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Palladium-Catalyzed Decarboxylative Acylation of *N*-Nitrosoanilines with α-Oxocarboxylic Acids

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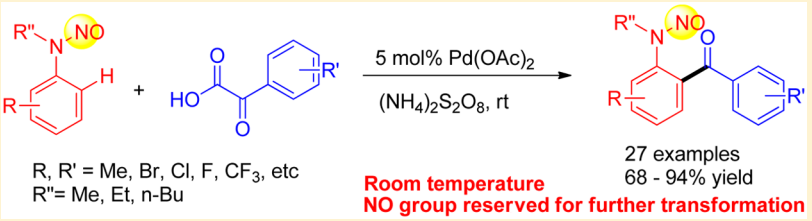
Supporting Information



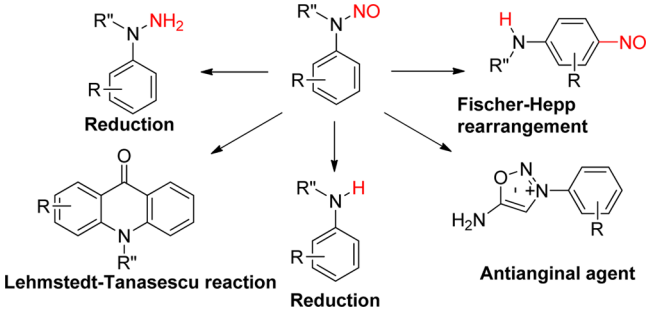
ABSTRACT: A palladium-catalyzed oxidative C−H bond decarboxylative acylation of *N*-nitrosoanilines using α-oxocarboxylic acid as the acyl source is described. The catalyst $Pd(OAc)_2$ and oxidant $(NH_4)_2S_2O_8$ enabled *ortho*-acylation of *N*-nitrosoanilines at room temperature, affording an array of *N*-nitroso-2-aminobenzophenones in moderate to excellent yields.

Aryl ketones are important structural motifs and resourceful intermediates for preparing natural products and biologically active compounds.[1] The traditional method for accessing aryl ketone is the Friedel−Crafts acylation of arenes in the presence of $AlCl_3$, which usually give poor regioselectivity when using substituted arenes,[2] or the oxidation of secondary alcohol by oxidant, which is limited to specific structures.[3] With the growing demand for aryl ketones in the synthesis of fine chemicals and pharmaceutical intermediates,[4] developing an efficient synthetic method with easily available acylating reagents under mild reaction conditions becomes more desirable.[5]

Transition-metal-catalyzed decarboxylative cross-coupling reactions have emerged as a promising tool for diaryl ketones in recent years. Goossen et al. first reported the Pd-catalyzed decarboxylative acylation for the formation of unsymmetric diaryl ketone with α-oxocarboxylic carboxylate salts as acyl anion equivalents.[6] Ge and co-workers disclosed that the *ortho*-acylation of acetanilides could be done by employing α-oxocarboxylic acid via a Pd-catalyzed decarboxylative acylation pathway.[7] After these pioneering works, a variety of directing groups, such as azos,[8] oximes,[9] acetamides,[10] and indoles,[11] etc., have been involved in the C−H bonds acylation with α-oxocarboxylic acids. In these reactions, aryl ketones with high selectivities and tolerance of functional groups were obtained. Despite these achievements, the decarboxylative cross-coupling reactions were still relatively unexplored. Many efficient and useful directing groups have not been involved in the decarboxylative acylation yet.

The *N*-nitroso group has been proven to be an efficient directing group for assisting C−H bond activation,[12] which is also an important moiety that can be transformed to a diversity of synthetically useful intermediates, such as amine, hydrazine, α-carbanion intermediates, diazonium salts, and *C*-nitroso compounds (Scheme 1).[13] Recently, we reported a palladium-catalyzed acylation of *N*-nitrosoanilines with toluene as acylation reagent, in which the nitroso group acted as a traceless directing group and provided a variety of *N*-alkyl-2-aminobenzophenones in good yields.[14] Considering the importance of *N*-nitroso group in organic synthesis, it is necessary to develop a mild method to keep *N*-nitroso group reserved during the C−H bonds activation for further transformation. In continuing our former works on palladium-catalyzed C−H activation,[15−17] herein we reported a palladium catalyzed decarboxylative *ortho*-acylation of *N*-nitrosoanilines with α-oxocarboxylic acids, providing the *N*-nitroso-2-aminobenzophenones in high yields at room temperature (Scheme 2).

