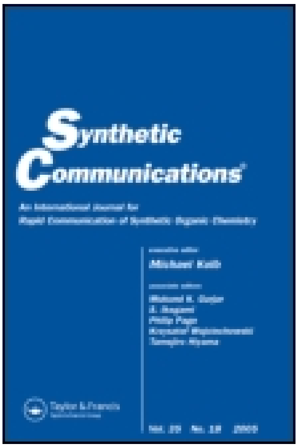

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Pd-Catalyzed Cross-Coupling of Acyl Chlorides with In Situ-Generated Alkynylzinc Derivatives for the Synthesis of Ynones

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Pd-CATALYZED CROSS-COUPLING OF ACYL CHLORIDES WITH IN SITU–GENERATED ALKYNYLZINC DERIVATIVES FOR THE SYNTHESIS OF YNONES

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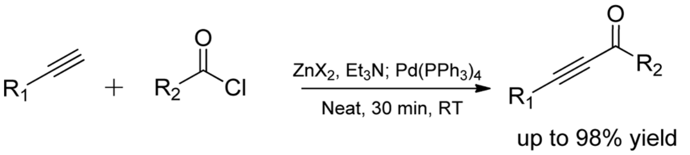
GRAPHICAL ABSTRACT



Abstract *A mild and operationally simple procedure by Pd-catalyzed cross-coupling of acyl chlorides with in situ–generated alkynylzinc derivatives was developed, giving the corresponding ynones in good yields.*

Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *full experimental and spectral details.*

Keywords Acyl chlorides; alkynylzinc; Pd-catalyzed; solvent-free; ynones

INTRODUCTION

Ynones are versatile building blocks for the synthesis of pharmaceutically significant and biologically active compounds, such as pyrroles,[1] pyrazoles,[2] isoxazoles,[3] pyrimidines,[4] quinolines,[5] and tetrahydro-β-carbolines.[6] Their preparation typically involves the reaction of alkynyl organometallic reagents of silver,[7] copper,[8] sodium,[9] lithium,[10] silicon,[11] tin,[12] cadmium,[13] or zinc[14] with acid chlorides and transition-metal-catalyzed carbonylation of haloalkanes with terminal alkynes in the presence of CO.[15] Most of the reported methods have poor yields, use harsh conditions, or require long reaction times. Among many synthetic strategies,

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the coupling reaction of acyl chlorides and terminal alkynes catalyzed by palladium catalysts has received much attention of late. However, these methods require preparation of some special heterogeneous catalysts[16] or conduct high temperatures.[17] We hope to explore a mild and operationally simple procedure for the synthesis of ynones using commercially available palladium catalysts.

The Pd-catalyzed cross-coupling of an organometal with an organic electrophile has emerged over the past 30 years as one of the most general and selective methods for carbon–carbon bond formation. Negishi et al.[18] reported a procedure for the synthesis of ynones by Pd-catalyzed cross-coupling of organozincs with acyl chlorides, but the procedure utilized organolithiums or Grignard reagents to form organozincs compounds and needs harsh conditions. Herein, we report the Pd-catalyzed cross-coupling of acyl chlorides with in situ–generated alkynylzinc derivatives for the synthesis of ynones. The reactions are performed as a mild and operationally simple procedure using reaction of free alkynes with acyl chlorides in the presence of premixed dry Et_3N, $ZnCl_2$ or $ZnBr_2$, and a suitable Pd catalyst.

RESULTS AND DISCUSSION

To reduce the chance of reaction between the acyl chloride component and the base,[19] we first tested the role of solvent for the coupling of benzoyl chloride (**1b**) with phenyl acetylene (**2a**) (Table 1). It was noted that dichloromethane (DCM) and Et_2O were good solvents for this coupling reaction. However, dipolar aprotic solvents, such as acetonitrile, dimethylformamide (DMF), and tetrahydrofuran (THF) gave inferior results with the formation of the corresponding anhydride as a by-product. To our surprise, when the reaction was performed under solvent-free conditions, the greatest yield of product was obtained. Consequently, all further reactions were performed neat under anhydrous conditions, and the results are recorded in Table 3.

