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Synthesis of Ynones by Palladium-Catalyzed Acylation of Terminal Alkynes with Acid Chlorides

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Phosphane-free oxime-derived palladacycle **2** is an efficient precatalyst for the copper-free acylation of terminal alkynes with different carboxylic acid chlorides in toluene in the presence of 3 equiv of TEA as base, giving the corresponding ynones in good yields. The coupling reaction can normally be performed under air or under inert atmosphere when very low catalyst loadings (10^{-3} mol % Pd) (turnover numbers (TONs) up to 23 000, turnover frequencies (TOFs) up to 958 h^{-1}) or sensitive carboxylic acid chlorides are used. In addition, $Pd(OAc)_2$ has been shown as an efficient catalyst for the ligandless process, although usually working under higher loading conditions. This new protocol allows one to perform the synthesis of ynones at 110 °C, at room temperature, or under microwave irradiation conditions.

Introduction

α,β-Acetylenic carbonyl derivatives have become compounds of considerable interest because of their widespread occurrence among natural products and their utility as synthetic intermediates. They have mainly been used in the preparation of heterocyclic derivatives, such as pyrroles,[1] furans,[2] furanones,[3] pyrazoles,[4] isoxazoles,[5] indolizidinones,[6] pyrimidines,[7] pyridopyrimidines,[8] pyridinones,[9] and quinolines.[10] Ynones and ynoates have also been employed in the synthesis of natural products with significant biochemical activity, such as nucleosides,[11] sex-pheromones,[12] alkaloids,[13] lembehynes B and C,[14] leukotriene B_4,[15] and incrustoporin.[16] Very recently, they have also been used in the synthesis of 1,3-diethynylallenes, a new family of modules for three-dimensional acetylenic scaffolding.[17]

Considerable effort has been devoted to the preparation of conjugated acetylenic carbonyl compounds based on a wide variety of synthetic approaches, including the oxidation of propargylic alcohols,[18] which are usually obtained by stoichiometric nucleophilic addition of metal acetylides to aldehydes[19] (Scheme 1, path a). Alternatively, to avoid the oxidation step, it is possible to carry out the addition of the corresponding metal acetylides[20] to carboxylic acid derivatives such as acid chlorides, acid anhydrides, esters, and acyl cyanides (Scheme 1, path b). α,β-Acetylenic carbonyl derivatives can also be synthesized using transition metal-catalyzed methods, such as the palladium-catalyzed[21] cross-coupling reaction of terminal alkynes,[22] or the metalated derivatives,[23] with

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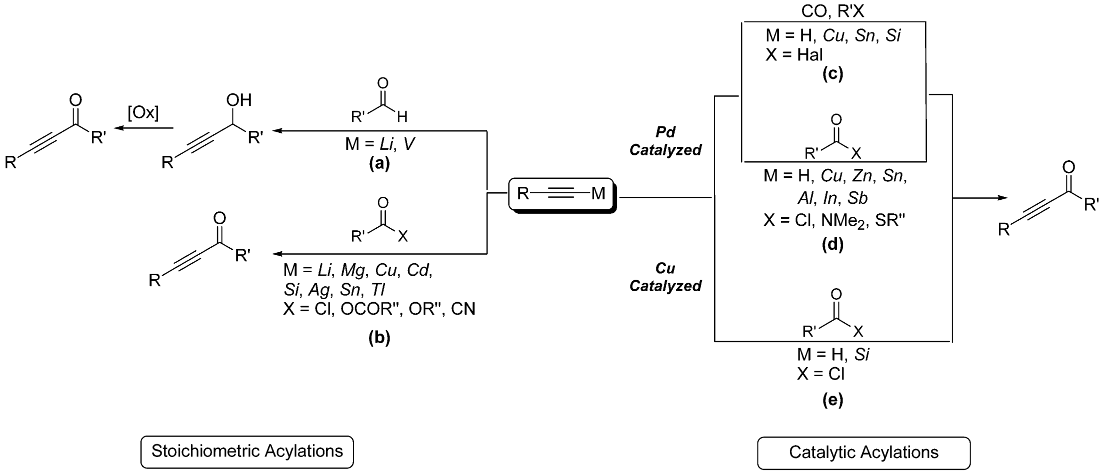
SCHEME 1. Synthesis of α,β-Acetylenic Carbonyl Derivatives



