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Room Temperature Palladium-Catalyzed Decarboxylative *ortho*-Acylation of Acetanilides with α-Oxocarboxylic Acids

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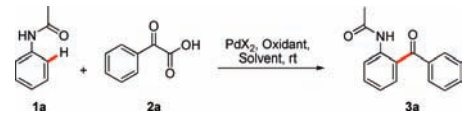
Abstract: A novel Pd-catalyzed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids is realized at room temperature. This reaction provides efficient access to *o*-acyl acetanilides under mild conditions.

Transition-metal-catalyzed decarboxylative coupling[1] is an attractive synthetic method for C−C bond formation since it does not require the use of stoichiometric organometallic coupling reagents and gives rise to CO_2 instead of often toxic metal compounds. Since the report of a palladium-catalyzed decarboxylative Heck-type of olefination of benzoic acids by Meyers,[2] extensive studies have been carried out in this area; representative examples are biaryl coupling by Goossen,[3] Forgione,[4] and Liu;[5] olefination by Satoh[6] and Wu;[7] alkynylation by Lee;[8] and aryl ketone and ester formation by Goossen[3e,9] and Liu.[10] Recently, decarboxylative arylation of unactivated arenes through Pd-catalyzed C−H activation was also developed.[11] It is of note that all of these processes suffer from high reaction temperature, which reduces their potential application. Therefore, the development of decarboxylative coupling under mild conditions is highly desirable.

Inspired by the recent studies in decarboxylative coupling of aryl halides with potassium α-oxocarboxylates[3e,9] and oxalate monoesters,[10] we report a room temperature, decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids *via* palladium-catalyzed C−H activation. This new method is complementary to the directed lithiation/acylation process[12] and provides *o*-acyl acetanilides, which are important structural units and synthetic intermediates in biologically active natural products and medicinal chemistry.[13]

Early studies showed that decarboxylation of α-oxocarboxylic acids could be catalyzed by a silver(I) salt with persulfate as the oxidant at room temperature.[14] Thus, our investigation began with decarboxylative coupling of acetanilide (**1a**) with phenylglyoxylic acid (**2a**) in the presence of 10 mol % $Pd(TFA)_2$, 20 mol % $AgNO_3$ and stoichiometric $(NH_4)_2S_2O_8$ in DCM at room temperature (Table 1, entry 1). To our delight, the desired product **3a** was obtained in 36% yield. Interestingly, it was then noted that $AgNO_3$ is not required for this reaction.[15] Optimization of the reaction conditions demonstrated that the reaction was most productive using diglyme as solvent and $(NH_4)_2S_2O_8$ as oxidant, providing **3a** in 93% yield at room temperature within 12 h (entry 5). Further study showed that both $[Pd(MeCN)_4](BF_4)_2$ and $Pd(OAc)_2$ are also efficient catalysts for this reaction while $PdCl_2$ gave only a trace amount of desired product **3a** (entries 17−19). It was also noted that both the amount of the catalyst and oxidant could be reduced at the expense of longer reaction time (entries 20 and 21).

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

Entry	PdX_2 (mol %)	Oxidant (equiv)	Solvents	Yield (%)[b]
1[c]	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	DCM	36
2	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	DCM	35
3[d]	−	$(NH_4)_2S_2O_8$ (2)	DCM	0
4[e]	$Pd(TFA)_2$ (10)	air	DCM	20
5	**$Pd(TFA)_2$ (10)**	**$(NH_4)_2S_2O_8$ (2)**	**diglyme**	**93(90[f])**
6	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	DME	82
7	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	EtOAc	34
8	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	DCE	18
9	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	*o*-xylene	trace
10	$Pd(TFA)_2$ (10)	air	diglyme	52
11	$Pd(TFA)_2$ (10)	O_2 (1 atm)	diglyme	55
12	$Pd(TFA)_2$ (10)	$K_2S_2O_8$ (2)	diglyme	65
13	$Pd(TFA)_2$ (10)	BzOOBz (2)	diglyme	61
14	$Pd(TFA)_2$ (10)	*t*BuOOBz (2)	diglyme	60
15	$Pd(TFA)_2$ (10)	$Ce(SO_4)_2$ (2)	diglyme	38
16	$Pd(TFA)_2$ (10)	Oxone (2)	diglyme	36
17	$[Pd(MeCN)_4](BF_4)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	diglyme	87
18	$Pd(OAc)_2$ (10)	$(NH_4)_2S_2O_8$ (2)	diglyme	75
19	$PdCl_2$ (10)	$(NH_4)_2S_2O_8$ (2)	diglyme	trace
20[g]	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (1.2)	diglyme	85
21[h]	$Pd(TFA)_2$ (5)	$(NH_4)_2S_2O_8$ (2.0)	diglyme	82

[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), PdX_2 (0.03 mmol), oxidant (0.6 mmol), 3 mL of solvent, rt, 12 h unless otherwise noted. [b] Yields and conversions are based on **1a**, determined by crude ^1H NMR using dibromomethane as the internal standard. [c] 36 h with 20 mol % $AgNO_3$. [d] 36 h, without palladium. [e] 36 h, without $(NH_4)_2S_2O_8$. [f] Isolated yield. [g] $(NH_4)_2S_2O_8$ (0.36 mmol), 24 h. [h] $Pd(TFA)_2$ (0.015 mmol), 24 h.

