
13	none	MeCN	60	63

<sup>a</sup> Reaction conditions: 2-phenylimidazo[1,2-*a*]pyridine (**1a**; 0.3 mmol), *t*-BuONO (**2**; 0.6 mmol), solvent (2 mL), 18 h; under air.

<sup>b</sup> Isolated yield.

Having obtained the optimized reaction conditions (MeCN as solvent, at 80 °C, under an air atmosphere), we next turned our attention toward the scope and limitations of the transformation, with the results summarized in Scheme 1. Imidazo[1,2-a]pyridines carrying electrondonating or electron-withdrawing aryl substituents performed well in the reaction, with the corresponding 3-nitroso products obtained in good to excellent yields. Notably, strongly electron-withdrawing groups such as trifluoromethyl and nitro were well tolerated in this transformation, with 3x-z afforded in 77-81% yields. 2-(1-Naphthyl)imidazo[1,2-*a*]pyridine could also be employed in the reaction to generate the desired product 3f in good yield. Notably, 2-(2-furyl)imidazopyridines were also compatible with the reaction conditions (3v and 3w). Although imidazopyridines bearing aryl groups at the C-2 position performed well in this reaction, unfortunately, 2-alkyl-substituted imidazopyridines were poor substrates, giving only traces of 4 (Scheme 1). The structure of **3n** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2) (see

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Supporting Information for details). Various other functional groups, such as methyl, methoxy, chloro, and bromo, were found to be compatible with the present protocol. We also investigated the synthetic applicability of the present method by carrying out a gram-scale reaction between 1a and **2** in the usual laboratory flask: 1.11 grams of **3a** was obtained in 83% yield without loss of efficiency (Scheme 1). Thus, this protocol is expected to serve as a practical and efficient access to 3-nitrosoimidazopyridines.



Figure 2 X-ray crystal structure of compound 3n (CCDC 1412151)

We attempted the synthesis of 3-aminoimidazopyridines by using the present method. As shown in Scheme 2, 3j was transformed into 5 in 92% yield in the presence of tin(II) chloride in ethanol.<sup>34</sup> Therefore, the present method is a useful approach to 3-aminoimidazopyridine derivatives from 3-H imidazopyridines.<sup>35</sup>

To gain a deeper understanding of the reaction mechanism, a radical inhibitor, 2,6-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) (4 equiv), was added to the reaction system under the standard conditions; this led to inhibition of the reaction (Scheme 3, a). This indicated that the reaction proceeds via a radical pathway. Furthermore, when the reaction was carried out under an oxygen atmosphere, the desired nitrosation product **3a** was obtained in 80% vield, but no nitration product 6 was observed (as determined by HPLC-MS); this was guite different from the previous reports that the nitroso radical NO<sup>•</sup> could easily be oxidized to the nitro radical NO<sub>2</sub>• under air or an oxygen atmosphere<sup>36</sup> (Scheme 3, b).

As illustrated in Scheme 4, two possible mechanisms for the direct transformation are proposed, on the basis of the preliminary results described above and some previous reports.<sup>14c,37</sup> In path A, heating of *tert*-butyl nitrite leads to the generation of the active nitroso radical I and the tertbutoxy radical II. Subsequently, the nitroso radical reacts with 2-phenylimidazo[1,2-*a*]pyridine (1a) to form the radical intermediate III. Then III is transformed into carbocation intermediate IV via a single-electron transfer (SET) process with the assistance of the tert-butoxy radical II. Finally, the desired product **3a** is generated through the elimination of a proton from intermediate IV. As a complementary mechanism (path B), heterolysis of tert-butyl nitrite generates an electrophilic nitroso cation (V). Subsequently, electrophilic addition of the electrophilic V to 1a also leads to the intermediate carbocation IV.

Heruntergeladen von: Flinders University of South Australia. Urheberrechtlich geschützt.



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In summary, a new catalyst-free system for the nitrosation of imidazopyridines was developed. The nitrosation reaction proceeded well under neutral conditions to give the 3-nitrosoimidazopyridines in good to excellent yields. Notably, no metal catalysts, no acids, and no strong oxidants were required in the transformation. The developed method provided an alternative and highly attractive route to various potentially biologically active 3-nitrosoimidazopyridines from easily available imidazo[1,2-*a*]pyridines and *tert*-butyl nitrite.