Scheme 1. Transformation of the Nitroso Group



We began to investigate the practicability of using α-oxocarboxylic acid as the acyl source in the coupling of *N*-nitrosoanilines (Table 1). *N*-Methyl-*N*-nitrosoaniline and phenylglyoxylic acid were used as the prototypical substrates in the model reaction. As we expected, the desired product **3ab**

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Scheme 2. Palladium-Catalyzed Acylation of *N*-Nitrosoanilines

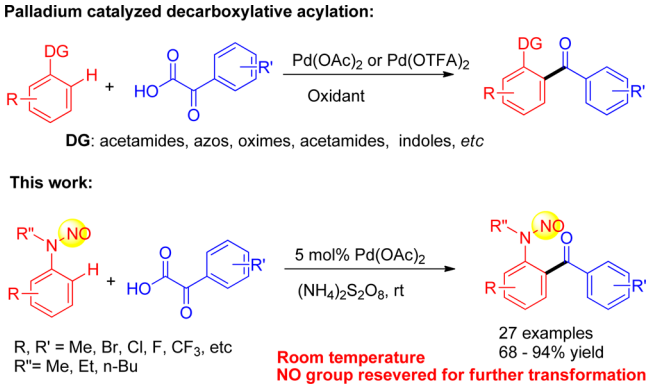
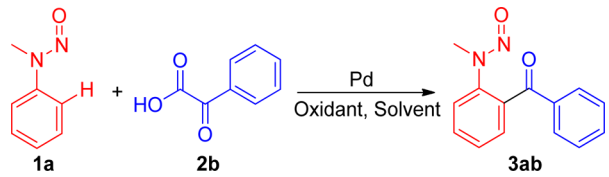


Table 1. Initial Optimization of Reaction Conditions[a]



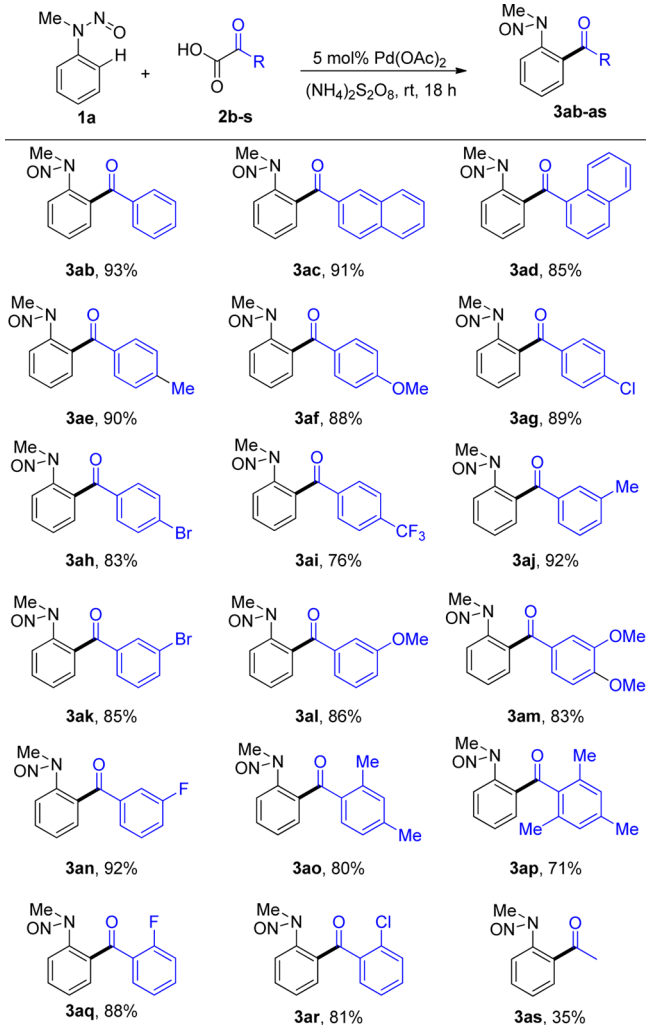
entry	metal	oxidant (equiv)	*T* (°C)	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$ (4)	80	DCE	73
2	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	80	DCE	81
3	$Pd(OAc)_2$	Ag_2CO_3 (4)	80	DCE	13
4	$Pd(OAc)_2$	BQ (4)	80	DCE	trace
5	$Pd(OAc)_2$	$Cu(OAc)_2$ (4)	80	DCE	trace
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	80	diglyme	90
7	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	80	dioxane	65
8	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	80	THF	84
9	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	80	DMF	79
10	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	120	diglyme	88
11	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (4)	rt	diglyme	96
12	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$ (2)	rt	diglyme	97 (93)[c]
13	$Pd(TFA)_2$	$(NH_4)_2S_2O_8$ (2)	rt	diglyme	83
14	$PdCl_2$	$(NH_4)_2S_2O_8$ (2)	rt	diglyme	56
15	$Pd(MeCN)_2Cl_2$	$(NH_4)_2S_2O_8$ (2)	rt	diglyme	79
16	$Pd(OAc)_2$[d]	$(NH_4)_2S_2O_8$ (2)	rt	diglyme	92

[a]Reaction conditions: *N*-methyl-*N*-nitrosoaniline **1a** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), phenylglyoxylic acid **2b** (2 mmol), and solvent (4 mL) were stirred for 18 h under air. [b]GC yields were reported. [c]Isolated yield in the parentheses. [d]2 mol % of $Pd(OAc)_2$ was used, 48 h.

