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Palladium-Catalyzed Carbonylative Cyclization of Terminal Alkynes and Anilines to 3-Substituted Maleimides

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Abstract. Herein, we describe an interesting palladium-catalyzed protocol for the carbonylative synthesis of 3-substituted maleimides. By annulation of simple anilines with terminal alkynes under carbon monoxide pressure, the desired 3-substituted maleimides can be obtained in 50-85% yields. Additionally, with the addition of phosphine ligand, maleic acid isoimide can be obtained from the same substrates as well. With the presence of $K_2S_2O_8$, the obtained maleic acid isoimide can be completely transformed to the corresponding maleimide.

Keywords: carbonylation; annulation; heterocycles synthesis; palladium catalyst; maleimides

Introduction

Maleimide is an important class of nitrogen-containing heterocycles with many potent applications in various areas (Figure 1).[1] Among all the maleimide analogues, 3-substituted maleimides are even more attractive. For example, biologically active α-2-adrenoceptor antagonist can be directly produced from the corresponding 3-substituted maleimide by asymmetric hydrogenation.[2] Additionally, they are ready for further modifications at the 4th position to produce the corresponding non-symmetrical 3,4-disubstituted products.[3] Although their obvious importance, synthetic methodologies for 3-substituted maleimides construction are still very limited. The known procedures are mainly based on the cross-coupling of aryl halides or aryldiazonium salts with maleimides.[4] Obviously, special effort should be given to overcome challenges between conversion and overreaction (give 3,4-disubstituted product).

On the other hand, transition-metal-catalyzed carbonylative transformations have found tremendous applications in organic synthesis. Through CO incorporation, a wide range of carbonyl-containing compounds can be prepared easily.[5] By using the proper substrates, heterocycles can be prepared in an atom-economical manner as well.[6,7] Among them, our group recently developed a rhodium-catalyzed carbonylation procedure for the synthesis of substituted maleimides.[6h] However, this procedure failed with terminal alkynes and only internal alkynes can be transformed and the products are limited to 3,4-disubstituted maleimides. More recently, Alper's group achieved a procedure on palladium-catalyzed chemo- and regioselective aminocarbonylation of alkynes with aminophenols.[11] The desired *α,β*-unsaturated amides were obtained in good to excellent yields. Additionally, Dyson, Liu and co-workers developed a palladium-catalyzed aminocarbonylation procedure for the synthesis of succinimide derivatives from alkynes and amines in the presence of *p*-TsOH.[6p] Inspired by these achievements and also as our continues interest in carbonylative synthesis of heterocycles, we describe here the first example on palladium-catalyzed carbonylative annulation of simple anilines and terminal alkynes. 3-Substituted maleimides were prepared in moderate to good yields.

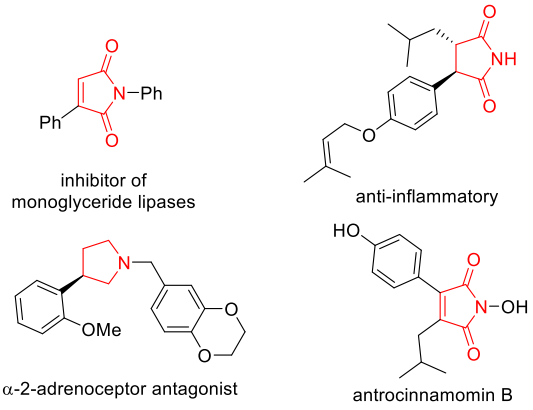

Figure 1. Selected examples of biologically active molecules featuring maleimides and derivatives.

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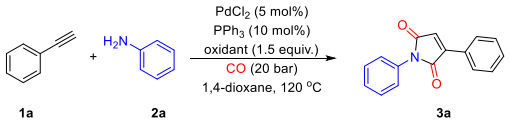
Results and Discussion

