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Graphical Abstract

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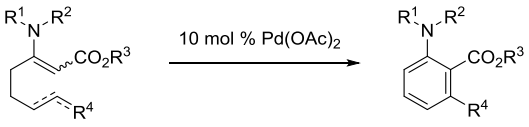

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Pd(OAc)$_2$-catalyzed one-pot preparation of anthranilates from acyclic unsaturated β-enamino esters

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ABSTRACT

A one-pot synthesis of anthranilates from acyclic unsaturated β-enamino esters with a catalytic amount of Pd(OAc)$_2$ was achieved for the first time. The substrates for the key catalytic reaction were easily prepared from acetoacetate esters and amines, and functionalized anthranilates were obtained in moderate to good chemical yields. A simple assembly of a ^{13}C-labeled anthranilate was demonstrated by applying this protocol. In addition, bioactive NNI-5 was synthesized using this catalytic process.

Introduction

Some synthetic anthranilic acid derivatives exhibit divergent biological activities. For instance, NNI-5 (**1**) shows antiviral properties[1] against the hepatitis C virus (HCV) which could have a significant impact for the approximately 71 million people living with chronic HCV infection.[2] Another example of biological activity is AAL993 (**2**), a vascular endothelial growth factor (VEGF) kinase inhibitor, which shows potent antiangiogenic and antitumor activities.[3] Compound **3**, which is a new class of malonyl-CoA decarboxylase inhibitor, possesses antiobesity and antidiabetic properties.[4] Finally, compound **4**, a *Staphylococcus aureus* Sortase A inhibitor, is a promising antibacterial agent[5] (Figure 1).

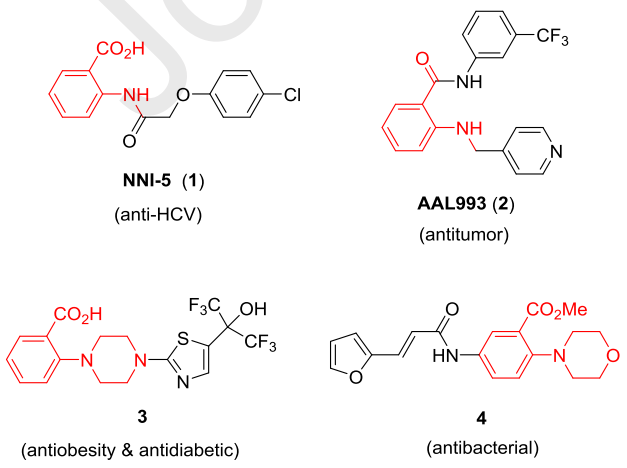
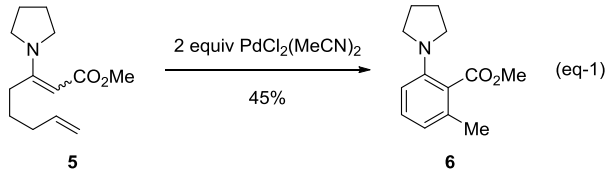
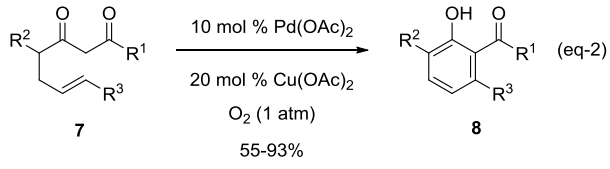


Figure 1. Structures of some bioactive anthranilic acid derivatives

***Ishikawa and Saito* (2001)**



***Our catalytic cycloaromatization* (2019)**



Scheme 1. Cycloaromatization reactions.