was obtained in 73% yield in the presence of oxidant $K_2S_2O_8$ (Table 1, entry 1). A screening of oxidants showed that $(NH_4)_2S_2O_8$ gave the best results while Ag_2CO_3, BQ (1,4-benzoquinone), and $Cu(OAc)_2$ were found to be inferior (entries 1–5). Commonly used organic solvents were screened. Diglyme gave a higher yield, while other solvents such as DCE, DMF, dioxane, and THF afforded lower yields (entries 6–9). Lowering the reaction temperature to room temperature gave the desired product in 96% yield, while raising the temperature to 120 °C only gave 76% yield (entry 10 and 11). These results were possibly due to the minimization of reagent decomposition. Decreasing the stoichiometry of oxidant has no negative effect on the yields (entry 11 and 12). Further studies showed that the catalyst $Pd(OAc)_2$ gave better results than $Pd(TFA)_2$, $PdCl_2$, and $Pd(MeCN)_2Cl_2$ (entries 12–15). We also tested the influence of catalyst loading and found that the reaction proceeded smoothly at room temperature in the presence of 2 mol % $Pd(OAc)_2$ with an extended reaction time (entry 16).

With our optimized reaction conditions in hand, we next began to explore its versatility in the decarboxylative acylation utilizing differently substituted α-oxocarboxylic acids (Table 2). 1-Naphthalenyl and 2-naphthalenyl oxocarboxylic acid gave good product yields (**3ac,ad**). Electron-donating *p*- or *m*-methoxyphenylglyoxylic acid gave slightly a lower yield of the

Table 2. Palladium-Catalyzed Acylation of *N*-Methyl-*N*-nitrosoaniline with Substituted α-Oxocarboxylic Acids[a]



[a]Reaction conditions: *N*-methyl-*N*-nitrosoaniline **1a** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), substituted glyoxylic acid **2b–s** (2 mmol), $(NH_4)_2S_2O_8$ (2 mmol), and diglyme (4 mL) were stirred for 18 h under air. Isolated yields are reported. Reaction times were not optimized for every substrate.

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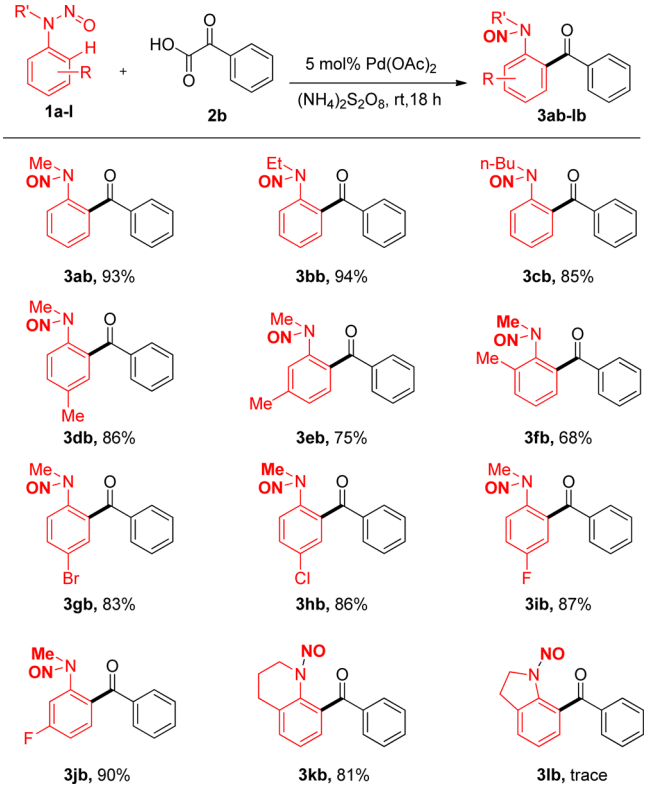
product (**3af**,**al**,**am**). The reaction showed good tolerance toward the halogen groups. Fluoro/chloro/bromo-substituted phenylglyoxylic acids were good coupling partners and gave the desired products in high yields (**3ag**,**ah**,**ak**,**an**,**aq**,**ar**). Worthy of mention was that the bromo group remained intact during the reaction (**3ah**,**ak**), which may offer potentially structural transformation via traditional metal-catalyzed cross-coupling reactions.[18] *Ortho*-subsituted substrates were also found to be favored (**3ao**−**ar**), although the yield was lower compared with others. The electron-withdrawing group trifluomethyl-substituted phenylglyoxylic acid gave the desired products in good yields (**3ai**). Furthurmore, we employed various aliphatic α-oxocarboxylic acids in the reaction, but only the 2-oxopropanoic acid could be involved in the reaction and afforded the desired product in low yield (**3as**).

