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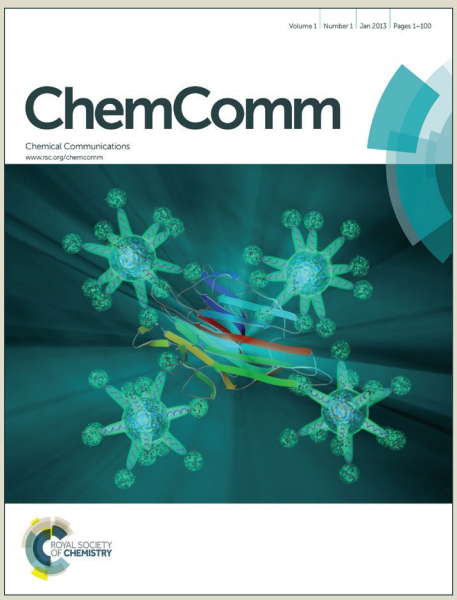

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Palladium-catalyzed C-H bond carboxylation of acetanilides: an efficient usage of *N, N*-dimethyloxamic acid as the carboxylate source

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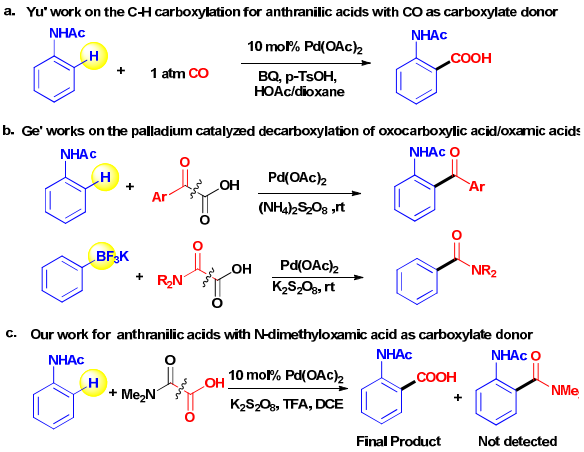
***N, N*-Dimethyloxamic acid can be successfully employed as carboxylate precursor in the palladium-catalyzed direct C–H carboxylation of acetanilides. The reaction proceeds smoothly under mild conditions over a broad range of substrates with high functional group tolerance, affording substituted *N*-acyl anthranilic acids in moderate to high yields.**

Anthranilic acid is an important structural motif found in various natural products and pharmaceutically chemical entities.[1] It is also known to be crucial synthetic precursor for a wide range of biologically active compounds including quinazoline, quinoline, benzoxazinone, and acridinone alkaloids.[2] Traditionally, anthranilic acids are synthesized by the reduction of 2-nitrobenzoic acids in the presence of metal catalyst, of which the starting material 2-nitrobenzoic acids are usually toxic and unstable;[3] or the Hofmann rearrangement of phthalamic acids, in which the products are limited to specific structures.[4] Given the prevalence of anthranilic acid moiety in medicinally relevant compounds, it would be desirable to develop a concise and highly efficient method to generate anthranilic acids.

Transition-metal-catalyzed direct C-H bond functionalization has become a cutting-edge methodology for the synthesis of structurally similar, yet diversified organic molecules in recent years.[5] Since the pioneer work of Fujiwara and co-workers,[6] C-H bonds carbonylation have been widely applied in the synthesis of carboxylic acids, esters, amides, and ketones. A number of directing groups, such as carboxylic acids,[8] hydroxyl groups,[9] acetanilides,[10] phosphinic acids[11] and oximes[12] could be involved in the C–H bonds carbonylation efficiently. In 2010, Yu and co-workers reported a palladium catalyzed C-H carboxylation of acetanilides with CO as the carboxylate donor (Scheme 2a), providing *N*-acyl anthranilic acid derivatives in good yields.[7] However, the current investigations mainly focus on the usage of CO as carboxylate source. The development of other efficient carboxylate agent has not been reported yet. In continuation of our previous works,[13-15] we report herein that *N,N*-dimethyloxamic acid, an easily obtained reagent,[16,17] could act as an efficient carboxylate agent in the palladium-catalyzed coupling of acetanilides for obtaining anthranilic acid derivatives (Scheme 2c).



Scheme 1: Palladium catalyzed C-H bonds functionalization of acetanilides.