The research on anthranilic acid (2-aminobenzoic acid) began with its isolation from indigo by Fritzsche in 1841.[6] Anthranilic acid was industrially synthesized from phthalic anhydride, available through oxidation of *o*-xylene via phthalamide.[7] Most substituted anthranilic acid derivatives have been prepared from benzenoids, such as isatins[8] and benzoic acids.[9] Recently, a myriad of different synthetic approaches to anthranilic acid derivatives with or without transition metals[10,11] have been reported. To the best of our knowledge, only Ishikawa and Saito have succeeded in a palladium-assisted anthranilate synthesis using acyclic unsaturated β-enamino ester **5** (Scheme 1, eq-1).[12]

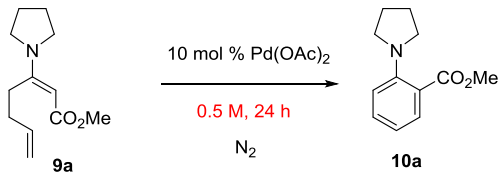
As a variety of substrates suitable for this process (**5** → **6**) are easi

adaptable to a wide variety of substituted anthranilate syntheses. However, there are still some challenges regarding its chemical yield and catalyzation. We became interested in applying our catalytic cycloaromatization protocol (**7** → **8**)[13] shown in eq-2 (Scheme 1) to unsaturated *β*-enamino esters for the construction of anthranilates.

Results and Discussion

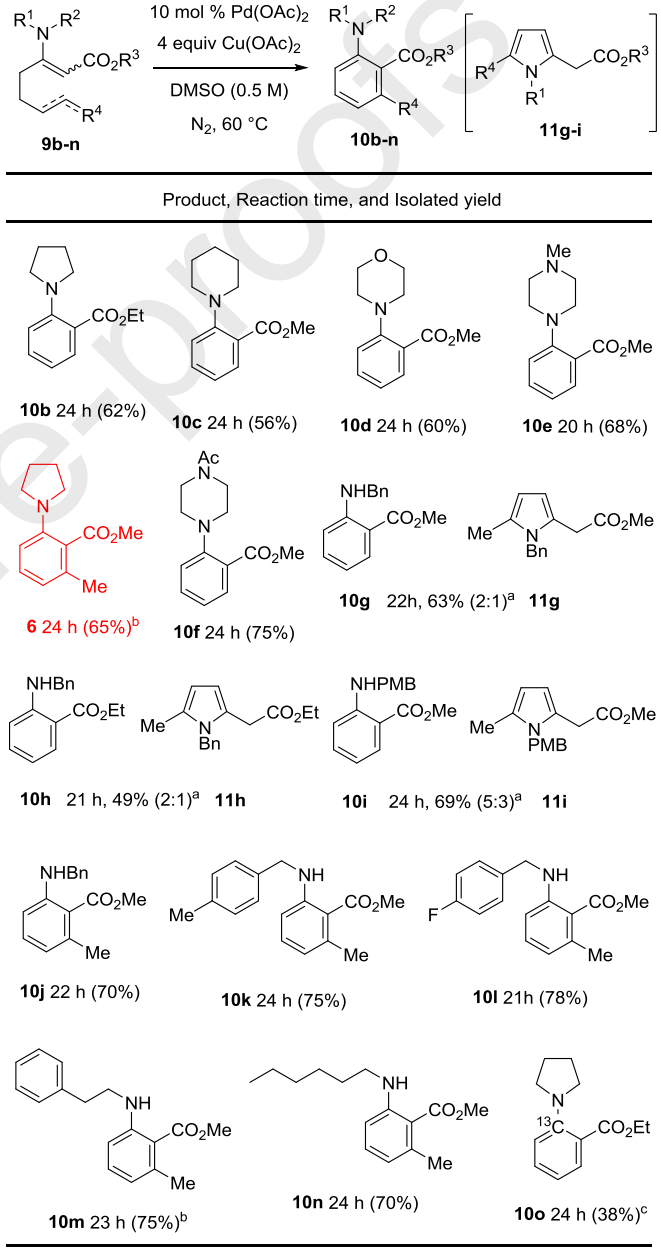
Our screening began with an effort to optimize the reaction conditions for the one-pot synthesis of anthranilates using a catalytic amount of $Pd(OAc)_2$. Methyl (*E*)-3-(pyrrolidin-1-yl)hepta-2,6-dienoate (**9a**) was chosen as a model compound for the optimization process. The requisite substrate **9a** was synthesized using mono-alkylation of acetoacetate-dianions[14] and enamine formation.[15] A variety of different reaction parameters, such as the reoxidant, solvent, and temperature were evaluated (Table 1). To begin, **9a** was subjected to our catalytic cycloaromatization conditions[13] to afford the desired anthranilate **10a** in a 44% yield (Table 1, entry 1). There is no experimental evidence so far, however, in contrast to hydrocarbons, whether nitrogen-containing compounds might participate in palladium catalysts as a ligand or nitrogen-containing substrates. It is also unknown whether their intermediates may be further oxidized under an aerobic atmosphere, and eventually those interactions could cause the reduction of the chemical yields of anthranilates. Although 1,4-benzoquinone (BQ) did not work at all as a reoxidant (Table 1, entry 2), three equivalent $CuCl_2$ functioned to a small degree (Table 1, entry 3). When less than two equivalent $Cu(OAc)_2$ was used, **10a** was obtained in about 10% yield (Table 1, entry 4). However, three equivalent $Cu(OAc)_2$ proved to be effective, and **10a** was isolated in a 75% yield (Table 1, entry 5). Toluene, 1,2-dimthoxyethane (DME), and MeCN were unsuitable for this catalytic process (Table 1, entries 6-8). It was found that DMF can be used as an alternative solvent for DMSO (Table 1, entry 9). However, when the reaction was performed at 60 ˚C to clearly produce **10a** (Table 1, entry 10), the higher temperature (120 ˚C) reduced the chemical yield. The reoxidation process in this catalytic system did not proceed smoothly at 120 ˚C, most likely due to the partial formation of palladium black, and eventually the chemical yield was reduced to 55% (Table 1, entry 11). The best yield (83%) was obtained using four equivalent $Cu(OAc)_2$ as a reoxidant (Table 1, entry 12). When the amount of catalyst was lowered to 5 mol %, the yield also dropped to 51% (Table 1, entry 13). The reaction hardly proceeded in the absence of the reoxidant (Table 1, entry 14) or $Pd(OAc)_2$ (Table 1, entry 15). Although **9a** disappeared by TLC-monitoring, no by-product was isolated. It was found that the coexistence of oxygen and $Cu(OAc)_2$ not only cancelled each efficacy, but also somehow caused uptake of the reaction substrate **9a** (Table 1, entry 16). Additionally, several other palladium catalysts, including $PdCl_2$ (12%) and $Pd(TFA)_2$ (15%), were also examined in this process, but none proved to be better than $Pd(OAc)_2$.