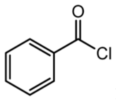
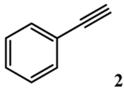
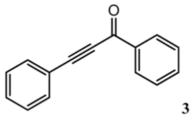
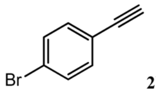
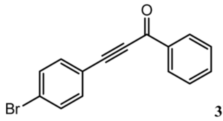
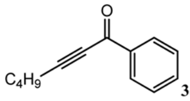
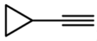
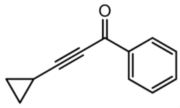
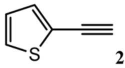
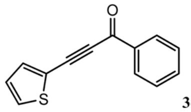
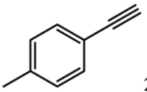
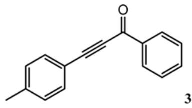
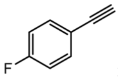
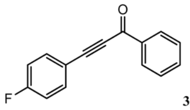
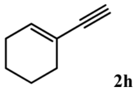
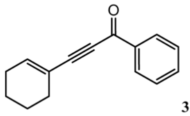
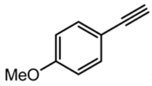
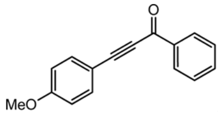
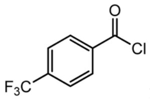
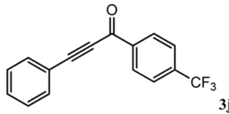
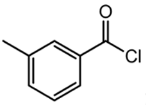
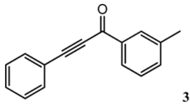
A classical catalyst ($Pd(PPh_3)_4$) for Negishi reaction was employed in this work and compound **3a** was obtained in excellent yield without formation of benzoic anhydride (Entry 1, Table 2). The reaction did not proceed without the Pd catalyst and yielded only benzoic anhydride (Entry 2, Table 2). In 2006, S. S. Palimkar[20] reported the palladium(II) acetate-catalysed acylation of terminal alkynes for the synthesis of ynones using Et_3N as base, but in our hand, only 60% yield of **3a** and

Table 1. Coupling reaction of benzoyl chloride (**1b**) with phenyl acetylene (**2a**) in the presence of different solvents[a]

Entry	Solvent	Yield[b] (%)
1	Acetonitrile	47
2	DMF	52
3	THF	58
4	DCM	85
5	Et_2O	83
6	Neat	95

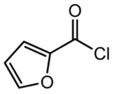
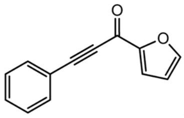
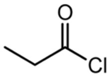
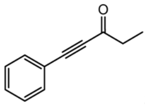
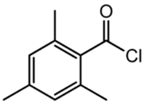
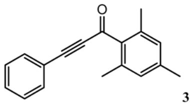
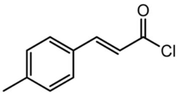
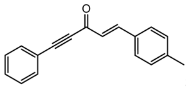
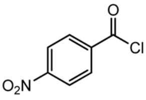
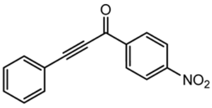
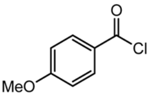
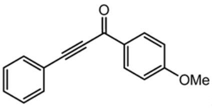
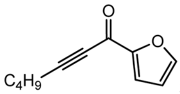
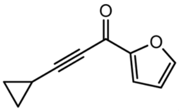
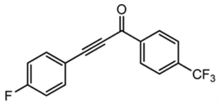
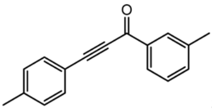
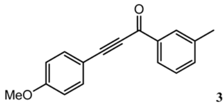
[a] Reaction conditions: acid chloride (1 mmol), 1-alkyne (1 mmol), $Pd(PPh_3)_4$ (0.5 mol %), $ZnCl_2$ (1.2 mmol), and Et_3N (2 mmol), 30 min.
[b] Isolated yields.

