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Palladium-catalyzed decarboxylative *ortho*-acylation of *N*-nitrosoanilines with α-oxocarboxylic acids

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ABSTRACT

A palladium-catalyzed efficient C–H acylation reaction of *N*-nitrosoanilines with α-oxocarboxylic acids has been developed. The reaction proceeded smoothly with potassium persulfate as the oxidant to afford acylated *N*-nitrosoanilines in moderate to good yields with a broad substrate scope and good regioselectivity.

Introduction

In recent decades, transition-metal-catalyzed direct C–H bond functionalization has been successful as a valuable tool for the modular and facile synthesis of structurally similar, yet diversified organic molecules.[1] Among them, transition-metal-catalyzed decarboxylative cross-coupling reactions involving the use of readily available α,β-unsaturated and aryl carboxylic acids as potential coupling partners, in place of aryl halides or organometallic reagents, has attracted much attention. In general, directing groups are necessary to facilitate the *ortho* C–H bond activation in the presence of transition metals (e.g., Pd, Ir, Rh, Ru, Cu, Fe, etc.) and lead to a versatile C–H bond functionalization upon trapping with appropriate electrophiles or nucleophiles under basic or oxidative conditions respectively.[2] *N*-Nitroso compounds can coordinate with transition metal catalysts, because the nitroso group possesses a lone pair of electrons.[3] This character makes it possible as a directing group to realize the C–H bond activation in the transition-metal-catalyzed reactions.

N-Nitrosoanilines are a class of very useful medicinal compounds and synthetic materials for the preparation of various nitrogen-containing compounds.[4] They are also important precursors to synthesize other organic compounds such as hydrazines[5] and sydnones.[6] Recently, C–H activation reactions of *N*-nitrosoanilines have attracted interest of organic chemists. The Zhu and Li groups reported the Rh-catalyzed *ortho*-olefination[7] and *ortho*-alkynylation,[8] respectively. The Zhu[9] and Huang[10] groups independently described the Rh-catalyzed cyclization of *N*-nitrosoanilines with alkynes for the synthesis of indoles. The Sun group[11] and we[12] disclosed the $Pd(OAc)_2$-catalyzed *N*-nitroso-directed *ortho*-alkoxylation and *ortho*-acyloxylation of arenes, respectively. More recently, the Sun group also reported the Rh-catalyzed cyanation of *N*-nitrosoanilines.[13] Kwong, Luo and co-workers[14] reported the palladium-catalyzed reaction of *N*-nitrosoanilines with toluene derivatives, and *N*-alkyl-2-aminobenzophenones were unexpectedly obtained. However, the palladium-catalyzed decarboxylative acylation of *N*-nitrosoanilines has been unknown until now. In recent years, our group has investigated the palladium-catalyzed sp^2 C–H activation reactions,[12,15], and have successfully realized the *ortho*-acylation with oxime and azo as the directing groups.[15i,j] In continuation of our interest in sp^2 C–H bond activation, herein we report a palladium-catalyzed *ortho*-acylation of *N*-nitrosoanilines using nitroso as the directing group with α-oxocarboxylic acids.[16]

Results and discussion

In our initial investigation, we chose the reaction of *N*-nitrosoaniline **1a** with α-oxocarboxylic acid **2a** as the model reaction. Firstly, 1,4-dioxane was chosen as the solvent. To our delight, product **3a** was isolated in 53% yield in the presence of $K_2S_2O_8$ and $Pd(OAc)_2$ (Table 1, entry 1). Different oxidants, such as $Na_2S_2O_8$, 1,4-benzoquinone (BQ), and $PhI(OAc)_2$, were explored.

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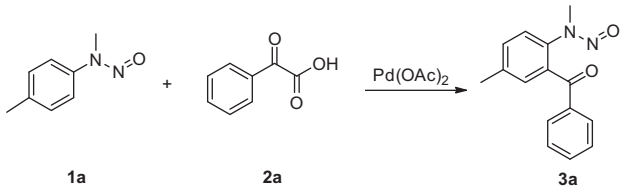
Table 1
Optimization of the reaction conditions[a]