Initially, phenylacetylene (**1a**) and aniline (**2a**) were selected as the model substrates to establish this catalytic system (Table 1, also see SI). As shown in Table 1, the desired 1,3-diphenyl-*1H*-pyrrole-2,5-dione (**3a**) could not be detected with BQ (1,4-benzoquinone), Ag_2CO_3, Ag_2O, $Cu(OAc)_2$, or DTBP (di-*tert*-butyl peroxide) as the oxidant (Table 1, entries 1-5). To our delight, 45% yield of the desired product **3a** was obtained in the presence of 5 mol% of $PdCl_2$, 10 mol% of PPh_3 and 1.5 equiv. of $K_2S_2O_8$ under CO gas pressure (20 bar) in 1,4-dioxane at 120 °C for 24 h. Other solvents including toluene, DMF, DMSO, THF, and CH_3CN were tested as well, and 1,4-dioxane was found to be the most effective solvent (Table 1, entry 6). To our surprise, 55% yield of the desired product **3a** can be obtained in the absence of ligand (Table 1, entry 13, SI). Notably, 46% yield of the desired product can still be obtained with only 2.5 mol% of the catalyst (Table 1, entry 14). The ratio of the two substrates were checked as well, and the yield of **3a** can be improved to 63% with slightly excess (1.2 equiv.) of aniline (Table 1, entry 16). Notably, **3a** can be obtained in 71% yield by using 1 mol% of PTSA as the additive (Table 1, entry 17).

Table 1. Screening of Reaction Conditions.[a]



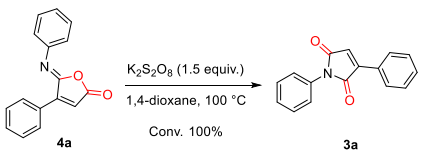
Entry	Catalyst	Ligand	Oxidant	Solvent	Yield[b]
1	$PdCl_2$	PPh_3	BQ	dioxane	trace
2	$PdCl_2$	PPh_3	Ag_2CO_3	dioxane	n.r.
3	$PdCl_2$	PPh_3	Ag_2O	dioxane	n.r.
4	$PdCl_2$	PPh_3	$Cu(OAc)_2$	dioxane	n.r.
5	$PdCl_2$	PPh_3	DTBP	dioxane	n.r.
6	$PdCl_2$	PPh_3	$K_2S_2O_8$	dioxane	45%
7	$PdCl_2$	PPh_3	$K_2S_2O_8$	Toluene	13%
8	$PdCl_2$	PPh_3	$K_2S_2O_8$	DMF	trace
9	$PdCl_2$	PPh_3	$K_2S_2O_8$	DMSO	trace
10	$PdCl_2$	PPh_3	$K_2S_2O_8$	THF	35%
11	$PdCl_2$	PPh_3	$K_2S_2O_8$	CH_3CN	29%
12	$PdCl_2$	PPh_3	$K_2S_2O_8$	DME	13%
13	$PdCl_2$	-	$K_2S_2O_8$	dioxane	55%
14[c]	$PdCl_2$	-	$K_2S_2O_8$	dioxane	46%
15[d]	$PdCl_2$	-	$K_2S_2O_8$	dioxane	56%
16[e]	$PdCl_2$	-	$K_2S_2O_8$	dioxane	63%
17[e,f]	$PdCl_2$	-	$K_2S_2O_8$	dioxane	71%

[a] Reaction conditions: phenylacetylene **1a** (0.4 mmol), aniline **2a** (0.2 mmol), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), oxidant (0.3 mmol), 1,4-dioxane (2 mL), 20 bar CO at 120 °C, 24 h.
[b] GC yield by using hexadecane as an internal standard.
[c] $PdCl_2$ (2.5 mol%).
[d] $PdCl_2$ (10 mol%).
[e] Phenylacetylene **1a** (0.2 mmol), aniline **2a** (0.24 mmol).
[f] *p*-Toluenesulfonic acid monohydrate (1 mol%) as the additive.

Interestingly, a 1:1.2 ratio mixture of the two products **3a** and **4a** were formed when 2,6-dimethoxy-1,4-benzoquinone used as the oxidant in the presence of 10 mol% PPh_3, (Table 2, entry 1). The molecular structure of the product **4a** was confirmed by X-ray diffraction (Figure 2), and known as maleic acid isoimide which is widely used as reactive intermediates for polyamides, polymerizable surfactants, and *β*-lactams synthesis.[8] They are usually prepared by condensation reaction.[9] To the best of our knowledge, this is the first example on palladium-catalyzed carbonylative annulation of simple aniline and terminal alkyne to synthesize maleic acid isoimide.

