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Pd/Cu-catalyzed oxidation of alkynes into 1,2-diketones using DMSO as the oxidant

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ABSTRACT

A facile and practical method for the palladium/copper-catalyzed transformation of internal alkynes into 1,2-diketones has been described, affording the desired products in moderate to excellent yields. The mechanistic studies were also preliminarily pursued using diphenyl sulfoxide as the oxidant, and the diphenyl sulfide was isolated as the reduced product.

1. Introduction

1,2-Dicarbonyl derivatives are very useful building blocks in the construction of a variety of organic intermediates,[1] especially in the synthesis of biologically active heterocyclic compounds,[2] such as imidazoles, quinoxalines, and indolone-*N*-oxide.[3] Some of these compounds show good antitumor activity or/and can be used as selective cyanide anion indicators or photoinitiators.[4]

Over the past decade, lots of synthetic protocols for the preparation of 1,2-diaryldiketones have been reported.[5] Since the internal alkynes as the starting material could be easily accessible via Sonogashira coupling,[6] the direct oxidation of internal alkynes into 1,2-dicarbonyl derivatives appears to be one of the most straightforward methods. Great progress on this type of transformation has been made during the last few years. For example, Yusubov and Chi introduced the $PdCl_2$ catalyzed oxidation of internal alkynes in DMSO, while the scope of this reaction was quite narrow and only two examples (1-phenylprop-1-yne and 1-phenylpent-1-yne) were involved.[5m] Subsequently, Wan's group reported palladium-catalyzed synthesis of 1,2-diketones via the oxidation of internal alkynes using oxygen as the oxidant.[5d] And then, Li and co-workers described a Au/Ag-catalyzed protocol, which could undergo in mild conditions using diphenyl sulfoxide as oxidant, which enlightened us on the essence of sulfoxide in these reactions.[5b] Inspired by these promising reports, our work was focused on the direct palladium/copper-catalyzed oxidation of internal alkynes into 1,2-dicarbonyl derivatives in DMSO. In this transformation, the DMSO would also behave as an oxidant.

2. Results and discussion

In our initial study, we launched our efforts to transform 1,2-diphenylethyne (**1a**) to the benzil (**2a**), and the product (**2a**) could be obtained in a yield of 17% in DMSO after 20 h using $Pd(OAc)_2$ as the catalyst in the absence of the cocatalyst (Table 1, entry 1). Gratifyingly, with the addition of the cocatalyst (e.g., $FeCl_3$ and $CuBr_2$), the yield of the desired product could increase dramatically, albeit the reaction did not occur at all with AgOAc as the cocatalyst (Table 1, entries 2–4). Especially, with $CuBr_2$ as the cocatalyst, the benzil (**2a**) could be afforded in a yield of 99% (Table 1, entry 4), while the desired product was not observed at all in the absence of the palladium catalyst (Table 1, entry 5). These results indicated that both of the palladium and copper species played a critical role on the catalytic efficiency (Table 1, entries 1–5). However, when the reaction time or temperature decreased to 12 h and 80 °C, the reaction only gave the benzil in yields of 78% and 72%, respectively (Table 1, entries 6 and 7). This oxidative reaction could also be performed in DMSO under the nitrogen atmosphere,