Various substituted *N*-nitrosoanilines (**1a**−**k**) were also examined, and the results are compiled in Table 3. Different

Table 3. Pd-Catalyzed *Ortho*-Acylation of Substituted *N*-Alkyl-*N*-nitrosoanilines[a]



[a]Reaction conditions: substituted *N*-nitrosoaniline **1a**−**l** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), phenylglyoxylic acid **2b** (2 mmol), $(NH_4)_2S_2O_8$ (2 mmol), and diglyme (4 mL) were stirred for 18 h under air. Isolated yields were reported. Reaction times were not optimized for each substrate.

alkyl-substituted *N*-nitrosoanilines reacted well with the phenylglyoxylic acid under the optimal conditions (**3ab**−**cb**). A variety of functional groups, including F, Br, and Cl, were tolerated under these reaction conditions, and no significant electronic effect was found (**3gb**−**jb**). We tested *N*-nitrosoanilines with the methyl group substituted at different positions and proved that the steric hindrance would affect the yields greatly. For the *meta*-substituted substrates, the acylation only happened on the position with less steric hindrance. To our surprise, the *o*-methyl-*N*-nitrosoaniline was compatible in this catalyst system and gave moderate yield, which is not common in the decarboxylative acylation.[7−11] We also tried to apply this system in the acylation of *N*-nitroso-1,2,3, 4-tetrahydroquinoline and *N*-nitrosoindoline. The results showed that the *N*-nitroso-1,2,3,4-tetrahydroquinoline allowed the acylation and gave the corresponding benzophenone in high yield (**3kb**), while the 1-nitrosoindoline could not be involved in the reaction (**3lb**).

The acylation of *N*-methyl-*N*-nitroso-4-chloroaniline **3h** was performed in gram scale, giving the desired product **3hb** with 82% yield (Scheme 3). Furthermore, we conducted some transformations of the compound **3hb** to access some biologically active compounds. For example, the nitroso group of **3hb** could be removed to give the *N*-methyl-4-chloro-2-aminobenzophenones, which could lead to the top-selling drug diazepam **4** via sequential cyclization with ethyl glycinate.[19] Besides that, both the indoline **5** and indole **6** could be synthesized from the compound **3hb** via simple procedures.[20]

Although a reaction mechanism is not clear at this stage, we suggest that this transformation began with the *ortho*-palladation of *N*-nitrosoaniline **1a** with $Pd(OAc)_2$ to provide the 5-membered palladacycle,[7,12] which can be subsequently reacted with α-oxocarboxylic acids to afford cyclopalladated complex (Scheme 4). Decarboxylation of the cyclopalladated complex followed by reductive elimination provides our desired product **3ab**. Finally, the regenerated Pd(0) catalyst can be reoxidized to the active Pd(II) catalyst in the presence of $(NH_4)_2S_2O_8$.

In summary, we have succeeded in showing that α-oxocarboxylic acids could act as the acyl sources in the oxidative coupling of *N*-nitrosoanilines at room temperature. A wide range of *N*-nitroso-2-aminobenzophenones were obtained in moderate to high yield. Fluoro, bromo, chloro, methoxy, trifluoromethyl groups were compatible in this catalytic system. We believe this strategy for accessing *N*-nitroso-2-aminobenzophenones will be useful in the synthesis of various biologically active compounds and natural products.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. Thin-layer chromatography was performed on precoated silica gel 60 F_{254} plates. Silica gel (230−400 mesh) was used for column chromatography. ^1H NMR spectra were recorded on a 400 MHz spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm) or with TMS (δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer and the spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak). Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on an IT-TOF mass spectrometer.

General Experimental Procedures and Characterizations. *Palladium-Catalyzed Acylation of N-Nitrosoanilides.* Substituted *N*-nitrosoanilide (1.0 mmol) and the $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) were loaded into a seal tube equipped with a Teflon-coated magnetic stir bar. Diglyme (4.0 mL) was added into the tube. The solution was stirred for about 1−2 min until the solid was dissolved. Substituted phenylglyoxylic acid (2.0 mmol) and $(NH_4)_2S_2O_8$ (2.0 mmol) were loaded into the tube. The tube was stirred at room temperature for 18 h. After completion of the reaction as judged by TLC, the reaction was quenched with saturated K_2CO_3 and diluted with EtOAc. The organic layer was separated, washed with brine, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The crude products