organic halides in the presence of carbon monoxide (Scheme 1, path c). However, to avoid the use of toxic CO, phosphane-based palladium-catalyzed carbon monoxide-free protocols have been developed using carboxylic acid derivatives as CO source[24] and the corresponding copper,[7a,25] zinc,[26] tin,[27] aluminum,[28] indium,[29] or antimony[30] acetylides, generated either catalytically, for copper acetylides, or stoichiometrically (Scheme 1, path d). Similarly, the Cu(I)-catalyzed acylation of terminal alkynes and alkynylsilanes with acid chlorides, employing toluene[31] or an amine, such as triethylamine (TEA) for terminal alkynes[11b,32] and 1,3-dimethylimidazolidinone (DMI) for alkynylsilanes,[33] as solvent (Scheme 1, path e), has also been reported. The main disadvantage of this Cu(I)-catalyzed protocol is the high catalyst loadings required (5−20 mol %).

From a synthetic point of view, mainly the palladium and/or copper-catalyzed processes have become of interest.[34] To the best of our knowledge, only one report has appeared in the literature on the reaction coupling of terminal alkynes with alkyl chloroformates to afford ynoates (Scheme 1, path d), employing, as a unique catalyst, high loadings (2.2 mol % Pd) of different phosphane-containing palladium complexes including Herrmann's palladacycle **1** (Figure 1).[35] However, the acylation of terminal alkynes with carboxylic acid chlorides under palladium catalysis conditions to give ynones has not been described.

Very recently, we have shown that oxime-based palladacycles are very efficient precatalysts in several carbon−carbon bond forming processes such as the Mizoroki−Heck,[36a,b,37c] Suzuki−Miyaura,[36a,c,37a,b] Ullmann,[36a,c] Sonogashira−Hagihara,[36d,e] Sila−Sonogashira,[36e] and Glaser type[36e] reactions, in both organic[36] and aqueous[37] solvents. In this work, we describe a novel, straightforward copper-free method for the preparation of ynones through the palladium-catalyzed reaction of 1-alkynes with different carboxylic acid chlorides, employing palladacycle **2** derived from 4,4′-dichlorobenzophenone (Figure 1) or $Pd(OAc)_2$ under ligandless, mild, and convenient reaction conditions.

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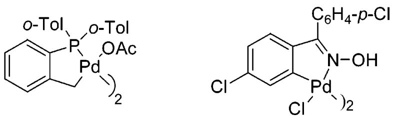
TABLE 1. Reaction Conditions Optimization[a]

entry	Pd catalyst (mol % Pd)	solvent	base (equiv)	additive (mol %)	T^b (°C)	t (h)	yield^c (%)
1	**2** (1)	NMP	Bu_4NOAc (1.5)		110	23	
2	**2** (0.5)	TEA			80	1	97 (66)
3	**2** (0.1)	TEA			80	1	30
4	**2** (2.5)	CH_3CN	TEA (1)		110	7	90
5	**2** (2.5)	CH_3CN	TEA (1)	CuI (2)	110	7	69^d
6	**2** (2.5)	CH_3CN	TEA (1)	CuI (5)	110	7	71^e
7	**2** (0.1)	toluene	TEA (2)		110	4.5	91 (60)
8	**2** (0.5)	toluene	i-Pr_2NEt (2)		110	2	45
9	**2** (0.1)	toluene	Bu_3N (2)		110	4	9
10	**2** (0.1)	toluene	DBU (2)		110	1	
11	**2** (0.1)	toluene	K_2CO_3 (2)		110	4	
12	**2** (0.5)	toluene	TEA (2)		110	1	>99 (70)^f
13	**2** (0.2)	toluene	TEA (0.5)		110	1	32
14	**2** (0.2)	toluene	TEA (1)		110	1	57
15	**2** (0.2)	toluene	TEA (3)		110	1	97 (75)
16	$Pd(OAc)_2$ (0.2)	toluene	TEA (3)		110	1	95 (70)
17	**2** (10^{-2})	toluene	TEA (3)		110	24	65^{g,h}
18	$Pd(OAc)_2$ (10^{-2})	toluene	TEA (3)		110	24	54^g
19	**2** (10^{-3})	toluene	TEA (3)		110	24	23^{g,i}
20	**2** (0.2)	toluene	TEA (3)		25	25	41^g
21	**2** (0.5)	toluene	TEA (3)		25	23	96^g
22	**2** (0.2)	toluene	TEA (3)		80	0.1	88^j