Table 1. $Pd(OAc)_2$-catalyzed cyclization of unsaturated *β*-enamino esters **9a**.



entry	reoxidant (equiv)	solvent	temp (˚C)	isolated yield (%)
1[a]	O_2 (1 atm)	DMSO	45	44
2	BQ (3)	DMSO	45	0
3	$CuCl_2$ (3)	DMSO	45	20
4	$Cu(OAc)_2$ (2)	DMSO	45	10
7	$Cu(OAc)_2$ (3)	DME	45	10
8	$Cu(OAc)_2$ (3)	MeCN	45	36
9	$Cu(OAc)_2$ (3)	DMF	45	62
10	$Cu(OAc)_2$ (3)	DMSO	60	76
11	$Cu(OAc)_2$ (3)	DMSO	120	55
12	$Cu(OAc)_2$ (4)	DMSO	60	83[e]
13[b]	$Cu(OAc)_2$ (4)	DMSO	60	51
14	none	DMSO	60	trace
15[c]	$Cu(OAc)_2$ (4)	DMSO	60	0
16[d]	$Cu(OAc)_2$ (4)	DMSO	60	12

[a]The reaction was run for 28 h. [b]5 mol % $Pd(OAc)_2$. [c]In the absence of $Pd(OAc)_2$. [d]Under O_2 (1 atm) atmosphere. [e]10 mol % $PdCl_2$ (12%) and $Pd(TFA)_2$ (15%).