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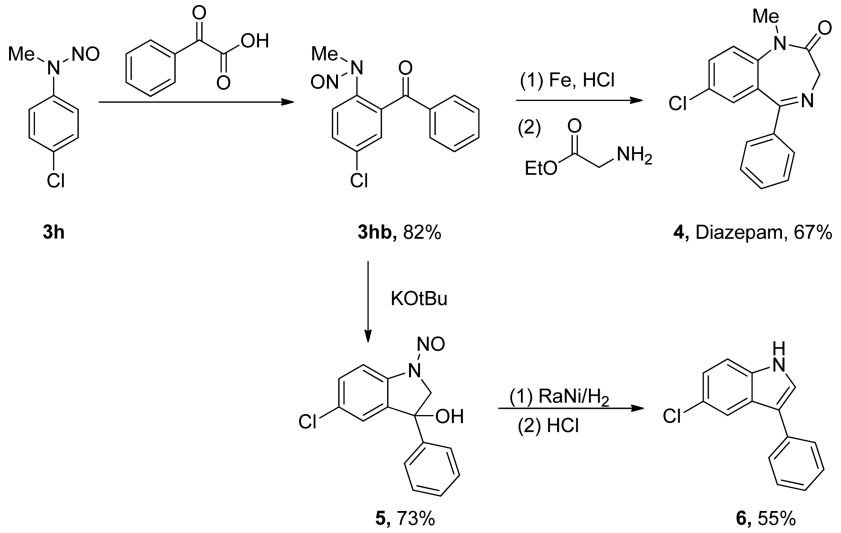
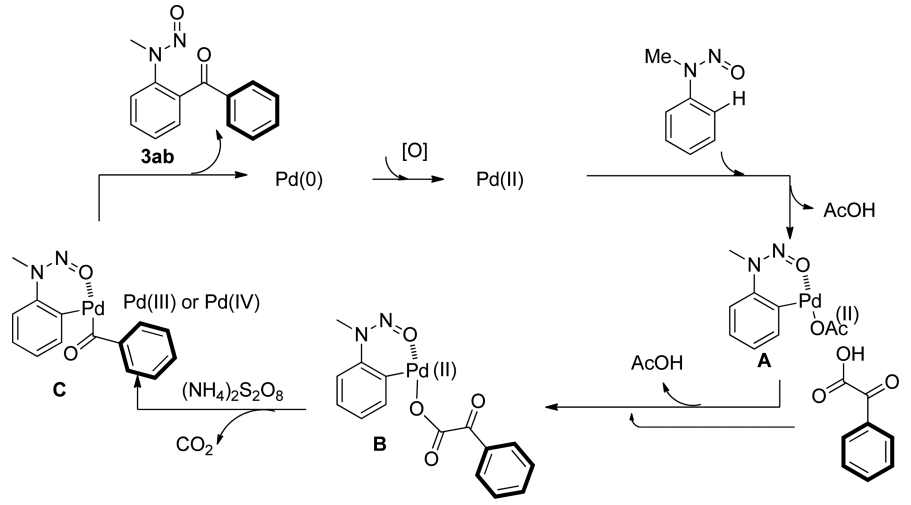
Scheme 3. Synthetic Transformation of *N*-Methyl-*N*-nitroso-2-aminobenzophenones



Scheme 4. Proposed Reaction Mechanism



were purified by flash column chromatography (EtOAc/petroleum ether 1:5) on silica gel (230−400 mesh) to afford the desired product.

*N-(2-Benzoylphenyl)-N-methylnitrous amide (Table 2, product **3ab**):* yellow oil, 93% (223 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.0 Hz, 2H), 7.68−7.64 (m, 1H), 7.62 (d, J = 6.1 Hz, 1H), 7.53 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.41−7.35 (m, 2H), 3.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 140.7, 136.9, 134.3, 133.4, 131.6, 130.2, 129.6, 128.5, 128.5, 128.1, 123.2, 34.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{12}N_2O_2Na$ 263.0791, found 263.0783.

*N-(2-(2-Naphthoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ac**):* yellow oil, 91% (264 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 7.4 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.77−7.69 (m, 2H), 7.63−7.60 (m, 1H), 7.57 (dd, J = 8.0, 4.9 Hz, 3H), 7.44 (d, J = 8.0 Hz, 1H), 7.42−7.37 (m, 1H), 3.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 140.7, 135.7, 134.4, 134.2, 132.3, 131.9, 131.6, 130.3, 129.5, 128.7, 128.6, 128.1, 127.8, 126.9, 124.7, 123.3, 34.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{14}N_2O_2Na$ 313.0947, found 313.0940.

*N-(2-(1-Naphthoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ad**):* yellow oil, 85% (247 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.76−7.69 (m, 2H), 7.62−7.58 (m, 1H), 7.54 (d, J = 6.8 Hz, 3H), 7.42 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 3.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 141.1, 138.7, 135.2, 133.5, 132.0, 131.1, 130.3, 128.4, 128.2, 128.1, 126.7, 125.8, 123.9, 123.8, 116.8, 99.9, 34.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{14}N_2O_2Na$ 313.0947, found 313.0939.

*N-Methyl-N-(2-(4-methylbenzoyl)phenyl)nitrous amide (Table 2, product **3ae**):* yellow oil, 90% (229 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (m, 1H), 7.63−7.57 (m, 3H), 7.52 (t, J = 7.5 Hz, 1H), 7.45−7.41 (m, 1H), 7.19 (d, J = 7.9 Hz, 2H), 3.24 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 144.4, 140.6, 134.5, 134.3, 131.4, 130.1, 129.8, 129.2, 128.0, 123.4, 34.6, 21.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0936.

*N-(2-(4-Methoxybenzoyl)phenyl)-N-methylnitrous amide (Table 2, **product 3af**):* yellow oil, 88% (238 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.9 Hz, 2H), 7.67−7.61 (m, 1H), 7.60−7.56 (m, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 163.9, 140.5, 134.8, 132.1, 131.2, 129.9, 129.6, 128.1, 123.6, 113.8, 55.5, 34.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_3Na$ 293.0897, found 293.0889.

*N-(2-(4-Chlorobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ag**):* yellow oil, 89% (245 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.61−7.58 (m, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 3.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 140.5, 139.9, 135.3, 133.7, 131.8, 130.9, 130.1, 128.9, 128.0, 122.9, 34.3;

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HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2ClNa$ 297.0401, found 297.0392.