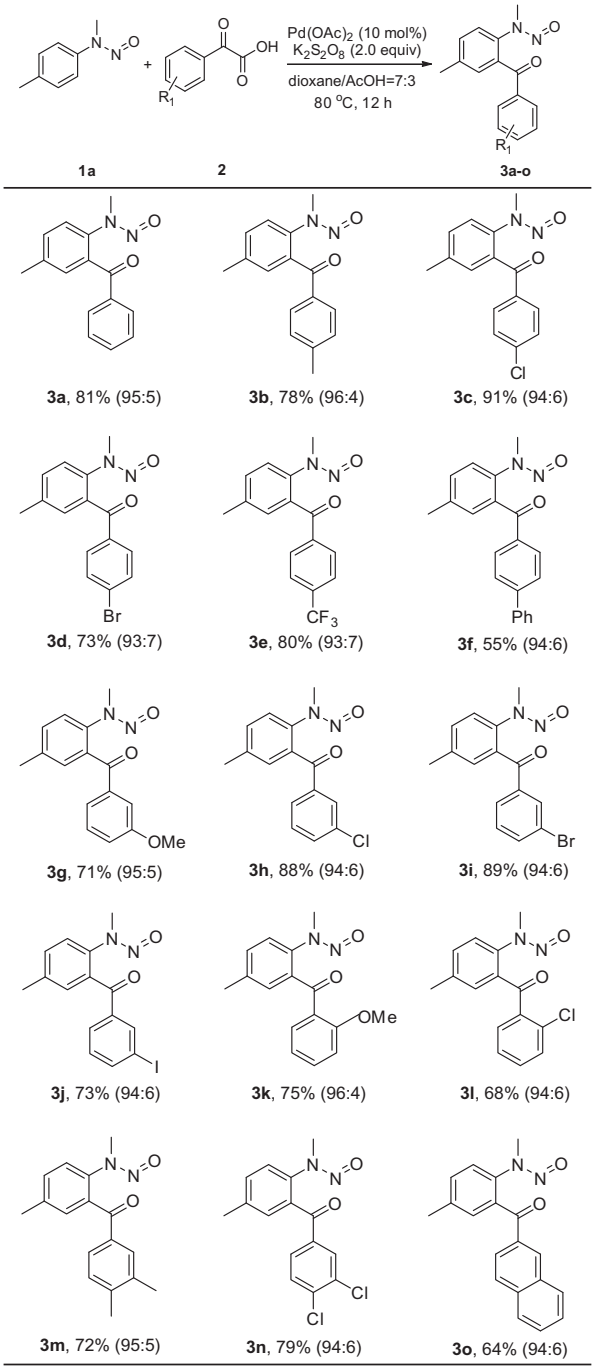
Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	$K_2S_2O_8$		1,4-Dioxane	53
2	$Na_2S_2O_8$		1,4-Dioxane	45
3	$PhI(OAc)_2$		1,4-Dioxane	Trace
4	BQ		1,4-Dioxane	Trace
5	$K_2S_2O_8$		$ClCH_2CH_2Cl$	39
6	$K_2S_2O_8$		CH_3CN	35
7	$K_2S_2O_8$		DMF	36
8	$K_2S_2O_8$		DMSO	Trace
9	$K_2S_2O_8$		NMP	Trace
10	$K_2S_2O_8$	$Cu(OAc)_2$	1,4-Dioxane	Trace
11	$K_2S_2O_8$	Ag_2CO_3	1,4-Dioxane	Trace
12	$K_2S_2O_8$	Ag_2O	1,4-Dioxane	Trace
13	$K_2S_2O_8$	PTSA	1,4-Dioxane	15
14	$K_2S_2O_8$	TFA	1,4-Dioxane	35
15	$K_2S_2O_8$	AcOH	1,4-Dioxane	61
16	$K_2S_2O_8$		1,4-Dioxane/AcOH (9:1)	75
17	$K_2S_2O_8$		1,4-Dioxane/AcOH (7:3)	81
18	$K_2S_2O_8$		1,4-Dioxane/AcOH (5:5)	77
19[c]	$K_2S_2O_8$		1,4-Dioxane/AcOH (7:3)	62
20[d]	$K_2S_2O_8$		1,4-Dioxane/AcOH (7:3)	69

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), oxidant (0.2 mmol), additive (0.2 mmol), solvent (1 mL), 80 °C, 12 h.
[b] Isolated yield based on **1a**.
[c] 70 °C.
[d] 90 °C.

Unfortunately, it was found that they were less effective, and **3a** was obtained in lower yields (Table 1, entries 2–4 vs. entry 1). Among all of the examined oxidants, $K_2S_2O_8$ was the best for this catalytic reaction. Other different solvents including $ClCH_2CH_2Cl$, CH_3CN, DMF, DMSO, and NMP were screened, and it was found that they were less effective, and deteriorated the product yield of **3a** (Table 1, entries 5–9). The addition of common additives, such as $Cu(OAc)_2$, Ag_2CO_3, Ag_2O, PTSA, and TFA, to the reaction resulted in a reduced yield of **3a** (Table 1, entries 10–14). Addition of AcOH moderately improved the yield of **3a** (Table 1, entries 15–18), indicating that AcOH was beneficial to this transformation. After further screening of the reaction media, the yield was increased to 81% with a 1,4-dioxane/AcOH mixture (7/3, v/v) (Table 1, entry 17). Lower temperature suppressed the efficiency, whereas higher temperature did not lead to a better result (Table 1, entries 19 and 20). Therefore, the optimal conditions for the palladium-catalyzed *ortho*-acylation of **1a** with **2a** were as follows: 10 mol % of $Pd(OAc)_2$ as the catalyst, 2.0 equiv of $K_2S_2O_8$ as the oxidant, and 1.5 equiv of α-oxocarboxylic acid as the partner of *N*-nitrosoaniline. The reaction was performed best at 80 °C for 12 h in a 1,4-dioxane/AcOH mixture (7/3, v/v).