Inspired by Ge's work that both the α-oxocarboxylic acids and oxamic acids could be involved in the palladium catalyzed cross coupling reaction through a decarboxylation way,[17,18] we envisioned that *N*-acyl-2-aminobenbenzamides could be generated *via* a similar mechanism in the palladium catalyzed cross coupling of acetanilides with oxamic acids. To our surprise, when we used the *N, N*-dialkyloxamic acid in the palladium catalyzed C-H bond activation of acetanilides, we obtained the *N*-acyl anthranilic acid as the final product, instead of the decarboxylated product. We next tested different oxamic acid derivatives in the coupling. Both the *N, N*-diaryloxamic acid and *N*-monoalkyloxamic acid provided desired product with low yield while 2-ethoxy-2-oxoacetic acid, oxalic acid, and 2-amino-2-oxoacetic acid gave no conversion (entries 3-7). Then we began to explore the reaction conditions with *N, N*-

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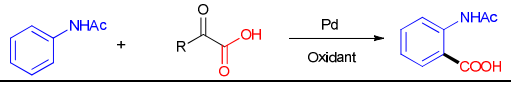
dimethyloxamic acid as carboxylate agent. A screening of metal catalysts revealed that $Pd(OAc)_2$ and $Pd(TFA)_2$ were applicable catalysts (entries 8-11). The effectiveness of oxidants was also examined and demonstrated that $K_2S_2O_8$ was the most suitable oxidant in this reaction (entries 12-15). Further screening of solvent revealed that 1, 2-Dichloroethane was the most effective solvent while other solvents gave lower conversion (entries 16-18). In addition, the reaction temperature of 80 °C was found to be optimal. Lowering the reaction temperature decreased the substrate conversion (entries 19-20). Additives such as TFA, AcOH, and TsOH were added to improve the yields (entries 21-23). We were delighted to find that the yield could get up to 73% in the presence of TFA (0.5 equiv.). We also conducted a control reaction with TFA but without *N, N*-dimethyloxamic acid added, which proved that TFA could not act as a carboxylate donor. The reaction with 5 mol% catalyst was performed and could get 58% yield with a longer time (entry 24).

Table 1: Scope of Pd-catalyzed oxidative *ortho*-carboxylation of acetanilide[a]