Table 2. Synthesis of ynones by coupling of acid chlorides with terminal alkynes[a]

Entry	Acyl chloride	Alkyne	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	95
2	**1a**	 **2b**	 **3b**	89
3	**1a**	C_4H_9—≡ **2c**	 **3c**	88
4	**1a**	 **2d**	 **3d**	94
5	**1a**	 **2e**	 **3e**	87
6	**1a**	 **2f**	 **3f**	89
7	**1a**	 **2g**	 **3g**	93
8	**1a**	 **2h**	 **3h**	95
9	**1a**	 **2i**	 **3i**	96
10	 **1b**	**2a**	 **3j**	90
11	 **1c**	**2a**	 **3k**	95

(*Continued*)

Table 2. Continued

Entry	Acyl chloride	Alkyne	Product	Yield^{b} (%)
12	 **1d**	**2a**	 **3l**	89
13^{c}	 **1e**	**2a**	 **3m**	55
14	 **1f**	**2a**	 **3n**	85
15	 **1g**	**2a**	 **3o**	95
16	 **1h**	**2a**	 **3p**	91
17	 **1i**	**2a**	 **3q**	92
18	**1d**	**2c**	 **3r**	93
19	**1d**	**2d**	 **3s**	98
20	**1b**	**2 g**	 **3t**	93
21	**1c**	**2f**	 **3u**	92
22	**1i**	**2i**	 **3v**	88

[a] Reaction conditions: acid chloride (1 mmol), 1-alkyne (1 mmol), Pd(PPh$_3$)$_4$ (0.5 mol %), ZnCl$_2$ (1.2 mmol), and Et$_3$N (2 mmol), 30 min.

[b] Isolated yields.

[c] Use DIEA as base.

Table 3. Coupling reaction of benzoyl chloride (**1b**) with phenyl acetylene (**2a**) in different conditions[a]

Entry	Catalysts	Yield[b] (%)
1	Pd(PPh$_3$)$_4$	95/0
2	—[c]	0/37
3	Pd(OAc)$_2$[d]	60/26
4	Pd(PPh$_3$)$_4$[e]	50/35

[a] Reaction conditions: acid chloride (1 mmol), 1-alkyne (1 mmol), Pd catalyst (0.5 mol %), $ZnCl_2$ or $ZnBr_2$ (1.2 mmol), and Et_3N (2 mmol), 30 min.

[b] Ynones yield/anhydride yield.

[c] No catalyst was used.

[d] Palimkar's method.

26% yield of benzoic anhydride were obtained (Entry 3, Table 2). Similarly, only 50% yield of **3a** and 35% yield of benzoic anhydride were obtained without $ZnCl_2$ or $ZnBr_2$ (Entry 4, Table 2) in this paper. So our method is highly effective for the coupling reaction of acyl chlorides and terminal alkynes.

To examine the scope of this coupling reaction, various benzoyl chlorides **1** containing either electron-withdrawing or electron-donating groups were coupled with different terminal alkynes **2** (Table 3). The results show that this reaction is equally facile with both electron-donating and electron-withdrawing substituents present on the acyl chloride and affords excellent yields of the corresponding ynones. The reaction is tolerant of a wide range of functional groups on the acetylene (Table 3), in particular aryl, alkyl, and heterocycle groups are compatible, all giving isolated purified products in high yields. Hetero-aryl acid chloride (furoyl chloride (Table 3, entry 12)) and α,β-unsaturated acyl chloride (p-methyl cinnamic chloride (Table 3, entry 15)), reacted smoothly with phenyl acetylene to give the isolated products in 89% and 95%, respectively. In the case of propionyl chloride, **1e**, a bulky diisopropylethylamine (DIEA) was employed instead of Et_3N to avoid direct reaction of the amine with the linear aliphatic acyl chloride[19,21], whereupon a satisfactory isolated yield of **3m** was obtained (Table 3, entry 13).

In conclusion, we have developed a simple, efficient, and rapid solvent-free synthesis of ynones at room temperature by the coupling of acyl chlorides with in situ–generated alkynylzinc derivatives, catalyzed by Pd(PPh$_3$)$_4$ using Et_3N as the base. The simple procedure, short reaction times, good selectivity, and excellent isolated yields make this method well suited for the generation of a combinatorial library of ynones.

EXPERIMENTAL

A mixture of $ZnCl_2$ or $ZnBr_2$ (1.2 mmol) in Et_3N (202 mg, 2 mmol) was stirred for 10 min at room temperature. The reaction mixture was then successively treated with alkyne (1 mmol), Pd(PPh$_3$)$_4$ (6 mg, 0.5 mol%) and acyl chloride (1 mmol), stirred for 30 min at room temperature, diluted with Et_2O, washed with aqueous NH_4Cl and then with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum to give the product, which was further purified by column chromatography using hexane/EtOAc (20:1) as eluent.

Please see the Supporting Information, available online, for complete experimental details.

ACKNOWLEDGMENTS

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