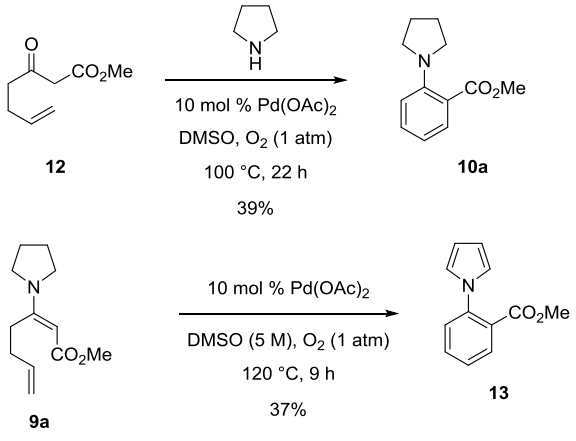


PMB: *p*-methoxybenzyl; (a) DMSO (0.75 M), 45 ˚C. (b) 40 mol % $Pd(OAc)_2$, 3 equiv $Cu(OAc)_2$. (c) 20 mol % $Pd(OAc)_2$.

Scheme 2. Substrate scope.

The scope and limitations of this catalytic reaction were next investigated using various unsaturated *β*-enamino esters **9b-o**. The results are summarized in Scheme 2.When ethyl (*E*)-3-(pyrrolidin-1-yl)hepta-2,6-dienoate (**9b**) was used, the yield fell to 62%. Even if the pyrrolidine ring portion of the reaction substrate was changed to a piperidine ring or a morpholine ring, the corresponding cyclized products **10c** and **10d** were obtained

in the same manner, although there was a slight decrease in yiel
(**9e**) and methyl (*E*)-3-(4-acetylpiperazin-1-yl)hepta-2,6-dienoate (**9f**) gave rise to the corresponding cyclization products **10e** and **10f** in 68% and 75% yields, respectively. On the other hand, methyl (*Z*)-3-(benzylamino)hepta-2,6-dienoate (**9g**) provided a separable 2:1 mixture of **10g** and **11g** in 63% yield. Similarly, ethyl (*Z*)-3-(benzylamino)hepta-2,6-dienoate (**9h**) and methyl (*Z*)-3-((4-methoxybenzyl)amino)hepta-2,6-dienoate (**9i**) produced a mixture of anthranilates **10h-i** and *N*-benzylpyrrole derivatives **11h-i**, respectively. Compounds **11g-i** were obtained by cyclization reactions of the allyl moiety and secondary amine part of substrate **9g-i** in a *5-exo-trig* mode earlier than the usual cycloaromatization reaction for **10g-i**. To avoid the above side reactions, methyl (*Z*)-3-(benzylamino)octa-2,7-dienoate (**9j**) was prepared and subjected to this catalytic process. As expected, the desired methyl 2-(benzylamino)-6-methylbenzoate (**10j**) was obtained in 70% yield as the sole product. Compounds **10k** and **10l** were synthesized in good yields in the same manner. To expand the versatility of this reaction, it was performed using methyl (*Z*)-3-(phenethylamino)octa-2,7-dienoate (**9m**) and methyl (*Z*)-3-(hexylamino)octa-2,7-dienoate (**9n**). As a result, it was found that the desired products **10m-n** were obtained in good yields and the usefulness of this reaction was clarified. It has also been confirmed that compound **6** can be obtained in a yield of 65% using this protocol. Although the detailed reason is not clear, the catalytic cyclization of acyclic unsaturated *β*-enamino esters having secondary amines tends to proceed smoothly compared with the reaction substrates having tertiary amines, most likely due to the reduced steric hindrance between the amine moieties and ester groups. To investigate the pharmacokinetics of biologically active anthranilic acid derivatives, the synthesis of ^{13}C-labeled anthranilates is essential. Therefore, ethyl (*E*)-3-(pyrrolidin-1-yl)hepta-2,6-dienoate-3-^{13}C (**9o**) was synthesized and subjected to the reaction. To complete the reaction in this case, 20 mol % of palladium acetate was required and **10o** was synthesized in 38% yield. It should be noted that although there is room for yield improvement, it was also possible to synthesize **10a** directly from acetoacetate **12** using similar reaction conditions, and when this reaction was carried out at a high concentration and high temperature, further oxidized pyrrole **13** was obtained from **9a**. (Scheme 3). When the two conversion reactions shown in Scheme 3 were performed using $Cu(OAc)_2$ as a reoxidizing agent instead of oxygen, the yield of **10a** was reduced to 29%, and **13** was not obtained at all. Compounds **10a** and **13** were treated with $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMSO at 100 ° C and 120 ° C, respectively. As a result, **10a** and **13** were recovered intact. Although there is no evidence to support the following speculation, in the one-pot synthesis of **10a**, pyrrolidine reacted with $Cu(OAc)_2$ to dilute its catalytic effect. On the other hand, under the higher concentration and temperature, only the uptake of **9a** by $Cu(OAc)_2$ proceeded. Further elucidation of the detailed reaction mechanism is required.