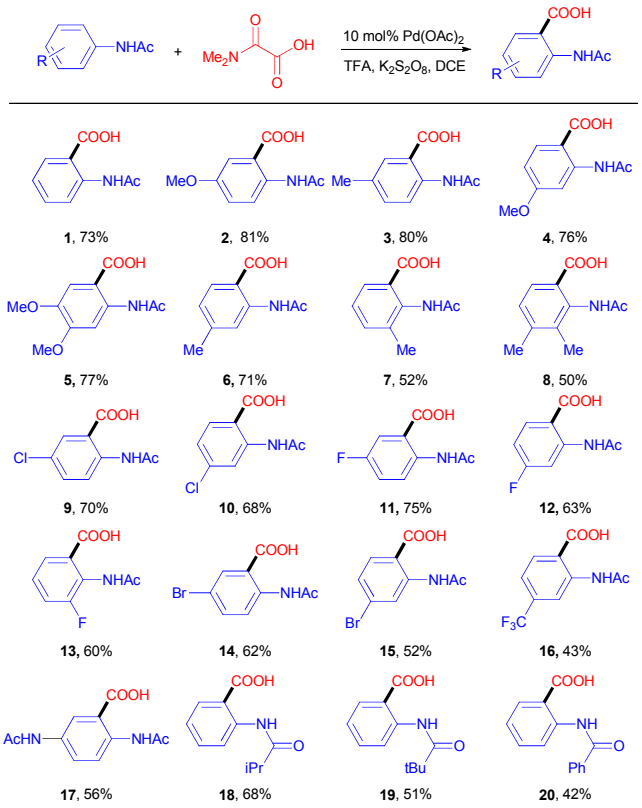


Entry	R	Conditions	%yield[b]
1	NEt_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	46
2	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	51
3	NPh_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	4
4	NHMe	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	5
5	NH_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	0
6	OEt	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	0
7	OH	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 80°C	0
8	NMe_2	$Pd(TFA)_2$, $K_2S_2O_8$, DCE, 80°C	50
9	NMe_2	$PdCl_2$, $K_2S_2O_8$, DCE, 80°C	18
10	NMe_2	$Pd(CH_3CN)_2Cl_2$, $K_2S_2O_8$, DCE, 80°C	32
11	NMe_2	$Pd(PPh_3)_4$, $K_2S_2O_8$, DCE, 80°C	9
12	NMe_2	$Pd(OAc)_2$, $(NH_4)_2S_2O_8$, DCE, 80°C	23
13	NMe_2	$Pd(OAc)_2$, Ag_2CO_3, DCE, 80°C	0
14	NMe_2	$Pd(OAc)_2$, $Cu(OH)_2$, DCE, 80°C	0
15	NMe_2	$Pd(OAc)_2$, BQ, DCE, 80°C	0
16	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, diglyme, 80°C	21
17	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DMSO, 80°C	33
18	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, Dioxane, 80°C	9
19	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 100°C	42
20	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, 60°C	28
21	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, TFA, 80°C	78(73)[c]
22	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, TsOH, 80°C	65
23	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, AcOH, 80°C	67
24	NMe_2	$Pd(OAc)_2$, $K_2S_2O_8$, DCE, TFA, 80°C	58[d]

[a] Reaction conditions: Acetaniline (1.0 mmol), $Pd(OAc)_2$ (10 mol%), Oxidant (2.0 mmol), oxamic acid (2.0 mmol), solvent (2.0 mL) were stirred for 24 h under air. [b] GC yields were reported. [c] Isolated yields were reported in the parentheses. [d] 5% mol $Pd(OAc)_2$ was used in 48 h.

The scope of this reaction was then investigated under the preliminary optimized conditions. A range of acetanilides were examined and the results are listed in Table 2. The *p*-methoxyl and methyl substituted acetanilide gave high yields of the corresponding products (**2** and **3**). For the 3-substituted acetanilides, the coupling only took place on the less hindered side presumably due to the steric hindrance (**4 -6, 10, 12,15,16**). It was worth noting that *ortho*-substituted substrates were feasible coupling partners in this catalytic system (**7, 8, 13**). Fluoro/chloro/bromo substituted acetanilides were compatible substrates (**9–15**), although the yields were lower than those of other substituted acetanilides. In particular, the bromo group remained intact during the course of the reaction (**14, 15**), which may potentially offer further structural fine-tuning by using other traditional cross-coupling reactions.[19] We also carried out the reaction with diacetanilides, only the *para*-diacetanilides gave the desired product with 56% yield (**17**). Apart from the acetamido group, other directing amido moieties were tested in this *ortho*-carboxylation reaction, *iso*-propyl groups gave the best results while the *tert*-butyl and phenyl moiety gave lower yield of the desired products **(18-20)**.

Table 2: Scope of acetanilides in the Pd-catalyzed oxidative *ortho*-carboxylation[a]



[a] Reaction conditions: Acetaniline (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 mmol), *N, N*-dimethyloxamic acid (2.0 mmol), TFA (0.5 equiv.), DCE (2.0 mL) were stirred at 80 °C for 24 h under air. Isolated yields were reported.

With the substituted *N*-acyl-anthranilic acids in hand, we also explored their potential biological activity (SP, Figure 1). Tranilast, an anthranilic acids derivative, has been reported processing the ability to inhibit the aggregation of *β*-amyloid (Aβ) peptides *in vitro*.[20] It has been well known that the formation and accumulation of aggregations of A*β* peptides in the brain are critical factors in the development and progression of Alzheimer's disease.[21] Among the 20 anthranilic acids we obtained, 10 of them showed better inhibitory activity of *β*-amyloid (A*β*) peptides than that of the positive control curcumin (EC_{50} 3.9 μM)[22] and compound 3 showed the best activity.

Control experiments were performed to identify the possible reaction mechanism (Scheme 2). The 5-membered palladcycle **P1** was prepared and reacted with the acetanilide under