*N-(2-(4-Bromobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ah**):* yellow oil, 83% (265 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 1H), 7.62−7.54 (m, 5H), 7.53 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 3.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 140.5, 135.7, 133.7, 131.9, 131.7, 131.0, 130.1, 128.6, 128.0, 122.9, 34.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2BrNa$ 340.9896, found 340.9884.

*N-Methyl-N-(2-(4-(trifluoromethyl)benzoyl)phenyl)nitrous amide (Table 2, product **3ai**):* yellow oil, 78% (240 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.74−7.68 (m, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.55 (td, J = 7.5, 1.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 140.6, 139.9, 134.3, 133.3, 132.0, 130.1, 129.7, 128.0, 125.5 (d, J = 3.7 Hz). 122.6, 119.2, 33.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{11}N_2O_2F_3Na$ 331.0665, found 331.0663.

*N-Methyl-N-(2-(3-methylbenzoyl)phenyl)nitrous amide (Table 2, product **3aj**):* yellow oil, 92% (234 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 14.5, 7.7 Hz, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 3.24 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 140.7, 138.4, 136.8, 134.4, 134.3, 131.5, 130.2, 130.0, 128.3, 128.0, 127.0, 123.3, 34.6, 21.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0940.

*N-(2-(3-Bromobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ak**):* yellow oil, 85% (270 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.71 (dd, J = 7.7, 1.4 Hz, 1H), 7.68−7.66 (m, 1H), 7.64 (d, J = 1.0 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.57−7.52 (m, 1H), 7.45−7.42 (m, 1H), 7.31−7.25 (m, 1H), 3.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 140.6, 138.8, 136.1, 133.4, 132.2, 131.9, 130.2, 130.1, 128.1, 128.0, 122.8, 122.7, 34.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2BrNa$ 340.9896, found 340.9886.

*N-(2-(3-Methoxybenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3al**):* yellow oil, 86% (232 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.63 (m, 1H), 7.61 (d, J = 6.1 Hz, 1H), 7.52 (t, J = 7.0 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.32−7.29 (m, 1H), 7.28−7.23 (m, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.07 (dd, J = 8.1, 1.6 Hz, 1H), 3.80 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 159.7, 140.6, 138.2, 134.3, 131.5, 130.2, 129.4, 128.0, 123.2, 122.5, 120.0, 113.5, 55.5, 34.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_3Na$ 293.0897, found 293.0892.

*N-(2-(3,4-Dimethoxybenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3am**):* yellow oil, 83% (249 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 1H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.58−7.53 (m, 1H), 7.50−7.42 (m, 2H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.93 (d, J = 7.3 Hz, 6H), 3.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 153.8, 149.2, 140.5, 134.7, 131.2, 129.9, 129.7, 128.0, 125.5, 123.7, 111.2, 109.9, 56.1, 56.0, 34.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{16}N_2O_4Na$ 323.1002, found 323.0993.

*N-(2-(3-Fluorobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3an**):* yellow oil, 80% (215 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.9, 5.4 Hz, 2H), 7.70−7.65 (m, 1H), 7.59 (dd, J = 7.7, 1.7 Hz, 1H), 7.54 (dd, J = 7.4, 1.1 Hz, 1H), 7.43 (dd, J = 8.0, 1.1 Hz, 1H), 7.07 (dd, J = 8.9, 8.3 Hz, 2H), 3.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 167.1, 164.5, 140.5, 134.0, 133.3 (d, J = 3.0 Hz), 132.2, 132.1, 131.6, 130.0, 128.0, 123.1, 115.7 (d, J = 22.1 Hz). 34.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2FNa$ 281.0697, found 281.0684.

*N-(2-(2,4-Dimethylbenzoyl)phenyl)-N-methylnitrous amide (Table 2, **product 3ao**):* yellow oil, 80% (215 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (t, J = 7.4 Hz, 2H), 7.53−7.49 (m, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.05 (s, 1H), 6.88 (d, J = 9.5 Hz, 1H), 3.15 (s, 3H), 2.47 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 142.5, 140.7, 139.9, 136.0, 134.4, 132.8, 131.7, 130.7, 130.5, 128.2, 125.7, 123.3, 34.5, 21.4, 20.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{16}N_2O_2Na$ 291.1104, found 291.1101.

*N-Methyl-N-(2-(2,4,6-trimethylbenzoyl)phenyl)nitrous amide (Table 2, product **3ap**):* yellow oil, 71% (200 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.60 (m, 2H), 7.50 (td, J = 7.6, 1.3 Hz, 1H), 7.40 (dd, J = 7.8, 1.2 Hz, 1H), 6.85 (s, 2H), 3.32 (s, 3H), 2.30 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 141.2, 139.5, 136.3, 135.6, 135.4, 133.3, 132.1, 129.4, 128.9, 127.0, 35.6, 21.1, 20.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}N_2O_2Na$ 305.1260, found 305.1249.

*N-(2-(2-Fluorobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3aq**):* yellow oil, 88% (227 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.75−7.70 (m, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.55 (td, J = 7.5, 1.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 167.1, 164.6, 140.5, 134.0, 132.3 (d, J = 9.5 Hz), 132.2, 131.6, 130.0, 128.0, 123.1, 115.8, 115.6, 34.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2FNa$ 281.0697, found 281.0686.