All commercially available reagents and chemicals were purchased from chemical suppliers and used as received without further purification. All the imidazopyridines were synthesized according to a previously reported method.<sup>13b</sup> Column chromatography was performed on silica gel (200–300 mesh). MS and HRMS were carried out by ESI on a TOF mass analyzer. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded of samples dissolved in CDCl<sub>3</sub> with TMS as internal standard at room temperature.

#### 3-Nitrosoimidazo[1,2-a]pyridines 3; General Procedure

A 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with substituted imidazopyridine **1** (0.3 mmol), *t*-BuONO (**2**; 0.6 mmol), and MeCN (2 mL). The tube was sealed and then the mixture was allowed to stir under an air atmosphere at 90 °C for 18 h. After completion of the reaction, the resulting solution was cooled to r.t., and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography (silica gel, PE–EtOAc) to provide the desired product **3**.

### 3-Nitroso-2-phenylimidazo[1,2-*a*]pyridine (3a)<sup>38</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 54 mg (81%); green solid; mp 163–165 °C (Lit.<sup>38</sup> 165 °C);  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.93 (d, J = 8.0 Hz, 1 H), 8.67 (d, J = 8.0 Hz, 2 H), 7.85–7.83 (m, 2 H), 7.60–7.54 (m, 3 H), 7.27–7.24 (m, 1 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 160.0, 153.4, 145.7, 136.2, 131.6, 131.5, 130.8, 128.9, 126.5, 119.6, 117.5.

ESI-HRMS: m/z calcd for  $C_{13}H_{10}N_3O$  [M + H]<sup>+</sup>: 224.0824; found: 224.0829.

#### 3-Nitroso-2-p-tolylimidazo[1,2-a]pyridine (3b)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 58 mg (82%); green solid; mp 218–219 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.95 (d, *J* = 4.0 Hz, 1 H), 8.59 (d, *J* = 8.0 Hz, 2 H), 7.84–7.82 (m, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.26–7.24 (m, 1 H), 2.47(s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 160.1, 153.3, 145.9, 142.3, 136.1, 130.8, 129.7, 128.8, 126.5, 119.3, 117.4, 21.6.

ESI-HRMS: m/z calcd for  $C_{14}H_{12}N_3O$  [M + H]<sup>+</sup>: 238.0980; found: 238.0987.

#### 3-Nitroso-2-*m*-tolylimidazo[1,2-*a*]pyridine (3c)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 61 mg (86%); green solid; mp 148–149 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.94 (d, *J* = 4.0 Hz, 1 H), 8.48 (m, 2 H), 7.85 (t, *J* = 8.0 Hz, 2 H), 7.47–7.40 (m, 2 H), 7.27–7.24 (m, 1 H), 2.49 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 160.3, 153.4, 145.7, 138.6, 136.1, 132.5, 131.4, 131.2, 128.8, 128.2, 126.5, 119.5, 117.5, 21.5.

ESI-HRMS: m/z calcd for  $C_{14}H_{12}N_3O$  [M + H]\*: 238.0980; found: 238.0981.

#### 2-(4-Chlorophenyl)-3-nitrosoimidazo[1,2-a]pyridine (3d)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 55 mg (71%); green solid; mp 223–225 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.12 (d, *J* = 8.0 Hz, 1 H), 8.65 (d, *J* = 8.0 Hz, 2 H), 7.91–7.80 (m, 2 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.30–7.27 (m, 1 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.6, 153.2, 145.6, 138.3, 136.2, 132.0, 130.0, 129.2, 126.5, 119.7, 117.5.

ESI-HRMS: m/z calcd for  $C_{13}H_9CIN_3O$  [M + H]<sup>+</sup>: 258.0434; found:258.0434.

### 2-(2-Bromophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (3e)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 66 mg (73%); green solid; mp 143–145 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.86 (d, J = 4.0 Hz, 1 H), 7.98–7.87 (m, 3 H), 7.84–7.62 (m, 1 H), 7.54–7.44 (m, 2 H), 7.36 (t, J = 8.0 Hz, 1 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 162.2, 161.0, 153.4, 145.1, 135.7, 134.2, 133.9, 133.0, 131.4, 126.7, 119.9, 117.9.