As shown in Table 2, a variety of substituted phenylglyoxylic acids, including methyl, methoxy, halogen, trifluoromethyl, and nitro groups, were compatible under the optimal reaction conditions. Although sterically hindered substrates failed for Pd(0)/Cu(I)-catalyzed decarboxylative acylation in a previous report,[9a] a good yield was obtained in this case (**3n**). Furthermore, aliphatic α-oxocarboxylic acids were also compatible in this reaction, giving good to excellent yields (**3q**−**u**).

The results of substituted acetanilide (**1b**−**t**) compatibility are presented in Table 3. In general, electron-donating groups provided higher yields when compared with electron-withdrawing groups at the *m*- and *p*-positions (**4b**−**k**). Although this reaction does not work well with strong electron-withdrawing groups at the *m*-position, good yields were obtained with *p*-substituted compounds (**4i**−**k**). Furthermore, *m*,*p*-disubstitued acetanilines also provided good yields (**4l**−**p**). Unfortunately, *o*-substituted acetanilides failed for the coupling reaction under the current catalyst system. It is noted that the acetamido group

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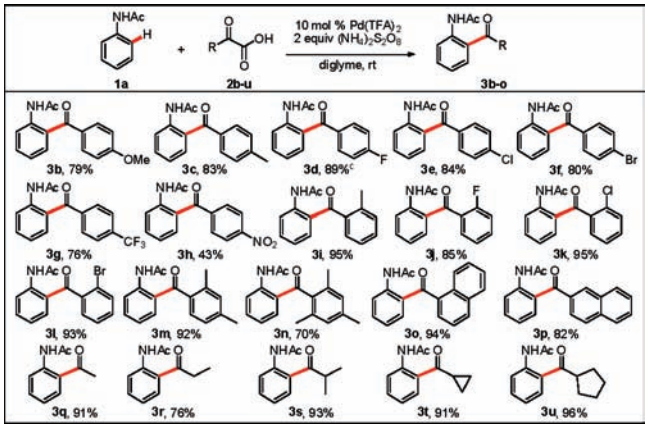
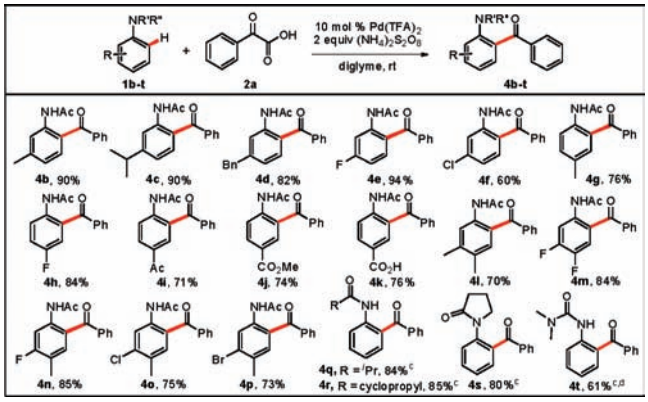
Table 2. Scope of α-Oxocarboxylic Acids[a,b]



[a] Conditions: **1a** (0.3 mmol), **2b**−**u** (0.6 mmol), $Pd(TFA)_2$ (0.03 mmol), $(NH_4)_2S_2O_8$ (0.6 mmol), 3 mL of diglyme, rt, 9−36 h. [b] Isolated yields based on **1a**. [c] $(NH_4)_2S_2O_8$ (0.36 mmol).

Table 3. Scope of Anilides[a,b]

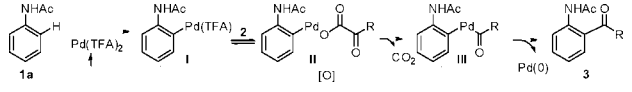


[a] Conditions: **1b**−**t** (0.3 mmol), **2a** (0.9 mmol), $Pd(TFA)_2$ (0.03 mmol), $(NH_4)_2S_2O_8$ (0.6 mmol), 3 mL diglyme, rt, 7−48 h. [b] Isolated yields based on **1**. [c] **2a** (0.6 mmol). [d] In AcOH/THF (1:1, v/v).

is not necessary for this transformation since other amides or urea also provided good to high yields (**4q**−**t**).

Although the reaction mechanism is not clear at this stage, it is believed that this transformation is initiated by *o*-palladation of the acetanilide **1** and subsequent anion exchange with α-oxocarboxylic acids (Scheme 1). Decarboxylation[15b] of intermediate **II** followed by reductive elimination provides the desired product **3**.

Scheme 1. Proposed Catalytic Cycle of Decarboxylative Coupling



In summary, an efficient approach for the direct *ortho*-acylation of acetanilides has been developed based on a Pd-catalyzed C−H activation process at room temperature. This novel method provides easy access to *o*-acyl acetanilides under mild conditions.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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