*N-(2-(2-Chlorobenzoyl)phenyl)-N-methylnitrous amide (Table 2, product **3ar**):* yellow oil, 81% (223 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.68 (m, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 3H), 7.34−7.30 (m, 1H), 3.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 141.9, 141.0, 137.4, 134.4, 132.8, 132.4, 131.3, 131.3, 130.5, 128.6, 126.8, 124.1, 34.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2ClNa$ 297.0401, found 297.0394.

*N-(2-Acetylphenyl)-N-methylnitrous amide (Table 2, product **3as**):* yellow oil, 35% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.7, 1.6 Hz, 1H), 7.67−7.62 (m, 1H), 7.53 (td, J = 7.6, 1.2 Hz, 1H), 7.38 (dd, J = 7.9, 1.0 Hz, 1H), 3.45 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 139.8, 135.5, 132.2, 129.2, 128.6, 124.5, 34.9, 29.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_9H_{10}N_2O_2Na$ 201.0634, found 201.0638.

*N-(2-Benzoylphenyl)-N-ethylnitrous amide (Table 2, product **3bb**):* yellow oil, 94% (239 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.4, 1.3 Hz, 2H), 7.71−7.66 (m, 1H), 7.61 (dd, J = 7.6, 1.6 Hz, 1H), 7.57−7.51 (m, 2H), 7.47 (m, 1H), 7.41 (t, J = 7.7 Hz, 2H), 3.87 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 139.6, 136.9, 134.9, 133.3, 131.3, 130.1, 129.8, 128.4, 127.9, 123.4, 41.7, 11.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0950.

*N-(2-Benzoylphenyl)-N-butylnitrous amide (Table 2, product **3cb**):* yellow oil, 85% (240 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.4, 1.3 Hz, 2H), 7.65 (ddd, J = 8.0, 7.3, 1.7 Hz, 1H), 7.58−7.55 (m, 1H), 7.52 (dd, J = 7.4, 1.2 Hz, 2H), 7.45 (dd, J = 3.3, 0.7 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 3.82−3.73 (m, 2H), 1.51−1.43 (m, 2H), 1.26 (dd, J = 15.1, 7.5 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 139.9, 136.9, 134.7, 133.4, 131.3, 130.1, 129.8, 128.4, 127.8, 123.3, 46.3, 28.3, 20.4, 13.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}N_2O_2Na$ 305.1260, found 305.1252.

*N-(2-Benzoyl-4-methylphenyl)-N-methylnitrous amide (Table 2, product **3db**):* yellow oil, 86% (219 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.44−7.36 (m, 3H), 7.31 (d, J = 8.1 Hz, 1H), 3.21 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 138.4, 137.0, 133.7, 133.3, 132.2, 130.6, 130.2, 129.6, 128.5, 123.3, 34.7, 21.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0944.

*N-(2-Benzoyl-5-methylphenyl)-N-methylnitrous amide (Table 2, product **3eb**):* yellow oil, 75% (191 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.1 Hz, 2H), 7.54−7.50 (m, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.36−7.32 (m, 1H), 7.24 (s, 1H), 3.22 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 142.5, 140.8, 133.7, 133.2, 130.4, 130.1, 129.6, 129.2, 128.7, 128.4, 124.0, 34.7, 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0944.

*N-(2-Benzoyl-6-methylphenyl)-N-methylnitrous amide (Table 2, product **3fb**):* yellow oil, 68% (173 mg); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, J = 7.2 Hz, 2H), 7.56−7.51 (m, 2H), 7.49−7.44 (m, 1H), 7.44−7.42 (m, 1H), 7.41−7.38 (m, 2H), 3.25 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 139.5, 137.9, 136.9, 136.1, 133.6, 133.5, 130.1, 128.8, 128.4, 127.3, 36.4, 17.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0947, found 277.0939.

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*N-(2-Benzoyl-4-bromophenyl)-N-methylnitrous amide (Table 2, product **3gb**):* yellow oil, 83% (265 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.5, 2.3 Hz, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.70 (m, 2H), 7.58−7.53 (m, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 8.5 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 139.6, 136.3, 135.7, 134.4, 133.7, 132.9, 129.6, 128.6, 124.5, 121.7, 34.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2BrNa$ 340.9896, found 340.9885.

*N-(2-Benzoyl-4-chlorophenyl)-N-methylnitrous amide (Table 2, product **3hb**):* yellow oil, 86% (236 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.68 (m, 2H), 7.65−7.61 (m, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.58−7.54 (m, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 139.1, 136.3, 135.5, 134.0, 133.7, 131.5, 130.0, 129.6, 128.6, 124.4, 34.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2ClNa$ 297.0401, found 297.0393.

*N-(2-Benzoyl-4-fluorophenyl)-N-methylnitrous amide (Table 2, product **3ib**):* yellow oil, 87% (225 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.4, 1.3 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 2.1 Hz, 1H), 7.43−7.41 (m, 1H), 7.41−7.39 (m, 1H), 7.40−7.36 (m, 1H), 7.33 (dd, J = 8.3, 2.7 Hz, 1H), 3.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 160.3, 136.3 (d, J = 18.1 Hz), 133.8, 129.6, 128.6, 125.6 (d, J = 8.7 Hz), 118.6, 118.3, 117.2, 117.0, 34.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2FNa$ 281.0697, found 281.0689.