Figure 2. ORTEP representation of **4a** (CCDC 1843193). Displacement ellipsoids correspond to 30% probability.[12]

In order to improve the chemoselectivity of **4a**, we subsequently screened various ligands. As shown in Table 2, diphosphine ligands were less effective on this transformation, in the respect of both reactivity and selectivity (Table 2, entries 5-7). Monophosphine with bulky substitution, such as tri-*tert*-butylphosphine and **L2**, facilitated the formation of **3a** (Table 2, entries 4 and 11). Remarkably, the yield of **4a** can be improved to 33% when we use 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane[10] (CYTOP 292, **L8** here) as the ligand (Table 2, entry 17). The yield and chemoselectivity can be further improved with NPh_3 (10 mol%) as the additive (Table 2, entry 21, **3a**/**4a** = 1:3.3, 41% yield of **4a**). Further increase the loading of phosphine ligand resulted in decreased substrates conversion (Table 2, entry 25). And the ratio of **3a** and **4a** did not change by prolong the reaction time even to 40 hours. *However, we failed to drive the selectivity fully to produce maleic acid isoimide.* Here, it is also important to mention that maleic acid isoimide **4a** can be completely transformed to **3a** with $K_2S_2O_8$ as the promotor in 1,4-dioxane at 100°C for 8 h. (Scheme 1).



Scheme 1. The conversion from **4a** to **3a**. Determined by GC and TLC after reaction.

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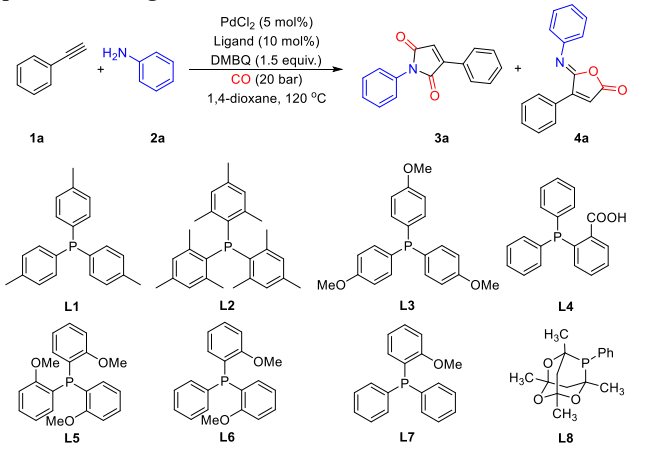
With the optimized conditions in hand (Table 1, entry 17), a range of substituted alkynes and amines were investigated. As summarized in Scheme 2, a series of terminal alkynes and anilines were smoothly transformed under identical conditions and gave the desired products in 50-85% yields. For anilines, the electronic properties of the substituent on the aromatic ring have little influence on the reaction outcomes. Both electron-withdrawing and electron-donating groups were well tolerated. Anilines with fluoro, chloro, and bromo substituents were also well tolerated and provide the corresponding products in moderate to good yields (**3d**, **3e**, and **3f**). These halogen substituents are ready for further transformations by cross-coupling reactions. However, our procedure failed when quinolin-5-amine and 2-methylbenzofuran-5-amine were tested with phenylacetylene under our standard conditions. Cyclohexylamine, as an example of aliphatic amine, was tested under our standard conditions as well. However, no desired product can be detected but the phenylacetylene homo-coupling product and together with a small amount of N^1,N^2-dicyclohexyloxalamide.

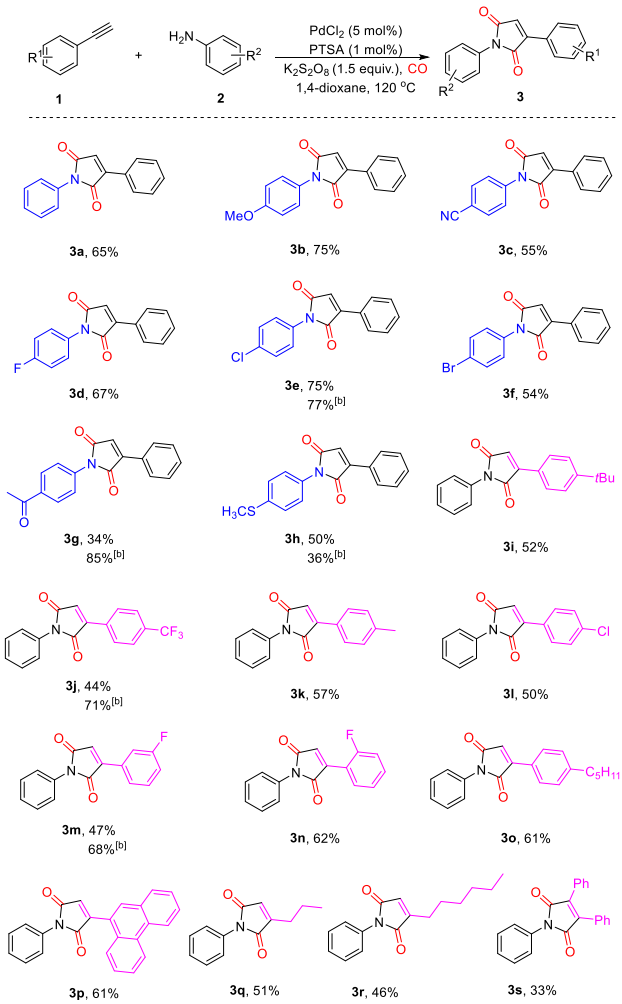
Table 2. Optimization of reaction conditions using 2,6-dimethoxy-1,4-benzoquinone as the oxidant in the presence of ligands.[a]