ESI-HRMS: m/z calcd for  $C_{13}H_9BrN_3O$  [M + H]<sup>+</sup>: 301.9929; found: 301.9931

#### 2-(1-Naphthyl)-3-nitrosoimidazo[1,2-a]pyridine (3f)<sup>39</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 65 mg (79%); green solid; mp 206–207 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.98 (d, J = 4.0 Hz, 1 H), 8.78 (d, J = 8.0 Hz, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 8.09 (d, J = 8.0 Hz, 1 H), 8.00–7.89 (m, 3 H), 7.69–7.60 (m, 3 H), 7.34 (t, J = 8.0 Hz, 1 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 162.6, 154.3, 145.3, 135.9, 133.4, 131.4, 128.6, 127.3, 126.3, 125.9, 125.1, 119.0, 117.7.

ESI-HRMS: m/z calcd for  $C_{17}H_{12}N_3O$  [M + H]<sup>+</sup>: 274.0980; found: 274.0977.

# 2-(4-Chlorophenyl)-7-methyl-3-nitrosoimidazo[1,2-*a*]pyridine (3g)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 62 mg (76%); green solid; mp 213–214 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.81 (d, *J* = 8.0 Hz, 1 H), 8.64 (d, *J* = 8.0 Hz, 2 H), 7.60 (s, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 2.56(s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.9, 153.1, 149.0, 146.3, 138.2, 131.9, 130.1, 129.1, 126.1, 121.5, 116.5, 22.3.

ESI-HRMS: m/z calcd for C<sub>14</sub>H<sub>11</sub>ClN<sub>3</sub>O [M + H]<sup>+</sup>: 272.0591; found: 272.0588.

# 2-(3-Bromophenyl)-7-methyl-3-nitrosoimidazo[1,2-a]pyridine (3h)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 70 mg (74%); green solid; mp 219–221 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.79 (d, J = 8.0 Hz, 1 H), 8.82 (s, 1 H), 8.65 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.61 (s, 1 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 2.57 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.4, 153.1, 149.0, 146.1, 134.3, 133.6, 133.2, 130.3, 129.4, 126.0, 122.9, 121.7, 116.6, 22.3.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}BrN_{3}O$  [M + H]<sup>+</sup>: 316.0085; found: 316.0089.

#### 2-(4-Methoxyphenyl)-7-methyl-3-nitrosoimidazo [1,2-a]pyridine (3i)<sup>40</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 57 mg (71%); green solid; mp 208–209 °C;  $R_f = 0.3$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.84 (d, *J* = 8.0 Hz, 1 H), 8.66 (d, *J* = 8.0 Hz, 2 H), 7.53 (s, 1 H), 7.06–7.01 (m, 3 H), 3.91 (s, 3 H), 2.92 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 162.8, 160.1, 153.0, 149.0, 146.8, 132.6, 126.3, 124.3, 120.8, 116.2, 114.4, 55.5, 22.3.

ESI-HRMS: m/z calcd for  $C_{15}H_{14}N_3O_2$  [M + H]<sup>+</sup>: 268.1086; found: 268.1081.

#### 8-Methyl-3-nitroso-2-phenylimidazo[1,2-a]pyridine (3j)<sup>25d</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 65 mg (91%); green solid; mp 140–141 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.78 (d, *J* = 8.0 Hz, 1 H), 8.69 (d, *J* = 8.0 Hz, 2 H), 7.62–7.53 (m, 3 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 2.74 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 159.2, 153.8, 145.6, 135.4, 131.9, 131.3, 130.8, 128.7, 127.9, 124.2, 119.4, 16.5.

ESI-HRMS: m/z calcd for  $C_{14}H_{12}N_3O$  [M + H]<sup>+</sup>: 238.0980; found: 238.0981.