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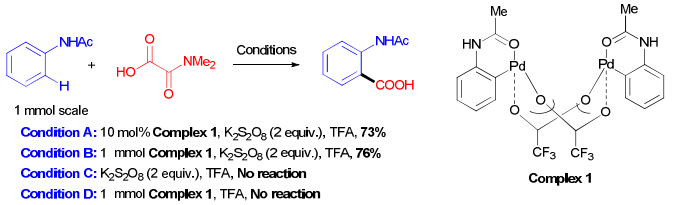
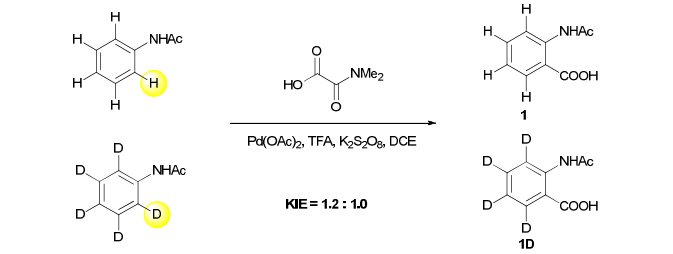
different conditions.[22] The desired product was obtained with 73% yield using catalytic complex **P1** and 76% yield with stoichiometric complex **P1**, which confirmed that the complex **P1** might be the actual intermediate during the catalysis (Scheme 2, condition A and B). We conducted the reaction under typical condition but without the Pd catalyst, the *N,N*-dimethyloxamic acid turned to the *N, N*-dimethylformamide in the presence of $S_2O_8^-$,[23] but no conversion of the acetanilide was observed, which proved that the Pd catalyst was necessary for the C-H bond activation (Scheme 2, condition C). When the reaction was carried with stoichiometric complex **P1** but without $K_2S_2O_8$, no desired product was observed. These results, coupled with the fact that the complex **P1** can be easily generated at low temperature, suggest that the critical step of the reaction may actually involve a transient Pd (III) or Pd(IV) intermediate (Scheme 2, condition D).[24, 25] The reaction could not proceed when using CO_2 instead of *N,N*-dimethyloxamic acid as the carboxylate agent, which may exclude the possibility that the intermediate **A** reacted with the CO_2 released from *N,N*-dimethyloxamic acid during the reaction.



Scheme 2: Control experiments

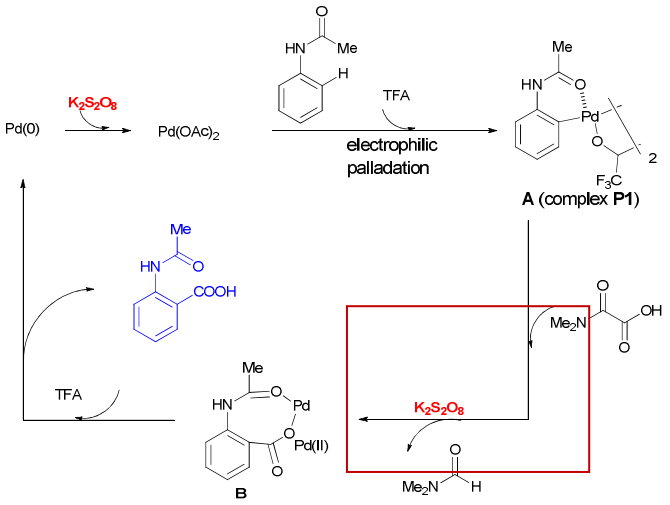
We also carried out an intermolecular kinetic isotope effect experiment by reacting *N, N*-dimethyloxoamic acid with acetanilides or d_5- acetanilides, respectively(Scheme 3). The (k_H/k_D) value was determined to be 1.2, which proved that the C-H bond cleavage of acetanilide is not involved in the rate-determining steps of the reaction.



Scheme 3: Control experiments and the KIE studies

Base on the above experiments and previous literatures,[7, 8, 26, 27] we suggested that the reaction mechanism began with the *ortho*-palladation of acetanilide with $Pd(OAc)_2$ to generate a palladacyclic intermediate **A** (Scheme 4). The resultant complex subsequently reacted with *N, N*-dimethyloxamic acid, affording the intermediates **B** through an acyl radical mediated process in the presence of $K_2S_2O_8$. The Pd(II) complex **B** liberated the desired product with the formation of Pd(0) species under acidic conditions. Finally, The regenerated Pd(0) catalyst was reoxidized to Pd(II) catalyst in the presence of $K_2S_2O_8$, thus completing the catalytic cycle. We also monitored the existence of *N, N*-dimethylformamide during the reaction by GC-MS. Yet, other alternative pathways cannot be excluded.

In conclusion, we have developed a novel palladium catalyzed cross-coupling of acetanilides and *N,N*-dimethyloxamic acid for the direct accessing to anthranilic acids. This is the first example of using *N,N*-dimethyloxamic acid as carboxylate agent in the C-H bonds carboxylation. Fluoro, bromo, chloro, and methoxy groups at different positions of arene are compatible in this catalytic system. An array of substituted *N*-acyl-anthranilic acids were obtained in moderate to high yields. We believed this new synthetic methods with *N, N*-dimethyloxamic acid as carboxylate agent would stimulate chemists to advance other relevant catalytic carboxylation processes.



Scheme 4: A plausible reaction mechanism

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