Entry	Ligand	Add.[c]	Conv.[b]	3a:4a [b]	Yield 4a[b]
1	PPh_3	-	48%	1:1.2	26%
2	PCy_3	-	30%	3.3:1	7%
3	TFP	-	48%	2.2:1	15%
4	$P(n\text{-}Bu)_3$	-	51%	9:1	5%
5	DPEPhos	-	34%	3.8:1	7%
6	dppp	-	22%	4.5:1	4%
7	BINAP	-	44%	7.8:1	5%
8	JohnPhos	-	13%	>99:1	-
9	$P(O)Ph_3$	-	67%	8.5:1	7%
10	L1	-	54%	1.1:1	26%
11	L2	-	42%	6:1	6%
12	L3	-	44%	1:1.1	23%
13	L4	-	50%	7.3:1	6%
14	L5	-	41%	1.2:1	19%
15	L6	-	42%	2:1	14%
16	L7	-	31%	1.2:1	14%
17	L8	-	49%	1:2	33%
18	L8	Et_3N	11%	>99:1	-
19	L8	DBU	-	-	-
20	L8	TBAC	18%	5:1	3%
21	L8	NPh_3	53%	1:3.3	41%
22[d]	L8	NPh_3	54%	1:1.7	34%
23[e]	L8	NPh_3	46%	1:1.1	24%
24[f]	L8	NPh_3	44%	1:4.5	36%
25[g]	L8	NPh_3	44%	1:3	33%

[a] Reaction conditions: phenylacetylene **1a** (0.4 mmol), aniline **2a** (0.2 mmol), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), DMBQ (0.3 mmol), 1,4-dioxane (2 mL), 20 bar CO at 120 °C, 20h. DMBQ = 2,6-dimethoxy-1,4-benzoquinone, TFP = tri-(2-furyl)-phosphine, DPEPhos = bis(2-diphenylphosphinophenl)ether, JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl, $P(O)Ph_3$ = triphenylphosphine oxide, TBAC = tetrabutyl ammonium chloride.
[b] Determined by GC using hexadecane as an internal standard.
[c] 10 mol% additive.
[d] Reaction at 100 °C.
[e] 15 bar CO.
[f] 15 mol% L8.
[g] 20 mol% L8.

Scheme 2. Substrates scope of anilines and terminal alkynes.



Reaction conditions: terminal alkynes **1a** (0.4 mmol), anilines **2a** (0.48 mmol), $PdCl_2$ (5 mol%), PPh_3 (10 mol%),