### 8-Methyl-3-nitroso-2-p-tolylimidazo[1,2-a]pyridine (3k)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 68 mg (90%); green solid; mp 181–182 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.73 (d, *J* = 8.0 Hz, 1 H), 8.56 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 2.68 (s, 3 H), 2.41 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 159.2, 153.6, 145.6, 141.9, 135.4, 130.7, 129.5, 129.1, 127.7, 124.2, 119.1, 21.6, 16.5.

ESI-HRMS: m/z calcd for  $C_{15}H_{14}N_3O$  [M + H]<sup>+</sup>: 252.1137; found: 252.1130.

#### 6-Methyl-3-nitroso-2-p-tolylimidazo[1,2-a]pyridine (31)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 64 mg (85%); green solid; mp 197–199 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.81 (s, 1 H), 9.54 (d, J = 8.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 2.45 (s, 3 H), 2.40 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 159.8, 153.2, 144.8, 142.0, 138.6, 130.6, 130.1, 129.6, 128.9, 124.8, 116.5, 21.6, 18.3.

ESI-HRMS: m/z calcd for  $C_{15}H_{14}N_3O$  [M + H]<sup>+</sup>: 252.1137; found: 252.1133.

#### 6-Methyl-3-nitroso-2-o-tolylimidazo[1,2-a]pyridine (3m)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 61 mg (81%); green solid; mp 218–220 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.82 (s, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.46–7.34 (m, 3 H), 2.62 (s, 3 H), 2.45 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 163.4, 153.7, 144.3, 138.4, 138.2, 133.1, 131.1, 130.3, 130.2, 125.6, 124.5, 116.8, 21.0, 18.3.

ESI-HRMS: m/z calcd for  $C_{15}H_{14}N_3O$  [M + H]\*: 252.1137; found: 252.1139.

# 6-Methyl-3-nitroso-2-(3-chlorophenyl)imidazo[1,2-*a*]pyridine (3n)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 67 mg (83%); green solid; mp 206–208 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz,  $CDCI_3$ ):  $\delta$  = 9.79 (s, 1 H), 8.65 (s, 1 H), 8.57 (d, J = 8.0 Hz, 1 H), 7.76–7.69 (m, 2 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.48 (t, J = 8.0 Hz, 1 H), 2.45 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 157.9, 153.1, 144.4, 138.6, 134.9, 133.4, 131.2, 130.8, 130.3, 130.0, 128.8, 124.7, 116.8, 18.4.

ESI-HRMS: m/z calcd for C<sub>14</sub>H<sub>11</sub>ClN<sub>3</sub>O [M + H]<sup>+</sup>: 272.0591; found: 272.0595.

# 6-Methyl-3-nitroso-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine (30)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 60 mg (74%); green solid; mp 212–213 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.81 (s, 1 H), 8.62 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 2 H), 2.45 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 158.3, 153.1, 144.5, 138.6, 138.0, 131.8, 130.6, 130.2, 129.1, 127.4, 116.7, 29.7.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}CIN_{3}O$  [M + H]<sup>+</sup>: 272.0591; found: 272.0597.

# 2-(4-Bromophenyl)-6-methyl-3-nitrosoimidazo[1,2-*a*]pyridine (3p)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 70 mg (74%); green solid; mp 176–178 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.77 (s, 1 H), 8.52 (d, J = 8.0 Hz, 2 H), 7.72–7.64 (m, 4 H), 2.43 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.2, 153.1, 144.5, 138.6, 132.0, 131.9, 131.7, 130.6, 130.5, 127.4, 126.6, 124.7, 116.7, 18.4.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}BrN_{3}O$  [M + H]<sup>+</sup>: 316.0085; found: 316.0078.

# 2-(3-Bromophenyl)-6-methyl-3-nitrosoimidazo[1,2-a]pyridine (3q)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 68 mg (72%); green solid; mp 186–187 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.80 (s, 1 H), 9.81 (d, J = 8.0 Hz, 2 H), 8.63 (d, J = 8.0 Hz, 1 H), 7.77–7.69 (m, 3 H), 7.42 (t, J = 8.0 Hz, 1 H), 2.46 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.2, 153.1, 144.5, 138.6, 132.0, 131.9, 131.7, 130.6, 130.5, 127.4, 126.6, 124.7, 116.7, 18.4.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}BrN_{3}O$  [M + H]<sup>+</sup>: 316.0085; found: 316.0081.