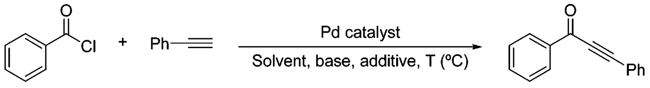
[a] Reaction conditions: phenylacetylene (0.5 mmol), benzoyl chloride (1 mmol), base, Pd catalyst, solvent (2 mL). [b] Bath temperature. [c] Conversion determined by GC on the basis of phenylacetylene using decane as internal standard. In parentheses, isolated yield after florisil chromatography. [d] A 4% yield of 1,4-diphenylbutadiyne was also obtained. [e] A 6% yield of 1,4-diphenylbutadiyne was also obtained. [f] Average of two runs. [g] The reaction was carried out under argon atmosphere employing dry toluene and dry TEA. [h] TON (moles of product per mole of Pd) = 6500. [i] TON = 23 000; TOF = 958 h^{-1}. [j] The reaction was performed under microwave irradiation conditions (120 W, hold time of 5 min).



1 **2**

FIGURE 1. Palladacycle catalysts for acylation of terminal alkynes.

SCHEME 2. Reaction Conditions Optimization



3a

Results and Discussion

The coupling between phenylacetylene and benzoyl chloride was chosen as a model reaction to find out the optimum reaction conditions (Scheme 2 and Table 1). It was observed that the usual conditions described for the copper- and amine-free Sonogashira type coupling between terminal alkynes and aryl halides catalyzed by oxime-derived palladacycles,[36d,e] that is, *N*-methylpyrrolidinone (NMP) as solvent and tetrabutylammonium acetate (TBAOAc) as base at 110 °C in the presence of 0.5 mol % **2**, failed for the acylation process (Table 1, entry 1). However, when the reaction was performed in TEA as solvent at 80 °C[25] in the presence of 0.25 mol % compound **2**, an excellent 97% conversion of 1,4-diphenyl-2-propyn-1-one (**3a**) was obtained (Table 1, entry 2). Unfortunately, under these reaction conditions, the conversion decreased significantly to 30% when the catalyst loading was reduced to 0.1 mol % Pd (Table 1, entry 3). Other solvents such as CH_3CN in the presence of 1 equiv of TEA under reflux conditions required higher catalyst loadings (2.5 mol % Pd) (Table 1, entry 4). The presence of CuI as cocatalyst (Table 1, entries 5 and 6) had a deleterious effect over the reaction scope, and the formation of 1,4-diphenyl-1,3-butadiyne as byproduct was also observed.[36e] The employment of toluene as solvent in the presence of 2 equiv of TEA led to a very efficient process (91% reaction conversion after 4.5 h), even under low catalyst loadings (Table 1, entry 7). When the coupling reaction was carried out in toluene in the presence of other bases, such as Hünig's base, tri-*n*-butylamine (n-Bu_3N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or K_2CO_3, very poor results were obtained (Table 1, entries 8−11). Finally, the use of toluene as solvent, 3 equiv of TEA, and 0.2 mol % Pd at 110 °C provided the most appropriate conditions, leading to a longer lifetime for the catalyst (Table 1, entries 12−15).

With respect to the palladium catalyst, the use of $Pd(OAc)_2$ was also efficient under the above-mentioned optimized conditions (Table 1, entry 16). Under lower catalyst loadings (10^{-2} mol % Pd) (Table 1, entries 17 and 18), palladacycle **2** was slightly more active than $Pd(OAc)_2$. However, higher turnover numbers (TONs up to 23 000) and turnover frequencies (TOFs up to 958 h^{-1}) were observed employing palladacyle **2** (10^{-3} mol % Pd) (Table 1, entry 19), with $Pd(OAc)_2$ failing under these low loading conditions. Under such very low catalyst loadings, it was necessary to work under anhydrous conditions (argon atmosphere and dry solvent and base), to avoid the formation of undesirable benzoic anhydride. This deleterious side reaction is an important obstacle for the palladium-catalyzed process, since carboxylic acid anhydrides are nonreactive substrates in the acylation process under the tested reaction conditions.[38] However, under anhydrous conditions, the formation of benzoic anhydride was nearly completely inhibited and the rate of the acylation process increased.