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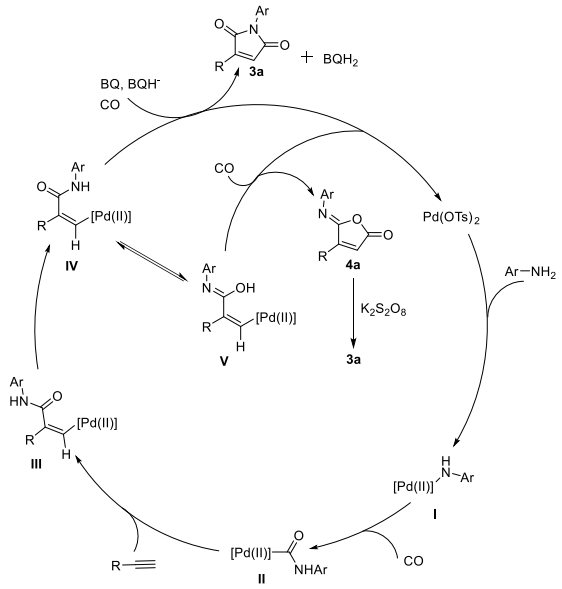
$K_2S_2O_8$ (0.6 mmol), PTSA (1 mol%), 1,4-dioxane (4 mL), 20 bar CO at 120 °C, 24 h. [b] Terminal alkynes **1a** (0.4 mmol), anilines **2a** (0.2 mmol), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), 2,6-dimethoxy-1,4-benzoquinone (0.6 mmol), PTSA (10 mol%), 1,4-dioxane (4 mL), 20 bar CO at 120 °C, 24 h.

Subsequently, a series of alkynes were also tested. Substrates with electron-donating or electron-withdrawing group were well tolerated and the corresponding 3-substituted maleimides were obtained in good yields (**3i** and **3j**). Furthermore, phenylacetylene bearing substituents with halogen at the *ortho*-, *para*- or *meta*-position of the phenyl ring were converted into the corresponding products in good yields as well (**3l**, **3m** and **3n**). 9-Ethynylphenanthraene substituted with a sterically hindered group can also gave the desired product in 61% yield **(3p)**. Additionally, aliphatic terminal alkyne can be successfully applied as well and give the target product in good yields (**3q**, **3r**). Additionally, internal alkyne can also be applied and gave the desired 3,4-disubstituted products in moderate yield (**3s**). However, no desired products could be detected when 3-ethynylpyridine, 3-ethynylthiophene and 3-methoxyprop-1-yne were tested with aniline under our best conditions.

Concerning the reaction pathway, based on our results and literatures,[11] a possible reaction mechanism is proposed and shown in Scheme 3. The reaction started with $Pd(OTs)_2$ which was produced in-situ from $PdCl_2$ and PTSA, after X ligand exchange with aniline to give the amino-palladium complex **I**. Then CO coordinates and inserts to produce complex **II**. After interaction with alkyne, vinyl palladium complex **III** will be formed. After rotation and the second CO insertion, the final maleimide will be eliminated after reductive elimination.[13] Then the formed Pd(0) will be re-oxidized and gave the active Pd(II) for the next catalytic cycle. In the case of using $K_2S_2O_8$ as the oxidant, **4a** can be transformed into **3a** completely. However, DMBQ cannot promote such transformation.



Scheme 3. Proposed Mechanism.

Conclusion

In summary, we have developed an interesting palladium-catalyzed carbonylative annulation procedure for the synthesis of 3-substituted maleimides from simple anilines and terminal alkynes. By modifying the reaction conditions, maleic acid isoimide can be formed as well which can be further transformed into the corresponding maleimides in the presence $K_2S_2O_8$. Notably, to the best of our knowledge, this is the first example on palladium-catalyzed carbonylative synthesis of 3-substituted maleimides from anilines and terminal alkynes.

Experimental Section

General produce of palladium-catalyzed carbonylative annulation.

A 7 mL screw-cap vial was charged with $PdCl_2$ (3.6 mg, 0.02 mmol, 5 mol%), *p*-toluenesulfonic acid monohydrate (0.8 mg, 1 mol%), $K_2S_2O_8$ (162 mg, 0.6 mmol) and an oven-dried stirring bar. The vial was closed by Teflon septum and phenolic cap and connected with atmosphere with a needle. Then a 1,4-dioxane (4 mL) solution of phenylacetylene (0.4 mmol) and aniline (0.48 mmol) was injected by syringe. The vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 mL) under argon atmosphere. At room temperature, the autoclave is flushed with carbon monoxide for three times and 20 bar of carbon monoxide was charged. The autoclave was reacted at 120 °C for 24 hours. After the reaction had finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The reaction mixture was diluted with water and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was adsorbed on silica gel and the crude product was purified by column chromatography using *n*-pentane/EtOAc as eluent.

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[12] CCDC 1843193 (**4a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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FULL PAPER

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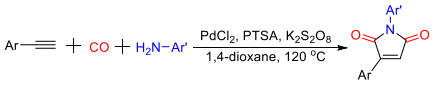

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