#### 6-Chloro-3-nitroso-2-phenylimidazo[1,2-a]pyridine(3r)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 52 mg (68%); green solid; mp 214–216 °C;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 10.00 (s, 1 H), 8.64 (d, *J* = 8.0 Hz, 2 H), 7.78 (s, 2 H), 7.63–7.54 (m, 3 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 2.46 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.8, 153.1, 143.8, 136.6, 131.8, 131.3, 130.8, 128.9, 127.4, 124.4, 117.8.

ESI-HRMS: m/z calcd for  $C_{13}H_9CIN_3O$  [M + H]<sup>+</sup>: 258.0434; found: 258.0436.

# 6-Chloro-2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (3s)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 60 mg (69%); green solid; mp 225–227 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 10.01 (s, 1 H), 8.66 (d, *J* = 8.0 Hz, 2 H), 7.82 (m, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 158.7, 153.1, 143.7, 138.6, 136.8, 131.9, 129.8, 129.3, 127.7, 124.4, 117.8.

ESI-HRMS: m/z calcd for  $C_{13}H_8Cl_2N_3O$  [M + H]<sup>+</sup>: 292.0044; found: 292.0048.

#### 6-Bromo-3-nitroso-2-phenylimidazo[1,2-a]pyridine (3t)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 65 mg (72%); green solid;  $R_f = 0.4$  (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.11 (s, 1 H), 8.67 (d, *J* = 8.0 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.63–7.56 (m, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 159.6, 153.0, 144.0, 138.9, 131.8, 131.3, 130.8, 128.9, 126.4, 118.1, 113.9.

ESI-HRMS: m/z calcd for  $C_{13}H_9BrN_3O$  [M + H]<sup>+</sup>: 301.9929; found: 301.9931.

### 6-Bromo-3-nitroso-2-*m*-tolylimidazo[1,2-a]pyridine (3u)

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 69 mg (73%); green solid; mp 225–226 °C;  $R_f$  = 0.4 (PE–EtOAc, 2:1).

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<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.09 (s, 1 H), 8.46 (s, 2 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.45–7.43 (m, 2 H), 2.49 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 159.8, 153.0, 143.9, 138.9, 138.7, 132.7, 131.2, 131.1, 128.9, 128.1, 126.4, 118.0, 113.8, 21.5.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}BrN_{3}O$  [M + H]<sup>+</sup>: 316.0085; found: 316.0081.

#### 2-(2-Furyl)-3-nitrosoimidazo[1,2-a]pyridine (3v)<sup>41</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 40 mg (63%); green solid; mp 195–197 °C;  $R_f$  = 0.3 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.89 (d, J = 8.0 Hz, 1 H), 7.88–7.84 (m, 4 H), 7.27 (s, 1 H), 6.72 (s, 1 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  = 151.2, 147.2, 146.7, 146.5, 136.4, 126.5, 119.4, 118.9, 117.6, 113.4.

ESI-HRMS: m/z calcd for  $C_{11}H_8N_3O_2[M + H]^+$ : 214.0617; found: 214.0610.

#### 2-(2-Furyl)-7-methyl-3-nitrosoimidazo[1,2-a]pyridine (3w)<sup>25d</sup>

Column chromatography (silica gel, PE–EtOAc, 3:1); yield: 45 mg (66%); green solid; mp 221–222 °C;  $R_f$  = 0.3 (PE–EtOAc, 2:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.77 (s, 1 H), 7.85–7.81 (m, 2 H), 7.58 (s, 1 H), 7.07 (s, 1 H), 6.69 (s, 1 H), 2.54 (s, 3 H).

 $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.4, 149.2, 147.0, 146.7, 130.9, 128.8, 126.0, 121.2, 118.7, 116.5, 113.3, 22.3.

ESI-HRMS: m/z calcd for  $C_{12}H_{10}N_3O_2$  [M + H]<sup>+</sup>: 228.0773; found: 228.0779.