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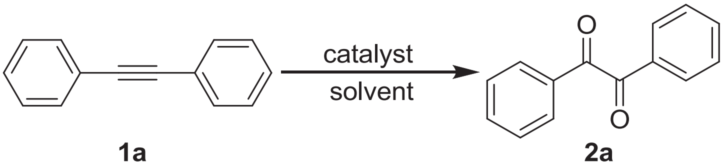
Table 1
Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	*t* (h)	*T* (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	DMSO	20	120	17
2	$Pd(OAc)_2/AgOAc$	DMSO	20	120	0
3	$Pd(OAc)_2/FeCl_3$	DMSO	20	120	93
4	**$Pd(OAc)_2/CuBr_2$**	**DMSO**	**20**	**120**	**99**
5	$CuBr_2$	DMSO	20	120	0
6	$Pd(OAc)_2/CuBr_2$	DMSO	12	120	78
7	$Pd(OAc)_2/CuBr_2$	DMSO	84	80	72
8[c]	$Pd(OAc)_2/CuBr_2$	DMSO	20	120	95
9	$PdCl_2/CuBr_2$	DMSO	20	120	90
10	$Pd(PPh_3)_2Cl_2/CuBr_2$	DMSO	20	120	90
11	$Pd(dba)_2/CuBr_2$	DMSO	20	120	70
12	$Pd(OAc)_2/CuBr_2$	Dioxane	20	100	0
13	$Pd(OAc)_2/CuBr_2$	DMF	20	120	0
14	$Pd(OAc)_2/CuBr_2$	DMA	20	120	0

Bold values in entry 4 represents the optimal conditions.

[a] Reaction conditions: 0.5 mmol **1a** and 10 mol % of catalyst in 2 mL solvent in air.

[b] Isolated yield.

[c] Under the nitrogen atmosphere.

generating the benzil in 95% yield (Table 1, entry 8). Then, other palladium catalysts were evaluated and the benzil was formed in moderate to good yields (Table 1, entries 9–11). Some other solvents such as dioxane, DMF and DMA were also examined, and no product was detected (Table 1, entries 12–14).

With the optimized reaction conditions in hand, the scope of the oxidation of alkynes was explored (Tables 2 and 3). Generally, the substituent and electronic effects have no significant influence on this transformation, and the reaction could tolerate a broad scope of substituents such as MeO, CHO, NO_2, CN, $SiMe_3$, and F, affording the desired products in moderate to good yields (Table 2). It should be noted that the oxidation of some heterocyclic and fused aromatic ring alkynes could also afford the corresponding 1,2-dicarbonyl derivatives in good yields (Table 3, entries 1–3). However, when one of the two substituents is an alkyl group (**1r**), the oxidation only gave the product in a low yield of 33% (Table 3, entry 4).

This oxidative reaction could generate the benzil in 95% yield under the nitrogen atmosphere, which suggested that the solvent (DMSO) may serve as an oxidant (Table 1, entry 8). To clarify the mechanism of the oxidation of internal alkynes, mechanistic studies were also pursued (Scheme 1). According to this hypothesis, the reductive product of DMSO would be dimethyl sulfide. But unfortunately, dimethyl sulfide is quite volatile, which is difficult to be detected. So we took diphenyl sulfoxide (**3**) instead of DMSO, and diphenyl sulfide (**4**) as the reductive product could be detected and isolated easily. However, diphenyl sulfoxide is a solid and cannot be used as the solvent, and thus the reaction was performed

Table 2
Oxidation of alkynes[a]

Entry	R¹	R²	Substrate	Product/yield[b] (%)
1	H	Me	**1b**	**2b**, 83
2	H	*tert*-Butyl	**1c**	**2c**, 78
3	H	MeO	**1d**	**2d**, 70
4	H	*n*-$C_5H_{11}O$	**1e**	**2e**, 85
5	H	NO_2	**1f**	**2f**, 65
6	H	CN	**1g**	**2g**, 75
7	H	CHO	**1h**	**2h**, 88
8	H	F	**1i**	**2i**, 80
9	H	$SiMe_3$	**1j**	**2j**, 90
10	Et	Me	**1k**	**2k**, 91
11	Et	MeO	**1l**	**2l**, 87
12	*n*-C_5H_{11}	MeO	**1m**	**2m**, 71
13	*tert*-Butyl	CN	**1n**	**2n**, 75

[a] Reaction conditions: 0.5 mmol alkyne, 10 mol % of $Pd(OAc)_2$ and 10 mol % of $CuBr_2$ in 2 mL DMSO at 120 °C in air for 20 h.

[b] Isolated yield.