With the optimized reaction conditions in hand, we next explored the scope of the α-oxocarboxylic acid derivatives as the simple acyl source (Table 2). The results indicated that *N*-nitrosoaniline **1a** could react with various phenylglyoxylic acids to generate the corresponding products **3a–o** in 55–91% yields (Table 2). The reaction tolerated a variety of functional groups including chloro, bromo, iodo, and methoxy groups. As for the substitution pattern of reagent **2**, higher yields were obtained with *para*-substituted phenylglyoxylic acids containing methyl, halo, and trifluoromethyl groups in comparison with that bearing aryl group (Table 2, **3b–e** vs. **3f**). *Meta*-substituted phenylglyoxylic

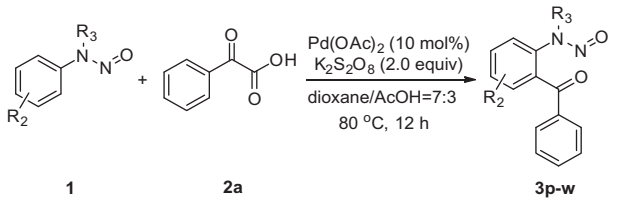
Table 2
Palladium-catalyzed direct *ortho*-acylation of *N*-nitrosoaniline **1a** with α-oxocarboxylic acids **2**[a,b]



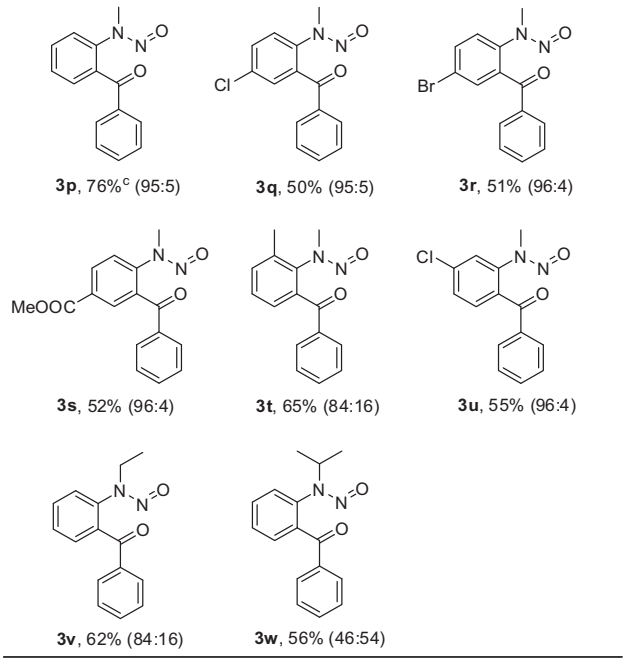
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), $K_2S_2O_8$ (0.6 mmol), dioxane/AcOH (7:3, 3 mL), 80 °C, 12 h. Isolated yield based on **1**.
[b] Ratios of the *syn* to *anti* isomers relative to the N–N bond are shown in parentheses, determined by the ^1H NMR spectra.

acids worked well in the reaction to give the desired products **3g–j** in good to excellent yields (71–89%). The reaction could also be applied to *ortho*-substituted phenylglyoxylic acids to afford **3k** and **3l** in moderate to good yields (68–75%). Furthermore, it was found that disubstituted phenylglyoxylic acids showed good reactivity and provided products **3m** and **3n** in good yields (72–79%). It should be noted that when 2-(naphthalen-1-yl)-2-oxoacetic acid was employed as the acyl source, the corresponding product **3o** was obtained in 64% yield.

Table 3
Palladium-catalyzed direct *ortho*-acylation of *N*-nitrosoanilines **1** with α-oxocarboxylic acid **2a**[a,b]



1 2a 3p-w



3p, 76%[c] (95:5) **3q**, 50% (95:5) **3r**, 51% (96:4)

3s, 52% (96:4) **3t**, 65% (84:16) **3u**, 55% (96:4)

3v, 62% (84:16) **3w**, 56% (46:54)

[c] **2a** (0.45 mmol), 80 °C.
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (0.03 mmol), $K_2S_2O_8$ (0.6 mmol), dioxane/AcOH (7:3, 3 mL), 100 °C, 12 h. Isolated yield based on **1**.
[b] Ratios of the *syn* to *anti* isomers relative to the N–N bond are shown in parentheses, determined by the ^1H NMR spectra.