*N-(2-Benzoyl-5-fluorophenyl)-N-methylnitrous amide (Table 2, product **3jb**):* yellow oil, 90% (232 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 2H), 7.65 (dd, J = 8.6, 6.1 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.24 (td, J = 8.2, 2.3 Hz, 1H), 7.17 (dd, J = 9.1, 2.3 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 165.2, 162.6, 136.9, 133.5, 132.4 (d, J = 9.6 Hz), 130.1 (d, J = 3.5 Hz,), 129.5, 128.6, 115.0, 114.8, 110.6, 110.3, 34.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{11}N_2O_2FNa$ 281.0697, found 281.0689.

*(1-Nitroso-1,2,3,4-tetrahydroquinolin-8-yl) (phenyl)methanone (Table 2, product **3kb**):* yellow oil, 81% (216 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.66 (m, 2H), 7.48 (dd, J = 10.4, 4.4 Hz, 1H), 7.44−7.37 (m, 3H), 7.36 (d, J = 3.1 Hz, 1H), 7.36−7.32 (m, 1H), 3.72 (t, J = 6.5 Hz, 2H), 2.91−2.80 (m, 2H), 2.11−2.00 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 139.9, 136.9, 134.7, 133.4, 131.3, 130.1, 129.8, 128.4, 127.8, 123.3, 46.3, 28.3, 20.4, 13.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_2Na$ 289.0947, found 289.0942.

*Typical Experimental Procedure for the Synthesis of Compound **4**.* A mixture of Fe powder (4 mmol), NH_4Cl (3 mmol), and compound **3hb** (1 mmol) were weighted in a flask. Ethanol (8 mL) was added, and the mixture was stirred at 80 °C for 6 h. After compound **3hb** disappeared in the TLC, glycine ethyl ester hydrochloride (1.2 mmol) and AcOH (2 mmol) were added. The mixture was then refluxed for 3 h. After removal of the solvent, the residue was diluted with NH_4OH (to reach pH = 8). CH_2Cl_2 was added to extract the crude product. The crude product was crystallized from ether/hexane (1:1) to obtain pure compound **4**.

*7-Chloro-1-methyl-5-phenyl-1H-benzo[e][1,4]diazepin-2(3H)-one (Scheme 3, compound **4**):* white soild, 67% (190 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 1.7 Hz, 2H), 7.51 (dd, J = 8.8, 2.5 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.41 (dd, J = 8.2, 6.5 Hz, 2H), 7.30 (d, J = 6.2 Hz, 1H), 7.29 (s, 1H), 4.83 (d, J = 10.8 Hz, 1H), 3.77 (d, J = 10.8 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.0, 142.6, 138.2, 131.5, 130.7, 130.1, 130.0, 129.5, 129.3, 128.4, 122.5, 57.0, 34.9.

*Typical Experimental Procedure for the Synthesis of Compound **5**.* Potassium *tert*-butoxide (1.1 mmol) was added to the solution of compound **3hb** (1 mmol) in 40 mL of tetrahydrofuran. The mixture was stirred at −10 °C for 30 min. After that, 20 mL of glacial acetic acid was added, and the reaction mixture was then partitioned betweed ether and water. The organic phase was separated, dried over sodium sulfate, and evaporated. The residue was crystallized from ether/hexane (1:1) to give the compound **5** (73%) as a white solid.

*5-Chloro-1-nitroso-3-phenylindolin-3-ol (Scheme 3, compound **5**):* white soild, 73% (201 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 8.6 Hz, 1H), 7.58 (dd, J = 8.5, 2.1 Hz, 1H), 7.42−7.31 (m, 5H), 7.15 (d, J = 2.1 Hz, 1H), 6.69 (s, 1H), 4.34 (d, J = 14.7 Hz, 1H), 4.23 (d, J = 14.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.3, 140.7, 139.4, 131.4, 130.6, 128.8, 128.0, 126.0, 125.8, 113.7, 77.5, 63.4.

*Typical Experimental Procedure for the Synthesis of Compound **6**.* Raney nickel (0.2 mmol) was added to the solution of compound **3hb** (1 mmol) in 10 mL of tetrahydrofuran. The system was stirred at room temperature for 1 h until uptake of hydrogen had stopped. After the catalyst by filtration was removed, the filtrate was evaporated under reduced pressure and redissolved in 5 mL of methanol. Two drops of concentrated hydrochloric acid was added. The mixture was then stirred at 100° h for 5 min. Water was added to the mixture, and the final product compound **6** was precipitated as a white solid (55%).

*5-Chloro-3-phenyl-1H-indole (Scheme 3, compound **6**):* white soild, 55% (125 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.66−7.60 (m, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.39 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.20 (dd, J = 8.6, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 134.8, 128.9, 127.7, 127.5, 126.9, 126.3, 123.0, 122.8, 119.3, 118.3, 112.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02535.

^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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