## $\label{eq:constraint} 7-Methyl-2-(4-nitrophenyl)-3-nitrosoimidazo [1,2-a] pyridine~(3x)$

Column chromatography (silica gel, PE–EtOAc, 4:1); yield: 60 mg (77%); green solid; mp 212–213 °C;  $R_f$  = 0.3 (PE–EtOAc, 3:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.77 (d, *J* = 8.0 Hz, 1 H), 8.62 (d, *J* = 8.0 Hz, 2 H), 7.56 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 2.54 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 158.8, 153.1, 149.0, 146.2, 138.1, 131.9, 130.1, 129.0, 126.0, 121.5, 116.5, 22.3.

ESI-HRMS: m/z calcd for  $C_{14}H_{11}N_4O_3$  [M + H]<sup>+</sup>: 283.0831; found: 283.0827.

# 3-Nitroso-2-[4-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyridine (3y)

Column chromatography (silica gel, PE–EtOAc, 4:1); yield: 65 mg (74%); green solid; mp 170–172 °C;  $R_f = 0.3$  (PE–EtOAc, 3:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.90 (d, *J* = 4.0 Hz, 1 H), 8.82 (d, *J* = 8.0 Hz, 2 H), 7.91–7.85 (m, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.84–7.30 (m, 1 H).

 $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.4, 145.4, 136.1, 134.9, 133.0 (q, J = 34.3 Hz), 131.0, 126.4, 126.7 (q, J = 271.2 Hz), 125.6 (q, J = 4.2 Hz), 120.7, 117.7.

ESI-HRMS: m/z calcd for  $C_{14}H_9F_3N_3O$  [M + H]<sup>+</sup>: 292.0698; found: 292.0664.

### 6-Methyl-3-nitroso-2-[4-(trifluoromethyl)phenyl]imidazo[1,2a]pyridine (3z)

Column chromatography (silica gel, PE–EtOAc, 4:1); yield: 78 mg (81%); green solid; mp 205–207 °C;  $R_f$  = 0.4 (PE–EtOAc, 4:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.76 (s, 1 H), 8.76 (d, *J* = 8.0 Hz, 2 H), 7.79–7.68 (m, 4 H), 2.45 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 157.5, 153.2, 144.3, 138.6, 135.0, 132.5 (q, *J* = 32.2 Hz), 131.0, 130.8, 126.7 (q, *J* = 271.2 Hz), 125.5 (q, *J* = 4.2 Hz), 124.5, 122.7, 116.9, 18.3.

ESI-HRMS: m/z calcd for  $C_{15}H_{11}F_3N_3O$  [M + H]<sup>+</sup>: 306.0854; found: 306.0843.

### 8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (5)

Nitroso compound **3j** (94 mg, 0.4 mmol) was added to a solution of  $SnCl_2$ ·H<sub>2</sub>O (5 equiv) in EtOH (2 mL). After the mixture had stirred at 80 °C for 2 h, the suspension was cooled to r.t. The precipitate that formed was filtered, washed extensively with EtOH (10 mL), and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography (silica gel, EtOAc); this provided the desired product **5**.

Yield: 83 mg (93%); mp 209–211 °C;  $R_f = 0.7$  (EtOAc).

<sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 8.51 (s, 1 H), 7.90 (d, J = 8.0 Hz, 2 H), 7.57–7.54 (m, 3 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 5.90 (br, 2 H), 2.58 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ): δ = 136.9, 130.3, 129.2, 128.2, 128.1, 128.0, 127.9, 127.6, 123.8, 122.0, 114.9, 16.5.

ESI-HRMS: m/z calcd for  $C_{14}H_{14}N_3$  [M + H]<sup>+</sup>: 224.1188; found: 224.1185.

# Acknowledgment

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21302110, 21302109 and 21375075), the Taishan Scholar Foundation of Shandong Province, the Natural Science Foundation of Shandong Province (ZR2013BQ017 and ZR2013BM007), the Project of Shandong Province Higher Educational Science and Technology Program (J13LD14), and the Scientific Research Foundation of Qufu Normal University (BSQD 2012021). We thank Pengfei Sun in this group for reproducing the results of **3a** and **3q**.

# **Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560508.

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Heruntergeladen von: Flinders University of South Australia. Urheberrechtlich geschützt.

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