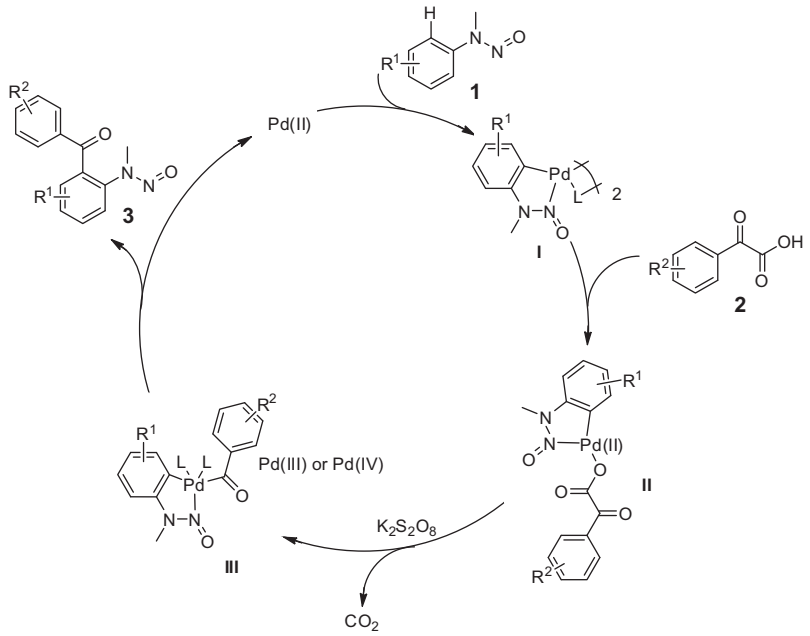
Next, the performance of some representative *N*-nitrosoanilines were examined under the optimized reaction conditions, and the results are shown in Table 3. *N*-Nitrosoaniline with no functional group reacted with phenylglyoxylic acid **2a** to provide product **3p** in 76% yield. When halo, methyl, and ester groups were introduced into the phenyl rings of *N*-nitrosoanilines, acylated products **3q**–**u** were obtained in moderate yields (50–65%). It is worthy mentioning that **3u** was exclusively formed, indicating that the reaction was very selective and did not occur at the *ortho* position of the chloro atom due to steric hindrance. In addition, substrates with *N*-ethyl and *N*-isopropyl groups instead of *N*-methyl could also be employed to react with **2a**, providing **3v** and **3w** in 62% and 56% yields, respectively.

It should be pointed out that there are two isomers, that is, *syn* and *anti* isomers for *N*-nitrosoanilines including both starting materials and products. The isomer is defined as the *syn* configuration when the *N*-alkyl group is cis to the *N*-nitroso oxygen atom. The *syn* to *anti* isomeric ratios of products **3a**–**w** are shown in the parenthesis for each product in Tables 2 and 3. Compared with **3p**, **3v** and **3w** showed decreasing *syn* to *anti* isomeric ratios due to the increasing steric hindrance between the *N*-alkyl and *N*-nitroso oxygen atom.

On the basis of our experimental results and the previous literature,[7,9,13,17] a plausible mechanism is shown in Scheme 1. Firstly, this transformation is believed to start with the *ortho*-palladation of **1** with $Pd(OAc)_2$ to provide the five-membered palladacycle **I**,[7,9,13] which subsequently undergoes anion exchange with **2** to afford intermediate **II**, followed by oxidation in the presence of $K_2S_2O_8$ and concurrent decarboxylation to furnish the Pd(III) or Pd(IV) intermediate **III**. Finally, product **3** is generated by reductive elimination with the simultaneous release of a Pd(II) species to complete the catalytic cycle. Alternatively, the reaction mechanism involving a Pd(0/II) catalytic cycle cannot be excluded.[18]

Conclusion

In summary, we have developed a novel Pd-catalyzed decarboxylative *ortho*-acylation of *N*-nitrosoaniline compounds with α-oxocarboxylic acids using $K_2S_2O_8$ as a convenient oxidant. The



Scheme 1. Plausible catalytic cycle for the Pd-catalyzed reaction of *N*-nitrosoanilines with α-oxocarboxylic acids.

reactions of *N*-nitrosoaniline compounds with a variety of α-oxo-carboxylic acids proceeded smoothly to generate the corresponding products in good yields. The reaction was highly efficient and provided a series of *ortho*-acylated *N*-nitrosoanilines, tolerating a wide range of functional groups.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.009.

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