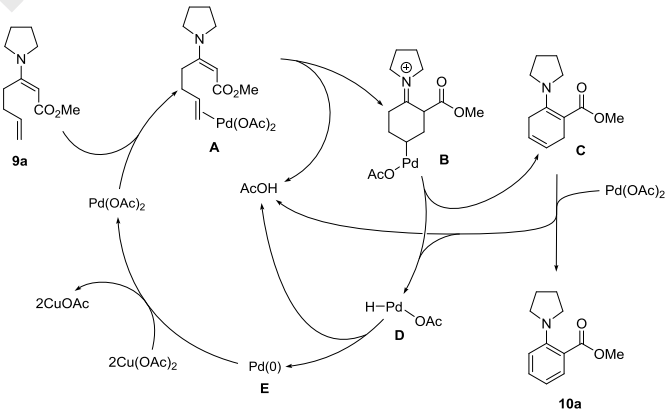


Scheme 3. Some aspects of the catalytic reaction.

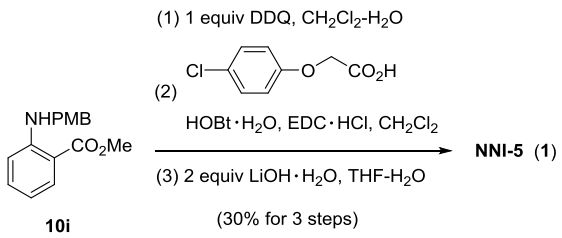
In order to clarify the reaction mechanism, the reaction was quenched when the starting material **9a** was still remaining. The ^{1}H NMR of the crude product showed only the presence of **9a** and **10a**, likely because the reaction intermediates were very unstable. Although there is no evidence, the presumed reaction mechanism is shown in Scheme 4. After activation of an isolated olefin in **9a** by $Pd(OAc)_2$, an enamine in **A** attacks the terminal carbon to generate the alkyl palladium intermediate **B**. *β*-elimination of acetoxypalladium(II) hydride (**D**) produces 1,4-diene **C**, which was subsequently oxidized by $Pd(OAc)_2$ to furnish anthranilate **10a**. Reductive elimination of AcOH from intermediate **D** provides Pd(0) **E**, which was oxidized by $Cu(OAc)_2$ to create $Pd(OAc)_2$. Although this reaction could be an equilibrium process, this equilibrium reaction should be terminated once the aromatic compound is formed, so only the thermodynamically stable anthranilate **10a** is formed.

Since compound **10i**, convertible to bioactive NNI-5 (**1**), was obtained through the present investigation, we embarked on the synthesis of NNI-5 (**1**). Namely, DDQ oxidation of **10i** led to methyl 2-aminobenzoate,[16] which was subjected to a Steglich reaction[17] with 1.5 equivalent 2-(4-chlorophenoxy)acetic acid followed by hydrolysis to afford NNI-5 (**1**) in 30% yield, over three steps (Scheme 5).

In conclusion, a wide array of acyclic unsaturated *β*-enamino esters, easily prepared from unsaturated 3-keto esters and amines, provided the corresponding anthranilates in moderate to good chemical yields in the presence of catalytic amounts of $Pd(OAc)_2$. Commercially available ethyl 3-oxobutanoate-3-^{13}C was transformed to ethyl 2-(pyrrolidin-1-yl)benzoate-2-^{13}C using this catalytic process. Finally, the total synthesis of bioactive NNI-5 was demonstrated by use of our synthetic substrate.



Scheme 4. Possible reaction mechanism.



Scheme 5. Synthesis of NNI-5 (**1**).

Dedication

Dedicated to the memory of Professor Hideo Nemoto (1943-2018).

Declaration and Competing Interest

The authors declare no conflict of interest.

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- One-pot synthesis of anthranilates from unsaturated *β*-enamino esters
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