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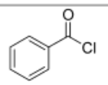
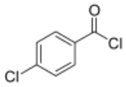
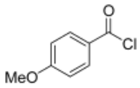
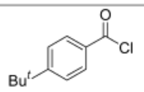
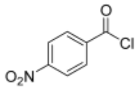
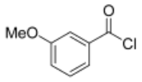
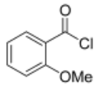
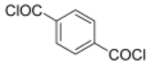
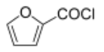
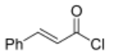
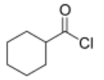
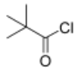
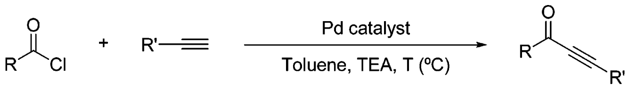
TABLE 2. Palladium-Catalyzed Acylation of Terminal Alkynes with Acid Chlorides[a]

Entry	Pd catalyst (mol% Pd)	RCOCl	Alkyne	T (°C)	t (h)	Product no.	Product Yield (%)[b]
1	**2** (0.2)		Ph—≡	110	1	**3a**	97 (75)
2	$Pd(OAc)_2$ (0.2)			110	1	**3a**	95 (70)
3	**2** (0.5)			25	23	**3a**	96[c]
4	$Pd(OAc)_2$ (0.5)			25	23	**3a**	99[c]
5	**2** (0.2)		TIPS—≡	110	7	**3b**	82 (61)
6	$Pd(OAc)_2$ (0.2)			110	7	**3b**	56
7	**2** (0.5)			25	24	**3b**	21[c]
8	$Pd(OAc)_2$ (0.5)			25	24	**3b**	19[c]
9	**2** (0.5)		C_6H_{13}—≡	110	6	**3c**	63 (35)[f]
10	$Pd(OAc)_2$ (0.5)			110	6	**3c**	73[c]
11	**2** (0.5)			25	23	**3c**	6[c]
12	$Pd(OAc)_2$ (0.5)			25	23	**3c**	6[c]
13	**2** (0.2)		Ph—≡	110	2.5	**3d**	99 (72)
14	**2** (0.2)		Ph—≡	110	4	**3e**	93 (70)
15	**2** (0.2)		Ph—≡	110	7	**3f**	87 (55)
16	**2** (0.2)		Ph—≡	110	4	**3g**	62
17	**2** (0.2)		Ph—≡	110	10	**3h**	56
18	**2** (0.2)		Ph—≡	110	13.5	**3i**	99
19	**2** (0.2)		Ph—≡	110	21	**3j**	68 (20)[c,d]
20	**2** (0.2)		Ph—≡	110	4	**3k**	84 (50)
21	**2** (0.2)		Ph—≡	110	3	**3l**	97 (77)[e]
22	**2** (0.2)		Ph—≡	110	4	**3m**	94 (60)
23	**2** (0.2)		Ph—≡	110	4	**3n**	100 (99)[f]

[a] Reaction conditions: alkyne (0.5 mmol), aroyl chloride (1 mmol), TEA (1.5 mmol), Pd catalyst, toluene (2 mL). [b] Conversion determined by GC on the basis of the starting alkyne using decane as internal standard. In parentheses, isolated yield after florisil chromatography. [c] The reaction was carried out under argon atmosphere, employing dry toluene and dry TEA. [d] 2.5 equiv of phenylacetylene was used. [e] Isolated yield when the reaction was scaled up to 5 mmol of alkyne. [f] The crude product was pure by ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectroscopy.

SCHEME 3. Palladium-Catalyzed Acylation of Terminal Alkynes with Acid Chlorides



3

Catalyst **2** also promoted the acylation coupling at room temperature, though it was again necessary to work under inert reaction conditions and higher catalyst loading (0.5 mol % Pd) (Table 1, entries 20 and 21). The coupling reaction can also be performed under microwave irradiation,[39] which drastically reduced the reaction time to 5 min (Table 1, entry 22).

The application of the palladium-catalyzed protocol to the general synthesis of ynones was studied with different acyl chlorides and terminal alkynes (Scheme 3 and Table 2). Thus, the cross-coupling reaction between benzoyl chloride and different terminal alkynes such as phenylacetylene, tris(isopropylsilyl)acetylene, and 1-octyne was first evaluated at 110 °C and at room temperature, employing palladacycle **2** or $Pd(OAc)_2$ as precatalyst (Table 2, entries 1−12). In general, at 110 °C, the reaction was faster when phenylacetylene was used as sp counterpart. At this temperature, the coupling of benzoyl chloride and 1-octyne had to be performed in the presence of higher catalyst loading (0.5 mol % Pd) and under argon atmosphere to avoid the formation of the corresponding anhydride (Table 2, entries 9 and 10). With respect to the palladium catalyst, both $Pd(OAc)_2$ and oxime-derived palladacycle **2** gave very similar and satisfactory results, working at 110 °C. When the reactions were performed at room temperature, only phenylacetylene gave high yields of the corresponding alkynone. Other aroyl chlorides such as 4-chlorobenzoyl, 4-anisoyl, 4-*tert*-butylbenzoyl, and 4-nitrobenzoyl chlorides were coupled with phenylacetylene at 110 °C in the presence of **2**, affording the corresponding products **3d**−**g** also with good yields (Table 2, entries 13−16). When the reaction was carried out with more sterically hindered *meta*- or *ortho*-substituted anisoyl chlorides (Table 2, entries 17 and 18), a decrease in the reaction rate was observed, although high conversions were still obtained. Terephthaloyl chloride reacted as well with an excess of phenylacetylene (2.5 equiv) to afford the corresponding diynone **3j** in a 68% conversion and a low 20% isolated yield, possibly due to the low stability of this compound (Table 2, entry 19). The heterocyclic derivative 2-furoyl chloride was likewise converted efficiently to the corresponding acetylenic derivative **3k** in a 50% isolated yield (Table 2, entry 20). Moreover, the reaction was very efficient in the case of using α,*β*-unsaturated acyl chlorides, such as cinnamoyl chloride, which afforded the corresponding

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(39) For the microwave-assisted Pd/Cu-catalyzed acylation coupling, see: Wang, J.-X.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* **2001**, *31*, 3337−3343. For the microwave-assisted Cu-catalyzed acylation coupling, see: Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* **2001**, *31*, 3527−3532.

product **3l** in a 97% conversion (77% isolated yield), even when the reaction was scaled up to 5 mmol of alkyne and carried out under air (Table 2, entry 21). This result shows the practical significance of the described methodology. Finally, it is also noteworthy to mention that the coupling reaction with phenylacetylene took place also with alkylic acid chlorides such as cyclohexanecarbonyl chloride and pivaloyl chloride with very good conversions and isolated yields (Table 2, entries 22 and 23).

With respect to the reaction mechanism, the absence of copper as cocatalyst in the process seems to point out a possible attack of an incipient acetylide anion on the acyl palladium intermediate, followed by reductive elimination of the ynone, as initially proposed by Cassar[40] and Heck[41] for the palladium-catalyzed cross-coupling reaction of terminal alkynes with aryl halides.

Conclusions

It can be concluded that the palladium-catalyzed acylation of terminal alkynes with carboxylic acid chlorides can be performed under mild copper- and phosphane-free conditions, employing either oxime-derived palladacycle **2** or $Pd(OAc)_2$ as catalyst in toluene as solvent and TEA as base. In general, palladacycle **2** performs better than $Pd(OAc)_2$ under very low catalyst loading conditions at 110 °C, whereas $Pd(OAc)_2$ gives very similar results at room temperature. The reaction coupling can normally be performed under air, although inert atmosphere has to be used under very low catalyst loadings or in the presence of sensitive carboxylic acid chlorides. The optimized protocol allows one to carry out the acylation reactions under microwave irradiation as well. This study shows the first example of a copper-free and non-phosphane-based palladium-catalyzed protocol for cross-coupling carboxylic acid chlorides and terminal alkynes to afford the corresponding ynones in good yields.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Acylation Coupling of 1-Alkynes and Carboxylic Acid Chlorides. A reaction tube from the carousel reaction equipment was charged with phenylacetylene (56 μL, 0.5 mmol), decane (97 μL, 0.5 mmol), benzoyl chloride (116 μL, 1 mmol), TEA (212 μL, 1.5 mmol), **2**[36b] (0.408 mg, 0.0005 mmol, 0.2 mol % Pd), and toluene (2 mL). The mixture was stirred at 110 °C or at rt in air or under argon atmosphere (see Tables 1 and 2), and the reaction progress was analyzed by GLC. After completion, the crude reaction mixture was extracted with water and EtOAc (3 × 15 mL). The organic phases were dried with $MgSO_4$ and evaporated (15 mmHg), and the resulting crude material was purified by florisil chromatography (hexane/EtOAc), affording pure diphenylpropynone (**3a**).

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Supporting Information Available: General experimental methods, typical experimental procedures, and analytical and spectral characterization data for all synthesized compounds (Table 2). This material is available free of charge via the Internet at http://pubs.acs.org.

JO035761+

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[40] Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253−257.

[41] Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259−263.